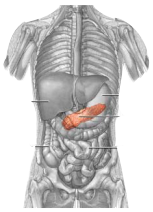
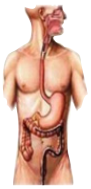
EMJ

December 2012
emjreviews.com

Gastroenterology





Inside: Review of the 20th United European Gastroenterology Week 2012, Amsterdam.

Page 8

Editorial Panel

GASTRO ENTEROLOGY

Prof. Abe Fingerhut,

FACS, FRCPS (g), FRCS (Ed), President ESTES 2010 - 2011 (European Society for Trauma and Emergency Surgery); President European Association for Endoscopic Surgery 2009 - 2011; Professor, First Surgical Department Hippokrateon Hospital, University of Athens, Athens, Greece

Prof. Najib Haboubi,

President Association of Coloproctology of Great Britain & Ireland 2009/2010; Honorary Professor University of Salford Manchester, Visiting Professor of Health Sciences, John Moore's University, and Liverpool, UK. Department of Pathology, University Hospital of South Manchester

Prof. Mark Hull,

Professor of Molecular Gastroenterology, Leeds Institue of Molecular Medicine, St. James's University Hospital

Dr. Tamara Matysiak-Budnik,

Professor of Gastroenterology, University of Nantes, France Council Member, European Association for Gastroenterology, Endoscopy and Nutrition (EAGEN)

Dr. László Madácsy,

Internal Medicine, Nuclear Medicine, Gastroenterology Specialist, Member of the Board, Hungarian Society of Gastroenterology, Board Member, MGT Endoscopic Section, Member of the Board, MGT Capsule Endoscopy Working Group, Committee member, Endoscopic ESGE European Society Education, Honorary associate professor, University of Szeged

Dr. Fabio Marra,

Associate Professor of Medicine, University of Florence, School of Medicine

Dr. Soren Meisner,

Head of Endoscopy Unit, Surgical Department K, Bispebjerg Hospital, Member of the Stoma Research Board, Chairman of the Danish Society for Gastroenterology's 'Endoskopiudvalg', Member of the Board, DMCG-PAL, Member of the Board, Scandinavian Association for Digestive Endoscopy, Member of ANDRE, Nordic Group for Research and Development in Advanced Therapeutic Endoscopy

Prof. Dr. István Rácz,

Professor of Medicine, 1st Department of Internal Medicine and Gastroenterology, Petz Aladár County and Teaching Hospital, Gyor, Hungary

Prof. Davor Stimac,

Head of Gastroenterology, Internal Clinic Department at University Hospital Rijeka; Former President of Croatian Society of Gastroenterology, Current President of Croatian Pancreatic Club; Member of European Board of Gastroenterology

Contents

EMJ

EUROPEAN MEDICAL JOURNAL - GASTROE

editor@congressreviews.com
www.emjreviews.com

Carlton House
101 New London Road
Chelmsford
Essex
CM2 0PP

Publisher
Editorial Director
Editor
Assistant Editor
Medical Writers

Project Manager

GASTRO ENTEROLOGY

Welcome...

I am very pleased to welcome you to our very first edition of ***European Medical Journal – Gastroenterology.*** This publication aims to provide readers with high quality articles, written on a variety of interesting and current topics by some of the leading healthcare professionals in the field of Gastroenterology.

This inaugural edition features articles on topics such as pancreatic disorders, gastro-oncology, and endoscopy which we hope will grab both your interest and attention.

As well as providing what aims to be an array of thought provoking articles, ***European Medical Journal – Gastroenterology*** also presents a review of the 20th United European Gastroenterology Week which took place during October in the cultural city of Amsterdam. This year, UEG celebrated its 20th year as one of the largest Gastroenterology congresses, which sees more than 12,000 visitors attend each year. This year's congress offered a fantastic insight into new technologies and advances in the field of Gastroenterology and as expected was a great success.

I hope that ***European Medical Journal – Gastroenterology*** becomes a useful and interesting tool for healthcare professionals by continuing to provide fascinating articles and unique, in house congress reviews.

At ***European Medical Journal***, we are pleased to receive feedback, topic suggestions or any comments that you might have, especially for this first edition. In turn, we will aim to provide an unprecedented, ongoing and captivating series.

Christine Dutaut, Editor

FOREWORD

I have great pleasure in welcoming you to the first edition of ***European Medical Journal – Gastroenterology***.

EMJ endeavours to provide open-access journals with breaking news, analysis and access to information of unparalleled quality and this edition is of no exception. A stimulating mix of review articles, theoretical discussions and original research stand together with our congress review to promote discussion and inquiry.

Included is an in-depth review of the United European Gastroenterology Congress Week 2012, held in October in Amsterdam, with concise news coverage and insight into the key developments presented there. This year's Congress Week was a particularly special event celebrating twenty years of the assembly of top experts from around the globe to present, discuss and analyse research and treatment advances in the field of gastroenterology to continuously broaden knowledge and the ability to treat liver and gastrointestinal diseases.

Summarising developments and celebrating clinical advances from the past twenty years, particular focus for future research was placed upon endoscopy and digestive cancers. Furthermore, UEG expressed their keen intent in the widespread promotion of colorectal cancer screening and awareness of the disease which has become one of the most common cancers in the EU.

This edition of ***European Medical Journal – Gastroenterology*** also includes comprehensive, informative articles authored by key opinion leaders on the current research of conditions such as acute pancreatitis and advanced cholangiocarcinoma. An extensive spectrum of information and diverse treatments such as gut-directed hypnotherapy and the first in-human study of an electronic capsule are discussed, as well as the role of environmental risk factors such as obesity, poor diet, smoking, lack of exercise in digestive cancers.

It is essential that physicians are kept up-to-date and informed and ***EMJ*** are fully committed to advancing learning, knowledge and research worldwide. We sincerely hope that ***European Medical Journal – Gastroenterology*** will assist physicians, clinicians and leading industry professionals to continuously develop their effectiveness and productivity.

Dorothy James, Editorial Director

20th United European Gastroenterology Week

Amsterdam, The Netherlands, October 20-24, 2012

Welcome to the *European Medical Journal* revi Gastroenterology Week

The United European Gastroenterology society proudly celebrated its 20th UEG Week during October in Amsterdam this year. The congress saw a large number of participants attend from 125 different countries.

As one of the most renowned gastroenterology societies, UEG unites many leading European societies whose primary concern lies with digestive and liver disease – just some of its founding members include the European Association for the Study of the Liver (EASL), European Society of Gastrointestinal Endoscopy (ESGE) and International Society of Digestive Surgery, European Federation (EFISDS).

UEG aims to constantly advance the understanding of digestive and liver disease and also aims to raise awareness and the level of care in gastroenterology. In order to achieve this, UEG offer various different education and training courses offered by respected experts in the field of gastroenterology, as well as holding their annual congress – UEG Week.

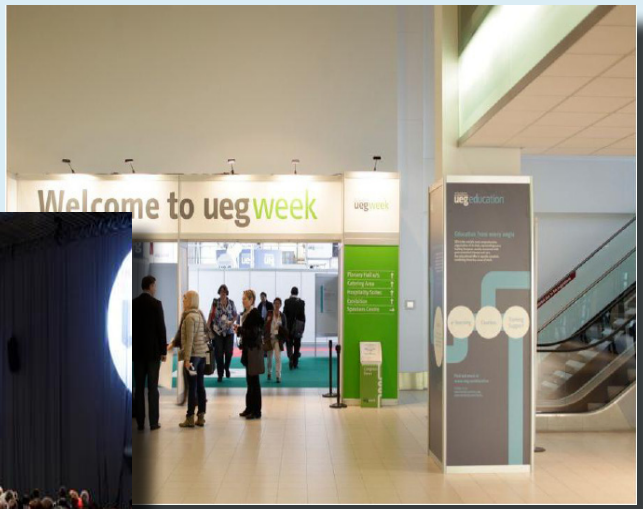
UEGW has developed over the decades into one of the most recognised annual Gastroenterology

iew of the 20th United European

congresses. The event has been known to attract large numbers of healthcare professionals concerned with digestive and liver disease, and this year was no exception as it saw UEG's best ever turnout.

This year, over 14,000 people descended into the cultural city of Amsterdam between the 20-24th of October. Amsterdam is one of the most diverse cities in the world and boasts the largest number of landmarks and museums per square mile than any other city in Europe, making it the perfect location for informal business meetings. The Rijksmuseum, Anne Frank House and the Van Gogh museum are just some of the attractions that can be found in this historical city. The city is also host to The Netherlands largest convention centre, the RAI, which hosted UEGW 2012.

UEG Week saw researchers from around the world present their latest research; it also featured a postgraduate course which attracted some of the leading lecturers for two days of interactive learning. Some of the 'special themes' demonstrated at UEGW included 'the modern role of multidisciplinary care' and 'the effect of obesity and alcohol on GI and liver disease' both very current topics affecting many gastroenterologists today.



CELEBRATING 20 YEARS OF U
A NEW JOURNAL AND RENEW
COLORECTAL CANCER IN EUR

The 20th anniversary of United European Gastroenterology (UEG) represents a significant milestone in the history of the organisation. Twenty years ago almost to the day, scientists and clinicians gathered in the ancient city of Athens to take part in the First United European Gastroenterology Week, where seven major European societies came together to form the United European Gastroenterology Federation (UEGF, now UEG). At the 20th UEG Week (UEG Week 2012) held in Amsterdam, the Netherlands, UEG President Professor Colm O'Morain, a gastroenterologist from Trinity College in Dublin, Ireland, told journalists that planning for the next 20 years has already begun. "UEG is very proud to celebrate its past, but looks forward with confidence to the future," he said. "The last year has witnessed major developments throughout the organisation, helping to build on our reputation as a driving force in Europe representing specialists in digestive and liver diseases. We now have a new corporate identity, a new central office in Vienna, a new UEG journal under development, and a very long list of what we want to achieve over the next 20 years."

UEG past and present

When UEG (then the UEGF) was founded in 1992, its main aim was to foster European co-operation in gastroenterology, primarily by organising an annual meeting where European researchers could present their work. Today, with 15 European and 41 national societies on-board, UEG's broader mission is to improve standards of care in gastroenterology and promote greater understanding of digestive and liver diseases amongst both the general public and within the medical profession. This,

> ***"Although our flagship event is still the annual UEG Week meeting, whi leading congress on the internatio as an organisation, we are active t the year campaigning for better ca tients with digestive disorders"***

says Prof. O'Morain, can only be achieved by the year round commitment of a dedicated team of volunteer officers supported by a professional secretariat.

"Although our flagship event is still undoubtedly the annual UEG Week meeting, which is now a leading congress on the international circuit, as an organisation, we are active throughout the year campaigning for better care for patients with digestive disorders," he said. "We have become increasingly successful at a political level and are proud to have influenced European affairs in terms of promoting colorectal cancer screening and a healthy lifestyle. However, we still have a very long way to go."

UEG and the fight against colorectal cancer

UEG is committed to working across the European Union (EU) to raise awareness of colorectal cancer (CRC) and encourage more countries to implement CRC screening programmes. According to Prof. O'Morain, CRC is now one of the most common cancers in the EU, with 400,000 new cases of CRC and 200,000 CRC related deaths reported in the EU each year.

UEG WITH A NEW HEADQUARTERS, VED DETERMINATION TO FIGHT OPE

> ***undoubtedly ich is now a nal circuit, hroughout re for pa-***
>
> ***Prof O'Moran***

"We know that CRC is associated with environmental risk factors such as smoking, obesity, a lack of exercise and a poor diet, so it is important we help to educate the general public about how they can reduce their risk of developing this type of cancer," said Prof. O'Morain. "CRC screening programmes are another vital way of reducing the number of deaths from CRC in Europe, and we are pleased that some EU countries have now introduced CRC screening within their populations."

Prof. O'Morain expressed his disappointment over the recent failure of the European Commission to support further action to reduce the impact of CRC and other cancers of the digestive system, pointing out that only 8 of the 27 EU Member States had introduced nationwide population-based CRC screening programmes so far. "It doesn't make any sense," he told journalists. "On the one hand, you have the European Parliament officially adopting a Written Declaration to fight colorectal cancer in the EU – supported by almost all MEPs – and on the other hand, you have the European Commission believing they have done enough already to reduce the impact of digestive cancer.

"We need the political will to succeed in providing colorectal cancer screening for everyone in Europe and we intend to do everything in our power to achieve that goal."

BOWEL CANCER SCREENING PROGRAMME V EACH YEAR IN THE NETHERLANDS

A national programme for bowel cancer screening, which is being introduced across the Netherlands in 2013, looks set to prevent thousands of deaths from this common type of cancer. The programme has taken 10 years to plan and organise, however, according to Professor Ernst Kuipers, Chief of the Department of Gastroenterology and Hepatology at the Academic Hospital in Rotterdam, speaking to journalists at the 20thUnited European Gastroenterology Week in Amsterdam, the Netherlands, the wait will have been worth it. "We are extremely pleased that after very careful preparation and analysis of extensive pilot studies[(1)], our national screening programme has been given the go-ahead," he said. "It is likely to have a significant impact on colorectal cancer mortality in the Netherlands and is of major importance for the population in our country."

Bowel cancer in the Netherlands

Bowel cancer is one of the most common types of cancer in the Netherlands. Over 12,000 new cases of bowel cancer are diagnosed each year, and without intervention this figure is expected to reach 14,000 per year by 2015.[(1)]Around 4,800 people die as a result of the condition every year.[(1)]

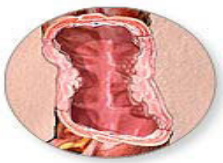
Bowel cancer usually starts as polyp – a small growth on the surface of the large intestine. Only a small proportion of polyps grow into tumours, however, over time, those that do can invade the intestinal wall and eventually spread to other organs. 9 out of 10 cases of bowel cancer develop in people over the age of 55 years.

"The early stages of bowel cancer are relatively easy to treat, with a good chance of achieving a cure," explains Prof. Kuipers. "Important warning signs are unexplained changes in bowel habit, such as the development of constipation or diarrhoea, blood in the stools, persistent abdominal pain and/or weight loss for no obvious reason, and anaemia."

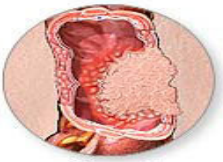
How is bowel cancer detected?

Bowel cancer is usually detected using two types of tests: a faecal occult blood test (FOBT) and colonoscopy. The FOBT is done on a stool sample collected using a home kit and can detect invisible traces of blood in the stool, which may indicate the presence of a polyp or cancerous lesion. If the FOBT is found to be positive, the individual is referred for colonoscopy, which allows the whole of the large intestine to be examined using an endoscope.

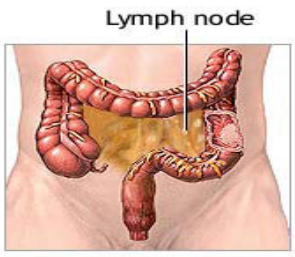
"Colonoscopy is the gold standard for detecting polyps and bowel cancer," says Prof. Kuipers. "Most polyps can be removed during the initial colonoscopy procedure, thereby significantly reducing the risk of them progressing to bowel cancer."



Stage I



Stage II



Stage III

VILL SAVE THOUSANDS OF LIVES

> ***"The early stages of bowel cancer are relatively easy to treat, with a good chance of achieving a cure. Important warning signs are unexplained changes in bowel habit, such as the development of constipation or diarrhoea, blood in the stools, persistent abdominal pain and/or weight loss for no obvious reason, and anaemia."***
>
> ***Prof. Kuipers***

The national screening programme

The national bowel cancer screening programme in the Netherlands will screen men and women aged 55–75 years every 2 years using a self-administered highly sensitive immunochemical FOBT. Stool samples will be taken at home using a special kit and sent to a laboratory for testing. People with a positive FOBT will be invited for a colonoscopy examination. The programme will be introduced in phases, with the first batch of invitations due to go out in September 2013 to people aged 65–75 years.

"This is a massive undertaking," says Prof. Kuipers. "Once the programme is up and running, more than 2 million people will be invited for screening each year and approximately 1.3 million FOBTs are expected to be analysed. This is likely to result in around 70,000 colonoscopies every year, which will have a significant impact on gastroenterologists around the country, increasing the colonoscopy workload by around 50%."

Prof. Kuipers believes that gastroenterologists will do everything they can to deliver a first-class service and meet the strict quality assurance standards required.

"In the long term, this national screening programme will benefit about 2,400 people a year who would otherwise die from bowel cancer, and an even larger number who would otherwise have required intensive oncological treatment," he says. "As gastroenterologists, we are proud to be part of this new public health initiative, which should improve bowel cancer outcomes in the Netherlands forever."

Reference

1. National Institute for Public Health and the Environment. Feasibility Study Into Population Screening for Bowel Cancer; 2011.

DYSFUNCTION OF GUT–BRAIN SIGNALLING PLA UNEXPLAINED GI SYMPTOMS AND FOOD INTAK

The importance of interactions between the digestive system and the brain has been recognised for centuries. Now, scientists believe that a dysfunction in gut–brain signalling plays a major role in the generation of unexplained gastrointestinal (GI) symptoms and in food intake disorders such as obesity and eating disorders.[1-2] Dr Lukas Van Oudenhove from the University of Leuven in Belgium – and a UEG 'Rising Star'* – says that while knowledge about the common neurobiological substrate being involved in processing gut–brain signals is rapidly growing, researchers must now work together to develop a fully integrated view of these disorders, including clarifying the role of psychological factors such as anxiety and depression. "An integrated view of both functional GI and food intake disorders is needed to make progress in unravelling their poorly understood pathogenesis," he told journalists at the 20th United European Gastroenterology Week in Amsterdam. "Unfortunately, research is currently being hampered by dualism, with some scientists focusing exclusively on peripheral mechanisms, while others are focussing only on central mechanisms."

Gut–brain signalling in health

The gut–brain axis is a bidirectional neurohumoral signalling system that continuously provides information on the homeostatic condition of the body to the brain. In the brain, this information is integrated with exteroceptive signals (olfactory, visual etc) as well as input from the brain reward system and affective and cognitive brain circuits. This system, which intrinsically links homeostatic signals to emotions, motivates the organism to take action and maintain its integrity when homeostasis is disturbed or threatened, thereby increasing the chances of survival.

As Dr Van Oudenhove explained to journalists, in health, food digestion and absorption remains largely unperceived, with only a small fraction of the continuous stream of interoceptive gut–brain signals – those requiring a behavioural response (e.g. pain and hunger) – reaching consciousness. This, he said, is due to a sensory filtering process that involves both the reward system and 'top-down' projections from affective and cognitive circuits in the brain. Profound changes in gut–brain signalling, most notably plasma levels of gut peptides, follow the cycles of hunger and food intake.

"Together with the neural pathways signalling gastric distention and digestion of nutrients, these peptides are critical players in homeostatic gut–brain signalling that control feeding behaviour," he said.

> ***"Research is currently being hampered by dualism, with some scientists focusing exclusively on peripheral mechanisms, while others are focusing only on central mechanisms."***
>
> **Dr van Oudenhove**

Gut–brain signalling dysfunction

Abnormalities in gut–brain signalling can result in dysregulation of food intake Including abnormal appetite and feeding behaviour. Similarly, the unpleasant subjective experience of visceral pain results from a dysfunction of the sensory filtering process, allowing non-noxious stimuli in the gut to be perceived as painful. Visceral pain, which may result from this signalling dysfunction, is a core symptom of functional GI disorders such as functional dyspepsia (FD) and irritable bowel syndrome (IBS). "So when things go wrong with the signalling pathways between the gut and the brain, we see visceral pain syndromes developing

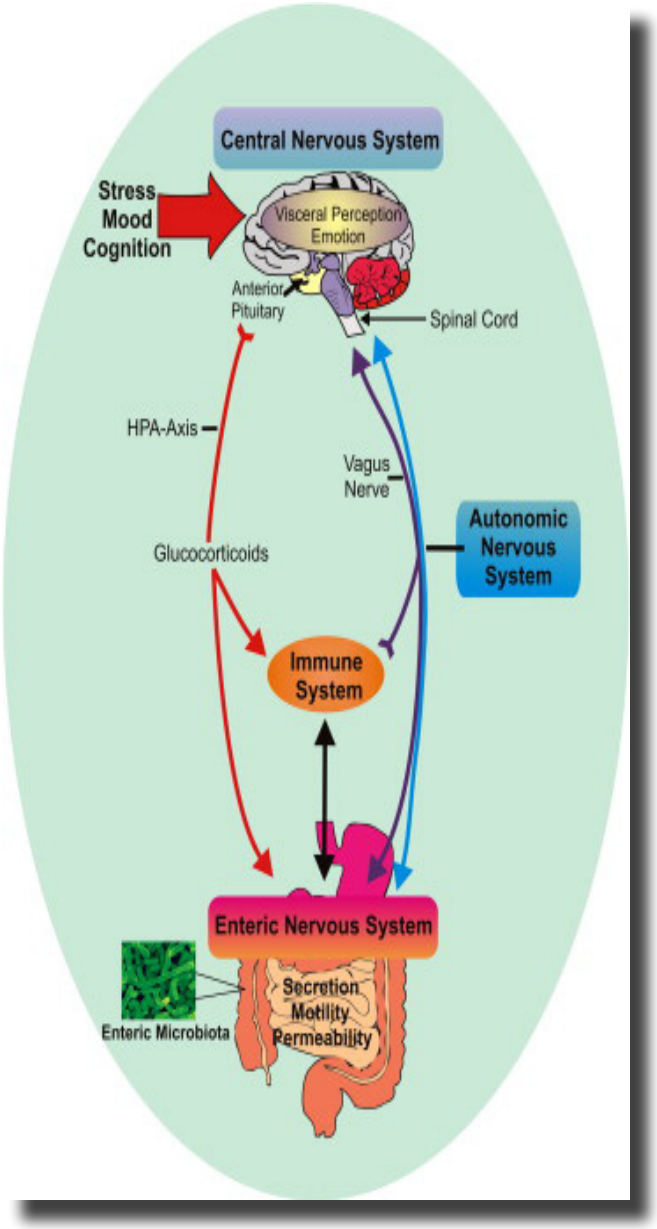
YS MAJOR ROLE IN DEVELOPMENT OF E DISORDERS

that may ultimately be diagnosed as FD or IBS," explained Dr Van Oudenhove. "We can also observe unexplained weight loss or the development of obesity, which are both hallmarks of food intake dysregulation."

Taking an integrated approach

Dr Van Oudenhove is keen to encourage an integrative approach to the study of visceral pain and food intake, combining neurophysiological, psychological/ behavioural and biochemical methods to investigate the interaction between peripheral and central mechanisms – an approach currently being taken in his own research centre. Recent research in which Dr Van Oudenhove has been involved has already helped to better define the associations between psychological factors and gastric sensitivity and how nutrient intake affects gut–brain signalling and emotion. He hopes these and other studies will eventually lead to the identification of novel treatment targets for functional GI and food intake disorders.

"Identifying novel treatment targets is extremely important given the currently limited treatment options for these disorders," he says. "These might include targeting psychological processes using psychotherapeutic techniques as well as targeting central and peripheral biological mechanisms with pharmacological treatments or even novel brain stimulation techniques," he concluded.



References

1. Van Oudenhove L, Vandenberghe J, Demyttenaere K, et al. *Psychosocial factors, psychiatric illness and functional gastrointestinal disorders: a historical perspective. Digestion 2010;82:201–10*

2. ***Mayer EA.*** *Gut feelings: the emerging biology of gut-brain communication. Nat Rev Neurosci 2011;12:453–66*

*UEG's 'Rising Star' initiative provides an internationally-renowned platform for young gastroenterologists to present their research findings to a large, experienced audience. The 'Rising Stars', who must be ≤40 years of age, are selected by the UEG National Societies Committee and the Scientific Committee.

MINIMALLY INVASIVE SURGERY: "THE GREATEST SURGICAL PRACTICE SINCE THE 1950s"

The introduction of minimally invasive surgery two decades ago has been coined "the greatest revolution in surgical practice since the 1950s" by Professor of Surgery, Jaap Bonjer from the VU University Medical Centre in Amsterdam, the Netherlands. Speaking to journalists at the 20th United European Gastroenterology Week in Amsterdam, Prof. Bonjer highlighted the benefits of minimally invasive surgical techniques and urged healthcare professionals to work together to integrate care, minimise post-surgical complications and speed patient recovery. "Two of the most significant developments in surgical practice over the past 20 years have been the introduction of minimally invasive surgery and the use of post-operative fast-track therapy," he said. "We need to take a more integrated approach to patients who undergo surgery, with healthcare professionals combining treatment methods such as these to optimise patient outcomes."

> ***"I would like to see the scope of minimally invasive surgery broadened by embedding innovative technology into the training of healthcare professionals."***
> ***Prof Bonjer***

Minimally invasive surgery

Minimally invasive surgery uses relatively small incisions in the skin, small-calibre instruments, and a video endoscope to facilitate meticulous dissection and reduce damage to healthy tissues during the procedure. Minimally invasive surgery has in many circumstances replaced traditional open surgery, which is associated with significant post-operative pain, prolonged hospitalisation and a tendency towards the development of incisional hernias.

"The merit of minimally invasive surgery is the reduction of surgical trauma by avoiding large incisions and using fine instruments in an operating field magnified by video-endoscopic imaging," explained Prof. Bonjer.

Removal of the gallbladder (cholecystectomy) was the first type of surgery in which a minimally invasive technique was applied and it is now the standard surgical approach used for this operation. Hiatal hernia repair, weight loss surgery, and removal of adrenal tumours are also now preferentially performed minimally invasively. As Prof. Bonjer explained, although it had been anticipated in the early 1990s that minimally invasive surgery would also quickly replace open colorectal surgery and open inguinal hernia repair – two very common procedures in general surgery – adoption by surgeons has been relatively slow.

"The benefits of using laparoscopic resection of either colon cancer or rectal cancer were debated for many years," he said. "Only when randomised studies generated long-term survival rates similar to those after open surgery was the surgical community adequately reassured, which is reflected in the growing number of laparoscopic colorectal procedures now being performed. In the Netherlands, for example, half of all colorectal surgeries were completed laparoscopically in 2011." Rates of conversion to open surgery are relatively low with these procedures (<15% with colon surgery and <20% with rectal surgery).

Post-operative fast-track therapy

According to Prof. Bonjer, a good recovery after surgery reflects the combination of good quality pre-operative care, surgery and post-operative care. He said protocols had now been established to optimise the condition of the patient before surgery and to accelerate post-operative recovery. These protocols are referred to as "Enhanced Recovery After Surgery (ERAS)" programmes or fast-track programmes and involve using carbohydrate-

T REVOLUTION IN

loaded fluids before surgery, limiting the use of fluids during and after surgery, early post-operative feeding and early mobilisation.

