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NOVEL DEVELOPMENTS IN DIAGNOSIS AND THERAPY OF EARLY GASTROINTESTINAL CANCER - ROLE OF INFLAMMATION AND IT'S CONTROL

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Proceedings of the EAGE Postgraduate Workshop in Gastroenterology NOVEL DEVELOPMENTS IN DIAGNOSIS AND THERAPY OF EARLY GASTROINTESTINAL CANCER – ROLE OF INFLAMMATION AND ITS CONTROL

Professional meeting in friendly atmosphere

Bled, Slovenia, 2005

NOVEL DEVELOPMENTS IN DIAGNOSIS AND THERAPY OF EARLY GASTROINTESTINAL CANCER - ROLE OF INFLAMMATION AND IT'S CONTROL

Course organizers:
L. Lundell (S),
P. Malfertheiner (D),
G. N. J. Tytgat (NL),
S. Markovic (SLO).

08:30–09:15 **Gastroesophageal Reflux disease and esophageal cancer**
G. N. J. Tytgat (NL)

09:15– 10:00 **Are all PPIs the same in the short and long-term perspective**
K. Andersson (S)

10:00– 10:20 **H. Pylori inflammation and gastric cancer**
P. Malfertheiner (D)

10:20– 10:40 **H. Pylori inflammation and gastric Malt lymphoma**
B. Dragosics (A)

10:40 – 11:00 **Changing views of gastric cancer in Slovenia**
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F. Szalay (H)

11:30 – 12:00 **BREAK**

12:00 – 12:30 **Chronic colonic inflammation and cancer**
B. Vucelic (CRO)

12:30 – 13:00 **Relationship between chronic inflammation and cancer**
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13:30 – 14:30 **BREAK**

14:30 – 15:00 **Chronic pancreatitis and pancreatic cancer**
P. Malfertheiner (D)

15:00 – 15:30 **From liver injury to hepatocellular cancer**
S. Markovic (SLO)

15:30 – 16:00 **Treatment of hepatocellular cancer**
E. Gadzijev (SLO)

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16:30 – 17:00 **Current chemopreventive possibilities**
C. Beglinger (CH)

17:00 – 17:30 **Current role of endoscopy and surgery in early digestive cancer**
L. Lundell (S)

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20:00 **GALA DINNER • GRAND HOTEL TOPLICE**

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Contents

Gastroesophageal reflux disease and oesophageal cancer

Emer G. N. J. Tytgat
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During the last decades, the incidence of oesophageal adenocarcinoma has increased almost 400%. Most of those cancers are believed to develop from a precursor lesion, the so called Barrett's oesophagus. Barrett's oesophagus is a condition in which the normal squamous lining of the distal oesophagus has been replaced by columnar epithelium often with intestinal metaplasia. Malignant degeneration of Barrett's oesophagus is thought to be a multi-step process in which intestinal metaplasia progresses through low grade dysplasia and high grade dysplasia into intramucosal and ultimately invasive carcinoma. Endoscopic surveillance, aimed at identifying patients with early and durable malignancy, is currently considered the monitoring technique of choice in patients with Barrett's oesophagus.

Early neoplastic lesions are difficult to identify. In the absence of visible abnormalities, four quadrant biopsies are randomly taken for every two centimetres length of Barrett epithelium.

In the last decade, many new endoscopic techniques have been evaluated for their potential role in improving the accuracy of the detection of early neoplasia. High-resolution endoscopes with high-quality CCD-chips (above 850,000 pixels) and a variable focal distance are now commercially available. High-resolution endoscopy can adequately distinguish areas of intestinal metaplasia from areas with gastric type mucosa. The detection of early neoplasia can be further enhanced by the use of dyes, such as methylene blue and indigo carmine. Methylene blue is a vital stain that is absorbed in areas of intestinal metaplasia. Methylene blue staining is time consuming and operator dependent. Some therefore prefer to combine high-resolution endoscopy with indigo carmine contrast staining.

Narrow band imaging (NBI) is a high-resolution endoscopic technique that aims at enhancing the fine structure of the mucosal surface without the use of dyes. The mucosa is sequentially illuminated with red, green and blue light. The reflected red, green and blue light images are detected by a monochromatic CCD-chip that sends these images to an image-processor that is synchronised with the rotary RGB-band pass filters. Apart from the standard RGB-band pass filters for white light endoscopy, the NBI system has a special set of RGB

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filters in which the band-pass ranges have been narrowed and the relative contribution of blue light has been increased. NBI improves the recognition of mucosal and vascular patterns in Barrett's oesophagus.

Tissue autofluorescence occurs when tissues are exposed to light of a short wavelength (usually ultraviolet or blue light, as certain endogenous biological substances (fluorophores) are excited causing them to emit fluorescent light of a longer wavelength). Early neoplastic changes cause a different autofluorescent wave pattern than normal tissue.

The incidence of high-grade dysplasia and early cancer in Barrett patients is currently estimated at 0.5% per year and the cost-effectiveness of any surveillance strategy has been questioned. The vast majority of Barrett patients will never develop oesophageal cancer, thus including them in an expensive and labour intensive endoscopy programme using high-tech imaging techniques is even more questionable. Hopes are set, therefore, on the detection of molecular markers to identify those patients that are truly at risk for malignant degeneration.