"An important component of fast-track protocols is communicating clearly and in a timely manner with the patient and providing detailed information on the expected peri-operative course," said Prof. Bonjer. "Dedicated teams of healthcare professionals are required to apply fast-track protocols."

Benefits of combining both approaches

Prof. Bonjer noted that some surgeons had previously suggested that combining open surgery with fast-track protocols would yield outcomes at least similar to those of minimally invasive surgery. However, this was not supported by several studies comparing minimally invasive and open surgery, with or without fast-track protocols, which Prof. Bonjer described, highlighting one recent study performed by Dutch investigators in patients undergoing segmental resection of the colon as a treatment for cancer.[1] In this study, he said, laparoscopic resection combined with a fast-track protocol was associated with a significantly shorter stay in hospital, with patients in this treatment group discharged an average of 2 days earlier than patients treated with open surgery and a fast-track protocol.[1]

"Personally, I would like to see the scope of minimally invasive surgery broadened by embedding innovative technology into the training of healthcare professionals," said Prof. Bonjer. "I would also like to see dedicated multidisciplinary teams of healthcare professionals collaborating to integrate care for their surgical patients. Finally, I think funding of surgical interventions should be weighted according to outcome to encourage greater use of minimally invasive techniques and programmes that enhance recovery such as the fast-track programmes."

Reference

1. Vlug MS, Wind J, Hollmann MW, et al. *Laparoscopy in combination with fasttrackmultimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann Surg 2011;254:868-75*

IMMIGRANT DISEASES IN GASTROENTEROLOGY AND HEPATOLOGY: WHAT CAN WE LEARN FROM THE DUTCH EXPERIENCE?

Immigrants to Europe from other parts of the world may bring with them a range of different clinical challenges for gastroenterologists and other specialists working in digestive disorders. Studies undertaken in the Netherlands suggest that people from different ethnic backgrounds present with a unique spectrum of gastrointestinal illnesses, with some being more common and some less so than the indigenous population. Speaking to journalists at the 20th United European Gastroenterology Week in Amsterdam, Dr Ruud Loffeld from the Zaans Medical Centre in Zaandam, the Netherlands, said clinicians needed to be aware of these differences and to adapt their clinical approach accordingly. "People originating from other parts of the world can suffer from different diseases of the gastrointestinal tract," he said. "So in areas with high levels of immigration, clinicians can expect to see changing patterns of morbidity that may affect their daily practices."

Immigration and the Netherlands

According to Dr Loffeld, the Netherlands has always attracted a high level of immigration, with people from all parts of the world flocking to the country. One region in particular (the Zaanstreek region north of Amsterdam) is home to a large number of Turkish immigrants, who now make up around 10% of the region's population. This, says Dr Loffeld, presents a unique opportunity to study differences in gastrointestinal diseases in patients of Turkish descent compared with native Dutch people.

"The Turkish people in the Zaanstreek region are now third- or even fourth generation immigrants, and they all visit the local community hospital," Dr Loffeld explained. "This has enabled us to undertake a range of epidemiological studies over the years that have helped to define more clearly ethnic differences in the occurrence and consequences of common gastrointestinal disorders. "In our region, for example, the vast

majority of patients with hepatitis B or C are of Turkish descent, primarily because the prevalence of these conditions is higher in Turkey and intrafamilial infection is common. Fortunately, most of these patients are asymptomatic and have no liver damage."

Disease of the upper gastrointestinal tract

As Dr Loffeld explained, one of the most striking differences between Turkish immigrants and native Dutch people in terms of upper gastrointestinal tract conditions is in peptic ulcer disease. Studies have found that Turkish ulcer patients are mostly men, significantly younger than Dutch ulcer patients, and predominately Helicobacter pylori positive.[1] He said the prevalence of ulcer disease and H. pylori infection is decreasing in both populations,[2-3] however, unfortunately, the prevalence of reflux disease appears to be increasing amongst Turkish people.[3]

"Our studies suggest that the acquisition rate of H. pylori is decreasing in both Turkish and Dutch populations, with the prevalence of infection now less than 10% in the Dutch population living in this region,"[3] said Dr Loffeld. "At current rates of infection, however, it is likely to take until 2027 before this low level is achieved in the Turkish population.[3] "Of course, it doesn't help that resistance to some antibiotics used to treat H. pylori is particularly high in people of Turkish descent living in our region."[4]

Disease of the colon

Several differences in diseases of the colon between Turkish and Dutch populations living in the Zaanstreek region have also emerged. In one study,[5] the prevalence of diverticulosis of the colon (a common condition in which there are anatomical abnormalities in the colon wall leading to small pouches developing) was found to be extremely low. Another more recent study found that colorectal adenomas (pre-cancerous growths) and colorectal cancer are very rare in Turkish people, however, when colorectal cancer does occur in this population, it tends to strike at a younger age and be more aggressive.[6]

"From all of these studies, it is clear that different patterns of gastrointestinal disease emerge with different ethnic groups," concluded Dr Loffeld. "Clinicians should be aware of these differences in their daily practices.

> ***"People originating from other parts of the world can suffer from different diseases of the gastrointestinal tract, so in areas with high levels of immigration, clinicians can expect to see changing patterns of morbidity that may affect their daily practices."***
>
> ***Dr. Loffeld***

References

1. Loffeld RJ, van der Putten AB. *The occurrence of a duodenal or gastric ulcer in two different populations living in the same region: a cross-sectional endoscopical study in consecutive patients. Neth J Med 2001;59:209-12*

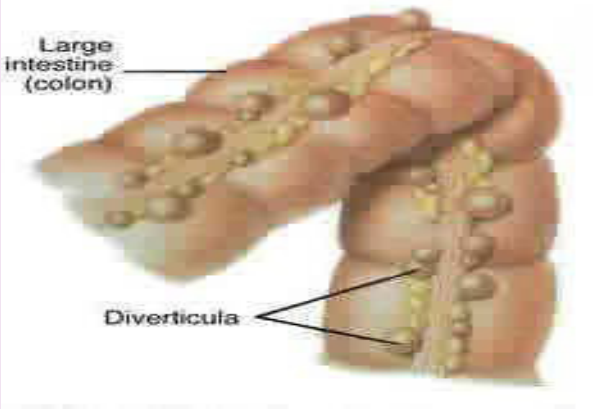
2. Loffeld SM, Loffeld RJ. *Changing morbidity pattern in oesophagus, stomach and duodenum in Turkish patients: a time-trend analysis. Neth J Med 2010;68:280-4*

3. Loffeld RJ, van der Putten AB. *Changes in prevalence of Helicobacter pylori infection in two groups of patients undergoing endoscopy and living in the same region in the Netherlands. Scand J Gastroenterol 2003;38:938-41*

4. Loffeld RJ, Fijen CA. *Antibiotic resistance of Helicobacter pylori: a cross-sectional study in consecutive patients, and relation to ethnicity. Clin Microbiol Infect 2003;9:600-4*

5. Loffeld RJ. *Diverticulosis of the colon is rare amongst immigrants living in the Zaanstreek region in the Netherlands. Colorectal Dis 2005;7:559-62*

6. Loffeld SM, Loffeld RJ. *Colorectal cancer and adenomas are rare in individuals of Turkish descent living in the Zaanstreek region in the Netherlands. J Cancer Res Clin Oncol 2010;136:1439-43*



LANDMARK STUDY CONFIRMS SMOKING CESSATION IMPROVES SYMPTOMS OF GASTRO-OESOPHAGEAL REFLUX: LATEST RESULTS FROM THE HUNT STUDY

A landmark study conducted in Norway has demonstrated that smoking cessation can markedly improve gastroesophageal symptoms (GORS) in some patients.[1] The study, involving almost 30,000 people with symptoms of reflux, found that individuals who quit or reduced their smoking experienced almost a two-fold improvement in severe symptoms compared with those who continued to smoke on a daily basis. This, said Dr Eivind Ness-Jensen from the HUNT Research Centre at the Norwegian University of Science and Technology and Levanger Hospital, provides compelling evidence that smoking cessation should be advised as a treatment strategy for gastro-oesophageal reflux disease (GORD). "We have known for some time that tobacco smoking is a risk factor for GORS,"[2] he told journalists at the 20th United European Gastroenterology Week. "Now, it seems that quitting smoking may be one of the best ways to improve these troubling symptoms."

GORD and its symptoms

Gastro-oesophageal reflux disease (GORD) presents a considerable and growing health problem in Western societies, affecting up to 20% of the population.[3] Symptoms of GORD include heartburn and acid regurgitation that are not only distressing and painful, but are also known to significantly increase the risk of adenocarcinoma of the oesophagus – a type of cancer with a relatively poor prognosis.[4-5]Although genetic factors are thought to be involved in the development of GORD and its symptoms, reflux is most likely to be caused by lifestyle factors including obesity, tobacco smoking, a lack of physical exercise, a low fibre diet, and a high salt intake.[2] Treatment includes moderating lifestyle factors, use of over-the-counter medications such as antacids, proton-pump inhibitors (PPIs), H2-receptor antagonists, and surgery when all else fails.

"Anti-reflux medications can be very effective at improving the symptoms of GORD, however, for many people, the symptoms are so frequent and severe that they require long-term regular use of these medications, which is far from ideal for the individual and imposes a massive burden on healthcare providers," explained Dr Ness-Jensen. "The long-term use of PPIs have been associated with adverse events, including increased risk of pneumonia, Clostridium difficile infections, and fractures, so alternative, non-surgical treatment approaches are desperately needed as the prevalence of this condition continues to rise."[3]

The HUNT study

The HUNT study is a landmark, prospective, longitudinal, population-based public health survey that was set up in the early 1980s in the Norwegian county of NordTrøndelag. Almost 75,000 individuals (representing 88%) of the population aged ≥20 years were originally involved. The study included 29,610 individuals who provided information on their GORS status in 1995–7 and 2006–9, allowing the association between quitting or reducing daily tobacco smoking and GORS to be evaluated. *This has been nominated as one of the five Top Abstracts at this year's UEG Week.

According to Dr Ness-Jensen, who is helping to run the study and presented these results for the first time at UEG Week 2012,[1] the study findings were undisputable. "We found that amongst participants reporting severe reflux symptoms and using regular anti-reflux medication, reducing or quitting daily tobacco smoking was associated with a two-fold improvement in reflux symptoms compared with those participants who continued to smoke every day," he said. "The association was more than five-fold amongst participants with a normal BMI, but we found no association in overweight participants. This probably reflects the strong association between obesity and GORD." The results were adjusted for sex, age, alcohol consumption, education, and physical exercise.

good evidence for the benefits of smoking cessation in many individuals with GORS – especially those experiencing severe symptoms. "The health benefits of smoking cessation are well-known and cannot be emphasised too strongly," he said. "Now we have demonstrated another clear advantage of quitting smoking if you have severe symptoms of gastric reflux. "On the basis of this and other studies, we believe that all patients with GORD should be advised to stop smoking tobacco," he concluded.

References

***1. Ness-Jensen E, Lindam A, Lagergren J, et al**. Decreased gastroesophageal reflux symptoms after tobacco smoking cessation in a prospective population-based cohort study: the HUNT study. Presentation at UEW Week 2012. Abstract UEGW12-3114*

***2. Nilsson M, Johnsen R, Ye W, Hveem K, et al**. Lifestyle related risk factors in the aetiology of gastro-oesophageal reflux. Gut 2004;53:1730-5*

***3. Ness-Jensen E, Lindam A, Lagergren J, et al**. Changes in prevalence, incidence and spontaneous loss of gastro-oesophageal reflux symptoms: a prospective populationbased cohort study, the HUNT study. Gut 2011 Dec 21. [Epub ahead of print]*

***4. Lagergren J, Bergström R, Lindgren A, et al.** Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825-31*

***5. Rubenstein JH, Taylor JB**. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. Aliment Pharmacol Ther2010;32:1222-7*

GUT-DIRECTED HYPNOTHERAPY SUPERIOR TO STANDARD MEDICAL THERAPIES IN CHILDREN WITH CHRONIC ABDOMINAL PAIN

Gut-directed hypnotherapy offers renewed hope for long-term symptom control in children and adolescents with functional abdominal pain and irritable bowel syndrome (IBS). Results from a randomised, controlled study suggest that up to 85% of children with these conditions could be symptom-free after hypnotherapy,[(1)] with the vast majority in remission almost 5 years later.[(2)]

Speaking to journalists at the 20th United European Gastroenterology Week, Professor Marc Benninga, a paediatrician from the Academic Medical Centre in Amsterdam, and one of the study's authors, said this suggests gut-directed hypnotherapy could be a highly valuable therapeutic option for these common, recurrent conditions. "Only a few studies have been conducted evaluating pharmacological and behavioural therapies for chronic abdominal pain in young people," he said. "Although more research is needed, this study certainly supports use of gut-directed hypnotherapy as a treatment approach for these conditions."

Chronic abdominal pain in children

Chronic abdominal pain is a common complaint amongst children and adolescents, accounting for 2–4% of all paediatric office visits and one quarter of all referrals to gastroenterology clinics. The pain typically waxes and wanes and is poorly localised within the abdomen. Two of the most common causes of chronic abdominal pain are functional abdominal pain (pain that has no objective evidence of an underlying disorder) and IBS, with the highest prevalence between the ages of 4 and 6 years and in early adolescence. While both are usually benign conditions, the pain associated with them can profoundly affect everyday activities leading to school absenteeism and social isolation; the child may be in considerable distress, and the parents are often extremely worried.

"Studies of children with chronic abdominal pain have revealed that quality-of-life scores are comparable to those of children with inflammatory bowel diseases such as ulcerative colitis and Crohn's disease," explained Prof. Benninga. "This highlights the clinical significance of this problem, which deserves far more attention than it currently receives."

According to Prof. Benninga, the aetiology and pathogenesis of functional gastrointestinal

disorders are still largely unknown, however, a growing body of evidence suggests that the pain results from a miscommunication between the gut and the brain. He says gut hypersensitivity, a heightened perception of pain messages from the gut, and problems with gut motility may also play a role.

What is gut-directed hypnotherapy?

Gut-directed hypnotherapy was first developed in the UK over 20 years ago for the treatment of IBS in adults. The technique involves inducing a mild hypnotic state and teaching the individual to understand how their gut works and how to create relaxing images they can associate with normal bowel function. Although a number of studies have found that hypnosis helps some adults with IBS when standard treatment fails, Prof. Benninga's study is the first to report the long-term outcomes of gut-directed hypnotherapy in children.

The study recruited 52 young people aged 8–18 years with chronic functional abdominal pain or IBS.[1] The youngsters were randomised to receive either six sessions of gut-directed hypnotherapy or standard medical care including dietary changes, increased fibre and use of pain medication plus six sessions of supportive counselling. Pain severity and pain frequency decreased in both groups, however, there was a significantly greater reduction in pain scores in the hypnotherapy group (P<0.001).[1] At the 1-year follow-up, successful treatment was achieved in 85% of the hypnotherapy group compared with 25% of the standard therapy group (P<0.001).[1]

"We have followed most of these children for an average of around 5 years, and we recently reported that 68% of the hypnotherapy group were in clinical remission compared with 20% of those from the standard therapy group (P=0.005),"[2] said Prof. Benninga. "This tells us that the beneficial effects of gut directed hypnotherapy are not only substantial in the short term, but are longlasting, making it a highly valuable therapeutic option for children with long-lasting complaints of IBS or functional abdominal pain."

References

***1. Vlieger AM et al**. Hypnotherapy for children with functional abdominal pain or irritable bowel syndrome: a randomized controlled trial. Gastroenterology 2007;133:1430–6*

***2. Vlieger AM et al.** Long-term follow-up of gut-directed hypnotherapy vs. standard care in children with functional abdominal pain or irritable bowel syndrome. Am J*

FIRST IN-HUMAN STUDY WITH NEW ELECTRONIC CAPSULE CONFIRMS FEASIBILITY OF REMOTE-CONTROLLED DRUG DELIVERY TO THE SMALL INTESTINE

The feasibility of delivering oral drug treatments to specific areas of the gastrointestinal (GI) tract has been confirmed by a first study in man using a new type of ingestible electronic "capsule". Findings were presented at the 20th United European Gastroenterology Week.[1] Researchers used the new device to remotely control the delivery of a radioisotope to the small intestine, bringing the possibility of targeted oral treatments for localised GI conditions even closer. Speaking to journalists at the meeting, Dr Peter van der Schaar – a gastroenterologist from the St. Antonius Hospital, Nieuwegein, in the Netherlands, who was involved in the study – said: "Guided by pH sensors in the capsule, confirmed by imaging, we were able to release the test compound into a short segment of the small intestine in 9 out of 10 of our volunteers. The capsule was easy to swallow and demonstrated to be safe and well tolerated (no adverse events were reported)."

IntelliCap® system: a new technology

The technology used in the study was developed collaboratively by Philips Research and Medimetrics in both the Netherlands and USA, with assistance from gastroenterology centres in the Netherlands. The IntelliCap® capsule is a compact capsule (measuring 27x11mm) comprising a drug reservoir, pH and temperature sensors, and a microprocessor. It incorporates an electromotor and piston designed to expel the contents of the

drug reservoir when remote commands are received. The capsule communicates via a wireless transceiver to an external control unit worn by the individual.

"The real-time wireless data recorder enabled us to monitor the capsule's progress through the GI tract, providing continuous measurements of pH and temperature," explained Dr van der Schaar. "The pH profile was especially important in determining exactly where the capsule was within the intestine, as there are significant changes in pH from the stomach to the duodenum and from the small intestine to the colon. This helped us target the test compound delivery to a prespecified region of the small intestine."

Success in first in-human study

This first in-human study was designed to test the safety and functionality of the IntelliCap® system using a commonly-used medical radioisotope that can be visualised in the gut by nuclear imaging. Ten healthy volunteers ingested an IntelliCap®capsule containing 99mTc-pertechnetate (99Tc) in the morning of the study. They were monitored during the day, going home overnight, and returning to the study centre the following morning. Nuclear images were obtained at predetermined timepoints. As soon as the capsule was confirmed to have passed the pylorus (determined by the pH changes transmitted), the capsule, via remote command, expelled its payload, delivering 75% of the total volume of the drug reservoir.

"After we released the 99Tc from the capsule, we could clearly see both the capsule and the radioisotope within the small bowel during nuclear scanning," said Dr van der Schaar. "The capsule's pH readings correlated well with what we could visualise using nuclear imaging, demonstrating that pH monitoring is an effective way of determining the location of the capsule within the gut." As Dr van der Schaar pointed out, in 9 out of 10 of the volunteers, the capsule precisely released its payload into the small intestine, which was confirmed by imaging.

Professor Peter Siersema, head of the department of gastroenterology of the University Medical Center Utrecht, where the study was conducted, believes this technology could have many different applications in the non-invasive and local treatment of GI disorders, as well as in diagnostics. "If we can deliver drugs to well-defined regions of the GI tract, we may be able to offer oral treatments that achieve high drug concentrations where they are needed most, which could improve both their effectiveness and tolerability. Moreover, the IntelliCap® system could also play a role in drug development."

Reference

1. van der Schaar P, Broekhuizen-de Gast H, Nijsen J, et al*. Remotely controlled, small intestinal release of 99mTc-pertechnetate using an ingestible electronic device: the*

FAECAL MICROBIOTA TRANSPLANTATION AS A TREATMENT FOR ULCERATIVE COLITIS: DOES THE EVIDENCE STACK UP?

Faecal microbiota transplantation (FMT) has occasionally been used for decades to treat gastrointestinal (GI) disorders and there is growing interest in using this approach as a treatment for ulcerative colitis (UC). Initial case series in UC reported entirely positive outcomes, however, a recent study conducted at the Medical University of Vienna in Austria suggests the treatment may not be as effective as previously thought. Speaking to journalists at the 20th United European Gastroenterology Week, Professor Walter Reinisch from the Department of Gastroenterology and Hepatology at the Medical University Vienna said results from a study conducted at his centre suggested that only a small proportion of patients with UC might benefit from FMT treatment. "We have now used FMT to treat five patients with moderately to severely active UC and we found a positive clinical response in only one patient," he said. "Although plenty of donor derived bacteria were established in all patients, successful colonisation by beneficial bacteria was achieved only in the one patient who had a good clinical response."

What is FMT?

Faecal microbiota transplantation (FMT) has been used for over 40 years in a variety of GI disorders that are resistant to standard therapies.[1] Some of the most promising results have been reported in patients with antibiotic-resistant Clostridium difficile (C. difficile) -related GI conditions, for whom a complete cure appears to be possible.[1] The technique involves the introduction into the recipient's intestine of carefully screened donor faecal samples using enemas, colonoscopies or nasojejunal intubation. In some centres, the recipient's bowel may be cleansed prior to transplantation using bowel lavage techniques and/or antibiotics.

"The rationale behind using FMT in conditions thought to be associated with abnormal or dysfunctional microbiota is that you are potentially repopulating an unhealthy intestine with 'healthy' or 'normal' flora," explained Prof. Reinisch. "We know from recent gene sequencing studies that FMT can rapidly normalise the gut microbiota in patients being treated for C. difficile-related GI disorders."[1]

FMT in ulcerative colitis: the evidence to date

Ulcerative colitis (UC) is a debilitating and potentially serious inflammatory bowel disease that affects the lining of the colon and rectum and leads to symptoms of abdominal pain, blood in the stools, diarrhoea and fever. Standard treatments include anti-inflammatory drugs such as sulfasalazine and immune suppressants and/or modifiers including corticosteroids, azathioprine, cyclosporine and infliximab.

"Although the pathogenesis of UC is still poorly defined, there is substantial evidence that the underlying inflammatory processes are associated with a microbial dysbiosis, supporting the potential use of FMT in this condition," said Prof. Reinisch.

The literature contains a few accounts of the successful use of FMT in UC.[2-3]In the largest cohort described to date,[4] six patients with a long history of severe, recurrent UC received FMT via enema daily for 5 days. Symptoms were reported to have improved by Week 1 post-treatment, with complete reversal of symptoms in all patients by 4 months and no recurrence in a follow-up ranging from 1 to 13 years. No adverse effects of treatment were noted. "This study suggests that FMT is an excellent treatment for unresponsive UC, and the results encouraged us to try the treatment in some of our own refractory patients," said Prof. Reinisch.

In Prof. Reinisch's study,[1] five individuals with moderately to severely active UC who had failed standard therapies received FMT via nasojejunal tube and enema. Clinical activity, adverse events and the faecal bacterial community were monitored for up to 12 weeks. All patients developed a fever with a temporary increase of C-reactive protein (CRP) during FMT. Abundant donor-derived bacteria were able to establish in all the recipients, however, the efficiency and stability of colonisation was highly variable between patients. A clinical response was observed at 12 weeks in only one patient.

"Our results were far less conclusive than those reported previously and highlight the need to understand more about what factors predict a good clinical response to FMT in UC," noted Prof. Reinisch. "Stable microbiota transfer appears to be essential to achieve a good outcome in these individuals."Prof. Reinisch admitted he and his team were surprised and somewhat disappointed that more of their patients did not respond to FMT treatment. "We were expecting a more positive result than we observed in this study," he said. "However, for the one patient who did have a good response after years of suffering, this was an excellent result."

References

1. Landy J, Al-Hassi HO, McLaughlin SD, et al. *Review article: faecal transplantation therapy for gastrointestinal disease. Aliment Pharmacol Ther 2011;34:409-15*

2. Bennet JD, Brinkman M. *Treatment of ulcerative colitis by implantation of normal colonic flora. Lancet 1989;1(8630):164*

3. Borody TJ, Warren EF, Leis S, et al. *Treatment of ulcerative colitis using fecal bacteriotherapy. J Clin Gastroenterol 2003;37:42-7*

SIMPLE RISK ASSESSMENT TOOL HELPS IDENTIFY PEOPLE FOR PRIORITY COLORECTAL CANCER SCREENING

A simple scoring system has been developed by scientists in Asia that can help to identify people at greatest risk of developing advanced colorectal cancer (CRC). The system uses readily-available information such as age, gender, family and smoking history to predict the risk of developing CRC and it can be used to prioritise people for CRC screening. Professor Joseph Sung from the Chinese University of Hong Kong, who was involved in developing and testing the tool, told journalists at the 20th United European Gastroenterology Week that although the system was developed with Asia Pacific countries in mind, it could be used in other regions. "Colorectal cancer is the second most common cancer in many Asia Pacific countries, and because of the large population, screening for CRC imposes a heavy burden in these regions," he said. "We set out to develop and validate a clinical score predictive of risk for advanced CRC specifically for Asia, however, the system could be applied in many other areas of the world."

The Asia Pacific Colorectal Screening (APCS) score

Development of the CRC screening tool was driven by the Asia Pacific Working Group on Colorectal Cancer Screening, which was set up in 2005 by a group of experts from six Asian countries. As Prof. Sung explained, a worrying increase in the incidence and rates of mortality from CRC in Asia[1] had prompted the development of consensus recommendations for CRC screening.[2] These, he said, aimed to improve awareness amongst healthcare professionals of the changing epidemiology of, and screening tests available for, CRC.

"We knew we had to take action to try and halt these worrying trends," said Prof. Sung. "Our own epidemiological studies had found that, contrary to what we believed, the incidence of CRC is just as high in Asia as it is in the USA and Europe.[1] We found that right-sided colonic adenoma is common and that certain groups such as Japanese, Korean and Chinese are more susceptible to developing CRC than others. We also found that male gender, advancing age and a family history of CRC were the strongest predictors of the disease."

Development and validation study

Armed with this information, the Asia Pacific Working Group then developed a simple scoring system based on age, gender, family history of CRC and smoking history (Table 1).[3] Using the system, risk scores for each factor (based on previous studies in Asia Pacific subjects) are assigned in the range of 0 to 3, with a total APCS score ranging from 0 to 7: a score of 0–1 is considered "average risk", 2–3 is "moderate risk" and 4–7 is "high risk".

The tool was tested in a prospective study carried out in 17 specialist hospitals in 11 Asian cities and involving 2,752 asymptomatic individuals undergoing screening colonoscopy.

Applying the APCS score, to which the endoscopists were blinded, to a sub-set of 1,892 individuals (the validation sub-set), 559 individuals (29.5%) were found to be in the low risk category, 966 (51.1%) were in the moderate risk group and 367 (19.4%) were in the high risk group. The prevalence of advanced CRC in the three groups was found to be 1.3%, 3.2% and 5.2%, respectively.

"This study confirmed the value of the APCS score in stratifying risk of advanced CRC," said Prof. Sung. "People in the moderate risk group were 2.6-times more likely to have advanced CRC when screened than those in the average risk group. Those in the high risk group were 4.3-times more likely to have advanced CRC at screening."

Table 1. The Asia-Pacific Colorectal Screening (APCS) score for prediction of risk for advanced CRC[3]

Risk Factor	Criteria	Points
Age	< 50 years	0
	50-69 years	2
	≤ 70 years	3
Gender	Female	0
	Male	1
Family history of CRC in 1st degree relative	Absent	0
	Present	2
Smoking	Never	0
	Current or past	1

Using the APCS score to prioritise screening

Prof. Sung believes the APCS score will prove invaluable in identifying individuals for priority CRC screening. "Ideally," he said, "everyone over the age of 50 years should be screened for CRC. However, this is simply not practical in most Asian countries where the population is large and national healthcare systems and health insurance cover only a small proportion of the population. Using this simple risk stratification tool,

References

1. Sung JJ, Lau JY, Goh KL, et al. *Increasing incidence of colorectal cancer in Asia: implications for screening. Lancet Oncol 2005;6:871-6*

2. Sung JJ, Lau JY, Young GP, et al. *Asia Pacific consensus recommendations for colorectal cancer screening. Gut 2008;57:1166-76*

3. Yeoh KG, Ho KY, Chiu HM, et al. *The Asia-Pacific Colorectal Screening score: a validated tool that stratifies risk for colorectal advanced neoplasia in asymptomatic Asian subjects. Gut 2011;60:1236-41.*

PHARMACOSMOS PRESENT AT UEGW

Pharmacosmos had significant presence at the Congress from both the company's Sales and Marketing team as well as from the Medical Affairs team reflecting the importance of the gastroenterology specialist area with regard to Monofer®.

Special themes this year included the modern role of multidisciplinary care and the effect of obesity and alcohol on gastrointestinal and liver diseases. There was a focus on inflammatory bowel disease (including treatment advances), two full days of live endoscopy, more on the expanding role of gastroenterologists in gastrointestinal oncology and a plethora of state-of-the-art lectures by established names and rising stars from all over the world.

Pharmacosmos had a very interesting Monofer-booth which focused mainly on our future: "Monofer - high dose iv iron in just one visit" had the purpose of attracting as many customers as possible.

ABBOTT ANNOUNCES DATA EVALUATING REDUCTION OF STEROID USAGE WITH HUMIRA® (ADALIMUMAB) IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS

At the 20th UEG Week, Amsterdam, Abbott announced results from a post-hoc analysis of the 52-week HUMIRA® (adalimumab) ULTRA 2 study. Results of the analysis showed that patients with moderately to severely active ulcerative colitis (UC) who failed, were intolerant or had contraindications to certain other medicines and achieved a response to HUMIRA® at eight weeks, were able to reduce corticosteroid doses at week 52.

In addition, results showed:

• Of those patients who were randomised to HUMIRA® and responded at eight weeks, the rate of patients able to discontinue steroids was 45.6 percent vs. 22.9% of placebo -treated patients.

• 20 percent of the HUMIRA® -treated eight-week responders were able to discontinue steroids for over 90 days and achieve remission defined by a Full Mayo score (Mayo score ≤2 with no sub scores >1) vs. 5.7% of patients receiving placebo.

"The cumulative dosage of steroids used to help manage ulcerative colitis has been associated with steroid toxicity—which may induce several metabolic disorders and complications in various organ systems. This is a major concern in patients of all ages, but particularly in young adults," said lead investigator Gert Van Assche, M.D., Ph.D., Professor of Medicine, University of Toronto and University of Leuven. "These data suggest that adalimumab-treated patients were able to reduce steroid usage, which is an important goal in the long-term management of this disease."

UC is an inflammatory bowel disease marked by ulcers in the colon and that may lead to life-threatening complications. It is estimated that 25 % of patients with UC may undergo surgical removal of the colon during their lifetimes, leaving patients with a permanent colostomy or ileal pouch.

HUMIRA® was also found to have a positive effect on mucosal healing in patients with moderate to severe active UC. Of the 494 patients included in the analysis and who responded at eight weeks, significantly more patients treated with HUMIRA vs. placebo achieved clinically relevant rates of mucosal healing at week 52 (responders per Full Mayo score=40.8%; responders per Partial Mayo score=43.1%; placebo=15.4%, p<0.001). Similar treatment effects at week 52 were observed regardless of prior anti-TNF use.

"HUMIRA® is one of the most comprehensively studied biologics on the market. Our scientific experience with HUMIRA® serves as a strong foundation to help fulfill unmet clinical needs in the management of ulcerative colitis," said John Medich, Ph.D., Divisional Vice President, clinical Development Immunology, Abbott. "Abbott continues to support the medical community with research to explore treatments that will help improve patient outcomes."

> *"Our scientific experience with HUMIRA® serves as a strong foundation to help fulfill unmet clinical needs in the management of ulcerative colitis."*
>
> *John Medich*

ABBOTT RECEIVES POSITIVE OPINION FROM CHMP FOR HUMIRA® USE IN PEDIATRIC CROHN'S DISEASE

Last month, Abbott announced that the European Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion for HUMIRA® (adalimumab) for the treatment of pediatric patients aged 6 to 17 years with severely active Crohn's disease (CD) who failed, are intolerant to or have contraindications to conventional therapy.Following the CHMP's positive opinion, a final decision from the European Commission is anticipated in the next several weeks. Upon final decision, HUMIRA® will be the only biologic in the European Union (EU) for the treatment of pediatric CD offering at-home administration.

Pediatric CD is a chronic, debilitating condition of the gastrointestinal (GI) tract that affects up to 200,000 children worldwide. CD most commonly involves the end of the small intestine and the beginning of the large intestine. In addition to symptoms such as chronic abdominal pain, weight loss and loose stools, pediatric CD can affect children in several ways, including potentially contributing to malnutrition, failure to grow and/or delayed puberty.

"Severe pediatric Crohn's disease symptoms can be extremely disruptive to a child's daily life and there are limited treatment options available," said John Medich, Ph.D., Divisional Vice President, Clinical Development, Immunology, Abbott. "Abbott is pleased pediatric patients and their caregivers may soon have access to a therapy that can be administered at home to help with the challenges of managing this disease."

Upon final approval, HUMIRA® will be indicated for the treatment of severe active Crohn's disease in pediatric patients (6 to 17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies.

Crohn's disease is especially difficult in the pediatric population due to its disruptive nature during a key time in physical and social development and can limit patients' opportunity to form relationships with peers and participate in regular activities

Disease progression in children is different from adults, with children developing complications from CD at a faster rate. CD is especially difficult in the pediatric population due to its disruptive nature during a key time in physical and social development and can limit patients' opportunity to form relationships with peers and participate in regular activities. Since there is no known cure for CD, the treatment goal of pediatric CD is to induce and maintain clinical remission, with restoration and preservation of normal growth as additional therapeutic goals.

The filing was supported by a Phase 3 dosing study, the IMAGINE 1 trial, which evaluated weight-based dosing strategies of HUMIRA® to induce and maintain clinical remission in pediatric patients with moderately to severely active CD.

BIOGAIA'S PROBIOTIC SAFE AND EFFECTIVE IN PREMATURE INFANTS

(NEC) the most common gastrointestinal cause of death and illness in premature infants, decreased by 40% in the infants supplemented by Lactobacillus reuteri Protectis compared to placebo.

Results from the largest probiotic study to date in premature infants showed that necrotizing enterocolitis (NEC), the most common gastrointestinal cause of death and illness in premature infants, decreased by 40% in the infants supplemented by Lactobacillus reuteri Protectis compared to placebo. Further, in the infants below 1500 grams Lactobacillus reuteri Protectis reduced episodes of feeding intolerance by 43%.

The safety of Lactobacillus reuteri Protectis in this high-risk population was also confirmed, but there was no significant difference between the groups on the primary outcome, frequency of death or hospital acquired infection.

"Although our study was under-powered to show significant differences in the primary outcome, the trends are consistent with those observed in meta analyses on NEC and death", says Professor Mario A. Rojas, Department of Pediatrics, Wake Forest School of Medicine, Winston-Salem NC, United States. "Unfortunately the study was terminated early, but despite this it is now confirmed that treatment of premature infants with Lactobacillus reuteri Protectis is both safe and clinically relevant", says Peter Rothschild, Chief Executive Officer at BioGaia.

Largest probiotic study in premature infants

A total of 751 infants were included in the study, which was considerably less than the number planned (1,110) and required to reach significance in the outcome parameters. The study was terminated early, which was related to substantial drops in recruitment rate and funding restrictions from the independent funding institute.

In the multi-centre, double-blind, randomised, placebo-controlled trial in nine neonatal intensive care units in Colombia, infants born prematurely, with a birth weight of 2000 grams or smaller, were randomised to two groups, one that was given five drops daily ofLactobacillus reuteri Protectis (BioGaia ProTectis, n=372) and one that was given a corresponding placebo (n=378). The study was published online in *Pediatrics* on 15 October 2012.

Necrotising enterocolitis – a fatal disease

NEC is the death of intestinal tissue. It predominantly affects premature infants and often results in death or serious medical or neurodevelopmental complications, such as cerebral palsy (CP) and cognitive, visual or hearing impairment. The rate of NEC is highest in the smallest neonates (<1500 grams) where around 10% of the infants are infected. The death rate ranges between 20 and 30%, with the highest rate among infants requiring surgery.

Lactobacillus reuteri – a well researched probiotic

Lactobacillus reuteri is one of the world's most well researched probiotics, especially in young children. To date 92 clinical studies using BioGaia's human strains of Lactobacillus reuteri have been performed in more than 7,700 individuals of all ages. Half of the studies have been performed in premature babies, infants and children. Results are published in 63 articles in scientific journals (September 2012).

LILLY ANNOUNCES POSITIVE RESULTS FOR RAMUCIRUMAB AS SINGLE AGENT IN PHASE III GASTRIC CANCER TRIAL

Eli Lilly and Company announced in October that the REGARD trial, a Phase III study of ramucirumab (IMC-1121B) in patients with metastatic gastric cancer, met its primary endpoint of improved overall survival and also showed prolonged progression-free survival. This trial is the first Phase III data read-out for ramucirumab.

Ramucirumab is a fully human IgG1 monoclonal antibody receptor antagonist designed to bind the extracellular domain of vascular endothelial growth factor (VEGF) receptor-2, thereby blocking the interaction of VEGF ligands (VEGF-A, VEGF-C, and VEGF-D) and inhibiting receptor activation. VEGF receptor-2 is considered a primary mediator of angiogenesis. When activated by VEGF ligands, VEGF receptor-2 promotes endothelial cell proliferation and survival, migration, and vascular permeability.

The REGARD trial is a Phase III randomised, double-blinded study of ramucirumab and best supportive care (BSC) versus placebo and BSC in the treatment of metastatic gastric or gastroesophageal junction adenocarcinoma following disease progression on first-line platinum- or fluoropyrimidine-containing combination therapy. The primary endpoint of the REGARD trial is overall survival and secondary endpoints include: progression-free survival; proportion of participants who are progression-free at week 12; proportion of participants with objective response, or objective response rate; duration of response; and safety.

The REGARD trial compared ramucirumab and best supportive care to placebo and best supportive care as a second-line treatment in patients with metastatic gastric and gastroesophageal junction cancers. The most frequent adverse reaction (any grade) occurring at a higher rate on the ramucirumab arm was hypertension (12%). Other adverse reactions (> 5%) occurring at a higher rate on the ramucirumab arm compared to the placebo arm were diarrhea and headache.

“We are pleased with this data of ramucirumab used as monotherapy in a second-line setting in this difficult-to-treat disease. It reinforces our confidence in the ramucirumab development program, in which we currently have six Phase III studies ongoing in five tumor types — breast, colorectal, gastric, hepatocellular and lung cancer,” said Richard Gaynor, M.D., vice president, product development and medical affairs for Lilly Oncology.

REGARD is one of two ramucirumab Phase III studies in gastric cancer. RAINBOW, a Phase III trial of ramucirumab in combination with paclitaxel, completed patient enrolment last month.

Lilly plans to present data from the REGARD trial at an upcoming scientific meeting and will discuss submission plans with regulatory authorities.

GIVEN IMAGING REPORTS NEW STUDIES ON PILLCAM® COLON 2 PRESENTED AT UEG WEEK

In October Given Imaging Ltd. a world leader in GI medical devices and pioneer of capsule endoscopy, announced three new studies confirming the value of PillCam® COLON 2 in a range of clinical settings, including as an evaluation tool for triaging FIT-positive patients for subsequent colonoscopy, for patients who are unable to undergo standard colonoscopy, and to assess the extent and severity of ulcerative colitis.

"These new studies underscore the value of PillCam COLON 2 and demonstrate a variety of cases in which it is useful," said Juan Manuel Herrerías Gutiérrez, MD, Universidad de Sevilla. "Capsule colonoscopy can serve as a filter for standard colonoscopy, and can also be an alternative to standard colonoscopy both in patients who have ulcerative colitis and in those who cannot or choose not to undergo colonoscopy."

GIVEN IMAGING REPORTS DATA SHOWING GREATE CAPSULE ENDOSCOPY IN DETECTING AND MONITO DISEASE

Capsule endoscopy found to be superior to magnetic resonance enterography

On October 24th, Given Imaging Ltd. a world leader in GI medical devices and pioneer of capsule endoscopy, announced results of two studies suggesting an increased role for capsule endoscopy in detecting Crohn's lesions in the small bowel.

"Capsule endoscopy for the detection of Crohn's disease in the small bowel has been clinically validated by a substantial and growing body of peer-reviewed research," said presenter Roberta Pica, M.D., Department of Clinical Sciences, Gastroenterology Unit at the Sapienza University of Rome. "As physicians, it's important to gather as much information as possible about the structural changes in the lining of the patient's small and large intestines to determine an accurate diagnosis and proper course of treatment. In this new study, early evidence shows that capsule endoscopy, widely considered the gold standard in small bowel visualisation, is superior to magnetic resonance enterography (MRE) as a reliable tool to evaluate the type and extent of mucosal lesions associated with small bowel Crohn's disease. This information can lead to a more precise course of treatment with the goal to improve patient outcomes."

Dr. Pica and colleagues presented the results of a prospective study comparing use of wireless capsule endoscopy (WCE) to magnetic resonance enterography (MRE) in the small bowel of 16 consecutive patients with confirmed or suspected Crohn's disease. In 9 of 10 patients (90%), WCE detected significant lesions as indicated by the presence of erythema, aphthous, ulcers, fissures or mucosal hemorrhages, with 5 patients showing lesions in both the jejunum and ileum and 5 only of the terminal ileum. MRE was less accurate than WCE, detecting inflammatory lesions in 11 of 15 patients (73%), with 2 patients showing lesions in both the jejunum and ileum and 9 in only the terminal ileum. In a group of 9 patients who were evaluated with both examinations, WCE detected lesions in 8 patients (90%), while MRE detected lesions in 6 (67%). In addition, 2 patients had a false negative on MRE and showed significant lesions in the terminal ileum with capsule endoscopy, and capsule endoscopy was able to exclude a false positive diagnosis of lymphoma suggested by MRE. The authors concluded that both tools are complementary methods for diagnosing small bowel Crohn's disease, noting that WCE represents a reliable tool in the evaluation of mucosal lesions

for th
while
altera

Separ
Depa
Hosp
show
patie
and a
reten
major
with
collea
ileoco
endos
estab
ident
bowe
occur
capsu
repor
CE u
estab

GI EN IMAGING

R ROLE FOR RING CROHN'S

y for detecting Crohn's disease

e direct visualisation of the mucosal surface, MRE enables physicians to diagnose specific ations of the bowel wall.

rately, Efstathios Saprikis, M.D., 2nd rtment of Gastroenterology, Evangelismos ital, Athens, Greece, presented a poster ing that small bowel capsule endoscopy in nts with established Crohn's disease is safe associated with a low percentage of capsule tion. When capsule retention did occur, the rity of the cases were adequately managed conservative treatment. Dr. Saprikis and agues identified 301 patients who underwent olonoscopy prior to small bowel capsule scopy. Among the 301 eligible patients with lished Crohn's disease, capsule endoscopy ified signs of Crohn's disease in the small l in 196 (65.1%). Capsule retention only rred in five patients (1.66%). These reported ule retention rates are in line with previously rted data as well as society guidelines for se in patients with suspected Crohn's or lished Crohn's disease.

AMONG THE STUDIES PRESENTED ABOUT PILLCAM COLON 2 AT UEG WEEK WERE:

Preliminary Results of Capsule Colonoscopy as a Filter Test Prior to Standard Optical Colonoscopy in a FIT Positive Screening Cohort by Ronan Leen, MD, Tallaght Hospital Dept. of Gastroenterology, Dublin, Ireland, and colleagues.

Investigators examined patients who had tested positively with Fecal Immunochemical Testing (FIT) and concluded that since PillCam COLON 2 is safe and well-tolerated with a high NPV (negative predictive value), it could serve as a filter test to determine which FIT positive patients should get standard colonoscopy. Data show that 49% of subjects who undergo standard colonoscopy after positive FIT do not have polyps or colon cancer. The authors conclude that by using PillCam COLON 2 as a filter test to select patients for OC in a screening population, physicians can avoid prescribing unnecessary colonoscopies to those without polyps after positive FIT.

Second-Generation Colon Capsule Endoscopy for Colorectal Cancer Screening in Patients Unable or Unwilling to Perform Colonoscopy by Lucian Negreanu, MD, PhD., Emergency University Hospital Dept. of Internal Medicine 2 Dept. of Gastroenterology, Bucharest, Romania, and colleagues.

Researchers aimed to assess the feasibility, accuracy, and safety of PillCam COLON 2 in detecting lesions in patients unable or unwilling to undergo colonoscopy. The researchers included 75 patients with average or increased risk of colorectal neoplasia in their study, all of whom were unable or unwilling to have a standard colonoscopy. They found PillCam COLON 2 to be well-tolerated and to have good sensitivity for the detection of lesions, and concluded that it could be an adequate tool for colorectal examination in patients in which colonoscopy was not appropriate.

PillCam® COLON (C2) vs. Colonoscopy in the assessment of Colon Mucosa in Patients with Ulcerative Colitis (Preliminary Study) by Mileidis Esther Sanjuan Acosta, MD, University Hospital Virgen Macare Dept. of Digestive Health, Gastroenterology and Hepatology, Seville, Spain, and colleagues.

For the first time, researchers studied the correlation between PillCam® COLON 2 and colonoscopy in assessing the extent and degree of disease activity in patients with ulcerative colitis. Using statistical analysis to compare both techniques, the study authors found that the match was "very good" in terms of severity and extent when the procedures achieved a complete study of the colon. Thus, the study authors concluded that PillCam® COLON 2 was able to assess the severity and extent of ulcerative colitis at levels comparable to that obtained with colonoscopy.

IT SOLUSCOPE

Soluscope, leader in endoscope hygiene, announced in October the launch of IT Soluscope, its new technology platform designed to manage your endoscope reprocessing activity.

Network-linked with Soluscope medical devices, IT Soluscope provides accurate and real time information to hospital staff including devices status and endoscope availability.

IT Soluscope features a user-friendly interface displayed on a Panel PC placed as wished. It enables a centralised and permanent communication to equipment and improves productivity.

Intuitive
- **A cross criteria search tool in case of need,**
- **A remote access to equipment for online diagnosis service.**

Traceability
- **Automated recording of all traceability data on a secured server,**
- **Anywhere access to electronic data and easy sharing.**

Supervision
- **Shows all status of cycles performed by Soluscope AERs,**
- **Provides endoscope availability in DSC8000 storage cabinet,**
- **Displays Consumables status (installation-date, use-by-date etc.) enabling smooth working flows.**

IT Soluscope redefines endoscopy reprocessing activity and leverages connectivity and traceability for the safety of endoscopes, users and patients.

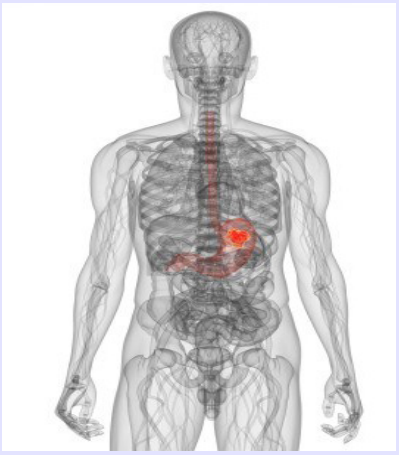
SPECTRASCIENCE WAVSTAT OPTICAL BIOPSY SYST

SpectraScience, Inc. a San Diego-based medical device company, featured its WavSTAT Optical Biopsy System in the PENTAX Medical booth at the United European Gastroenterology Week Conference (UEGW) in Amsterdam. PENTAX also highlighted the benefits of WavSTAT during a dinner presentation to more than 150 European physicians and medical professionals held during UEGW.

In June 2012, SpectraScience signed an exclusive five-year agreement with PENTAX Europe GmbH to distribute its WavSTAT Optical Biopsy System for use in colorectal cancer screening and diagnosis. The agreement, which includes the Company's new WavSTAT4 console and the disposable optical biopsy forceps, covers Europe as well as Turkey, Saudi Arabia, and South Af of minimally invasive surgical devi which are used with the WavST colorectal cancer.

"We are looking forward to support seeing firsthand how physicians r and benefits," said Michael Oliver Officer. "UEGW is an excellent venue sessions with PENTAX sales repre including Germany, France, the Uni Because UEGW is a pan-European

BIOHIT HAS BEEN GRANTED U.S. PATENT FOR THE INVENTION OF BINDING CARCINOGENIC ACETALDEHYDE IN THE GASTROINTESTINAL TRACT AND IN NUTRITION



Biohit Oyj has been awarded US patent 8,227,513 B2, which is valid until 3.4.2026. The object of this BioFood-invention comprises food compositions, to which one or more acetaldehyde-binding compositions are added. The purpose of the compositions is to reduce the amount of detrimental acetaldehyde in the area of the mouth, the pharynx, the oesophagus, the stomach, and the small and large intestines, and through this, to reduce the risk of developing cancers in these areas.

Group I human carcinogens such as acetaldehyde, asbestos, benzene and formaldehyde, regardless of the source, are bound to the uniform international principle. Exposure to them should be avoided by all means. Exposure to acetaldehyde has been shown to be one of the most significant factors causing cancer in the upper gastrointestinal tract (mouth, the pharynx, the oesophagus, the stomach). Nearly one and half a million people worldwide die from these cancers every year, thus they are the main cause of cancer–related death. In addition, these cancers have exceptional poor prognosis, and hence it is extremely important to prevent and diagnose them in the early phase.

Biofood method invented by Biohit Oyj is intended to reduce the food stuff mediated exposure to acetaldehyde. In addition, Biohit´s GastroPanel diagnosis method is developed to identify major risk groups for oesophageal and gastric cancer, for whom the avoidance of acetaldehyde is of particular importance.

TEM FEATURED AT UEG WEEK

frica. PENTAX is a leading provider ces, including flexible endoscopes, TAT System during screening for

ting PENTAX at the conference, and respond to WavSTAT's capabilities , SpectraScience's Chief Executive e to complement our recent training esentatives in key initial markets, ted Kingdom and The Netherlands. event, WavSTAT will be introduced

to customers in additional smaller markets, and we expect to get feedback that will help guide the product launch strategy. Following UEGW we plan to proceed with PENTAX sales force training in the Scandinavian countries, and then in southern Europe.

SpectraScience
INNOVATIONS IN CANCER DETECTION

Acute Pancreatitis – Beyond Gallstones and Alcohol

Omid Sadr-Azodi

Unit of Upper Gastrointestinal Research, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

Omid Sadr-Azodi, MD PhD

Abstract

Acute pancreatitis is the most common disorder of the pancreas. The incidence of the disease has increased markedly during the past decades. Whilst alcohol abuse and gallstone disease might explain a large proportion of the disease etiology, in one quarter of the patients, the cause remains unknown. Life-style and pharmaceutical drug use are potential risk factors for the disease. This brief review highlights the recent research on the role of these factors in the etiology of acute pancreatitis.

Disclaimer: There is no potential conflict of interest.
Citation: *European Medical Journal - Gastroenterology,* 2012:1:35-38

Epidemiology

Acute pancreatitis is the most common disorder of the pancreas. In 10–20% of patients the disease progresses to multi-organ failure with high mortality. During the past decades there has been a steady rise in the incidence of acute pancreatitis, particularly the non-severe acute pancreatitis, in many industrialized countries.[1-6] The incidence of acute pancreatitis was increased by 30% in the United States between 2000 and 2009,[6] 50% in Ireland between 1997 and 2004[1] and 75% in the Netherlands between 1992 and 2004.[2] In the United States, acute pancreatitis resulted in more than 270,000 hospital discharges in 2009 to a cost of 2.6 billion dollars.[6] Although a more frequent use of computerised tomography and pancreatic enzymes might have contributed to such an increase in the incidence, changes in life-style factors and pharmaceutical drug use might also be involved.

Lifestyle and acute pancreatitis

The pathophysiology of acute pancreatitis is complex and not fully understood.[7] The disease is initiated by uncontrolled activation of proteolytic enzymes and an autodigestive process that progresses to an inflammatory cascade.[7] Alcohol abuse and gallstone disease are acknowledged risk factors for the disease.[8] However, during recent years several other risk factors for the development of acute pancreatitis have been identified.

Smoking

Smoking is an acknowledged risk factor for the development of chronic pancreatitis.[9] In an autopsy study, pancreatic fibrosis was more common in smokers compared to non-smokers.[10] Smoking accelerates the progress of acute alcoholic pancreatitis to chronic pancreatitis[11] whereas smoking cessation seems to postpone this development.[12] The role of smoking in the development of acute pancreatitis has been investigated in a few studies.[13-15] Smokers have between 2–3 fold increased risk of acute pancreatitis. In the most recent report, current smokers with ≥20 pack-years of smoking had more than 2-fold (HR=2.29; 95% CI: 1.63, 3.22) increased risk of first attack of acute non-gallstone-related pancreatitis compared to never-smokers.[15] Smoking duration rather than number of cigarettes smoked per day seemed to be more influential in the development of acute pancreatitis. Interestingly, 20 years of smoking cessation decreased the risk of acute pancreatitis to the levels comparable to never-smokers. The same risk reduction was seen among individuals

who consumed <400 g of alcohol per month, corresponding to one standard drink of alcohol or less, after 10 years of smoking cessation.