The standard therapy for high-grade dysplasia and early cancer in Barrett patients has always been radical oesophagectomy. The five year survival rate after surgery in such patients is excellent. The mortality and morbidity of this procedure, however, are 3–5% and 40–50% respectively, even in expert centres. With oesophagectomy, the functional oesophagus is lost which may be associated with a reduced quality of life. Since the risk of lymph node involvement or metastasis to distant sites is small and negligible in such cases, local endoscopic therapy might be a less invasive treatment alternative. Such endoscopic mucosal resection for high-grade dysplasia or mucosal cancer should only be performed after extensive work-up using high-resolution endoscopy, a standard biopsy protocol, expert histopathological evaluation and endoscopic ultrasound. Endoscopic mucosal resection has a low complication rate and preserves the functional oesophagus. Other endoscopic ablation techniques should only be used as an adjunct to mucosal resection. After endoscopic treatment, rigorous follow-up is imperative since the current techniques are still associated with a high recurrence rate. In the future, they will be replaced by techniques that allow radical mucosal resection of the whole Barrett segment.

Are all proton pump inhibitors equal in their short- and long-term perspective

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It was not until the introduction of H_2 antagonists that patients suffering from gastro-oesophageal reflux disease (GERD) were offered any effective pharmacological help. Roughly 50% of patients had their erosive oesophagitis (EE) healed after an 8 weeks treatment period. With the appearance of more potent acid inhibitors it has been possible to raise the standards regarding clinical outcome for patients with GERD. It is well known that there is a good correlation between healing of EE and time with intragastric pH above 4 (1). Esomeprazole has in several studies been compared with all members of the proton pump inhibitors (PPIs) class (omeprazole, lansoprazole, pantoprazole and rabeprazole) regarding their ability to raise intragastric pH above 4. It has consistently been shown that esomeprazole is superior to the others in keeping a high pH for longer time. In a recent five-way crossover study this was again confirmed (2). Also when comparing intravenous infusion over a five day treatment period, esomeprazole was found to provide more effective control of intragastric pH than pantoprazole (3).

To patients, the most relevant endpoint is relief of symptoms. In some very large clinical studies esomeprazole has been compared with omeprazole, lansoprazole and pantoprazole in their ability to control symptoms. Regarding time to sustained symptom control as well as percentage of patients kept without symptoms during treatment, esomeprazole was found to be most effective. As previously mentioned, healing of EE correlates well with control of gastric acidity. Based on its superiority in controlling intragastric pH esomeprazole should be more effective also in healing of EE. In two large clinical studies comprising more than 2,700 patients, esomeprazole was shown to be significantly superior to omeprazole (4). In another major clinical study (n = 5,240), esomeprazole was compared to lansoprazole in their ability to heal EE.

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It was found that esomeprazole was more effective over the whole range of EE (LA grade A–D). In the more severe cases (grades C–D), esomeprazole was shown to heal approximately 15% more of the patients (5). Recently, similar data was reported from another major study (n = 3,151) comparing esomeprazole with pantoprazole (6). In a recent metaanalysis comparing the efficacy of omeprazole to heal EE during an 8-week treatment course with other available effective acid inhibitors, the only drug shown to be significantly superior was esomeprazole (7).

To keep patients in remission following healing, maintenance treatment is necessary in most patients. Following healing, esomeprazole has been shown to keep more patients in remission and more patients free from symptoms during 6 months maintenance treatment compared with lansoprazole (8) and to pantoprazole (9). In both studies greater consistency of maintenance treatment was seen across all grades of oesophagitis with esomeprazole.

In patient suffering from nonerosive reflux disease (NERD) PPIs have been shown to be superior to H_2 antagonists in controlling symptoms. Only few studies have been performed to compare the efficacy of the different PPIs in this group of patients and there is currently no evidence for any difference in efficacy.

In conclusion, when comparing the PPIs in standard doses, esomeprazole is more effective compared with any other PPI in the management of EE. In management of NERD, PPIs is the treatment of choice but no difference has been observed between them.

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Helicobacter pylori infection and gastric carcinogenesis

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The major and threatening complications from *Helicobacter pylori* infection is gastric cancer. The disease occurs usually at a more advanced age (> 50 years) and at the time of clinical presentation it is in most cases (~ 85%) a non curable condition. Frequently there are no premonition symptoms and therefore prevention strategies offer the best chance. H. pylori testing with treatment in case of a positive result in dyspeptic patients, although an important strategy, would not permit to prevent gastric cancer in a large number of patients as many are not dyspeptic before gastric cancer becomes apparent. Screen and treat would be the best strategic option but has currently the limits of therapy which is still complex and difficult to prescribe for asymptomatic persons with the scope of prevention. Moreover, these strategies would incur a huge burden of expenses currently not acceptable by health regulatory organs. The best imaginable approach for current application is test and treat complemented by a search and treat strategy in subsets of patients at risk.