Obesity

The rise in the incidence of acute pancreatitis has occurred alongside an increase in the prevalence of obesity in the Western World.[16-17] Therefore, it is intriguing to clarify the role of obesity in the development of acute pancreatitis. It is known that obesity is an independent predictor for the severity of acute pancreatitis. Apart from an increased risk of complications confined to the pancreas, i.e. pancreatic necrosis, abscess or pseudocysts, and systemic complications, i.e. circulatory shock, respiratory- or renal insufficiency, obese patients with acute pancreatitis have higher risk of death compared to non-obese patients.[18] However, these associations do not necessarily imply causality in the development of this disease. A recent meta-analysis indicated that obesity was an independent, although weak, risk factor for the development of acute pancreatitis.[19] However, none of the included studies distinguished between abdominal and total adiposity.[19] Fat tissue, particularly abdominal fat, is associated with a systemic inflammatory state.[20] Intra-pancreatic unsaturated fat has been shown to promote inflammatory response and oxidative stress resulting in cell necrosis.[21] In a recent study, the association between abdominal adiposity, assessed as waist circumference, and total adiposity, assessed as body mass index (BMI), and the risk of acute pancreatitis was clarified.[22] In this cohort study, 68,158 Swedish men and women were followed for mean 12 years. During this period 424 persons had a first attack of acute pancreatitis. The risk of acute pancreatitis was two-fold increased among individuals with a waist circumference >105 cm (HR= 2.37; 95% CI: 1.50, 3.74) compared to individuals with a waist circumference of 75.1–85.0 cm adjusted for potential confounders including BMI. This increased risk remained virtually unchanged when stratifying the analyses for sex or the severity of acute pancreatitis. Importantly, there was no such association between BMI and the risk of acute pancreatitis, when mutually adjusting for waist circumference.

Diet

The exocrine and endocrine functions of the pancreas are affected by the dietary components of food. Therefore, it is reasonable to assume that dietary habits could modulate the risk of acute pancreatitis, but very few studies have investigated this potential association. One study examined the association between vegetable and fruit consumption on the development of acute pancreatitis.[23] It is known that oxidative stress plays an important role in the pathogenesis of acute pancreatitis.[24] The high anti-oxidative content of vegetables and fruits could potentially protect against the development of non-gallstone-related acute pancreatitis. In this study, consumption of vegetables was found to reduce the risk of acute pancreatitis in a dose-response manner. Individuals with vegetable consumption in the highest quartile had almost 50% (HR=0.56; 95% CI: 0.37, 0.84) reduced risk of acute pancreatitis compared to the lowest quartile. This association was most clear among individuals who consumed >1 standard drinks of alcohol/ day and those with a BMI ≥25 kg/m2, i.e. individuals with higher baseline oxidative stress. Interestingly, there was no association between fruit consumption and acute pancreatitis. Although the anti-oxidative content of fruits is generally high, the high fructose content of fruits may counteract the protective effect of antioxidants.

Pharmaceutical drug use

Drug-induced acute pancreatitis has previously been considered as a rare cause of acute pancreatitis but recent reports have indicated that this form of acute pancreatitis might be the third most common cause of the disease, accounting for 3-5% of all cases.[25-26] More than 200 drugs have been proposed to induce acute pancreatitis.[27] The current knowledge is practically based on case-reports which cannot establish an association between a given drug and acute pancreatitis on the population level, since the disease being treated could be a risk factor for acute pancreatitis. Recently, a few population-based studies have been performed establishing an association between oral glucocorticoids,[28] tetracycline,[29] metronidazole,[30] and dismissing such association between antidopaminergic,[31] selective serotonin-reuptake inhibitors[32] and hormone replacement therapy[33]. Future population-based research will further clarify the role of different pharmaceutical drugs and acute pancreatitis.

Alcohol – unfinished business

Alcohol is an acknowledged risk factor for acute and

chronic pancreatitis. However, the role of drinking behaviour, amount and the type of alcohol consumed on acute pancreatitis is not fully studied. Among findings that tell against an association between alcohol and acute pancreatitis is the lack of an increased incidence of acute pancreatitis in conjunct to Munich Oktoberfest, during which 6.6 million litres of beer was sold.[34] In Stockholm County, the incidence of acute pancreatitis dropped between 1974 and 1987, during which sales of wine and beer increased while sales of spirit declined.[35] The overall alcohol sales were unchanged. Finally, consumption of spirit, but not wine or beer, was associated with increased risk of acute pancreatitis.[36] There was a dose-response association between the amount of spirit consumed on a single occasion and this risk. The average amount of alcohol consumption was not associated with acute pancreatitis. However, the average alcohol consumption was relatively low in the study population and may not be generalisable to individuals with high alcohol consumption. Future research should focus to clarify the role of alcohol type and drinking behaviour on the development of acute pancreatitis.

Clinical implications

The growing knowledge on the effect of lifestyle factors on the development of acute pancreatitis creates possibilities for both primary and secondary prevention of this disease. Acute pancreatitis shares similar risk factors for cancer and cardiovascular diseases. Therefore lifestyle change will provide general health benefits, including reduced risk of acute pancreatitis, to individuals with an unhealthy lifestyle. In patients who have already developed acute pancreatitis, it is reasonable to assume that continuous exposure to the risk factor will increase the risk of recurrent- and chronic pancreatitis. Yet, research on the secondary prevention of pancreatitis is scarce. Smoking cessation has been shown to reduce the progress of the pancreatic damage.[12] Therefore, as the least measure, smoking cessation should be provided to all smokers who have developed acute pancreatitis.

In conclusion, more knowledge on the risk factors of the disease will provide tools to improve the clinical management, particularly the secondary prevention, of acute pancreatitis.

References

***1. O'Farrell A, Allwright S, Toomey D, Bedford D, Conlon K**. Hospital admission for acute pancreatitis in the Irish population, 1997-2004: could the increase be due to an increase in alcohol-related pancreatitis? J Public Health (Oxf). Dec 2007;29(4):398-404.*

***2. Spanier BW, Dijkgraaf MG, Bruno MJ**. Trends and forecasts of hospital admissions for acute and chronic pancreatitis in the Netherlands. Eur J Gastroenterol Hepatol. Jul 2008;20(7):653-658.*

***3. Roberts SE, Williams JG, Meddings D, Goldacre MJ.** Incidence and case fatality for acute pancreatitis in England: geographical variation, social deprivation, alcohol consumption and aetiology--a record linkage study. Aliment Pharmacol Ther. Oct 1 2008;28(7):931-941.*

***4. Satoh K, Shimosegawa T, Masamune A, et al**. Nationwide epidemiological survey of acute pancreatitis in Japan. Pancreas. May 2011;40(4):503-507.*

***5. Sandzen B, Rosenmuller M, Haapamaki MM, Nilsson E, Stenlund HC, Oman M**. First attack of acute pancreatitis in Sweden 1988 - 2003: incidence, aetiological classification, procedures and mortality - a register study. BMC Gastroenterol. 2009;9:18.*

***6. Peery AF, Dellon ES, Lund J, et al**. Burden of Gastrointestinal Disease in the United States: 2012 Update. Gastroenterology. Aug 8 2012.*

***7. Waldthaler A, Schutte K, Malfertheiner P.** Causes and mechanisms in acute pancreatitis. Dig Dis. 2010;28(2):364-372.*

***8. Frossard JL, Steer ML, Pastor CM**. Acute pancreatitis. Lancet. Jan 12 2008;371(9607):143-152.*

***9. Andriulli A, Botteri E, Almasio PL, Vantini I, Uomo G, Maisonneuve P**. Smoking as a co-factor for causation of chronic pancreatitis: a meta-analysis. Pancreas. Nov 2010;39(8):1205-1210.*

***10. van Geenen EJ, Smits MM, Schreuder TC, van der Peet DL, Bloemena E, Mulder CJ.** Smoking is related to pancreatic fibrosis in humans. Am J Gastroenterol. Jun 2011;106(6):1161-1166; quiz 1167.*

***11. Maisonneuve P, Lowenfels AB, Mullhaupt B, et al**. Cigarette smoking accelerates progression of alcoholic chronic pancreatitis. Gut. Apr 2005;54(4):510-514.*

***12. Talamini G, Bassi C, Falconi M, et al.** Smoking cessation at the clinical onset of chronic pancreatitis and risk of pancreatic calcifications. Pancreas. Nov 2007;35(4):320-326.*

***13. Lindkvist B, Appelros S, Manjer J, Berglund G, Borgstrom A**. A prospective cohort study of smoking in acute pancreatitis. Pancreatology. 2008;8(1):63-70.*

***14. Tolstrup JS, Kristiansen L, Becker U, Gronbaek M.** Smoking and risk of acute and chronic pancreatitis among women and men: a population-based cohort study. Arch Intern Med. Mar 23 2009;169(6):603-609.*

***15. Sadr-Azodi O, Andren-Sandberg A, Orsini N, Wolk A**. Cigarette smoking, smoking cessation and acute pancreatitis: a prospective population-based study. Gut. Feb 2012;61(2):262-267.*

***16. Groves T**. Pandemic obesity in Europe. BMJ. Nov 25 2006;333(7578):1081.*

***17. Olshansky SJ, Passaro DJ, Hershow RC, et al**. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med. Mar 17 2005;352(11):1138-1145.*

***18. Martinez J, Johnson CD, Sanchez-Paya J, de Madaria E, Robles-Diaz G, Perez-Mateo M.** Obesity is a definitive risk factor of severity and mortality in acute pancreatitis: an updated meta-analysis. Pancreatology : official journal of the International Association of Pancreatology. 2006;6(3):206-209.*

19. Hong S, Qiwen B, Ying J, Wei A, Chaoyang T. *Body mass index and the risk and prognosis of acute pancreatitis: a meta-analysis. European journal of gastroenterology & hepatology. Nov 2011;23(12):1136-1143.*

20. Despres JP, Lemieux I*. Abdominal obesity and metabolic syndrome. Nature. Dec 14 2006;444(7121):881-887.*

21. Navina S, Acharya C, DeLany JP, et al. *Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity. Science translational medicine. Nov 2 2011;3(107):107ra110.*

22. Sadr-Azodi O, Orsini N, Andren-Sandberg Å, Wolk A*. Abdominal and total adiposity and the risk of acute pancreatitis – a population-based prospective cohort study. Am J Gastroenterology. 2012;In Press.*

23. Oskarsson V, Sadr-Azodi O, Orsini N, Andren-Sandberg A, Wolk A. *Vegetables, fruit and risk of non-gallstone-related acute pancreatitis: a population-based prospective cohort study. Gut. Jun 27 2012.*

24. Leung PS, Chan YC. *Role of oxidative stress in pancreatic inflammation. Antioxid Redox Signal. Jan 2009;11(1):135-165.*

25. Vinklerova I, Prochazka M, Prochazka V, Urbanek K*. Incidence, severity, and etiology of drug-induced acute pancreatitis. Dig Dis Sci. Oct 2010;55(10):2977-2981.*

26. Spanier BW, Tuynman HA, van der Hulst RW, Dijkgraaf MG, Bruno MJ. *Acute pancreatitis and concomitant use of pancreatitis-associated drugs. Am J Gastroenterol. Dec 2011;106(12):2183-2188.*

27. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. *Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol. Jun 2007;5(6):648-661; quiz 644.*

28. Sadr-Azodi O, Mattsson F, Bexelius TS, Lindblad M, Lagergren J, Ljug R. *Oral glucocorticoid use is associated with an increased risk of acute pancreatitis. Arch Intern Med [In Press]*

29. Ljung R, Lagergren J, Bexelius TS, Mattsson F, Lindblad M*. Increased risk of acute pancreatitis among tetracycline users in a Swedish population-based case-control study. Gut. Jun 2012;61(6):873-876.*

30. Norgaard M, Ratanajamit C, Jacobsen J, Skriver MV, Pedersen L, Sorensen HT. *Metronidazole and risk of acute pancreatitis: a population-based case-control study. Aliment Pharmacol Ther. Feb 15 2005;21(4):415-420.*

31. Boden R, Bexelius TS, Mattsson F, Lagergren J, Lindblad M, Ljung R. *Antidopaminergic drugs and acute pancreatitis: a population-based study. BMJ Open. 2012;2(3).*

32. Ljung R, Ruck C, Mattsson F, Bexelius TS, Lagergren J, Lindblad M. *Selective serotonin reuptake inhibitors and the risk of acute pancreatitis: a Swedish population-based case-control study. J Clin Psychopharmacol. Jun 2012;32(3):336-340.*

33. Tetsche MS, Jacobsen J, Norgaard M, Baron JA, Sorensen HT. *Postmenopausal hormone replacement therapy and risk of acute pancreatitis: a population-based case-control study. Am J Gastroenterol. Feb 2007;102(2):275-278.*

34. Phillip V, Huber W, Hagemes F, et al. *Incidence of acute pancreatitis does not increase during Oktoberfest, but is higher than previously described in Germany. Clin Gastroenterol Hepatol. Nov 2011;9(11):995-1000 e1003.*

35. Schmidt DN. *Apparent risk factors for chronic and acute pancreatitis in Stockholm county. Spirits but not wine and beer. Int J Pancreatol. Jan 1991;8(1):45-50.*

36. Sadr Azodi O, Orsini N, Andren-Sandberg A, Wolk A. *Effect of type of alcoholic beverage in causing acute pancreatitis. Br J Surg. Nov 2011;98(11):1609-1616.*

Challenging Propofol Sedation In Gastrointestinal Endoscopy: High Risk Patients And High Risk Procedures

Eduardo Redondo-Cerezo

MD, PhD, Endoscopy Unit, Gastroenterology Department, Hospital Universitario Virgen de las Nieves, Granada. Spain

Eduardo Redondo-Cerezo, MD, PhD

Abstract

Sedation is increasingly becoming a must for most endoscopic procedures. Non-anesthesiologist administration of propofol is the standard of practice in many European countries. Nevertheless, despite anesthesiology societies concerns about sedation guided by endoscopist, practitioners find some limits to propofol administration, related to high risk patients or high risk and complex procedures, which can be long lasting and technically challenging.

The main patient related risk factors for sedation are elderly patients, obesity, ASA≥3 patients, individuals with craniofacial abnormalities or with pharyngolaringeal tumors, patients with an acute gastrointestinal bleeding, under pain medications, sedatives, antidepressants, or who consume significant amounts of alcohol or drugs. Procedure related risk factors have more to do with the duration and complexity of the procedure than with other factors, in which considering a general anesthesia allows the endoscopist to concentrate on a difficult task.

Published papers addressing the most challenging sedation groups in endoscopy are exploring and even trespassing previously assumed frontiers, and new scenarios are opening to the endoscopist, increasing his/her autonomy, reducing costs and giving patients levels of comfort previously unknown.

In this review we analyse each risk group determining the ones in which a sedation protocol could be widely applied, and other in which the published evidence does not guarantee a safe endoscopist guided propofol sedation.

Disclaimer: No potential conflict of interest.
Citation: *European Medical Journal - Gastroenterology,* 2012:1:39-44

Introduction

Non-anesthesiologist administration of propofol (NAAP) is an expanding sedation regimen throughout Europe. Many patients have been successfully sedated with this drug, and the increasing population demands for comfort as well as the need to reduce costs in medical procedures determined its expanded use among medical practitioners not directly related with anesthetics departments or intensive care units .[1]

Still, anesthesiology societies have concerns regarding propofol use by non-anesthesiologists, but they are mostly based on expert opinion rather than in well designed studies.[2,3] Indeed, collaborative efforts between different endoscopy and anesthesiology societies have recently produced guidelines for the wide use of NAAP in endoscopy,[4] and a vast European and US NAAP experience has been published in different settings.[1,5-11] As time goes by, propofol use by gastroenterologists is spreading and showing its safety. Nevertheless, when a therapy or medical procedure spreads it also finds its burdens,

and sedation ones are the same as those found in anesthesiology and sedation in regular patients, in which elderly, comorbidities, cardiovascular or lung diseases can limit our possibilities. Certainly, the guidelines suggest endoscopist to be careful and even to refer some patients to an anesthesiologist before undergoing NAAP when some risk factors are found, including ASA category≥3, a Mallampati's class of 3, or other conditions at risk for airway obstruction, patients who chronically receive significant amounts of pain medications or in cases of predictable long-lasting procedures.[4]

High risk sedation has therefore two main groups of risk factors: patient dependent and procedure dependent. Regarding patient dependent risk factors, elderly patients,[8,9,12] obesity,[13] ASA≥3 patients, individuals with craniofacial abnormalities or with pharyngolaringeal tumors,[4] patients with an acute gastrointestinal bleeding[14] who are under pain medications, sedatives, antidepressants, or who consume significant amounts of alcohol or drugs are more difficult to sedate, and sometimes require the participation of an anesthesiologist. Procedure dependent factors are related to the duration of the procedure, painful maneuvers associated to endoscopy (e.g. percutaneous gastrostomy), the need of a motionless patient for complex techniques and the type of endoscopy required, upper or lower, because upper endoscopy causes more discomfort to patients and comprise a higher risk of airway complications.

It is essential for a gastroenterologist who usually, maybe daily, performs NAAP, to do so under a strict sedation protocol and always knowing when to require the assistance of an anesthesiologist. In a valuable effort, a multi-society joint in the US has established a curriculum for sedation in gastrointestinal endoscopy,[15] in which authors recommend to require this assistance in the following settings:

- Prolonged or therapeutic endoscopic procedures requiring deep sedation or general anesthesia.
- Anticipated intolerance, paradoxical reaction or allergy to standard sedation regimens.
- Increased risk of complications because of severe comorbidity (ASA class 4 and higher)
- Increased risk of airway obstruction
    - History of stridor
    - History of severe sleep apnea
- Dysmorphic facial features
    - Trisomy 21
    - Pierre-Robin syndrome
- Oral abnormalities
    - <3 cm oral opening in adults
    - Protruding incisors
    - Macroglossia
    - High arched palette
    - Tonsillar hypertrophy
    - Mallampati score of 4
- Neck abnormalities
    - Decreased hyoid-mental distance (3 cm in adults)
    - Short thick neck
    - Limited neck extension
    - Cervical spine disease (eg, advanced rheumatoid arthritis) or trauma
    - Severe tracheal deviation
- Jaw abnormalities
    - Retrognathia
    - Micrognathia
    - Trismus
    - Severe malocclusion

In general, we strongly agree with these limitations to NAAP. Nevertheless, recent reports provide new evidence to support the practice of NAAP in some previously considered high risk scenarios. In this review we are going to establish these situations in which the gastroenterologist could safely sedate a patient otherwise considered of high risk.

The first recommendation for a non-anesthesiologist who is planning to develop a NAAP protocol, is to undergo a structured training for this purpose, to receive an extensive instruction in basic life support and even in advanced cardiac life support (ACLS), if an ACLS caregiver is not immediately available in the endoscopy unit. Self training has been strongly discouraged in this item.[4] Thus, every gastroenterology or endoscopy training program should have a specific scheduled training in NAAP.

Patient Related Risk Factors

1. ASA≥3

Although some guidelines recommend the assistance of an anesthesiologist with these patients, the general recommendation in the main guidelines is to adjust propofol doses and maintain an adequate monitoring, because they are at a higher risk of sedation-related side effects.[4,16] In a paper focused on high risk octogenarian which underwent therapeutic endoscopy, 34/74 patients in the propofol group were ASA-III and 12/76 ASA-IV.[8] The authors observed a higher decrease in blood pressure and a higher oxygen desaturation rate with propofol, when comparing NAAP with a standard sedation with Midazolam. Nevertheless, NAAP was safe, with no major adverse events a no procedure interrupted due to sedation related events in ASA-III-IV patients. Of note, neither propofol doses (60-870 mg) nor mean examination times (47±16 minutes) were lower than what is expected for average risk patients. In another recent paper from our group, 138/456 ASAIII-IV patients were included in a study focused on EUS. Per protocol, high risk patients received between a quarter and half the dose of propofol comparing to average risk patients. As an obvious consequence to this dosage, we found that the total propofol dose was lower in high risk patients (164.8±84.3), finding no differences in procedure duration, recovery time, patients' and endoscopist's satisfaction with the procedure, and adverse events.[10] No major adverse events have been observed in our series.

Consequently, we think there is enough evidence to support cautious propofol sedation in patients with high anesthetic risk, under a strict sedation protocol (ASA-III/IV).

2. NAAP in the Elderly

Many studies have tested NAAP in high risk elderly patients, finding no differences with other sedation regimes regarding safety.[8,9,12] The first paper addressing this issue,[9] in which the authors included 1435 patients who were 70-85 years of age and 351 with more than 85 years, considered very old, is remarkable. In this study, the investigators found that doses could be reduced in these patients as much as a 35-40% of that administered to younger adults. They found a slightly increased rate of oxygen desaturation in old patients, but without clinical consequences, concluding that propofol is safe in this group of patients.

Interestingly, investigators agree in lowering initial propofol doses in the elderly, with repeated doses of 20 mg, normally following the 20/20 rule, which consists in a careful titration in steps of 10-20 mg against the clinical response, making pauses lasting at least 20 seconds between each bolus.[9,12] This schedule allows an effective and cautious sedation in old patients, leading to a safety comparable to young patients in the studies which specifically addressed this population.

3. Obese Patients

Obesity has been recognised as a potential risk factor for sedation in endoscopy,[17,18,19] and obese patients have a high prevalence of sleep obstructive apnea, which can make individuals more prone to hypoxemia when sedated. Indeed, propofol accentuates airway collapse, potentially increasing the risk of cardiopulmonary adverse events.[20] Data on the association of obesity and sedation-related outcomes in patients undergoing endoscopy are limited. A recent paper addressed the safety of propofol administered by anesthesiologist for endoscopy in obese patients. Although the author concluded that propofol sedation in this situation is safe, the frequency of every airway maneuvers to treat hypoxemia was significantly higher in obese patients, even with an anesthesiologist on charge.[13] In our experience, sedation in the very obese patient (BMI>35-40kg/m2) is challenging, because of propofol dosage, accumulation of the drug in the adipose tissue and frequent airway occlusion; for this reason we usually require an anesthesiologist for those patients.

4. Acute Gastrointestinal Bleeding

Propofol can cause a significant hypotension, and has been proscribed in situations as gastrointestinal bleeding, considered as a high risk situation.[21,22] No sedation at all or sedation with the assistance of an anesthesiologist has been advocated in these patients by many authors. A paper describes the safety of NAAP for patients with upper gastrointestinal bleeding, in 120 patients with average and high anesthetic risk.[14] Excluding unconscious patients or the ones who presented a severe cardiovascular depression, the authors found no significant differences in neither mean decrease in systolic blood pressure nor bradycardia, despite the mean time required to complete the endoscopic procedure and mean dosage of propofol were both significantly higher in the group with gastrointestinal bleeding. There were no differences in the frequency of hypoxemia between both groups, and the authors concluded that propofol sedation in patients with acute gastrointestinal bleeding is safe. Interestingly, the authors titrated propofol dosage by age, giving 0.8 mg/kg for patients <70 years of age and 0.6 mg/kg for patients aged ≥70 years or older, with subsequent boluses of 10 mg with the target of a moderate sedation.

Although we think gastrointestinal bleeding is a high risk condition, propofol might be safe in patients with no signs of hypovolemic shock and always with a careful administration scheme and monitoring.

5. Concomitant Pharmacologic Therapies

The use of some drugs, alcoholic drinks and medications like sedatives or antidepressants usually enhances propofol metabolism by the liver, requiring increasing doses of the drug, which can be difficult to titrate because patients can quickly shift from a mild sedation to a deep one and even apnea.[16] When we have this type of patient, we tend to apply in otherwise healthy individuals the usual induction doses. If the patient is adequately induced, we proceed with the procedure as regularly, if not we administer half the initial dose of propofol after about 90 seconds. If endoscopy is impossible after this second propofol infusion, we finish the procedure and ask for the participation of an anesthesiologist in a subsequent endoscopy.

In general, with this scheme, sedation is possible in most of the patients. We find more difficulties with heavy alcohol consumers, in which an anesthesiologist is frequently required. Of note, we have an anesthesiologist specially dedicated to endoscopy who hardly ever induces sedation but general anesthesia with orotracheal intubation, also in these patients, arguing a difficult control of the sedation level even when performed by anesthesiologists.

Procedure-Related Risk Factors

Some guidelines recommend evaluating the nature of endoscopic intervention, indication, duration, invasiveness and complexity before deciding between NAAP and general anesthesia.[16] The more complex procedures in endoscopy comprise those with interventional or advanced endoscopy, i.e. ERCP, EUS and some other. Many studies have shown that NAAP is safe and better than previous methods of sedation in those procedures. NAAP has been successfully tested in ERCP, EUS, double balloon enteroscopy (DBE) and other.[6-8,10,12,17-19] Nevertheless, in our opinion, some long lasting or potentially painful procedures are not suitable for NAAP, which can be applied if needed, but are performed with much more comfort for the endoscopist under general anesthesia. We think there is a subtle difference between what can be safely performed and what should be done in order to be more comfortable and aggressive when planning the goals of an intervention. In our practice, ERCP, a procedure which can be long-lasting and very complex is always performed under general anesthesia. The same happens with DBE, which takes a mean time of two hours and can be painful. We do sedate with propofol patients undergoing EUS with or without FNA. However, if we have to perform a pseudocyst drainage, a cholangiography guided by EUS, or other complex long-lasting procedures we opt for a general anesthesia. Indeed, in our experience, a regular EUS with or without FNA takes less than one hour,[10] a period of time in which the endoscopist can safely complete the procedure and sedate the patient. As a general rule, if something is foreseen to last more than an hour, or if it can be significantly painful, we do not despise the help of our anesthesiologist.

Conclusions

NAAP has spread in most of western countries,

with an especial impact in Europe. Trained nurses and clinicians have learnt to apply propofol and are doing it safely, with an increasing comfort for patients. With the growing experience in many centers, propofol use is expanding to patients with a theoretical higher risk, and endoscopists are in some cases toying with the burdens of safety. For this reason we have tried to address for practitioners what to do in some borderline situations in which evidence is far from pristine. In some aspects, as in patients with high anesthetic risk or in old patients there are data enough to begin a NAAP sedation protocol. In these groups, an accurate titration of the infused doses, with induction doses of about 0.5 mg/kg or less and reinfusions of half this first dose, is safe and valuable for an effective sedation. More concern arise in other situations, like in patients with an acute upper gastrointestinal bleeding, or in the very obese patients, in which caution is advised by some authors and, in our opinion, it is wise to require an anesthesiologist or to perform the procedure without sedation, if this is possible. Regarding procedure related risk, we consider a general rule to require an anesthesiologist for endoscopies with a high complexity or potentially long lasting. General anesthesia is always applied to patients undergoing ERCP in our unit, and, although NAAP is feasible and, indeed, we have sedated ERCP patients before, we really think it is much more comfortable for both the patient and the endoscopist to undergo general anesthesia. Anyway, improvements in sedation by non endoscopist, increasing needs to reduce healthcare costs and the demand of more comfort related to endoscopy by the population will for sure change the way we do things in the coming years.

References

***1. Heuss LT, Peter S**. Propofol use by gastroenterologists-the European experience. Gastrointest Endoscopy Clin N Am 2008; 18: 727-738.*

*2. **Werner C, Smith A, Van Aken H.** Guidelines on non-anaesthesiologist administration of propofol for gastrointestinal endoscopy: a double-edged sword. Eur J Anaesthesiol. 2011; 28: 553-5.*

***3. Pambianco DJ, Hardi R.** The debate for nonanesthesiologist-administered propofol sedation in endoscopy rages on. Gastrointest Endosc. 2011; 74: 449.*

***4. Dumonceau JM, Riphaus A, Aparicio JR et al;** NAAP Task Force Members. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology Guideline: Non-anesthesiologist administration of propofol for GI endoscopy. Endoscopy. 2010;42: 960-74.*

***5. Rex DK, Deenadayalu VP, Eid E et al.** Endoscopist-directed administration of propofol: a worldwide safety experience. Gastroenterology. 2009 Oct;137(4):1229-37.*

***6. Fatima H, DeWitt J, LeBlanc J, Sherman S, McGreevy K, Imperiale TF.** Nurse-administered propofol sedation for upper endoscopic ultrasonography. Am J Gastroenterol. 2008;103:1649-56.*

***7. Yusoff IF, Raymond G, Sahai AV.** Endoscopist administered propofol for upper-GI EUS is safe and effective: a prospective study in 500 patients. Gastrointest Endosc. 2004; 60: 356-60.*

***8. Schilling D, Rosenbaum A, Schweizer S et al.** Sedation with propofol for interventional endoscopy by trained nurses in high-risk octogenarian: a prospective, randomized controlled study. Endoscopy 2009; 41: 295-298.*

***9. Heuss LT, Schnieper P, Drewe J, et al.** Conscious sedation with propofol in elderly patients: a prospective evaluation. Aliment Pharmacol Ther. 2003; 17: 1493-1501.*

***10. Redondo-Cerezo E, Sánchez-Robaina A, Martínez Cara JG et al.** Gastroenterologist-guided sedation with propofol for endoscopic ultrasonography in average-risk and high-risk patients: a prospective series. Eur J Gastroenterol Hepatol. 2012; 24: 506-12.*

***11. Amorós A, Aparicio JR, Garmendia M et al.** Deep sedation with propofol does not precipitate hepatic encephalopathy during elective upper endoscopy. Gastrointest Endosc. 2009; 70: 262-268 .*

***12. Riphaus A, Stergiou N, Wehrmann T.1** Sedation with propofol for routine ERCP in high-risk octogenarians: a randomized, controlled study. Am J Gastroenterol. 2005; 100 1957-1963.*

***13. Wani S, Azar R, Hovis CE et al.** Obesity as a risk factor for sedation-related complications during propofol-mediated sedation for advanced endoscopic procedures. Gastrointest Endosc. 2011; 74: 1238-47.*

***14. Tohda G, Higashi S, Wakahara S et al.** Propofol sedation during endoscopic procedures: safe and effective administration by registered nurses supervised by endoscopists. Endoscopy. 2006; 38: 360-7.*

***15. Vargo JJ, DeLegge MH, Feld AD et al.** Multisociety sedation curriculum for gastrointestinal endoscopy. Gastrointest Endosc 2012; 76: e1-e25.*

***16. Riphaus A, Wehrmann T, Weber B et al.** S3-guidelines--sedation in gastrointestinal endoscopy. Endoscopy 2009; 41: 787-815.*

***17. Berzin TM, Sanaka S, Barnett SR, et al.** A prospective assessment of sedation-related adverse events and patient and endoscopist satisfaction in ERCP with anesthesiologist-administered sedation. Gastrointest Endosc 2011; 73: 710-7.*

***18. Cote GA, Hovis RM, Ansstas MA, et al**. Incidence of sedation-related complications with propofol use during advanced endoscopic procedures. Clin Gastroenterol Hepatol 2010; 8: 137-42.*

***19. Qadeer MA, Vargo JJ, Dumot JA, et al.** Capnographic monitoring of respiratory activity improves safety of sedation for endoscopic cholangio-pancreatography and ultrasonography. Gastroenterology 2009;136:1568-76; 1819-20.*

20. Hillman DR, Walsh JH, Maddison KJ et al. *Evolution of changes in upper airway collapsibility during slow induction of anesthesia with propofol. Anesthesiology 2009;111:63-71.*

21. Chen SC, Rex DK. *Review article: Registered nurse-administered propofol sedation for endoscopy. Aliment Pharmacol Ther 2004; 19: 147-155.*

22.Rex DK, Overley CA, Alker J. *Registered nurse-administered propofol sedation for upper endoscopy and colonoscopy: Why? When? How? Rev Gastroenterol Disord 2003; 3: 70-80.*

Endoscopic Assessment of Early Neoplasia in the Gastrointestinal Tract

P. Didden, MD[1], A.D. Koch, MD[1]

[1]*Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands*

Abstract

Endoscopic detection and evaluation of early neoplasia in the gastrointestinal tract should be carried out by systematic assessment of a standard set of lesional characteristics. First of all, attention should be given to the microvasculature and pit pattern of the mucosal surface. These features can distinguish neoplastic from non-neoplastic lesions and are used to assess the presence of dysplasia or malignancy. High resolution endoscopy combined with narrow band imaging usually provides sufficient detailed visualisation for characterisation. Secondly, estimating the risk of invasion beyond the mucosal layer is important, because the depth of invasion corresponds to the risk of lymph node metastasis. This prediction can be based on the gross morphology according to the Paris classification, but also size, the presence of converging folds with clubbing, ulceration and discoloration are considered predictive characteristics. This editorial provides a practical approach to assessing early neoplasia in the gastrointestinal tract. We would encourage endoscopists to appreciate these features systematically before proceeding to endoscopic or even surgical resection.

Disclaimer: There is no potential conflict of interest.
Citation: *European Medical Journal - Gastroenterology,* 2012:1:45-52

Introduction

By definition, all malignant tumours throughout the gastrointestinal tract arise from precursor lesions. Discrete premalignant epithelial changes are the first step in the progression to early carcinoma, ultimately leading to advanced cancers. Endoscopy is the most effective method to detect these precursor lesions or the neoplastic lesions restricted to the superficial layers. A neoplastic lesion is called "superficial" when the depth of penetration in the digestive wall is limited to the mucosa or submucosa, i.e. there is no infiltration of the muscularis propria.[(1)] The term early carcinoma refers to the same depth of invasion confined to the mucosa or submucosa, irrespective of lymph node metastasis. Because superficial neoplastic lesions are usually asymptomatic, they are often incidental findings or are detected during screening or surveillance programs. Accurate recognition and assessment of such lesions is essential and should be done carefully before endoscopic therapy is considered. Assessment of mucosal surface characteristics allows making a presumptive in vivo histological diagnosis. It can assist in differentiating between non-neoplastic and neoplastic (pre)malignant lesions. Additionally, the morphological features predict the extent of invasion into the submucosa which corresponds with the risk of lymph node metastasis. This information is crucial to determine the appropriateness of endoscopic resection and the need for en bloc or piecemeal resection. Despite improved quality with high-resolution (HR) images composed of 850K to 1 million pixels, detailed evaluation of such lesions can still be difficult and operator dependent. New endoscopic technologies have been developed in recent decennia aiming to improve detection, visualisation and characterisation of neoplastic lesions. High magnification endoscopes are capable of enlarging the image up to 150 times with the same pixel density, providing an even more detailed image.[(2)] Because most endoscopists are not familiar with the use and interpretation, magnifying endoscopy has not gained wide-spread acceptance in Western countries. Chromoendoscopy is an endoscopic intravital staining technique using absorptive and

contrast stains to enhance visual characteristics.[3]

Chromoendoscopy is usually applied in combination with optical magnification to improve examination, although its use has also been adopted in standard magnification endoscopy. Narrow band imaging (NBI) is a relatively new optical technology using special narrow band filters in the endoscopic system and highlights the superficial vasculature and mucosal pattern of gastrointestinal neoplasia.[4] Another diagnostic modality that is frequently performed in staging of digestive tract cancer is endoscopic ultrasound (EUS), either using radial or linear array ultrasonography endoscopes or more recently developed miniature ultrasound probes. High frequency ultrasound visualizes the distinctive layers of the gastrointestinal tract, allowing pre-treatment determination of the T-stage.

This review focuses on the different aspects of adequate assessment of superficial neoplastic lesions in the colon, stomach and esophagus, including Barrett's esophagus. It is written from a practical point of view and should be helpful in daily practice to every endoscopist using modern endoscopes. The value of HR endoscopy, chromoendoscopy and NBI is discussed, considering the wide availability of these techniques in both academic and community centres. Because high magnification endoscopy has been the first diagnostic modality providing detailed micromorphological differences, the yield of this technique is also described. Furthermore, the additional value of EUS is discussed.

Assessment of mucosal surface

Examining the mucosal surface is an important aspect in the endoscopic assessment of a superficial lesion. Most knowledge has been gained from examination of colorectal lesions. To classify colorectal neoplastic lesions, the pit pattern classification according to Kudo is usually applied.[5] The type of pit pattern can be assigned after closely examining the mucosal surface of the lesion (Fig.1). It appears valuable in the histological prediction according to five types of pit pattern. Lesions with type I and II are considered nontumorous epithelial tissue, i.e. normal or hyperplastic. In contrast, type IIIS, IIIL, IV and V are neoplastic adenomatous lesions, potentially harbouring carcinoma. Incorporating a technique during standard colonoscopy that can accurately differentiate between adenomatous and hyperplastic polyps is desired. This could prevent unnecessary removal of nonadenomatous polyps, resulting in decreased risk of complications and costs. The original Kudo classification was based on assessment using magnifying endoscopy with white light (WL) after spraying the lesion with indigo carmine or cresyl violet. Whereas this classification relies on the variation of intestinal crypt openings, NBI also provides detailed visualisation of the microvasculature. Because superficial vascular structures change during the process of tumour angiogenesis, proper recognition is an essential component of characterising neoplastic lesions. Several studies have shown that magnification in combination with NBI is able to satisfactorily differentiate neoplastic from non-neoplastic lesions.[6-7] Furthermore, it could possibly provide a prediction of submucosal invasion, in particular massive invasion depths.[8] Although these results are encouraging, magnifying endoscopy is not routinely available in most Western endoscopy centers. HR endoscopy is generally used instead because most endoscopists feel more comfortable with this technique. However, the diagnostic accuracy of HR endoscopy in distinguishing neoplastic colorectal lesions is suboptimal. Without the use of optical magnification,

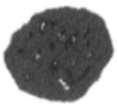
I		Round, regular (normal)
II		Stellar or papillary pits
IIIL		Large tubular or roundish pits
IIIS		Small tubular or roundish pits
IV		Branch-like or gyrus-like pits
V		Non-structural pits

Figure 1. Kudo's pit pattern classification. Adapted from reference [5]

assessment of the lesions with NBI alone seems to be an advancement. NBI without magnification has been compared with WL endoscopy in three large studies, both with HR images. For predicting adenomas, NBI was significantly superior to WL with a sensitivity ranging from 80-96% vs 38-69% and diagnostic accuracy ranging from 80-93% vs 61-77%.[9-11] The results of non-magnifying endoscopy using NBI with HR closely resembles the results obtained with magnifying endoscopy. It may represent a functional tool, which is able to assist endoscopists in making determinations regarding polyp histology prior to resection. One should be aware though that results do not indicate that this technique can replace histopathological examination. Furthermore, adequate interpretation of NBI produced images is preceded with a learning curve in which dedicated training and feedback is essential.[10]

For assessment of the mucosal surface of esophageal or gastric superficial lesions, still no internationally accepted validated classification system is available. However, adequate evaluation in these areas relies on the presence of distorted microvasculature and mucosal morphology, similar as in colorectal lesions.

In superficial esophageal squamous cell tumours, grading the microvasculature is based on different shapes of intraepithelial papillary capillary loops (IPCL), as suggested by two studies.[12-13] IPCL's were visualised using magnifying endoscopy in both studies. The reported level of distortion correlates to the degree of malignancy. It may even be possible to predict invasiveness based on these characteristics. Theoretically, NBI could have an additional value because it accentuates the vasculature. However, two studies have demonstrated that the use of NBI for differentiating superficial esophageal squamous cell carcinomas is not beneficial. Although a higher contrast ratio has been demonstrated with NBI compared to WL endoscopy, prediction of the depth of invasion is equally effective between both diagnostic modalities with an accuracy rate of approximately 80%.[14-15] Chromoendoscopy has not been investigated as a tool for differentiating early esophageal squamous cell cancers. On the other hand, lugol staining might improve visualization of the lateral margins of the lesion.[16]

Surveillance of Barrett's esophagus (BE) primarily focuses on the presence of high grade dysplasia (HGD) or carcinoma. Detailed observation of the mucosal morphology can assist in the distinction of HGD or carcinoma from nondysplastic specialized intestinal metaplasia (SIM). Several studies using magnifying endoscopy with NBI have demonstrated that HGD is associated with irregular/disrupted mucosal patterns and irregular/abnormal vasculature. NBI has also been evaluated as a potential diagnostic tool for BE, mostly in non-comparative studies. It seems effective in differentiating HGD or carcinoma from LGD with a reported sensitivity of 93-100% and specificity of 58-100%.[17-21] Only one randomised cross over trial evaluated the detection capability of NBI versus WL HR endoscopy in Barrett's esophagus.[20] In this study 28 patients referred for occult HGD underwent two separate endoscopies with an interval of 6-8 weeks. Although NBI detected a limited number of additional lesions, the sensitivity for identifying patients with HGD or carcinoma with NBI was similar compared to HR endoscopy. Also based upon our own experience, we would recommend WL HR endoscopy for evaluating BE using NBI as a supportive imaging technique. Standard resolution endoscopy should not be used for detection of dysplasia in BE as it is proven to be inferior compared to HR endoscopy with NBI.[22] The role of chromoendoscopy for the detection of dysplasia in BE is limited. A recent meta-analysis demonstrated no significant incremental yield with methylene blue compared to conventional random biopsies.[23] As for the methylene blue staining characteristics, it still remains unclear which staining pattern is predictive for HGD or early carcinoma and therefore routine use is not advocated at this time.[24-25]

With regard to early gastric neoplastic lesions, several Japanese researchers have adopted various classification systems, based on changes of microvascular architecture and glandular structure. Most studies have used magnifying endoscopy with NBI, demonstrating an accurate relationship of the type of microvessel pattern with the pathological diagnosis.[26-28] This classification corresponds with the histopathological differentiation grade as well as the presence of submucosal invasive cancer. In contrast to the esophagus, the additional value of NBI is more clearly established in evaluation of gastric lesions, although benefit has only been demonstrated in combination with magnifying endoscopy. Magnifying endoscopy with NBI allows for identification of small gastric lesions more accurately with a higher sensitivity compared to

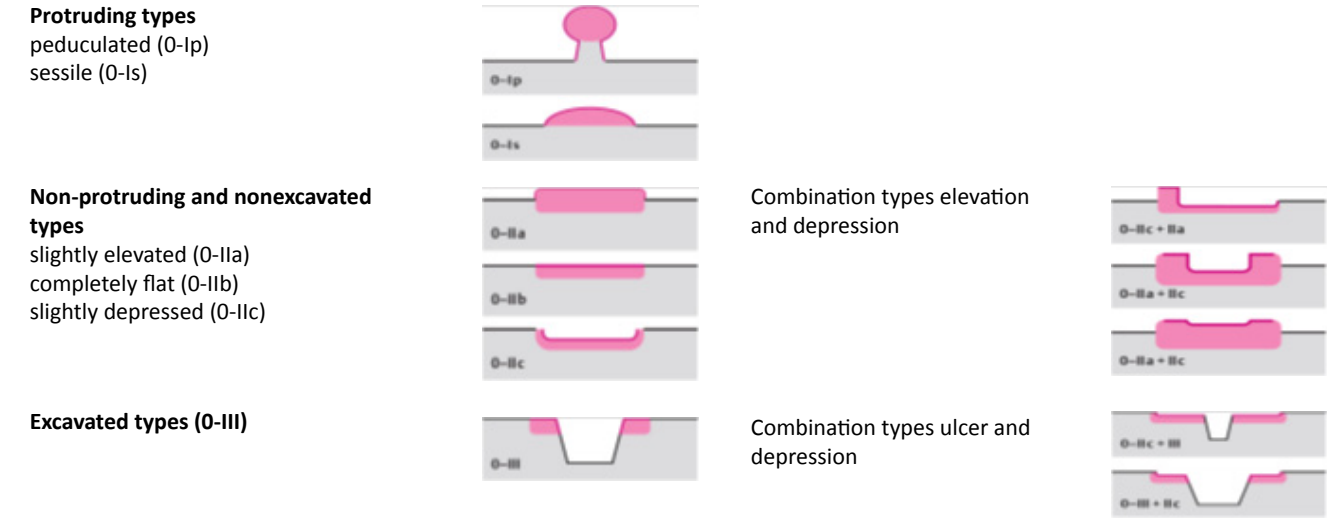


Figure 2. Paris Classification; Endoscopic appearance of superficial neoplastic lesions. Adapted from reference [35]

WL HR endoscopy.[29] Furthermore, several studies have shown a superior accuracy in the differential diagnosis of superficial gastric lesions.[30-31] One study of 204 gastric lesions, including 14 proven cancers, demonstrated a high diagnostic accuracy of predicting cancer (sensitivity 92.9% and sensitivity 94.7%) based on a triad (disappearance of fine mucosal structure, microvascular dilation and heterogeneity) observed using ME with NBI.[30] These results were significantly better compared to ME with WL (sensitivity 42.9% and sensitivity 61.0%). In a different study, ME with NBI was superior in distinguishing low grade adenoma from early gastric cancer.[31] The use of chromoendoscopy has been studied in early gastric cancer, with indigo carmine, methylene blue and Congo red as the most frequently used dyes. The clear benefit in increasing the detection of gastric lesions has never been confirmed in randomized trials. Instead, it can be helpful for determination of the lateral border of the lesion which is essential to achieve complete resections. Three studies have confirmed a better diagnostic performance of identifying the lateral margin in differentiated adenocarcinoma using a mixture of indigo carmine with acetic acid compared to HR WL endoscopy.[32-34] However, this advantage has not been confirmed in undifferentiated adenocarcinoma.[33]

Assessment of gross morphology

Besides the mucosal surface, another crucial element is the assessment of the gross morphological appearance. The most widely accepted classification system is the Paris classification (Fig.2).[1,35] Although initially used to assess superficial tumours in the stomach, this classification was later adopted for early neoplasia throughout the entire gastrointestinal tract. The classification assists in predicting the extent of invasion into the submucosa. Because this depth of invasion correlates with the risk of lymph node metastasis, appropriate treatment of each lesion is largely depending upon this assessment. Superficial lesions are classified as either protruding (0-I), non-protruding, non-excavated (0-II) or excavated and often ulcerated lesions (0-III). The protruding lesions (0-I) can further be divided in pedunculated (0-Ip) or sessile (0-1s) lesions. Type 0-II lesions are subdivided in 0-IIa, 0-IIb and 0-IIc, corresponding to slightly elevated, completely flat and slightly depressed type lesions respectively. Lesions which have both elevated and depressed components are classified into two groups: depressed lesions in which most of the surface is depressed and there is elevation in a portion of the peripheral ring are classified as 0-IIc + IIa, while elevated lesions with a central depression encircled by the elevated ring at the periphery are called 0-IIa + IIc. The combined patterns of excavation and depression are called 0-III + IIc or 0-IIc + III, depending on the relative surface area of the ulcer and of the depressed area.

The corresponding incidence of submucosal infiltration varies between the different subtypes and the location in the gastrointestinal tract.[35] True protruding (0-I) lesions in the stomach demonstrate a 57% relative frequency of submucosal invasion, whereas nonprotruding, nonexcavated lesions (0-II) demonstrate submucosal invasion in 20-40%.The

incidence also differs between the three subtypes of type 0-II lesions. Especially type 0-IIc lesions have a substantial risk of penetration into the submucosa with a reported incidence of 40%. In excavated gastric lesions (0-III), the muscularis propria is often already involved. Although the exact percentage of involvement of the muscularis propria is not reported in the literature, this number comes close to 100%. This latter assumption also accounts for excavated lesions in the large bowel, although exact numbers are lacking. In type 0-II colorectal lesions, the proportion of submucosal infiltration is highest (61%) for type 0-IIc lesions, similar to gastric neoplasia. Regarding early neoplasia of the esophageal squamous epithelium, submucosal invasion most frequently occurs in protruding (0-I) or excavated (0-III) types, both with an incidence of approximately 80%. However, one should be aware that also type 0-II lesions, especially 0-IIa, are at risk of submucosal invasion with a rate of 15-48%.

Representative frequencies in Barrett's esophagus cannot be provided as there is relative paucity on data regarding this subject.

Other neoplastic features

Additional characteristics which should be taken into account and include larger size, converging folds with clubbing, presence of discolorations (remarkable redness) and ulceration. These adverse features are associated with deeper invasion and higher risk of lymph node metastasis. The diameter of a lesion has been analysed as a prognostic factor for submucosal invasion in various studies. For instance, submucosal infiltration occurs in less than 1% when a colorectal lesion measures less than 10mm and this rate increases in proportion to the diameter. This applies for every morphological type, except for depressed (type 0-IIc) type lesions, of which also small diameter lesions are associated with a substantial risk of submucosal invasion.[1] In the stomach, small (<1 cm) lesions with submucosal invasion of more than 500µm (sm2) also carry a considerable risk of lymph node metastasis. The incidence even rises in larger lesions. On the other hand, when invasion into the submucosa is limited to the upper 500µm (sm1), the risk of lymph node metastasis is low, even when the diameter increases.[36] Thus, it is important to realise that further management should not solely be based on the size of a lesion. Another feature that should be taken into account is the relation with the peristaltic waves. Lesions that are confined to the mucosa tend to floatingly move over the peristaltic waves, whereas peristaltic waves seem to curve around tumours that have invaded the muscularis propria.

In most endoscopic resection techniques, submucosal injection of fluid is used to lift the lesion from the muscularis propria. The amount of lifting also provides information on the invasion depth of the lesion. Mucosal or superficial submucosal lesions usually demonstrate complete lifting, whereas the lesions which infiltrate into the deeper submucosal layers often lift incompletely. In the first situation the lesion is generally amenable for endoscopic resection, while in the latter the efficacy of an endoscopic approach is doubtful. A non-lifting sign most often represents invasion into the muscularis propria, precluding endoscopic resection. One should be aware that the presence of fibrosis, for example after previous attempts at removal, can also hinder complete lifting.

Endoscopic ultrasonography

In our opinion, the addition of EUS as a diagnostic modality does not substantially impact management decisions of early neoplastic lesions. Even the recently developed miniprobe EUS, which provides excellent resolution, is not more reliable than conventional endoscopy prior to treatment. A systematic review, evaluating the performance of EUS in gastric cancer, reported a diagnostic accuracy ranging from 65% to 92.1% for overall T staging.[37] When the accuracy of EUS is limited to early gastric cancer, the overall accuracy in differentiating mucosal (T1m) from submucosal (T1sm) lesions, is 67.4%, as shown in the largest series to date including 955 cases.[38] In this comparative study conventional endoscopy, using criteria predominantly based on the Paris classification, appeared superior with an accuracy rate of 73.7%. Approximately 40% of cases were assessed by a miniprobe, which indeed showed a significantly higher accuracy compared to radial EUS, but this was not different from conventional endoscopy. The imperfection of EUS can be explained due to various reasons. EUS has a tendency to overstage tumours due to ulceration and peritumoral inflammation. On the other hand, understaging can occur due to undetected microinvasion. The most important limitation of the miniprobe EUS is the restricted

field of visualisation. Therefore, there is a risk of misdiagnosing the invasiveness in larger lesions. In our opinion, EUS should not routinely be applied in pretreatment staging of early gastric cancer. The same limitations impede the regular use of EUS in early esophageal cancer. The diagnostic performance on determining the exact T-stage is unsatisfactory as demonstrated in a recent systematic review.[39] In our opinion, the role of EUS is also limited in early rectal cancer since careful conventional endoscopic assessment is usually sufficient to predict deep submucosal invasion. However, it should be noted that there are no comparative studies with regards to early esophageal and rectal cancer.

Criteria for endoscopic resection

Critical appraisal of all these aforementioned features enables us to choose the appropriate resection modality, either an endoscopic or surgical resection. Endoscopic resection can be performed using endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). While ESD allows radical, en bloc, resection independent of the size of the lesion, en bloc EMR can only be achieved in lesions <2 cm using a snare technique. The advantage of en bloc resection is accurate assessment of the depth of invasion in the obtained specimen.

This is less important in neoplastic lesions with predicted low- or high-grade dysplasia without submucosal invasion. These can safely be removed by piecemeal EMR for example using snare polypectomy. On the other hand, en bloc resection is indicated for lesions potentially harboring carcinoma based on endoscopic appearance. Current widely adopted guidelines suggest that ESD or en bloc EMR is justified for intramucosal, well or moderately differentiated carcinomas, because the incidence of submucosal lymphovascular involvement in these cases is close to zero. In case of submucosal ingrowth, the extent of infiltration into the submucosa is measured from the lower limit of the muscularis mucosae. It is well known that deeper invasion is clearly associated with a higher rate of lymphangitic spread. The currently adopted cut-off limit is dependent on the location in the gastrointestinal tract.[35] Invasion should be less than 200µm in the squamous epithelium of the esophagus, less than 500µm in the stomach or in Barrett's esophagus and less than 1000µm in non-pedunculated neoplastic lesions of the colon. Studies have shown that with only limited submucosal invasion, in the absence of other adverse qualitative criteria, the rate of nodal metastases is very low. Although the rate is not zero, and reported even up to 26% for esophageal squamous cell carcinoma[40] and up to 16% for Barrett's neoplasia based on limited data,[41] it is suggested that in these patients endoscopic resection is justified and surgery can be avoided.[35] Many endoscopists however tend to be more conservative. Usually in these esophageal cases invasion limited into the muscularis mucosae is accepted as a cut-off for endoscopic resection. In these cases, the risk of lymph node metastasis is negligible compared to mortality rates reported for esophageal resection. Thus, accurate histological examination of the obtained specimen by a dedicated pathologist is of major importance as it may guide further management.

Conclusion

Every endoscopist will encounter early neoplastic lesions on a regular basis, either as an incidental finding or during screening or surveillance endoscopy. Selecting the most appropriate resection method largely depends on accurate assessment of a standard set of lesional characteristics using the correct imaging techniques. Relying on glandular structure and microvasculature patterns, it is possible to categorize lesions as non-neoplastic or neoplastic lesions and to assess the presence of dysplasia or even malignancy. Magnifying endoscopy is capable of delivering the most detailed information. However, it is not widely available, is time-consuming, requires extensive training and should therefore only be used in the hands of experienced endoscopists. We believe that HR images are sufficient for accurate inspection of the vast majority of lesions. NBI may contribute to a more detailed visualisation and characterisation of microvessels, although improved accuracy has only been suggested in gastric and colorectal lesions. Another critical point of evaluation is the estimated risk of submucosal invasion, which is an important predictive factor for the development of lymph node metastasis. The value of EUS for staging depth infiltration in early neoplasia is limited and should not be routinely advocated at this time. However, assessment of the gross morphology according to the Paris classification as well as other endoscopic features, give a reliable real-time prediction of invasion into the submucosa or beyond. Appreciation

of the combination of these endoscopic findings should be used as a tool in deciding further treatment. It plays a pivotal role in the decision making which lesion can be safely resected in a piecemeal fashion and which lesion should be resected en bloc or even be referred for surgery.