According to epidemiological data approximately 70% of distal gastric cancers can be attributed to H. pylori. The evidence for H. pylori as the most important risk factor in gastric cancer is based on biological plausibility and on the beneficial effect of eradication on the progression from gastritis to gastric cancer. Experimental investigations in animal models and from numerous studies with human tissues and cells provide further support for the causal association of H. pylori with gastric cancer.

H. pylori infection interferes with cell biological phenomena that are linked with gastric carcinogenesis. It triggers hyperproliferative and apoptotic processes and takes direct command of the epithelial cell signalling including the modulation of tyrosine-kinase receptors, activation of cell dissociation as well as disruption of cell-cell interactions.

Only a subset of individuals will develop malignant H. pylori-related disease. At present, there are few predictors for an increased gastric cancer development

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among the infected. Microbial and host factors, together with the environment, seem to determine which groups of individuals will develop gastric cancer. Certain *microbial* virulence factors such as the Cag PAI (Pathogenicity island), Vac alleles as well as other bacterial molecules are more prevalently found in bacteria isolated from patients with gastric cancer.

Host genetic factors are related to functional polymorphisms of various genes and also contribute significantly to the clinical outcome of H. pylori infection. These factors relate to the host immune and inflammatory response against the bacterium. There is an important interaction between host genetic factors and H. pylori virulence determinants. Functional polymorphisms in the interleukin-1 beta (IL-1B-511/-31), tumour necrosis factor alpha (TNF-A-308) genes and others significantly increase the risk of non-cardia gastric cancer.

The risk appears to be significantly increased in the presence of certain genotypes of various pro-inflammatory cytokines and of H. pylori strains with higher virulence. Furthermore, the increased risk applies equally to intestinal and diffuse types of gastric adenocarcinoma.

Future tasks are: better definition of subjects at risk, identify the point of no return in the pathway of gastric carcinogenesis despite H. pylori eradication, and development of a novel therapy (the golden bullit).

A strategy scenario I could imagine is to screen all children at school age and treat all positive with a simple well tolerated new drug.

Helicobacter pylori inflammation and gastric MALT lymphoma

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Keywords: autoimmunity, gastric MALT lymphoma, genetic aberrations, *Helicobacter pylori*, oncogenetic pathways, virulence factors

Abstract

Half a century ago, Denis Burkitt's report of a lymphoma of the jawbone in an African boy has been the first one about an infection-associated human tumour in the history of medicine. Some decades later primary gastric lymphoma of the mucosa associated lymphoid tissue has been found to be closely associated to *Helicobacter pylori* (Hp) infection of the gastric mucosa. Moreover, early stages of lymphoma have been shown to completely regress after antibiotic eradication of the bacterium, thus providing strong evidence for a causal role of Hp in lymphomagenesis. The oncogenetic pathways, first, from infectious gastritis to "early" lymphoma and, second, from Hp dependency of lymphomatous proliferation to autonomous tumour growth are poorly understood. However, some more examples of infection-associated lymphomas are presented suggesting mechanisms like (i) tissue transformation to "altered self" creating new epitops for immunoresponse, (ii) enhancement of autoimmunoreactivity, (iii) production of idiotypic immunoglobulins, and (iv) T-cell directed specific B-cell proliferation with consecutive selection of a tumour clone. In contrast to Hp-associated gastric carcinogenesis, the main pathways to Hp-associated gastric MALT lymphoma may be determined by the immunoresponse with features of autoimmunoreactivity of the host combined with the Hp strain-induced release of highly genotoxic oxygen reactive species from neutrophilic leukocytes in the gastritic inflammatory infiltration.

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In the year 1958, surgeon Denis Burkitt observed highly malignant jawbone tumours in young African children and took them for sarcomas (1). Few years later, Epstein identified the lymphomatous nature of these tumours and successfully derived viral particles from the tumour cell culture (2). The first human infection associated tumour model was established. In fact, the prevalence of these specific tumours is restricted to the tropical climate zone of equatorial Africa and most likely dependent on vectors simultaneously transmitting Epstein Barr Virus (EBV) and malaria-plasmodia. Such co-infection, however, may substantially influence and, probably, alter the immunologic milieu in a host. This tumour model is classically addressing the question about the major players among the three actors – infectious agent, human being, and environment, respectively.

In 1983, a new infectious agent appeared on the medical stage (3). It was discovered in Australia, identified as *Helicobacter pylori* (Hp), and later on accepted as pathogenic for the gastric mucosa. In the very same year but on the opposite side of the globe, in England, a "distinctive lymphoma derived from the gastric MALT" was described (4). Ten years later, mucosal lymphoid follicles – acquired on occasion of Hp infection and switching the gastric mucosa secondarily into a lymphatic organ – revealed to be the "crucial link" between Hp infection and MALT lymphoma (5). In 1991, J. Parsonnet published very similar odds ratios for carcinoma and lymphoma, respectively, of persons with Hp infection as compared with persons without such infection (6). As a consequence, Hp was put into class I of carcinogens by the WHO. Since then, plenty of questions have arisen upon the pathways along which MALT lymphoma develops and why its incidence is low, whereas worldwide prevalence of Hp infection is high. Which factors select the type of disease associated with chronic Hp gastritis? The answer is very likely resulting from the dialogue between the Hp strain and the host. In fact, Hp is sending toxins into the gastric mucosa provoking specific T-cell response, cytokine production, and B-cell stimulation of the host. Extensive studies did not show a clear cut association of Hp virulence factors and lymphoma (7–9). Interestingly, for unknown reasons, an *H. heilmannii* infection is ten times more prone to be associated with MALT lymphoma than Hp, as demonstrated by the data from the Institute of Pathology in Bayreuth, BRD (10).

Fundamental insights into lymphomagenesis are given by the studies of human MALT lymphoma cell cultures (11). Tumour cells derived from three gastric resection specimens were proliferating in culture, exclusively, when transfected with the very same Hp strain isolated from the individual gastric mucosa before resection. Different strains, even associated with MALT lymphoma in other patients, did not raise the lymphoma cell culture, at all. In addition, removing of T-cells from the culture was followed by its decline, whereas leaving them within further promoted its growing. Furthermore, a tumour specific immunoglobulin could be gained from the supernatant of the cell culture, which was identified – by murine antibody testing – as idiotypic immunoglobulin known to be produced, exclusively, by B-cell clones of autoreactive type. These results strengthen the causal role of a distinctive Hp strain stimulating strain-specific T-cells and clonal B-cell proliferation in the host. The production of an idiotypic immunoglobulin is presuming the presence of a local epitop, probably strain-induced created in the culture environment. The coincidence of an Hp strain capable of inducing lymphoma, on one side, and a host inclining to immunologic autoreactivity, on the other, is very likely to be a rare event and might thus explain the rarity of these tumours. In literature, examples of infection-associated MALT lymphoma in patients with already established autoimmune disease have been reported (12–15).

In summary, several pathways of lymphomagenesis may exist, either persistent antigen presentation by an infectious agent, or an autoantigen per se might exert chronic immunostimulation. Moreover, it is likely that infection may induce structural tissue damage followed by "altered self" epitops, which are acting as autoantigens. Cause-specific T-cells and

cytokines in the host select a B-cell clone, which in an "autoimmune" reacting host within an appropriate microenvironmental setting – rich with inflammatory neutrophilic leukocytes derived genotoxic oxygen reactive species – may transform to lymphoma.

As to the issue of control of inflammation-associated diseases, in the case of MALT lymphoma, the complete remission of early tumour stages may be regarded the most spectacular argument for the causal role of Hp infection in lymphomagenesis. Reported in 6 cases already in 1993 (16), it holds true in more than 80% of cases till to date (17). Meanwhile, molecular biologic findings support the Hp-associated pathogenesis of MALT lymphoma (18, 19). Especially the t(11;18) has proven a valuable marker of predicting response to antibiotic therapy.

In conclusion, there is strong evidence for a causal role of Hp in the oncogenesis of a major subgroup of gastric MALT lymphomas. Pathogenesis might start with Hp infection in childhood or youth, persistently presenting bacterial antigens over decades and activating strain-specific T-cells in the host. Starting the cascade of immunoresponse resulting in lymphoma, however, might be dependent on an intimate crosstalk between the individual germ and its suitable host. Only in an appropriate setting the bacterial cytotoxins induce cytokines in the gastric mucosa, probably altering tissue structures consecutively provoking idiotypic monoclonal immunoglobulins with autoreactive effect. After transformation to "aberrant tumour clone", the proliferation might start to become autonomous and to be directed by the host, exclusively – according to Shakespeare's Othello – "...the germ has done its obligation, the germ may go...".

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Changing views of gastric cancer in Slovenia

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Key words: gastric cancer, surgical treatment, survival

Ključne besede: rak želodca, kirurško zdravljenje, preživetje

Abstract

Although declining in incidence in western countries during the last twenty years, gastric cancer remains an important cause of cancer-related death throughout the world. Prognosis of gastric cancer is poor, as it is usually diagnosed late. More attention should be paid to the early detection to improve the effectiveness of treatment and thus survival of patients who develop gastric cancer. Surgery remains the cornerstone of the management. The curative treatment of gastric cancer is now becoming the subject of a multidisciplinary approach. The results of individual surgical centers in Slovenia are comparable to the outcomes in leading centers in Europe.

Spreminjanje pogledov na raka želodca v Sloveniji

Čeprav njegova incidenca po svetu in pri nas upada, želodčni rak še vedno pomembno prispeva k umrljivosti za rakom. Prognoza je slaba, ker je pogosto odkrit v napredovalem stadiju. Rezultate zdravljenja je mogoče izboljšati le z zgodnejšim odkrivanjem. V zdravljenju je pomemben multidisciplinarni pristop. Glavno vlogo v zdravljenju ima še vedno kirurgija. Rezultati zdravljenja v posameznih centrih v Sloveniji so primerljivi z vodilnimi v Evropi.