References

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

2. "*Technology status evaluation report. High resolution and high-magnification endoscopy", Gastrointest Endosc 2000;52:864-6*

3. Fennerty M B, *"Tissue staining", Gastrointest Endosc Clin N Am, 1994;4:297-311*

4. Kuznetsov K, Lambert R, Rey J F, *"Narrow-band imaging: potential and limitations", Endoscopy, 2006;38:76-81*

5. Kudo S, Tamura S, Nakajima T, et al., *"Diagnosis of colorectal tumorous lesions by magnifying endoscopy", Gastrointest Endosc, 1996;44:8-14*

6. Hirata M, Tanaka S, Oka S, et al., *"Evaluation of microvessels in colorectal tumors by narrow band imaging magnification", Gastrointest Endosc, 2007;66:945-52*

7. Katagiri A, Fu K I, Sano Y, et al., *"Narrow band imaging with magnifying colonoscopy as diagnostic tool for predicting histology of early colorectal neoplasia", Aliment Pharmacol Ther, 2008;27:1269-74*

8. **Wada Y, Kashida H, Kudo S E, et al**., *"Diagnostic accuracy of pit pattern and vascular pattern analyses in colorectal lesions", Dig Endosc, 2010;22:192-9*

9. Rastogi A, Keighley J, Singh V, et al., *"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, 2009:104:2422-30*

10. Rogart J N, Jain D, Siddiqui U D, et al., *"Narrow-band imaging without high magnification to differentiate polyps during real-time colonoscopy: improvement with experience", Gastrointest Endosc, 2008;68:1136-45*

11. Sikka S, Ringold D A, Jonnalagadda S, et al., *"Comparison of white light and narrow band high definition images in predicting colon polyp histology, using standard colonoscopes without optical magnification", Endoscopy, 2008;40:818-22*

12. Arima M, Tada M, Arima H, *"Evaluation of microvascular patterns of superficial esophageal cancers by magnifying endoscopy", Esopaghus, 2005;2:191-7*

13. Inoue H, Honda T, Nagai K, et al., *"Ultra-high magnification endoscopic observation of carcinoma in situ of the esophagus", Dig Endosc, 1997;9:16-8*

14. Goda K, Tajiri H, Ikegami M, et al., *"Magnifying endoscopy with narrow band imaging for predicting the invasion depth of superficial esophageal squamous cell carcinoma", Dis Esophagus, 2009;22:453-60*

15. Yoshida T, Inoue H, Usui S, et al., *"Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions", Gastrointest Endosc, 2004;59:288-95*

16. Dawsey S M, Fleischer D E, Wang G Q, et al., *"Mucosal iodine staining improves endoscopic visualization of squamous dysplasia and squamous cell carcinoma of the esophagus in Linxian, China", Cancer, 1998;83:220-31*

17. Curvers W L, Singh R, Song L M, et al., *"Endoscopic tri-modal imaging for detection of early neoplasia in Barrett's oesophagus: a multi-centre feasibility study using high-resolution endoscopy, autofluorescence imaging and narrow band imaging incorporated in one endoscopy system", Gut, 2008;57:167-72*

18. Goda K, Tajiri H, Ikegami M, et al., *"Usefulness of magnifying endoscopy with narrow band imaging for the detection of specialized intestinal metaplasia in columnar-lined esophagus and Barrett's adenocarcinoma", Gastrointest Endosc, 2007;65:36-46*

19. Hamamoto Y, Endo T, Nosho K, et al., *"Usefulness of narrow-band imaging endoscopy for diagnosis of Barrett's esophagus", J Gastroenterol , 2004;39:14-20*

20. Kara M A, Ennahachi M, Fockens P, et al., *"Detection and classification of the mucosal and vascular patterns (mucosal morphology) in Barrett's esophagus by using narrow band imaging", Gastrointest Endosc, 2006;64:155-66*

21. Sharma P, Bansal A, Mathur S, et al., *"The utility of a novel narrow band imaging endoscopy system in patients with Barrett's esophagus", Gastrointest Endosc 2006;64:167-75*

22. Wolfsen H C, Crook J E, Krishna M, et al., *"Prospective, controlled tandem endoscopy study of narrow band imaging for dysplasia detection in Barrett's Esophagus", Gastroenterology 2008;135:24-31*

23. Ngamruengphong S, Sharma V K, Das A, *"Diagnostic yield of methylene blue chromoendoscopy for detecting specialized intestinal metaplasia and dysplasia in Barrett's esophagus: a meta-analysis", Gastrointest Endosc,2009;69:1021-8*

24. Canto M I, Setrakian S, Willis J E, et al., *"Methylene blue staining of dysplastic and nondysplastic Barrett's esophagus: an in vivo and ex vivo study", Endoscopy, 2001;33:391-400*

25. Horwhat J D, Maydonovitch C L, Ramos F, et al., *"A randomized comparison of methylene blue-directed biopsy versus conventional four-quadrant biopsy for the detection of intestinal metaplasia and dysplasia in patients with long-segment Barrett's esophagus", Am J Gastroenterol, 2008;103:546-54*

26. Nakayoshi T, Tajiri H, Matsuda K, et al., *"Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology (including video)", Endoscopy (2004), 36: pp. 1080-4.*

27. Yao K, Oishi T, Matsui T, et al., *"Novel magnified endoscopic findings of microvascular architecture in intramucosal gastric cancer", Gastrointest Endosc, 2002;56:279-84*

28. Yokoyama A, Inoue H, Minami H, et al., *"Novel narrow-band imaging magnifying endoscopic classification for early gastric cancer", Dig Liver Dis, 2010;42:704-8*

29. Ezoe Y, Muto M, Uedo N, et al., *"Magnifying narrowband imaging is more accurate than conventional white-light imaging in diagnosis of gastric mucosal cancer", Gastroenterology, 2011;141(3):2017-25*

30. Kato M, Kaise M, Yonezawa J, et al., *"Magnifying endoscopy with narrow-band imaging achieves superior accuracy in the differential diagnosis of superficial gastric lesions identified with white-light endoscopy: a prospective study", Gastrointest Endosc, 2010;72:523-9*

31. Maki S, Yao K, Nagahama T, et al., *"Magnifying endoscopy with narrow-band imaging is useful in the differential diagnosis between low-grade adenoma and early cancer of superficial elevated gastric lesions", Gastric Cancer (2012)*

32. Kawahara Y, Takenaka R, Okada H, et al., *"Novel chromoendoscopic method using an acetic acid-indigocarmine mixture for diagnostic accuracy in delineating the margin of early gastric cancers", Dig Endosc, 2009;21:14-9*

33. Lee B E, Kim G H, Park do Y, et al., *"Acetic acid-indigo carmine chromoendoscopy for delineating early gastric cancers: its usefulness according to histological type", BMC Gastroenterol, 2010;10:97*

34. Sakai Y, Eto R, Kasanuki J, et al., *"Chromoendoscopy with indigo carmine dye added to acetic acid in the diagnosis of gastric neoplasia: a prospective comparative study", Gastrointest Endosc, 2008;68:635-41*

35. *"Update on the paris classification of superficial neoplastic lesions in the digestive tract", Endoscopy, 2005;37:570-8*

***36. Gotoda T, Yanagisawa A, Sasako M, et al.**, "Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers", Gastric Cancer, 2000;3:219-25*

***37. Kwee R M, Kwee T C**, "Imaging in local staging of gastric cancer: a systematic review", J Clin Oncol, 2007;25:2107-16*

***38. Choi J, Kim S G, Im J P, et al.**, "Comparison of endoscopic ultrasonography and conventional endoscopy for prediction of depth of tumor invasion in early gastric cancer", Endoscopy, 2010;42:705-13*

***39. Young P E, Gentry A B, Acosta R D, et al.**, "Endoscopic ultrasound does not accurately stage early adenocarcinoma or high-grade dysplasia of the esophagus", Clin Gastroenterol Hepatol, 2010;8:1037-41*

***40. Kodama M, Kakegawa T**. "Treatment of superficial cancer of the esophagus: a summary of responses to a questionnaire on superficial cancer of the esophagus in Japan". Surgery, 1998;123:432-439*

***41. Leers JM, Demeester SR, Oezcelik A, et al**. "The prevalence of lymph node metastases in patients with T1 esophageal adenocarcinoma: a retrospective review of esophagectomy specimens". Ann Surg. 2011;253:271–278*

The Role of Environmental Factors in Digestive Cancer

René Lambert

Visiting Scientist, Screening Group. WHO, International Agency for Research on Cancer, Lyon, France

Abstract

Endoscopic detection and evaluation of early neoplasia in the gastrointestinal tract should be carried out by systematic assessment of a standard set of lesional characteristics. First of all, attention should be given to the microvasculature and pit pattern of the mucosal surface. These features can distinguish neoplastic from non-neoplastic lesions and are used to assess the presence of dysplasia or malignancy. High resolution endoscopy combined with narrow band imaging usually provides sufficient detailed visualisation for characterisation. Secondly, estimating the risk of invasion beyond the mucosal layer is important, because the depth of invasion corresponds to the risk of lymph node metastasis. This prediction can be based on the gross morphology according to the Paris classification, but also size, the presence of converging folds with clubbing, ulceration and discoloration are considered predictive characteristics. This editorial provides a practical approach to assessing early neoplasia in the gastrointestinal tract. We would encourage endoscopists to appreciate these features systematically before proceeding to endoscopic or even surgical resection.

Disclaimer: There is no potential conflict of interest.
Citation: *European Medical Journal - Gastroenterology,* 2012:1:53-62

Introduction

In a small (5%) percentage of cases, cancer occurs through the transmission of a dominant gene by one ascendant; the development of this hereditary cancer occurs independently of any causal factor. Sporadic cancer corresponds to the majority of cases; here the development of the tumor may result, in connection to environment and lifestyle, of a prolonged abnormal exposure to toxic or infectious factors. The susceptibility to these causal factors varies with the genetic profile of the concerned person, justifying the occurrence of familial, but not hereditary, cancer, i.e. cases of sporadic cancer occurring in first degree parents, exposed to similar risk factors in their family.

The role of environmental factors linked to lifestyle has been exposed in multiple publications.[1-8] Particularly D.M. Parkin wrote a complete special issue of the *British Journal of Cancer* on this topic in 2011,[8] analysing the role of 14 distinct toxic or infectious factors with a carcinogen impact, on 18 sites of cancer, out of which 7 were located in the digestive system. The study concerned only the population of England in 2010, a country with a westernised lifestyle. In synthesis in this European country, non optimal exposure to one, or too many, of these carcinogenic factors, occurred in 42.7% of the incident cases in the year 2010. Cancer prevention aims to reduce cancer mortality through early detection and appropriate treatment of the tumor at a curable stage. This strategy, called secondary prevention is often developed through screening in asymptomatic persons. Cancer prevention also occurs through the identification and elimination of these causal factors linked to lifestyle and environment: their control is primary prevention of cancer.

The worldwide risk of digestive cancer

Population based cancer registries give for most countries very precise information of the annual burden of cancer at each site. Annual incidence and mortality are displayed there. Cancer survival is estimated from registries with a continuous follow-up of cases included, at each successive year. Cancer registries produce observed values of incidence and mortality, but in many countries this only applies

to a fraction of the population. Estimated values of incidence and mortality in all the population of a country and at each tumor site are also found in the WHO-IARC database GLOBOCAN, recently re-edited for the year 2008.[9]

In each cancer population based registry and for each tumor site, the yearly number of new cases occurring in 100,000 persons of the concerned population, is the crude rate of incidence. The figure is influenced by the distribution of age classes in this population; therefore for comparison of the risk between different countries, the figures refer to a standard of population. The age standardised rate (ASR) of incidence per 100,000 persons refers to the repartition of age classes in the world population in 1960, and is adopted in the listing of registries edited at intervals by the WHO International Agency for Research on Cancer in Lyon; in the most recent edition, the data are listed from 225 registries in 60 distinct countries, for the period 1998-2002.[10]

In each cancer registry and at each tumor site, the annual number of deaths by cancer is displayed in the corresponding population. The crude mortality rate is the annual number of deaths per 100,000 persons of the concerned population occurring in a year. The mortality is also expressed as an ASR mortality per 100,000 persons.

Cancer survival is usually expressed at each tumor site in percent as a crude 5 years survival. The 5 years relative survival refers to survival rate taking into account the comparison with persons of same sex and age, not suffering from this cancer. Survival analysed in cancer registries is also estimated at each stage of the detected tumor, for 'localised' to 'distant' cancer.

Sites of digestive cancer considered in this review are listed according to their code in the International Classification of Diseases (ICD10). The tumor sites in the digestive tract include cancer in the esophagus (C-15), stomach (C-16), colon and rectum (C-18 to C-21). Outside of the digestive tract the major sites include cancer in the liver (C-22), gallbladder and biliary tract (C-23 and C-24), and pancreas (C-25). The frequency of digestive cancer is confirmed by the worldwide numbers of incident cases and of deaths by cancer which are estimated and displayed in the database GLOBOCAN 2008.[9] Globally they represent around 30% of incident cancer at all sites and 37% of the total number of deaths by cancer at all sites, as shown in Table 1. Other digestive tumors not considered in this review include cancer in the lips, mouth and tongue (C-00 to C-06), oropharynx (C10), pharynx and hypopharynx (C-12 to C14).

	N° incident cases in 2008	N° deaths in 2008
All cancers	12 661 000	7 564 000
Esophagus Ca.	481 000	406 000
Stomach Ca.	998 000	736 000
Colon, Rectum Ca.	1 234 000	608 000
Liver Ca.	749 000	695 000
Gallbladder Ca.	145 000	109 000
Pancreas Ca.	278 600	266 600

Table 1: Estimated Worldwide burden of digestive cancer in 2008 according to GLOBOCAN.[9] At each site, both sexes are included in the annual numbers of incident cases and of death by cancer. The global burden of digestive cancer - 3,885,600 cases and 2,820,600 deaths - amounts to 30.6% of the incident cases of cancer at all sites and 37.2% of mortality by all cancers.

Classification of countries through development

The countries of the world are classified in large geographic areas. The more developed countries, in their majority, are located in North America, Europe plus Australia and Japan. On the other hand, less developed countries are concentrated in Asia, Africa, Central and South America. Some countries, which are not yet classified as completely developed, like Brazil, Russia, India, and China, have a very fast improvement of their resources and are called "emerging" countries. The World Bank[11] is publishing a very precise list of the countries resources classified in 4 categories, with yearly revision of the figures. The list is based on the annual "per capita" income classified as Low, Middle-lower, Middle upper and High. The annual income per person is expressed in

Dollars, and the data for 2011 are given in Table 2.

Category of the country	GNI per capita
Low	$1005 or less
Lower middle	$1006 to $3975
Upper middle	$3976 to $12,975
High	$13,976 or more

Table 2: Amount in Dollars of the annual income per person (GNI per capita) in the population of a country for the year 2011, according to the listing of the World Bank. [11] Countries are distributed in 4 categories according to individual income.

At each site of digestive tumors there are considerable variations in the risk for incidence, mortality and survival between countries at different levels of development. The variation is a consequence of the relationship between the resources of a country and the global health status of the respective population. First, this applies to the role of causal factors of digestive cancer in relation to lifestyle and resources of the persons. Causal factors may have an impact on the risk of cancer with an increase or a decrease, depending on the tumor site and type. Second, the proportion of cases detected early, at a curable stage depends on the diffusion of screening strategies in the corresponding country. Indeed there are considerable variations in the survival of colorectal cancer according to its stage at detection. In the SEER registries of the USA [12-14] the 5 years survival is as high as 96% for stage I (localized) and as low as 6% for stage IV (distant). Third, the quality of an adapted treatment, particularly for endoscopic and surgical procedures, depends on the level of development. In the same registries, the 5 years survival increased at all sites of digestive cancer during two decades of progression in early detection and treatment, as shown in Table 3.

Site of cancer	Years 1980-84	Year 2002
Esophagus	6.9%	16.7%
Stomach	16.7%	25.7%
Colon & Rectum	53.9%	69.1%
Liver	3.8%	14.0%

Table 3: Increase in the 5 years relative survival from digestive cancer in both sexes during the period 1980-2000 in the USA in relation to development of screening and treatment at early stage, as shown in the SEER registries. [14]

In the less developed Sub-Saharan countries of the African continent, early detection of a cancer is not frequent and the overall survival is very low for most tumors. Furthermore the organisation of the sanitary system in the less developed countries is not homogenous, and the healthcare is better in urban than in rural sectors, where it is still deficient. This heterogeneity in healthcare in urban and rural sectors often persists in emerging countries in spite of their rapid development. On the other hand in the more developed countries classified in the higher category of the World Bank listing, healthcare is homogenously distributed with a generalised positive impact on cancer mortality and survival.

Environmental causal factors in digestive cancer

Causal factors promoting carcinogenesis are often present in the environment of the persons and their action occurs through modalities of the lifestyle. As a rule, lifestyle criteria correlate with economic resources and depend on the development in the concerned country which has a direct impact on the role of causal factors of cancer. Around the world the carcinogenic factors connected to lifestyle can be classified in 3 categories which may have an impact on the risk of digestive cancer:

1- Nutrition, with the quantitative and qualitative character of aliments absorbed in the diet, plays a determinant role in the risk for colorectal cancer.

2- Toxicity, with agents like alcohol and tobacco absorbed in complement to diet, increases the risk for digestive cancer at all sites. Toxic factors associated to tobacco and Betel Quid chewing, increase the risk of esophageal cancer. Aflatoxin as a food contaminant in the culture of corn in tropical and less developed countries specifically increases the risk for liver cancer.

3- Infection occurs by multiple modalities of contamination and is an important causal factor of digestive cancer. The infectious agents include for stomach cancer the bacteria Helicobacter pylori, for liver and bilary tract cancer with hepatocarcinoma and cholangiocarcinoma; the Hepatitis B and C Viruses, the infections by liver flukes like Opistorchis viverrini, and Clonorchis sinensis.

In a first analysis of the global burden of infection associated cancers in the year 2002,[7] it was

that a complete prevention of infectious factors would decrease the number of incident cancers by 7.7% in developed countries and by 26.7% in less developed countries. In a more recent analysis[4] of the global burden of cancers attributable to infections in 2008, infectious agents accounted for 16.1% of all cancers, i.e. 2,000,000 incident cases. The proportion was much higher in the less developed countries of Asia and Africa (22.9%), than in more developed countries of Europe and North America (7.4%). In the same analysis[4] the most frequent infectious agents playing a role in digestive cancer were the bacteria H. pylori with an estimated number of incident cases in 2008 at 660,000 and the Hepatitis B and C viruses with an estimated number of incident cases in 2008 at 600,000.

For these environmental causal factors, the role played in the etiology of digestive cancer differs in each region of the world, showing quantitative variations in the impact on the incidence of cancer. In more developed countries the majority of causal factors belongs to nutrition and diet with absorption of an excessive amount of calories, or to toxic agents like alcohol and tobacco. The conclusions of the recent analysis of these factors conducted at all sites of cancer in England[8] are also valid in the majority of developed countries in Europe and North America. On the other hand, infectious factors play a predominant role in less developed countries of the world, like H. pylori infection in Asia and Viral Hepatitis B in Africa.

A more or less important reduction in the risk of cancer may be obtained by the control of the causal factors linked to lifestyle of the population; this is primary prevention of cancer. The strategy of primary prevention and its efficacy varies of course with the nature of the causal factor and with the style of life in this country. The efficacy of primary prevention through control of noxious environmental factors depends of course on the level of healthcare and economic resources in the concerned country, it also depends on its interaction with the lifestyle of the persons. The generalised practice of a vegetarian diet in India achieves an effective and spontaneous primary prevention of colorectal cancer. In opposition the prevention of hepatocarcinoma in Africa requires a complex and diffuse intervention of vaccination against hepatitis Virus B in the population.

Causal factors at each site of digestive cancer

Esophageal cancer

In GLOBOCAN,[9] the worldwide number of incident cases of esophageal cancer occurring in 2008 was estimated for both sexes at 481,000, out of which 80,000 occurred in developed countries and 399,000 (83% of total) in developing countries. In the recent analysis[8] of environmental factors associated to esophageal cancer in England, tobacco smoking or chewing is present in 65.5% of cases and alcohol drinking in 20.6% of cases. There are two distinct tumor types in the esophagus: squamous cell cancer and adenocarcinoma. The incidence of adenocarcinoma is much lower than that of squamous cell cancer, but it tends to increase. Squamous cell cancer is more frequent in developing countries of Asia; the tumor arises from the normal squamous epithelium of the esophageal mucosa; alcohol and tobacco are acknowledged as causal factors of squamous cell cancer, and their control is recommended for primary prevention of this tumor. Adenocarcinoma, developed in a metaplastic columnar epithelium, also called Barrett esophagus, is in relation to chronic inflammation through gastro-esophageal reflux and is more frequent in developed countries of North America and Europe with a higher risk in Caucasians. The risk for this tumor is increased by smoking and higher in persons with excess weight and obesity at a young age. In addition to the control of acid reflux by proton pump inhibitors in persons with gastro-esophageal reflux, the primary prevention of esophageal adenocarcinoma through control of environmental factors, relies on the control of smoking and reduction of calories in the diet to prevent obesity. Early detection of esophageal squamous cell cancer through population based screening trials is organized of high risk areas in China and Southern Brazil and based on a balloon or sponge scrapping of the esophageal mucosa, followed by upper GI endoscopy in persons positive to the test. For esophageal adenocarcinoma, organised screening endoscopic trials are not recommended.

Stomach cancer

In GLOBOCAN,[9] the worldwide number of incident cases of stomach cancer occurring in 2008 was estimated for both sexes at 988,000, out of which 274,000 occurred in developed countries and 713,000

(70% of total) in developing countries. Gastric cancer, localised in the distal part of the stomach accounts for 80% of the cases, while proximal gastric cancer (also called cardia cancer) accounts for 20% of the cases. However in most countries, during the recent decades, the decreasing incidence of distal gastric cancer is in contrast with the increasing incidence of proximal gastric cancer at the cardia. In the analysis of the global burden of infection-associated cancers in 2002[7] the proportion of gastric cancers attributable to H. pylori infection was estimated at 61.4% in developed countries and 64.4% in developing countries; the global numbers are shown in Table 4. Therefore gastric cancer is the tumor site more frequently associated to an infectious agent. In a more recent worldwide analysis, conducted in 2008[4] the prevalence of the infectious agent in cases of non-cardia (distal) gastric cancer was estimated at 90% and 74.7% of incident cases of this tumor occurring in 2008 were classified as attributable to this infectious agent. In addition to infection of the gastric mucosa, nutritional factors such as a high intake of salt and nitrates and a low intake of fruit and vegetables, may increase the risk of cancer.

Countries	Sex	N° distal gastric cancer	N° attributable to H. pylori infection
Developed countries	Men	156 000	117 000
	Women	117 000	75 00
	Both	273 000	192 000
Developing countries	Men	324 000	254 000
	Women	187 000	146 000
	Both	511 000	400 000

Table 4: Estimation of the worldwide number of stomach cancer attributable to H. pylori infection in 2002 for developed and developing countries according to the worldwide analysis conducted by DM Parkin.[7] The figures are based on the following assumption: the proportion of adult persons infected by the bacteria is 58% in developed countries and 74% in developing countries.

The sequence of gastric carcinogenesis in relation to H. pylori infection as a cause of atrophic gastritis, a pre-neoplastic condition, has been described by Correa in the gastric lumen: the increased pH causes a growth of anaerobic bacteria with formation of carcinogenic compounds like the nitrosamines. The bacteria H. pylori has been classified as a carcinogen agent in a monography of the WHO-IARC agency in Lyon. Another infectious factor plays a role in addition to H. pylori in gastric carcinogenesis: Epstein-Barr virus is present in the tumor cells of about 10% of cases of gastric cancer.[15] This agent accounts for around 80,000 cases annually. Until recently the role of H. pylori infection in gastric carcinogenesis was limited to distal gastric cancer. More recently a positive association with this infectious factor was observed both for proximal and distal gastric cancer. Indeed cancer associated to Epstein Barr virus shows a more frequent localisation in the proximal stomach with a high proportion of diffuse type of tumors.

Non-cardia (distal) gastric cancer[16] occurs all over the world but the incidence is higher in countries of Eastern Asia and in South America as shown in Table 5.

	Men	Women
NorthAmerica		
USA : SEER 14 registries	7.2/100,000	3.4/100,000
South America		
Chile : Valdiva registry	43.1/100,000	16.0/100,000
Europe		
Denmark	7.1/100,000	3.2/100,000
Italy : Vénétie	15.7/100,000	7.3/100,000
Asia		
China : Shanghai registry	34.1/100,000	17.2/100,000
Japan : Osaka registry	51.3/100,000	19.8/100,000
Korea : Séoul registry	63.7/100,000	27.1/100,000

Table 5: The ASR incidence for gastric cancer in cancer registries from various countries for the period 1998-2002 according to 'Cancer Incidence in Five Continents'[10]

In Japan, this cancer accounts for a high proportion of cases at all tumor sites. Other regions at high risk of non-cardia gastric cancer include Eastern Europe and Western South America. The incidence of proximal gastric cancer is lower and the highest figures are

observed in North America and in Europe. Primary prevention of distal gastric cancer is focalised on the eradication of H. pylori infection at the individual scale in children. This is completed by the diffusion of a policy on healthy nutrition combining the reduction of salt and nitrites in the alimentation to an increased consumption of fruit and vegetables. This policy is currently applied in Japan, a country where the consumption of food preserved by salt was often combined with a low consumption of fruit, vegetables, and anti-oxidants. The changing style of life in nutrition in this country has a significant impact on the reduction of the risk. The preventive action of ascorbic acid, an anti-oxidant, is based on the inhibition of the endoluminal formation of carcinogens. Primary prevention of proximal (cardia) gastric cancer relies on the control of excess weight at a young age, to reduce gastro-esophageal reflux.

Secondary prevention of stomach cancer by organised screening for early detection at a curable stage is only justified in countries with a high incidence, like in Japan where there is a national screening policy. In this country the first test is photofluorography performed on seven small films easily swallowed, followed by gastroscopy in persons positive to the test.