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INTRODUCTION

Gastric cancer is the second leading cause of cancer-related death throughout the world (1). Incidence and mortality rate of gastric cancer have declined steadily in most countries, especially in the developed countries, such as the United States and Western Europe, while those of adenocarcinoma arising from gastric cardia and oesophagus have been stable or increased, especially among white males (2–4). In the United States, gastric cancer was the leading cause of cancer death in 1930, but it now ranks 14th in incidence and 8th as a cause of cancer mortality (5). The dramatically decreased incidence in gastric cancer seen in developed countries is mainly due to the marked reduction of well-differentiated 'intestinal type' adeno-carcinomas of the fundus and the antrum (6). The incidence of other tumour types affecting the fundus and the antrum ('diffuse', 'infiltrating' or 'poorly differentiated') has declined more slowly. Consequently, in low risk developed countries, the poorly differentiated tumour types tend to occur more frequently than the well differentiated intestinal tumours (6, 7).

Gastric carcinoma generally has a dismal prognosis. In western countries the disease is usually diagnosed late. In the United States, the overall 5-year survival is reported as 37, 18, 11, and 5% for stages II, IIIA, IIIB, and IV, respectively (8). Overall, 5-year survival resulting from a nationwide population-based Swedish study was 19.4% for noncardial stomach cancer and 10.4% for patients with cancer of the gastro-oesophageal junction (9). Similar figures are reported for other European countries (10). In surgical series, the 5-year survival goes from 55% for stage II tumours to 16% for stage IV (T4N1-3M0 or any TN3M0) disease (8, 11). In M1 tumours, a median survival of 7–9 months is observed with no survivors at 5 years (12, 13). In Japan, where detection programs have been established due to the very high incidence of the disease even in young adults, the diagnosis of stage IA and IB disease is more frequent with a 5-year survival of 75% and over (14, 15).

Most cancer statistics in Slovenia, a country of 2 million population, is based on the data of the Cancer Registry of Slovenia, which was founded in 1950. Nowadays in Slovenia, gastric cancer is because of its decreasing incidence the fifth most common cancer in men (after lung, skin, colorectal, and prostate), and the seventh in women (after breast, skin, colorectal, corpus uteri, lung, and cervix uteri). Regarding the mortality, it is on the forth place in men (after lung, colorectal, and prostate), as well as in women (after breast, colorectal and lung). However, in the 1950s and mid-1960s it was the leading cancer site in incidence as well as in mortality (16–19).

During the observed 40 years, the age distribution of patients has changed. In the period 1993–2001 the percentage of patients aged 80 years and more was much higher than in the period 1963–72 (4, 18, 19).

The exact causes of the decline of gastric cancer are not well understood, but must include improvements in the affluence of diet, food storage (e.g. refrigeration) and, possibly, the decline of *Helicobacter pylori* (HP) infection (20, 21).

DIAGNOSTICS

Endoscopic examination and biopsy of suspicious changes of the gastric mucosa took on the leading role in the diagnostics of stomach cancer in early 1970s. In preoperative disease staging, standard ultrasonography was introduced in the mid-1980s, whereas endoscopic ultrasonography came into use in the mid-1990s. In the 1980s, pathologists additionally standardized the analyses of resections by Lauren's histology classification for stomach cancer, malignancy stage (G) and UICC pTNM, and in the 1986, also by R classification. Multiple attempts to develop histological classifications with prognostic significance in gastric carcinoma have been made over the last 40 years. Among them, those developed by Lauren and the WHO's are the most commonly used (22). Lauren divided all gastric cancers into two main types: intestinal and diffuse (23). The

intestinal type has a glandular structure and is basically well delimited. The diffuse type is composed of small cells, which grow more or less diffusely into the surrounding gastric wall. The intestinal type is more frequent in males and at older ages while the diffuse type shows no difference between sexes and is more frequent in younger ages. Intestinal type is predominant in high-risk areas. It is also argued that the intestinal type is more influenced by environmental factors. However, several studies have failed to find difference in risk factors between diffuse and intestinal types (24, 25).

The WHO classification is based mostly on the morphology of cancer cells and divides gastric cancer histologically into tubular, papillary, mucinous and signet ring cell types (26). The WHO classification is less useful but remains the most widely used system worldwide (27).

In Slovenia, in the period 1993–97, 91% of cases were microscopically confirmed, the percentage of adenocarcinomas, non-differentiated cell carcinomas, non-Hodgkin lymphomas and leiomyosarcomas in these cases was 85%, 7%, 6%, and 0.6%, respectively. In the period 1998–2001, 95% of cases were microscopically confirmed, the percentage of adenocarcinomas, non-differentiated cell carcinomas, non-Hodgkin lymphomas and leiomyosarcomas in these cases was 84%, 7%, 8% and 1.3%, respectively.

The wider use of the Lauren histological classification as well as detailed reporting to the Cancer Registry started in the 1990s. With an increasing percentage of defined cases, a slightly lower percentage of intestinal type, and a slightly higher percentage of the diffuse type has been noticed in the late 1990s (16–18).

TREATMENT

Surgery has been the cornerstone of the curative management of gastric cancer for over a century. Oncological aspects of gastric surgery became the main concern in the 1940s. At that time, locoregional relapse was a major issue (28). Analysis of the patterns of local treatment failure revealed many recurrences in the region of the coeliac axis and splenic bed. This was the reason for proposing total gastrectomy with routine splenectomy and node dissection around the coeliac vessels and aorta (29).

In Slovenia until the early 1980s, the principal surgical treatment of stomach cancer involved resection with omentectomy (in principle, distal subtotal resection, total gastrectomy when otherwise not possible). A new strategy was initiated in 1982 that implied surgery planning depending upon the histology type (Lauren), subsite (thirds of the stomach), and depth of infiltration (sT). In 1986, systemic lymphadenectomy of the groups of lymph nodes I- and II-D2 was initiated (30). The proportion of total gastrectomies was gradually increasing from 5–10% to 30–40% (31).

In the first half of the 1990s, a multidisciplinary team of experts elaborated *Recommendations for a Comprehensive Approach to Patients with Digestive Cancer*. These recommendations were adopted by all professional boards and approved by the Health Council at the Ministry of Health of the Republic of Slovenia. They were published as a booklet and thus made available to all Slovenian physicians (32).

In 1995, two workshops and symposia on surgery of gastric cancer with the proceedings *Stomach Surgery* facilitated the implementation of this strategy also in the surgical departments of other hospitals (30). Though radical surgery is the sole treatment modality that offers the possibility of cure, about one third of patients with newly detected stomach cancer have never entered a surgical unit in this time. In 1993, only 72% (374/520) of patients with newly detected stomach cancer were treated at various surgical units, whereas in 2000, only 69% (330/480) (30). The high proportion of patients, not operated upon, definitely contributes to a poor five-year survival of patients with stomach cancer in Slovenia.

Currently, three major surgical strategic controversies are debated. The first deals with the extent of gastrectomy. The second questions the utility of extensive lymph node resection and the third issue has arisen more recently and deals with the best management of early gastric cancer.

Extent of gastrectomy

During the early 1980s, total gastrectomy was considered the standard curative treatment of gastric cancer. It was felt on the basis of some previous retrospective studies that subtotal gastrectomy was inadequate for controlling gastric carcinoma because of the high local recurrence rate (33). However, because of the high overall operative mortality (15% in specialized western centres going up to 29% in the hands of general surgeons), total gastrectomy never gained wide acceptance in western countries (34). Today, due to technical and medical improvements, the overall mortality rate associated with total gastrectomy has dropped considerably, but wide variations persist among countries, and between specialized and general surgical centres.

Quality of life is initially better (overall 6-month recovery) for distal gastric cancer patients who are treated by subtotal gastrectomy in terms of symptoms, daily living activities, anxiety, depression, and body mass index (35). However, this difference tends to vanish later on. Therefore, quality of life considerations should not offset oncologic safety requirements in the planning of curative surgery in gastric cancer.

Extent of lymph node resection

Lymph node metastasis decisively affects prognosis in stomach cancer. Operative clearance of the nodes is of utmost importance and requires a thorough surgical training if it is to be done effectively and safely. Removal of the perigastric lymph nodes only is called D1-resection. In D2-lymphadenectomy, removal of the lymphatic chains along the coeliac axis, the common hepatic and splenic artery, and at the hilus of the spleen is also performed. Earlier, splenectomy was performed in order to remove the splenic nodes (station 10). The left pancreatectomy was part of the removal technique of the lymph nodes of the splenic artery (station 11). In the meantime, several studies originating from western countries and Japan have demonstrated that systematic splenectomy and caudal pancreatectomy were not necessary and could increase the morbidity of the procedure (36).

The involvement of the splenic nodes (station 10) is most often seen in proximal tumours originating from the big curvature, while splenic artery lymph nodes (station 11) are most frequently involved by tumours situated in the middle of the stomach (37). Therefore, there is now general agreement to perform the resection of station 10 with splenectomy only in the presence of proximal lesions of the big curvature and macroscopic metastases to the splenic hilum (38). Similarly, with the introduction of new surgical techniques, station 11 resection no longer requires caudal pancreatectomy; it is now reserved to direct pancreatic invasion (39).

Nowadays, the D2 procedure is done to achieve accurate staging and regional disease control, and because of potential benefit to a subgroup of patients with occult disease in D2 nodes. D2 lymphadenectomy is safe if done by a skilled surgeon and if splenectomy and pancreatic resection are avoided. Splenectomy should be done only in cases of locally advanced tumour of the upper third of the stomach, tumours of the greater curvature, and those of the gastric cardia. The incidence of lymph node metastases is 10–25%, and if splenectomy is advised, the pancreas should be preserved (40).

In order to avoid unnecessary removal of lymph nodes that are not at risk of tumour, two new approaches emerged recently. The first technique uses a computerised database of information to convert a large amount of information and experience to a treatment decision for an individual patient. Depth of infiltration, tumour size, tumour location, grading, typing, and macroscopic appearance are used to predict the probability of nodal metastases

(41). The second approach uses information derived from dissection of the sentinel node. At present, clinical impact of both approaches is limited due to the low specificity and low positive predictive value (42).