Colorectal cancer

In GLOBOCAN,[9] the worldwide number of incident cases of colorectal cancer occurring in 2008 was estimated for both sexes at 1,234,000, out of which 727,000 occurred in developed countries and 506,000 (41% of total) in developing countries. Worldwide, colorectal cancer is the third most common cancer in men, and the fourth in women. In 95% of cases colorectal cancer occurs as a sporadic disease in adults of both sexes, aged 50 years or more. The site of colon cancer is in the ascending segment, right angle, transverse segment, left angle and descending segment of the large bowel, while rectum cancer is in the most distal part of the large bowel between the recto-sigmoid junction and the anal margin. The proportion of colorectal cancer attributable to lifestyle and environmental factors in England for the year 2010 is estimated at 54%.[8] These factors include a diet rich in calories of animal origin, with red and processed meat, overweight, inducing resistance to insulin and production of insulin-like growth factors like the IGF-1 which stimulates the proliferation of intestinal cells. Aromatic polycyclic molecules with a carcinogenic impact, develop within meat directly grilled. Another causal factor is a sedentary mode of life with decreased physical activity. All these environmental factors are closely related to the development of resources and of urbanised life; therefore the incidence of cancer in the colon and cancer in the rectum is higher in countries classified in the Upper Middle and in the High Income categories for their GNI per capita, than in those classified in the Lower middle and Low Income categories, which account for 82% of the world population. Data on the incidence of cancer in the colon and in the rectum in Cancer Registries are displayed for the period 1998-2002 in the last edition of 'Cancer Incidence in Five Continents'.[10] The ASR Incidence /100,000 of CRC for men is high in developed countries: 37.4 in Japan (Osaka registry), 38.4 in the USA (SEER 9 registries), 48.7 in France (Bas-Rhin registry). The figures for women are slightly lower but still high. Incidence is much lower, and under 10/100,000 in countries with low resources like in Zimbabwe (Harare registry) in Sub-Saharan Africa. Incidence of colorectal cancer increased in the two recent decades in urbanised areas of emerging countries like China and Brazil, reaching similar figures to those observed in the more developed countries.

A confirmation of the role of environmental factors linked to diet is shown by the stable and low incidence of colon cancer in India, a country where the diet is strictly vegetarian as a rule, during the same period; stability applies also to cancer at the rectum sub-site. The temporal trend for increasing incidence observed in North America, Europe, Japan and Australia in the period 1980-2000, is more marked for the colon than for the rectum sub-site. As an example, in Japan in the Osaka cancer registry[17] the trend in incidence during the period 1974-2003, shows a topographic shift in the distribution of colorectal cancer towards proximal colon. In summary colorectal cancer is a frequent tumor, with an incidence rate higher in developed than in developing countries, as shown by the estimates of GLOBOCAN.[9] In the year 2008 59% of cases occurred in developed countries which account for only 36% of the world population.

With respect to cancer survival, developing countries with low resources have not yet developed their National Health Care System and the efficacy in the diagnosis and treatment of colorectal cancer is

poor. Survival depends on the stage of the tumor at detection and is much higher for localised than for advanced cancer. The 5 years relative survival of colorectal cancer in registries from developed countries is displayed in the CONCORD study for the period 1990-94[18]: - for men the figures are: 51.9% in registries from USA, and 61.1% in registries from Japan. -for women the respective figures are 60.2%, and 77.3%. In registries from Europe slightly lower values are reported in the same study[18] for men and women at the colon and rectum sub-sites; with almost similar results in the period 1995-99.[19] In registries from Asia in the period 1990-2000[20] the 5 years relative survival from colon cancer is low at 32.3% in the Mumbai registry of India a country in the Lower middle category of the GNI per capita, and high at 65.7% in the Seoul registry of Korea, a country in the high category of the GNI per capita. An increase of the survival in the registries of 2 successive periods, suggests a progress in cancer prevention, either through early detection with more cases detected at stage I or II, or through improved treatment. In the period 1988-2001, the 5 years relative survival increased in the USA in relation to the progress in early detection and the figures in the SEER registries for both sexes at the colon and rectum sub-sites were 64.0% and 62.7% during the period 1988-2001.[12] In the less developed countries of the world survival is much lower: the 5-year relative survival in the period 1990-2000 in Uganda, a sub-Saharan country,[30] is in the range 7 to 11%, because detection often occurs at an advanced stage. Emerging and developing countries with middle and higher resources, have already built structures of health care and cancer control in urbanized areas. In China in the period 1990-2000, the 5 years relative survival for cancer in the colon and rectum is higher in the urbanised district of Shanghai, than in the rural district of Qidong.[20] Cancer survival can reach the same level as in developed countries, in the urbanised sectors of developing countries with enough resources; however, heterogeneity persists with lower figures in rural areas. Multiple publications address to incidence, mortality and survival of this tumor.[21-30]

Primary prevention of colorectal cancer is based on a reduction of the amount of calories, focused on proteins and fat and in increased physical activity and daily walking,[23-30] in order to reduce excess weight and obesity. These prescriptions can be integrated in a national policy creating awareness among the population on: 1 - restraining high consumption of sugar, and fat, 2 - increasing consumption of vegetal food including fruits, vegetables and whole grains, 3 - increased physical activity 4 - keeping an ideal bodyweight without obesity. An example of the impact of a spontaneous national primary prevention is given by India, an emerging country, where low incidence of colorectal cancer persists in spite of the development in urban districts, in relation to a generalised vegetarian alimentation.[23,24,28,30] In India, the stable and low incidence of colon cancer during the period 1973-2002 in the urban registry of Mumbai, is in contrast with the increasing trend occurring in Japan and in China, as shown in Table 6.

	Period 1973 - 1977	Period 1998 - 2002
Japan, Myagi registry		
Men	8.3/100,000	36.0/100,000
Women	7.3/100,000	21.5/100,000
China, Shanghai registry		
Men	6.7/199,000	15.8/100,000
Women	6.0/100,000	14.6/100,000
India, Mumbai registry		
Men	3.5/100,000	3.0/100,000
Women	3.5/100,000	2.4/100,000

Table 6: The ASR Incidence of colon cancer in men and women in cancer registries of Asia in two periods 1973 to 1977 and 1998 to 2002. The incidence increases in relation to the progression of the development in Japan and in China, but not in India according to 'Cancer Incidence in Five Continents.[10, and previous editions]

Secondary prevention of colorectal cancer is based on screening trials which are often offered in developed countries of Europe, North America and in Japan. Mass screening is proposed to all persons in the age range 40 to 70 years and repeated at regular intervals of 2 to 5 years. The strategy of early detection and treatment is based on a filter test, the Guaiac or Immunologic Fecal Occult Blood Test; colonoscopy, the detection test, is performed only in persons found positive to the test.[31] A 10% to 20% reduction in cancer mortality has been confirmed in the randomised trials conducted in the USA (Minnesota trial) and in Europe (Nottingham and Funen trials).

Countries	N° liver cancer	Attributable to HBV	Attributable to HCV	Attributable to HBV or HCV
Developed countries	119,800	26,000	22,000	48,000
Developing countries	515,000	393,000	172,000	475,000

Table 7: Estimation of the worldwide number of liver cancer, both sexes, attributable to infection by HBV and HCV in 2002 for developed and developing countries, according to a worldwide analysis.[7] Globally 85.5% of hepatocarcinoma are attributable to viral hepatitis and 90% of cases occur in developing countries of Africa and Asia.

The reduction in incidence did not occurr in the cost effective European trials in which the proportion of persons submitted to colonoscopy was small. Mass screening interventions addressed to the population of a country require an evaluation of the benefits and drawbacks. Benefits include a reduction in cancer mortality and increased survival.

Drawbacks include the morbidity of the endoscopic intervention and the inevitable over-detection of cancer in screened persons with a preclinical cancer, which would die from another cause. Non organized screening is also often proposed in developed countries to asymptomatic persons, in the age range 50-70 years; with the objective of early detection of cancer at a curable stage; this is called opportunistic screening. Primary colonoscopy is then directly performed, allowing also the detection and treatment of adenomatous premalignant lesions; then the development of colorectal cancer is prevented by the destruction of the precursors with an impact on cancer incidence. Indeed the trend to increased incidence of colorectal cancer in the USA during the last quarter of the XXth century is now inversed; a recent decline in incidence follows an increased endoscopic destruction of premalignant precursors.

Liver cancer

In GLOBOCAN,[9] the worldwide number of incident cases of Liver cancer occurring in 2008 was estimated for both sexes at 749,000, out of which 122,000 occurred in developed countries and 625,000 (83% of total) in developing countries. Liver cancer develops in chronic cirrhosis; toxic and infectious environmental factors linked to lifestyle play a major role in the development of this tumor. Among toxic factors is alcohol consumption, at the origin of the liver cirrhosis,[32] tobacco smoking increases the risk of cancer and is a frequent associated factor. The first step of alcohol toxicity on the liver is steatosis followed by fibrogenesis induced by alcetaldehydre. Aflatoxin, a mycotoxin produced by Aspergillus, is present in the soil and contaminates the crops during farming in the south of China and in Sub-Saharan African countries. The necrosis produced in the liver is followed by development of an hepatocarcinoma. Infectious agents with a carcinogen activity are hepatitis viruses. In the review of infectious associated tumors conducted in 2002,[7] the worldwide number of hepatocarcinomas attributable to virus B and C (HBV and HCV), is estimated at 340,000 for Hepatitis virus B, (54%) and at 195,000 for Hepatitis virus C (31%). The majority of the hepatocarcinomas (over 80%) attributable to viral hepatitis occurs in the less developed or developing countries, as shown in Table 7.

The HBV is a DNA virus with distinct genotypes present in Asia and in Africa and Europe;[33] the contamination occurs through sex, or injections. The integration of the DNA virus, behaving as an oncogene in the genoma of the host cells, insures the chronicity of infection. The proportion of hepatocarcinomas with a positive HBV serology is above 50% in China, Taiwan, Korea and Thailand. HCV is a RNA virus with two distinct genotypes.[34] The virus is not an oncogene and is not impacted in the cell DNA and replication occurs in the cytoplasma, with an interference on the regulation of the cell cycle. Contamination by HCV occurs through the deficient asepsy of injections. The proportion of hepatocarcinomas positive for HCV is near to 70% in Japan and in Egypt.[34]

Primary prevention of digestive cancer at all sites, including liver hepatocarcinoma, is possible worldwide through reduction of alcohol drinking and tobacco smoking or chewing. With respect to toxic factors like Aflatoxin, the prevention of the contamination of the crops of cereals and of milk of

animals is obtained through selection of the cultivar and pre-harvest treatments. Prevention against infectious agents is also a priority in Asia and in Africa, through vaccination against HBV. Concerning HCV, there is still no effective vaccine, but the use of safe blood products, disposable syringes and needles, and a strict asepsy for injections have dramatically reduced risk of infection.

Secondary prevention of liver hepatocarcinoma by screening asymptomatic persons or persons with chronic virus C Hepatitis is possible, using abdominal ultrasound and serum alpha-foetoprotein as filter tests.

Organized screening interventions have been successful in Japan and attempted in African countries. In persons with a positive filter test, confirmation of the diagnosis requires a tissue sampling by biopsy under ultrasound or CT scan. Conservative treatment of small tumors detected by screening is based on new techniques like radio-frequency or chemo-embolisation.

Gallbladder and biliary cancer

In GLOBOCAN,[9] the worldwide number of incident cases of cancer in the gallbladder and biliary tract occurring in 2008 was estimated for both sexes at 145,000, out of which 60,000 occurred in developed countries and 85,000 (58% of total) in developing countries. The role of infectious agents in the risk of cholangiocarcinoma is considered In the analysis of the global burden of infection-associated cancers in 2002[7]: in countries from Asia, liver flukes, which are endemic, may play a role: Opistorchis Viverrini in China , Korea, Vietnam and Opistrochis felineus in Thailand.

Pancreatic cancer

In GLOBOCAN,[9] the worldwide number of incident cases of pancreatic cancer occurring in 2008 was estimated for both sexes at 278,700, out of which 166,000 occurred in developed countries and 112,000 (40% of total) in developing countries. Pancreatic cancer incidence and mortality are higher in developed Western countries and in Japan. In Europe, rates are highest in the Nordic countries. In the USA, rates are particularly high in native Hawaiians and in African Americans. In the special issue of the *British Journal of Cancer*,[8] tobacco smoking is a significant environmental factor linked to the risk of pancreatic cancer. The presence of this toxic factor is acknowledged in 28.7% of the cases occurring in England. Another factor playing a role and linked to diet is the excess weight and obesity; sources of animal calories, proteins and fat, may play an important role in the etiology of pancreatic cancer. The presence of obesity is acknowledged in 12.2% of the cases occurring in England.

In conclusion

Environmental and preventable factors linked to lifestyle play a role in around 50% of digestive cancer at all sites. The burden of digestive cancer could be significantly reduced by an intervention on these factors. Toxic agents like alcohol and tobacco play a worldwide role. If they interfere with the risk of digestive cancer at all sites, their major promoting role is for esophageal cancer. Infectious agents like H. pylori for stomach cancer and Hepatitis B and C viruses for liver hepatocarcinoma, concern in priority the risk in regions of Asia and in Africa. Their role is more marked in the less developed countries.

There should be a joint action between policies of primary prevention and policies of secondary prevention. Both policies contribute to reduction of the risk and detection of cancer or precursors at an early curable stage, providing a safe and effective treatment. A good example is the role of colonoscopy in the prevention of colorectal cancer; this procedure offers a simple and non-aggressive treatment of the precursor adenomas and of superficial cancer detected in asymptomatic persons.

References

1. Boffetta P, Couto E, Wichmann J, et al. *Fruit and vegetable intake and overall cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). J Natl Cancer Inst. 2010;102(8):529-37.*

2. Cavaleiro-Pinto M, Peleteiro B, Lunet N, Barros H. *Helicobacter pylori infection and gastric cardia cancer: systematic review and meta-analysis. Cancer Causes Control. 2011 ;22:375-87*

3. Davies NJ, Batehup L, Thomas R. *The role of diet and physical activity in breast, colorectal, and prostate cancer survivorship: a review of the literature. Br J Cancer. 2011;105 Suppl 1:S52-73. doi: 10.1038/bjc.2011.423.*

4. De martel C. Ferlay J. Franceschi S. Vignat J. Bray F.Forman D. et al. *Global burden of cancers attributable to infections in 2008 : a review and synthetic analysis. Lancet Oncology 2012,13, 607-615.*

5. Franceschi S, Montella M, Polesel J et al. *Hepatitis viruses, alcohol, and tobacco in the etiology of hepatocellular carcinoma in Italy. Cancer Epidemiol Biomarkers Prev. 2006 ;15:683-689.*

6. E Riboli, R Lambert eds. *Nutrition and lifestyle: opportunities for cancer presention IARC Scientific publication 156 , IARC PRESS, Lyon 2002*

7. Parkin DM. *The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006; 118(12):3030-3044*

8. Parkin DM, Boyd L, Walker LC. *16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer. 2011;105 Suppl 2:S77-81*

9. Ferlay J, Shin HR, Bray F, et al. *GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 . IARC Lyon; 2010. Available from: http://globocan.iarc.fr*

10. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanu M, et al. eds *Cancer Incidence in Five Continents, Vol. IX , IARC Scientific Publications No. 160, IARC, Lyon, 2007.*

11. World Bank *list of economies (April 2012) http://shop.ifrs.org/files/CLASS.pdf and List of Countries by GDP (nominal) per capita. http://en.wikipedia.org/wiki/ List of countries by GDP (nominal) per capita.*

12. **Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, Horner M-J, eds**. *SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics. National Cancer Institute, SEER Program, NIH Pub. No. 07-6215, Bethesda, MD, 2007.*

13. SEER *Cancer incidence Public Use Database, 1973-1995.National Cancer Institute, 1998,National Institute of health, Bethesda , Md, USA*

14. SEER *Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/*

15. **Chen JN, He D, Tang F, Shao CK**. *Epstein-Barr virus-associated gastric carcinoma: a newly defined entity. J Clin Gastroenterol. 2012 ;46:262-71*

16. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, et al.(eds) Lambert R, Parkin DM *Screening, Surveillance & Prevention of Gastric Cancer in Gastrointestinal Oncology.D H Kelsen,JM Daly, SE Kern et al Eds. Lippincott Williams Wilkins Publ. 2002, 341-354*

17. Toyoda Y, Nakayama T, Ito Y, Ioka A, Tsukuma H. *Trends in colorectal cancer incidence by subsite in Osaka, Japan. Jpn J Clin Oncol. 2009 ;39:189-91*

18. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. *Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol. 2008 ;9: 730-56*

19. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R; et al. *.EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. Eur J Cancer. 2009 ;45:931-91*

20. Sankaranarayanan R, Swaminathan R, eds, *Cancer survival in Africa, Asia, the Caribbean and Central America: IARC Scientific Publications N° 162, IARC, Lyon, 2011*

21. **Lambert R, Saito H, Lucas E, Sankaranarayanan R**. *Survival from digestive cancer in emerging countries in Asia and Africa. Eur J Gastroenterol Hepatol. 2012 ;24:605-12.*

22. García-Alvarez A, Serra-Majem L, Ribas-Barba L, et al. *Obesity and overweight trends in Catalonia, Spain (1992-2003): gender and socio-economic determinants. Public Health Nutr. 2007;10(11A):1368-78.*

23. Nayak SP, Sasi MP, Sreejayan MP, Mandal S. *A case-control study of roles of diet in colorectal carcinoma in a South Indian Population. Asian Pac J Cancer Prev. 2009;10(4):565-8.*

24. Sinha R, Anderson DE, McDonald SS, Greenwald P. *Cancer risk and diet in India. J Postgrad Med. 2003;49(3):222-8.*

25. Sullivan R, Kinra S, Ekelund U, et al. *Socio-demographic patterning of physical activity across migrant groups in India: results from the Indian Migration Study. PLoS One. 2011;6(10):e24898.*

26. Wolin KY, Yan Y, Colditz GA, Lee IM. *Physical activity and colon cancer prevention: a meta-analysis. Br J Cancer. 2009;100(4):611-6.*

27. Lund Nilsen TI, Vatten LJ. *Colorectal cancer associated with BMI, physical activity, diabetes, and blood glucose. IARC Sci Publ. 2002;156:257-8.*

28. **van Duijnhoven FJ, Bueno-De-Mesquita HB, Ferrari P, et al.**. *Fruit, vegetables, and colorectal cancer risk: the European Prospective Investigation into Cancer and Nutrition. Am J Clin Nutr. 2009;89(5):1441-52.*

29. Mohandas KM. *Colorectal cancer in India: controversies, enigmas and primary prevention. Indian J Gastroenterol. 2011;30(1):3-6.*

30. Pathy S, Lambert R., Sauvaget C. , Sankaranarayanan R. *The incidence and survival rates of colorectal cancer in India remain low as compared to rising rates in East Asia". Diseases Colon rectum, 2012, 55,900-906*

31. **Winawer SJ, Krabshuis J, Lambert R, O'Brien M, Fried M**;*Cascade colorectal cancer screening guidelines: a global conceptual model. World Gastroenterology Organization Guidelines Committee. J Clin Gastroenterol. 2011 Apr;45(4):297-300.*

32. Voigt MD. *Alcohol in hepatocellular cancer. Clin Liver Dis. 2005;9:151-69*

33. Custer B, Sullivan SD, Hazlet TK et al. *Global epidemiology of hepatitis B virus. J Clin Gastroenterol. 2004 ;38 (10 Suppl): S158-S168*

34. Raza SA, Clifford GM, Franceschi S. *Worldwide variation in the relative importance of hepatitis B and hepatitis C viruses in hepatocellular carcinoma: a systematic review. Br J Cancer. 2007;96:1127-1134.*

Treatment of Advanced Cholangiocarcinoma: Current Status and Future Perspectives

Jan B. Kuhlmann

Senior Physician, Department of Gastroenterology, University Hospital Freiburg, Germany

Jan B. Kuhlmann

Abstract

Cholangiocarcinoma (CC) is a tumour with a poor prognosis. The treatment of CC is challenging as the tumour is usually diagnosed late and the treatments are not very effective except when complete surgical resection is possible. However in the majority of cases, surgical resection is not possible and palliation is the mainstay of treatment. Currently chemotherapy combining gemcitabine with a platinum agent is the recommended first-line treatment regimen for advanced CC. Since, CCs have only a limited tendency to metastasize locoregional therapy is an interesting approach. The aim of this short review is to give an update on standard and prospective treatment concepts in advanced cholangiocarcinoma based on a comprehensive review of the recent literature and guidelines.

Disclaimer: There is no potential conflict of interest.
Citation: *European Medical Journal - Gastroenterology* 2012:1:63-67

Introduction

Cholangiocarcinoma (CC) is a relatively rare, heterogenous tumour entity with a poor prognosis. It is distinguished by anatomic site and typically classified as either intrahepatic or extrahepatic cholangiocarcinoma. Intrahepatic cholangiocarcinomas (IHCC) are located within the hepatic parenchyma and have also been called "peripheral" CCs. CCs occurring anywhere within the common hepatic duct or the common bile duct are classified extrahepatic cholangiocarcinomas (EHCC). Perihilar CC (also called Klatskin tumour) belongs to the EHCC, and is the most common type, however incidence and mortality rate of IHCCs have increased markedly worldwide.[1]

Perihilar or extrahepatic CCs typically present with features of biliary obstruction. Intrahepatic CCs are usually more advanced at presentation. These tumours often present with systemic manifestations of malignancy including malaise, fatigue and weight loss. Some cases are detected incidentally as a result of scans performed for other indications.

Treatment of resectable tumours

Surgical resection offers the only curative option and usually requires a major hepatic resection in addition to resection of actual bile duct cancer. Unfortunately, curative resection is only possible in about 20% of patients because of locally advanced disease, distant metastases or co-morbidity in an elderly population.[2]

Resection involves a major operative procedure and requires appropriate surgical and anaesthetic experience. Surgical treatment depends on the site and extent of bile duct involvement by tumour. IHCCs are usually treated by resection of the involved segments or lobe of the liver. Distal CCs are managed by pancreatoduodenectomy, as with ampullary or pancreatic head cancer. Major hepatectomy for hilar CCs carries a considerable risk of hepatic insufficiency if there is a small future liver remnant. Portal vein embolisation of the lobe to be removed is a safe method for increasing the future liver remnant and permits curative hepatic resection to be carried out.[3] But even after resection, the rate

of recurrence is approximately 60% and the 5-year overall survival (OS) rates are 15-40% for IHCC and 23-50% for EHCC. [4]

Historically, liver transplantation for CC was associated with rapid recurrence of disease and poor survival rates.[5] However, increasing data suggest that liver transplantation for CC can be successful in rigorously selected patients undergoing neoadjuvant therapy in highly specialised centres.[6]

Adjuvant therapy

Because of the high recurrence rates radiotherapy (RT), radiochemotherapy (RCT) and chemotherapy (CT) alone have been investigated in an adjuvant setting to improve progression free survival. Their role, however, is still undefined, due to the limited number of patients evaluated, the prevalence of retrospective trials and the heterogeneity of stages and types studied.

Treatment of unresectable tumours

Endoscopic stenting

The median survival time of advanced CC undergoing supportive care alone is short.[7] Effective palliation to relieve the symptoms associated with jaundice and the prevention of biliary tract infection are fundamental goals for most patients with hilar CC. Relief of biliary tract obstruction by endoscopic or percutaneous placement of plastic or metal stents is regarded the optimal first-line palliation as this achieves similar survival to surgical bypass, but less procedure-related morbidity or mortality and at substantially lower costs.[8]

Photodynamic therapy

Photodynamic therapy (PDT) is a relatively new ablative therapy, involving intravenous injection of a photosensitising drug followed by selective irradiation with light of a specific wavelength to initiate localised drug activation, and has been used for palliation in patients with hiliar CC. The combination of PDT with biliary stenting was reported to improve the OS of patients with unresectable CCs in two small randomised clinical trials.[9,10] In contrast to these results, the preliminary data of the UK Photostent-02 trial demonstrated, that patients receiving PDT had no benefit in OS compared to patients treated with endoscopic stenting alone (5.6 vs. 8.5 months).[11] However fewer patients in the PDT group received additional palliative chemotherapy.

Chemotherapy

The recently published randomised, controlled phase III ABC-02 study, which enrolled 410 patients with locally advanced or metastatic CC, gallbladder cancer, or ampullary cancer, demonstrated that the combination of gemcitabine and cisplatin improves overall survival and progression-free survival by 30% over gemcitabine alone.[12] Median OS was 11.7 months and 8.1 months (hazard ratio=0.64; 95% CI, 0.52-0.8; P<0.001), and median progression-free survival was 8.0 months vs. 5.0 months (hazard ratio=0.63,;95% CI, 0.51-0.77; P<0.001), both in favour of the combination arm. Although the rate of neutropenia was higher in the group receiving gemcitabine and cisplatin, there was no significant difference in the rate of neutropenia-associated infections between the two arms.

A Japanese phase II trial of gemcitabine with cisplatin vs. gemcitabine alone found very similar results with median OS of 11.2 months in the combination arm. [13]

Oxaliplatin is widely used in clinical practice instead of cisplatin: the safety profile of the GEMOX regimen (gemcitabine and oxaliplatin) and the good response rates (RR) suggest that this is not a suboptimal treatment when compared to the standard schedule with cisplatin.[14]

Based on these results, currently chemotherapy combining gemcitabine with a platinum agent is the recommended first-line treatment regimen for advanced CC.

With respect to second-line palliative therapy, a recent retrospective analysis of 395 patients over 20 years at a single centre showed that after first-line chemotherapy, 25% of patients received a second-line regimen, and only 6% a third-line regimen.[15] Objective response rate (RR) and stable disease with second-line chemotherapy were 9% and 34%, respectively Median PFS and median OS measured from the initiation of second-line chemotherapy was 2.8 and 7.5 months, respectively.

New targeted agents (e.g. anti-angiogenic or EGFR/RAS/RAF/MEK pathway inhibitors) are urgently needed for a more effective therapy. These agents

are currently tested alone, or two of these together, or in combination with cytotoxic chemotherapy in clinical trials.

Locoregional therapies

CCs have only a limited tendency to metastasize, and only one-third of the patients had lymph node, hepatic, or peritoneal metastases at surgery.[16] Therefore, locoregional therapy is an interesting approach for treatment of this tumour.

Radiofrequency ablation (RFA)

Percutaneous image-guided radiofrequency ablation (RFA) is a minimally invasive technique that uses high frequency alternating current to heat tissue to the point of coagulation with the aim of local curation.