Early gastric cancer

Early gastric cancer is a well-known entity in Japan, where it represents up to 50% of the gastric neoplasms The prognosis of early gastric cancer is excellent with 10-year survival rates between 80 and 95% (43). With such good results, the debate is dominated by the desire not to 'overtreat' these patients (44). However, many studies have shown that up to 20% of the early lesions showing submucosal invasion can be associated with lymph node involvement, which bears a poorer prognosis (45). In Japan, surgeons favour endoscopic mucosal resection, which is thought to have high curative potential and to avoid the need for further radical surgery. However, such an approach should only be done if very accurate local staging has been achieved. In Slovenia, the incidence of early gastric cancer has increased, too. Among patients who underwent surgical procedure at our department, there were 20.5% of patients with early gastric cancer in the period 1998–2002.

GASTRIC SURGERY IN SLOVENIA

In the last observed period, patients underwent surgery at nine surgical departments of general hospitals in Slovenia. On average, one third of patients were operated on in the University Medical Centre (UMC), Department of Abdominal Surgery, in Ljubljana, the other third in two major regional hospitals, and the last third in the remaining six general hospitals. In the early 1990s, it was often stressed that the treatment of malignant diseases in the centres that can admit a critical number of patients is significantly more effective. In recent years, an increasing proportion of patients have been operated on at larger departments of three major hospitals in Slovenia. In smaller surgical departments, they practically do not operate any

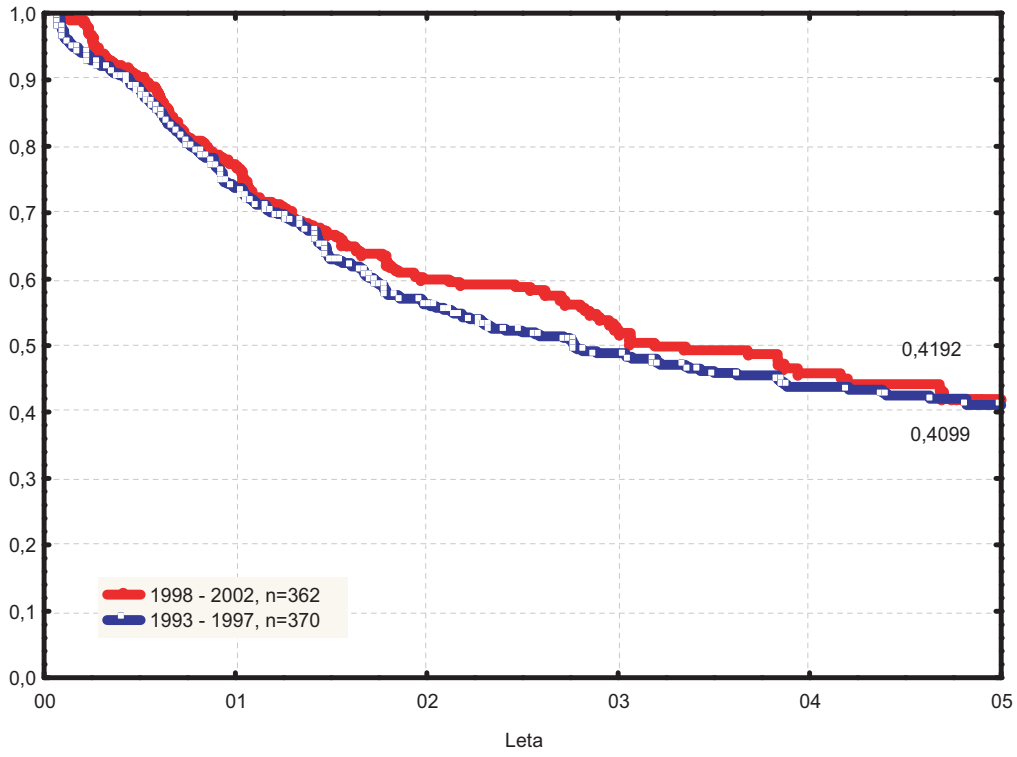

Figure 1. Five year survival of resected patients (R0, R1, R2). Comparision of two 5-year periods (1993–1997 and 1998–2002).

more on the patients with stomach cancer (30–33). In the period from January 1998 to December 2002, 474 patients underwent operation at the Department of Abdominal Surgery, UMC in Ljubljana. At the time of surgery 37.3% of them were older than 70 years, 32.7% were between 61 and 70 years of age, and 30% were younger than 61 years. In 392 cases potentially curative (R0) or palliative (R1, R2) resection was performed (resectability rate 82.7%). In 216 cases (55.1%) this was distal subtotal resection, in 172 (43.9%) total gastrectomy. In 4 cases (1.02%) endoscopic mucosectomy of an early cancer was done successfully. R0 resection was performed in 78.6% (305/392) of patients with postoperative mortality rate of 6.5% (20/305).

Despite all the efforts made in the field so far, the results of treatment on national level are unsatisfying. More attention should be paid to the early detection to improve the effectiveness of treatment and thus survival of patients who develop gastric cancer. Surgery remains the cornerstone of the curative management of gastric cancer. The morbidity and mortality of gastric cancer surgery is associated with the skills of surgeons and with the quality of training programmes. The curative treatment of gastric cancer is now becoming the subject of a multidisciplinary approach including surgery, radiation therapy and systemic therapy, as for colorectal cancer and some other solid tumours.