A study of 13 patients with 17 primary IHCCs treated with RFA reported a local control rate of 88% at a median follow-up of 19.5 months. Two local failures occurred, both in tumours larger than 5cm in diameter. The median OS after RFA was 38.5 months.[17] Only one major complication (liver abscess) occurred in 17 RFA sessions. Similiary results demonstrated a Chinese non-randomised study of 18 patients.[18]

Together, these findings indicate that RFA may provide successful local tumour control in patients with intermediate (3-5m) or small (<3cm) intrahepatic nodules. Tumour size larger than 5cm, tumour geometry, proximity to large intrahepatic vessels and subcapsular location are factors that usually lead to insufficient ablations and significantly influence outcome. To overcome this problem stereotactic RFA may be an applicable technique.[19] However this technique is very complex and may involve major complications.

Transcatheterarterial chemoembolisation (TACE)

Transcatheter arterial chemoembolisation of the liver has been shown to provide durable response in hepatocellular carcinoma.[20] This technique utilizes a dual therapeutic approach to target solid tumours - the infusion of multiple chemotherapeutic agents combined with hepatic artery embolisation. Chemoembolisation reduces oxygen and nutrient delivery to the tumour while concurrently providing a 10- to 25-fold increase in local chemotherapy concentration and reducing drug clearance from the liver. Severe toxicity is limited, as up to 85% of the administered drug is trapped in the liver. This makes the side effect profile of chemoembolisation attractive relative to systemic chemotherapy.

In several series of patients with IHCC TACE, using different chemotherapeutic agents, seemed to be safe and effective with a median OS of approximately 12-26 months[21-25]. All studies are limited by a low number of patients, the non-randomised, and partial retrospective design. TACE have been even studied in a adjuvant setting, however with no effect on survival.[26]

Drug eluting bead (DEB)-TACE

Chemoembolisation with drug-eluting beads combines the drug with the embolisation device by using the embolic device to reduce blood flow to the tumour whilst at the same time eluting a chemoherapeutic agent into the tumour via its own vasculature. Therefore, beads with the capability to elute drugs may offer the possibility to control precisely the release and dose of the chemotherapeutic agent into the tumour bed.

Aliberti et al.[27] demonstrated in 11 patients treated with DEB-TACE using doxorubicin a chemotherapeutic agent a median OS of 13 months. In another retrospective study DEB-TACE using irinotecan median OS was comparable to chemotherapy using the GEMOX regimen and even superior to conventional TACE using mitomycin C.[28] Further, Poggi et al.[29] reported an OS of 30 months in nine patients with intrahepatic CC, treated with a combination of oxaliplatin DEB-TACE and systemic chemotherapy (CHT) with oxaliplatin and gemcitabine. All studies are limited by a low number of patients and the non-randomised design.

Nevertheless, locoregional therapy with TACE, especially DEB-TACE seems to be active, and its combination with systemic CHT seems promising.[29] Therefore randomised prospective clinical trials enrolling a larger number of patients need to be carried out, comparing the efficacy of TACE or DEB-TACE using different chemotherapeutic agents (e.g. irinotecan, oxaliplatin, doxorubicin, and mitomycin C) and evaluate the combination of TACE with systemic CHT.

Radiation therapy

Data on external beam radiation therapy (EBRT) are limited. Due to the fact that whole-liver dose of extending 40 Gy often is associated with severe side effects, including life-threatening radiation induced liver disease EBRT is restricted to those patients with a small and focal tumour burden, where a sufficient volume of the liver remains untreated. Through the development of radiation therapy this problem may be overcome using stereotactic body radiotherapy. Barney et al. demonstrated in a study of 10 patients that a dose escalation up to 60 Gy (mean 55 Gy) is feasible and has promising local effects.[30] However another study reported of 22% serious gastrointestinal injury mainly biliary stenosis and duodenal/pyloric ulcerations after stereotactic radiotherapy.[31]

Transarterial radioembolisation

Liver tumours are generally radiosensitive and transarterial radioembolisation with yttrium-90 (90Y) microspheres has been demonstrated to be effective in unresectable HCC and metastases of the liver.[32]

In contrast to TACE, for intra-arterial radioembolisation to be effective, optimal perfusion and blood flow is required to allow the generation of free radicals by ionisation of water molecules near the tumour cell's DNA. In the presence of normal oxygen tension, permanent DNA damage is caused by one or both DNA strands, and apoptosis is initiated or reproductive death is eventually achieved.

In a series of 24 patients with unresectable IHCC, radioembolisation with 90Y microspheres induced >50% tumour necrosis and 100% tumour necrosis in 77% and 9% of patients respectively, with a median OS of 14.9 months.[33] In another study of 25 patients 90Y radioembolisation achieved in 24% partial remission and in 48% stable disease resulting in a median OS of 9.3 months.[34]

Conclusion

Most CCs are locally advanced or metastatic disease at the time of diagnosis. Even if it is resectable, long time survival rates are low.[4] Due to its low incidence and heterogeneity of this cancer, there are few high quality randomised clinical trials. Currently chemotherapy combining gemcitabine with a platinum agent is the recommended first-line treatment regimen for advanced biliary tract cancer.[12]

However, median OS is only approximately one year. Locoregional therapies such as RFA, TACE and transarterial radioembolisation have been shown to be safe and effective in IHCC. Most of these studies are not randomised, often combine gallbladder cancers with intrahepatic and extrahepatic CC, and involve small numbers of patients, making it difficult to draw definitive conclusions. Nevertheless liver directed therapy can make a meaningful contribution as part of oncologic treatment to reduce systemic side effect of CHT and prolong survival in advanced CC.

Therefore randomised prospective clinical trials enrolling a larger number of patients need to be carried out.

References

1. Patel T. *Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 2001;33(6):1353-7.*

2. Hezel AF, Zhu AX. *Systemic therapy for biliary tract cancers. Oncologist 2008;13(4):415-23.*

3. Benson AB, 3rd, Abrams TA, Ben-Josef E, Bloomston PM, Botha JF, Clary BM, et al. *NCCN clinical practice guidelines in oncology: hepatobiliary cancers. J Natl Compr Canc Netw 2009;7(4):350-91.*

4. Aljiffry M, Walsh MJ, Molinari M. *Advances in diagnosis, treatment and palliation of cholangiocarcinoma: 1990-2009. World J Gastroenterol 2009;15(34):4240-62.*

5. Meyer CG, Penn I, James L. *Liver transplantation for cholangiocarcinoma: results in 207 patients. Transplantation 2000;69(8):1633-7.*

6. Darwish Murad S, Kim WR, *Therneau T, Gores GJ, Rosen CB, Martenson JA, et al. Predictors of pretransplant dropout and posttransplant recurrence in patients with perihilar cholangiocarcinoma. Hepatology 2012;56(3):972-81.*

7. Park J, Kim MH, Kim KP, Park do H, Moon SH, Song TJ, et al. *Natural History and Prognostic Factors of Advanced Cholangiocarcinoma without Surgery, Chemotherapy, or Radiotherapy: A Large-Scale Observational Study. Gut Liver 2009;3(4):298-305.*

8. Khan SA, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP, et al. *Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. Gut 2012.*

9. Ortner ME, Caca K, Berr F, Liebetruth J, Mansmann U, Huster D, et al. *Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. Gastroenterology 2003;125(5):1355-63.*

10. Zoepf T, Jakobs R, Arnold JC, Apel D, Riemann JF. *Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. Am J Gastroenterol 2005;100(11):2426-30.*

11. Pereira S, Hughes, S.K. Roughton, M., O'Donoghue, P., Wasan, H.S., Valle, J., Bridgewater J. *. Photostent-02; Porfimer Sodium photodynamic therapy plus stenting versus stenting alone in patients (pts) with advanced or metastatic cholangiocarcinomas and other biliary tract tumours (BTC): A multicentre, randomised phase III trial. ESMO 2010 2010;Abstract No 8020.*

12. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al*. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362(14):1273-81.*

13. Okusaka T, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi A, et al*. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer 2010;103(4):469-74.*

14. Harder J, Riecken B, Kummer O, Lohrmann C, Otto F, Usadel H, et al*. Outpatient chemotherapy with gemcitabine and oxaliplatin in patients with biliary tract cancer. Br J Cancer 2006;95(7):848-52.*

15. Walter T, Horgan AM, McNamara M, McKeever L, Min T, Hedley D, et al*. Feasibility and benefits of second-line chemotherapy in advanced biliary tract cancer: A large retrospective study. Eur J Cancer 2012.*

16. Mosconi S, Beretta GD, Labianca R, Zampino MG, Gatta G, Heinemann V*. Cholangiocarcinoma. Crit Rev Oncol Hematol 2009;69(3):259-70.*

17. Kim JH, Won HJ, Shin YM, Kim KA, Kim PN. *Radiofrequency ablation for the treatment of primary intrahepatic cholangiocarcinoma. AJR Am J Roentgenol 2012;196(2):W205-9.*

18. Xu HX, Wang Y, Lu MD, Liu LN. *Percutaneous ultrasound-guided thermal ablation for intrahepatic cholangiocarcinoma. Br J Radiol 2012;85(1016):1078-84.*

19. Haidu M, Dobrozemsky G, Schullian P, Widmann G, Klaus A, Weiss H, et al. *Stereotactic radiofrequency ablation of unresectable intrahepatic cholangiocarcinomas: a retrospective study. Cardiovasc Intervent Radiol 2012;35(5):1074-82.*

20. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. *Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359(9319):1734-9.*

21. Herber S, Otto G, Schneider J, Manzl N, Kummer I, Kanzler S, et al. *Transarterial chemoembolization (TACE) for inoperable intrahepatic cholangiocarcinoma. Cardiovasc Intervent Radiol 2007;30(6):1156-65.*

22. Burger I, Hong K, Schulick R, Georgiades C, Thuluvath P, Choti M, et al. *Transcatheter arterial chemoembolization in unresectable cholangiocarcinoma: initial experience in a single institution. J Vasc Interv Radiol 2005;16(3):353-61.*

23. Kim JH, Yoon HK, Sung KB, Ko GY, Gwon DI, Shin JH, et al. *Transcatheter arterial chemoembolization or chemoinfusion for unresectable intrahepatic cholangiocarcinoma: clinical efficacy and factors influencing outcomes. Cancer 2008;113(7):1614-22.*

24. Vogl TJ, Schwarz W, Eichler K, Hochmuth K, Hammerstingl R, Jacob U, et al*. Hepatic intraarterial chemotherapy with gemcitabine in patients with unresectable cholangiocarcinomas and liver metastases of pancreatic cancer: a clinical study on maximum tolerable dose and treatment efficacy. J Cancer Res Clin Oncol 2006;132(11):745-55.*

25. Park SY, Kim JH, Yoon HJ, Lee IS, Yoon HK, Kim KP. *Transarterial chemoembolization versus supportive therapy in the palliative treatment of unresectable intrahepatic cholangiocarcinoma. Clin Radiol 2011;66(4):322-8.*

26. Wu ZF, Zhang HB, Yang N, Zhao WC, Fu Y, Yang GS. *Postoperative adjuvant transcatheter arterial chemoembolisation improves survival of intrahepatic cholangiocarcinoma patients with poor prognostic factors: results of a large monocentric series. Eur J Surg Oncol 2012;38(7):602-10.*

27. Aliberti C, Benea G, Tilli M, Fiorentini G*. Chemoembolization (TACE) of unresectable intrahepatic cholangiocarcinoma with slow-release doxorubicin-eluting beads: preliminary results. Cardiovasc Intervent Radiol 2008;31(5):883-8.*

28. Kuhlmann JB, Euringer W, Spangenberg HC, Breidert M, Blum HE, Harder J, et al*. Treatment of unresectable cholangiocarcinoma: conventional transarterial chemoembolization compared with drug eluting bead-transarterial chemoembolization and systemic chemotherapy. Eur J Gastroenterol Hepatol 2012;24(4):437-43.*

29. Poggi G, Amatu A, Montagna B, Quaretti P, Minoia C, Sottani C, et al. *OEM-TACE: a new therapeutic approach in unresectable intrahepatic cholangiocarcinoma. Cardiovasc Intervent Radiol 2009;32(6):1187-92.*

30. Barney BM, Olivier KR, Miller RC, Haddock MG. *Clinical outcomes and toxicity using Stereotactic Body Radiotherapy (SBRT) for advanced cholangiocarcinoma. Radiat Oncol 2012;7:67.*

31. Kopek N, Holt MI, Hansen AT, Hoyer M. *Stereotactic body radiotherapy for unresectable cholangiocarcinoma. Radiother Oncol 2010;94(1):47-52.*

32. Vente MA, Wondergem M, van der Tweel I, van den Bosch MA, Zonnenberg BA, Lam MG, et al. *Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis. Eur Radiol 2009;19(4):951-9.*

33. Ibrahim SM, Mulcahy MF, Lewandowski RJ, Sato KT, Ryu RK, Masterson EJ, et al. *Treatment of unresectable cholangiocarcinoma using yttrium-90 microspheres: results from a pilot study. Cancer 2008;113(8):2119-28.*

34. Saxena A, Bester L, Chua TC, Chu FC, Morris DL*. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. Ann Surg Oncol 2010;17(2):484-91.*

Buyer'sGuide

FeaturedSuppliers

Abbott is a global, broad-based health care company devoted to the discovery, development, manufacture and marketing of pharmaceuticals and medical products, including nutritionals, devices and diagnostics.

Almirall, S.A. is an international pharmaceutical company based on innovation and committed to health. Almirall research, develop, produce and market proprietary R&D medicines and those under licence with the aim of improving people's health and wellbeing.

FUJIFILM Europe GmbH owns highly versatile fundamental technologies, including organic and inorganic materials, analysis, thin-film formation and processing, image and software, optics, and mechatronics, developed in areas such as photosensitized materials and xerography

MSD range from developing new therapies that treat and prevent disease to helping people in need, they're committed to improving health and well-being around the world.

Olympus is a leading European healthcare and consumer electronics company and a leading manufacturer of innovative optical and digital equipment for the healthcare and consumer electronics sectors.

Pentax Europe GmbH provides endoscopic imaging devices and solutions to the global medical community. Specialising in the development of video and fibre endoscopy equipment for observation, therapeutic and research applications.

Shire aim to help people with life-altering conditions lead better lives. They focus on developing treatments for conditions where the impact of their drugs can make an immediate and tangible difference for patients. Including medicines for specialist conditions like ulcerative colitis.

Associations

UEG - United European Gastroenterology	www.ueg.eu
AOECS - Association of European Coeliac Societies	www.aoecs.org
ASGE - American Society for Gastrointestinal Endoscopy	www.asge.org
CCUVN - Crohn en Colitis Ulcerosa Vereniging	www.crohn-colitis.nl
DDW - Digestive Disease Week	www.ddw.org
EAES - European Association for Endoscopic Surgery	www.eaes.eu
EAGEN - EuropeanAssociation for Gastroenterology, Endoscopy and Nutrition	www.eagen.org
EASL -European Association for the Study of the Liver	www.easl.eu
ECCO - European Crohn's and Colitis Organisation	www.ecco-org.eu
EDS - European Digestive Surgery	www.edsurgery.org
EFCCA - European Federation of Crohn's & UlcerativeColitis Associations	www.efcca.org
EFISDS - International Society of Digestive Surgery	www.efisds.eu
EHSG - European Helicobacter Study Group	www.helicobacter.org
ENDO LIVE ROMA 2013	www.endoliveroma.it
EPC - European Pancreatic Club	www.e-p-c.org
ESCP - European Society of Coloproctology	www.escp.eu.com
ESDO - European Society of Digestive Oncology	www.esdo.eu
ESGAR - European Societyof Gastrointestinal and Abdominal Radiology	www.esgar.org

Associations

ESGE - European Society of Gastrointestinal Endoscopy	www.esge.com
ESNM - European Society of Neurogastroenterology and Motility	www.esnm.eu
ESPCG -European Society for Primary Care Gastroenterology	www.espcg.eu
ESPGHAN - European Society for Paediatric Gastroenterology, Hepatology and Nutrition	www.espghan.med.up.pt
EuropaColon	www.europacolon.com
Gastrointestinal Nursing	www.gastrointestinalnursing.co.uk
GCCA - Global Colon Cancer Alliance	www.globalcca.org
GEEW - Gastroenterology and Endotherapy European Workshop	www.live-endoscopy.com
OESO - World Organization for Specialized Studies on Diseases of the Esophagus	www.oeso.org
Rome Foundation	www.romecriteria.org
WEO - World Endoscopy Organization	www.worldendo.org
World Gastroenterology Organisation	www.worldgastroenterology.org

Buyer'sGuide

A. Menarini Farmaceutica Internazionale	www.menarini.com
Abbott EPD	www.abbottep.in
ACTIAL FARMACEUTICA Lda	www.ristomed.eu
Advanced Sterilization Products, a division of Medos International Sarl	www.aspjj.com/emea
Alfa Wassermann S.p.A.	www.alfawassermann.it
ALTON (Shanghai) Medical Instruments Co., Ltd	www.alton.com.cn
Apollo Endosurgery, Inc.	www.apolloendo.com
APTALIS Pharma SAS	www.aptalispharma.comfr
BALTON Sp. z. o. o.	www.balton.pl
Bedfont Scientific Ltd	www.bedfont.com
BIOCODEX	www.biocodex.com
BioGaia AB	www.biogaia.com
Biohit Oyj	www.biohit.com
biolitec biomedical technology GmbH	www.biolitec.de
Boston Scientific International S.A.	www.bostonscientific.com
BOWA - electronic GmbH & Co. KG	www.bowa.de
Bracco Suisse SA	www.bracco.com
BUHLMANN Laboratories AG	www.buhlmannlabs.ch
C 2 Therapeutics	www.c2therapeutics.com
Calpro	www.calpro.no
CAMPRO SCIENTIFIC / Quintron / Compact Science Systems	www.campro.eu
CapsoVision Inc.	www.capsovision.com

Buyer'sGuide

Casen Fleet	www.casenfleet.com
CBC (Deutschland) GmbH	www.cbc-de.com
COOK Medical	www.cookmedical.com
Covidien	www.covidien.com
DANONE	www.danone.co.uk
Dr. Falk Pharma GmbH	www.drfalkpharma.de
ELLA-CS, s.r.o.	www.ellacs.eu
EMcision International Inc.	www.emcision.com
EMED SP. Z O. O. SP. K.	www.emed.pl
ENDALIS SARL	www.endalis.com
EndoChoice	www.endochoice.com
EndoClot Plus Inc.	endoclot.com
Endo-Flex GmbH	www.endo-flex.de
Epigenomics AG	www.epigenomics.com
Era Endoscopy S.r.l.	www.endotics.com
Erbe Elektromediz GmbH	www.erbe-med.com
Ferring Pharmaceuticals	www.ferring.co.uk
Fischer ANalysenInstrumente	www.fan-gmbh.de
G- Flex Europe SPRL	www.g-flex.com
GE Healthcare	www3.gehealthcare.co.uk
GI Dynamics, Inc	www.gidynamics.com
Given Imaging GmbH	www.givenimaging.com
Hospira UKLtd	www.hospira.co.uk

GASTRO ENTEROLOGY

HUGER Endoscopy Instruments Co; Ltd	www.huger.cn
Immundiagnostik AG	www.immundiagnostik.com
INFAI GmbH	www.infai.de
Institut Allergosan	www.allergosan.at
IntroMedic. Co.,Ltd	www.intromedic.com
Janssen-Cilag B.V.	www.janssen-cilag.nl
Karl Storz GmbH & Co. KG	www.karlstorz.com
Kibion AB	www.kibion.se
Kimberly-Clark	www.kimberly-clark.com
KLS Martin Group - Gebr. Martin GmbH & Co. KG	www.klsmartin.com
LIFE PARTNERS EUROPE	www.lifeurope.com
Lumenis (Germany) GmbH	www.lumenis.com
M.I. Tech., Ltd	www.mitech-uk.com
Mauna Kea Technologies	www.maunakeatech.com
Mayoly- Spindler	www.mayoly-spindler.com
Mederi Therapeutics Inc.	www.mederitherapeutics.com
Medical Electronic Construction R&D sprl	www.mecbelux.com
Medical Innovations	www.medicalinnovations.co.uk
Medical Measurement Systems b.v.	www.mmsinternational.com
MediCapture	www.medicapture.com
Medi-GlobeGmbH	www.medi-globe.de
Hitachi Medical Systems Europe Holding AG	www.hitachi.com

Buyer'sGuide

Medigus	www.medigus.com
MEDITALIA S.a.S	www.meditaliasas.it
Medivators	www.medivators.com
Medspira	www.medspira.com
Medtronic International Trading Sarl	www.medtronic.co.uk
MEDWORK MEDICAL PRODUCTS AND SERVICES GMBH	www.medwork.eu
Merit Services, Inc. Endotek Division	www.merit.com
Micro-Tech (Nanjing) Co., Ltd.	www.micro-tech.com
MTW Endoskopie	www.mtw-endoskopie.de
NDS Surgical Imaging BV	www.ndssi.com
NIKKISO Europe GmbH	www.nikkiso-europe.eu
NinePoint Medical, Inc.	www.ninepointmedical.com
NISO BIOMED SRL	www.nisobiomed.com
Norgine Limited	www.norgine.com
Otsuka Pharmaceutical Europe, Ltd.	www.otsuka-europe.com
Ovesco Endoscopy AG	www.ovesco.com
PAULDRACH medical GmbH	www.pauldrach-medical.de
Peter Pflugbeil GmbH	www.pflugbeil.com
PharmacosmosA/S	www.pharmacosmos.com
Philips Medical Systems Nederland BV	www.healthcare.philips.com
Piolax Medical Devices, Inc.	www.piolax-md.co.jp
R-Biopharm AG	www.r-biopharm.com

GASTRO ENTEROLOGY

Robarts Clinical Trials	www.robartsclinicaltrials.ca
Ruhof Corporation	www.ruhof.com
S & G Biotech Inc.	www.sngbio.en.ec21.com
Sandhill Scientific	www.sandhillsci.com
Siemens Healthcare	www.medical.siemens.com
Soluscope SAS	www.soluscope.com
Sony Europe Limited	www.sony-europe.com
Spatz FGIA, Inc	www.spatzmedical.com
STARmed	www.starmed.co.uk
STEELCO S.p.A.	www.steelcospa.com
Strong Biotech Corp	www.strongbiotech.com
Sumitomo Bakelite Co., Ltd	www.sumibe.co.jp/english
Supersonic Imagine	www.supersonicimagine.fr
Symprove Limited	www.symprove.com
Taewoong Medical, Co. Ltd	www.taewoongtech.co.kr
Takeda Pharmaceuticals International GmbH	www.takeda.co.uk
Therakos Photopheresis	www.therakos.com
Tillotts Pharma AB	www.tillottsnordic.com
WIlson Instruments (SHA) Co., Ltd	www.wilson.sh.cn

Amsterdam Live Endoscopy

17-18th December, 2012

Amsterdam, Netherlands

Amsterdam Live Endoscopy offers you two full days with over thirty five endoscopic procedures televised in High Definition from AMC to the Okura hotel. It also offers you an option to listen to state-of-the-art lectures as well as to discuss subjects in small interactive breakout sessions with the best endoscopists of the world.

15th Dusseldorf International Endoscopy Symposium

31–2nd February, 2013

Dusseldorf, Germany

Aims to: Evaluate recent advances in endoscopy, assess their clinical utility and level of evidence. Apply new endoscopic techniques, instruments and accessories and compare them with traditional methods and devices. Choose the optimal endoscopic approach for specific case management. Manage failed interventions and complications and recognise the importance of an interdisciplinary approach.

8th European Crohn's and Colitis Organisation Congress of Inflammatory Bowel Diseases

14-16 February, 2013

Vienna, Austria

ECCO 2013 in Vienna will provide a unique opportunity to gain access to the latest and best scientific information and education in adult and paediatric gastroenterology, hepatobiliary disease, endoscopy, imaging and gastrointestinal surgery related to IBD. Our aims are to advance the understanding of digestive disorders, to improve the development of guidelines through the most robust process, to define better and valid outcomes for the therapy of IBD that will enhance patient care.

ESGE Live Demonstration, Dubai

22-23th March, 2013

Dubai, UAE

Through this workshop, the ESGE Society aims to exchange the expertise and knowledge of our health care professionals to improve the quality of life of the peoples worldwide and in particular the United Arab Emirates through fostering and maintaining high standards of care in gastroenterology and hepatology practice and endoscopy. The Society and its activities shall be so directed that they serve the Member Societies by collecting, collating and disseminating information concerning the educational, research and service provision aspects of gastroenterelogy & endoscopy practice and represent the consensus view of Member Organizations in the East Mediterranean region and national forums.

UPCOMINGEVENTS &CONGRESSES

Quality in Endoscopy: Upper GI Endoscopy and Neoplasia

19-20th April, 2013

Lisbon, Portugal

Leaders in this field alongside more junior colleagues will expound on state-of-the-art and future trends in upper GI endoscopy and the detection, staging and treatment of upper gastrointestinal neoplasia through lectures, case discussion, lively debates, and social networking. Participants, who are largely from the younger generation, will benefit from the highly communicative teaching with a strong, dedicated faculty.

EUS Live in Amsterdam, 16th Annual Course

6-7th June, 2013

Amsterdam, Netherlands

The 2013 issue of our course will focus on new developments but also teach and show techniques of experts in order to either learn EUS or to benchmark your performance. Our course is well known for its relaxed atmosphere and open discussions. Over the past years the course has grown to an attendance of around 200 people. We are not aiming to attract more than these 200 participants as this might result in a decreased learning experience for our participants, for you!

31st GEEW – Gastroenterology and Endotherapy European Workshop

17-19th June, 2013

Brussels, Belgium

The course will involve: Evaluation of established and most recent endoscopy techniques, assessing their clinical utility in a multidisciplinary setting. Descriptions of pre-therapeutic assessment and post-treatment follow up. Detailed technical teaching of various procedures. Scientific appraisals of technologies, evidence-based, with comparison with others approached. Recognition of the role of endoscopy in digestive diseases and its interaction with gastroenterology, surgery, oncology, radiology and transplantation. Teaching on prevention and treatment of complications. The intended audience includes gastroenterologists, surgeons, internists and oncologists, nurses and GI assistants, MD in training and medical students, biomedical engineers and industry partners

The World Congress of Gastroenterology, APDW/WCOG

21-24th September 2013

Shanghai, China

An outstanding scientific program has been developed that will combine current evidence and cutting-edge technology providing for a unique opportunity for learning and discussion.

EMJ

www.emjreviews.com

"providing professionals with the most salient and up-to-the-minute developments"

Click here to view all of our titles in convenient eBook format.

"A lively mix of review articles, case reports, practice guides, theoretical discussions and original research will ensure that readers are kept informed, and will also stimulate healthy discussion between specialties - the mark of a quality publication"

Professor Hamid Rushwan, FIGO Chief Executive.

To subscribe and receive the latest updates and publications from EMJ go to:

www.emjreviews.com

If you are interested in submitting a paper to EMJ please contact:

editor@congressreviews.com

You can also find us on:

Facebook, LinkedIn and Twitter