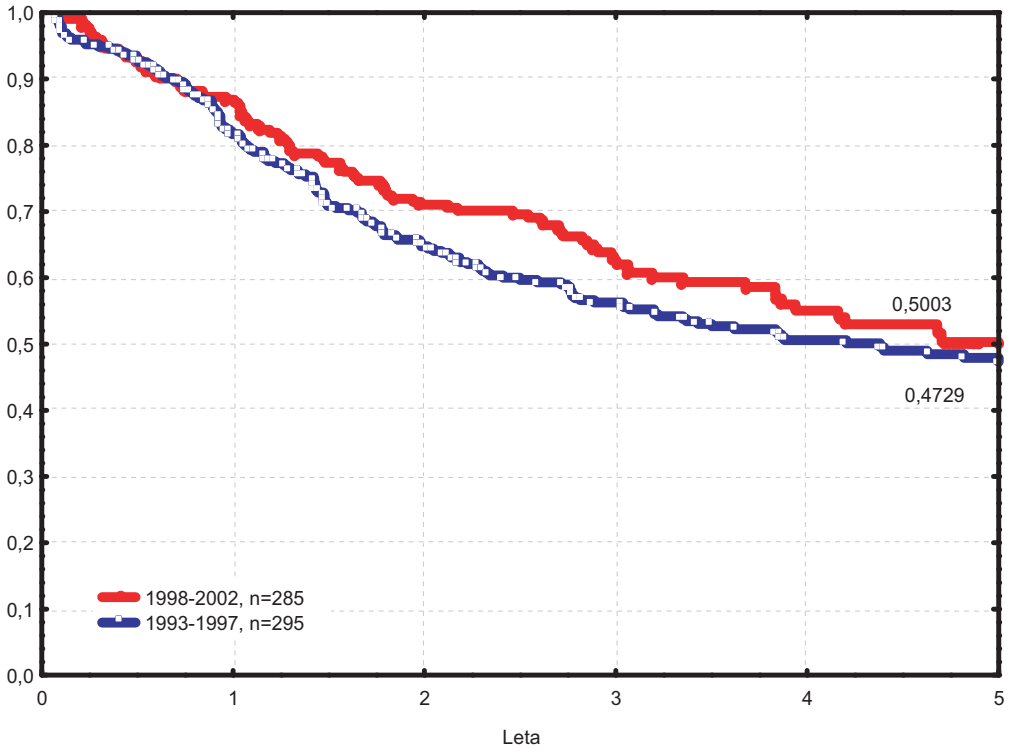

Figure 2. Five year survival of R0 resected patients. Comparision of two 5-year periods. (1993–1997 and 1998–2002).

Five-year survival rate of all resected patients (R0, R1, R2) was 41.92%, while in potentially curatively resected (R0) group it was 50.0%. According to the TNM stage 5-year survival was as follows: pS1 79.66%, pS2 41.09%, pS3 19.43%; in pS4 nobody survived longer than 3.5 years (Figures 1 and 2).

The benefits of our twenty-year endeavours to facilitate the access to endoscopic examinations, follow-up of high-risk patients, multidisciplinary approach to patients, standardized surgical treatment at major surgical units and at specialized cancer treatment departments will probably start to have an impact on the treatment results on the national level only in the next observation period.

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Chemoprevention of colorectal cancer

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INTRODUCTION

Colorectal cancer is the third most common cause of cancer-related death in the Western countries, following lung and prostate cancer in men, and lung and breast cancer in women (1). Colorectal carcinogenesis is a multistep process characterized by the successive accumulation of cancer-associated mutations (2). In greater than 95% of cases, an adenomatous polyp is the predecessor of a colorectal cancer (3), making the presence of a colorectal adenoma the best known predictive biomarker for the development of these malignancies (Figure 1). The rate at which adenomatous polyps progress to cancer is estimated at about 2.5 polyps per 1,000 per year (4). Approximately 50% of men and 30% of women develop adenomatous polyps of the colon by age 50 (5, 6), and the lifetime incidence of colorectal cancer in Western populations is approximately 6% (1). Removal of adenomatous polyps (pre-malignant lesions) through colonoscopy with endoscopic polypectomy is an effective method of cancer prevention (7), but it is invasive, costly, and not utilized on a population basis. Other strategies include prevention of the development of colorectal polyps and colorectal cancer through chemoprevention in the hope to reduce the need for colonoscopy in individuals with colorectal adenomas.

PREDICTORS OF COLORECTAL CANCER RISK

The identification of a surrogate endpoint biomarker (SEB) is important to the development of cancer chemoprevention methods. The ideal SEB is the one that can be measured with minimal morbidity in pre-malignant tissue and that accurately predicts colorectal cancer risk. Molecular analysis of colorectal neoplasia indicates that pre-malignant changes occur in the gastrointestinal epithelium long before an adenoma develops (2). These genetic changes may be modulated through exogenous factors (examples: changes in diet, or use of chemopreventive drugs) (8, 9).

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COLORECTAL CANCER PREVENTION

Endoscopic Polypectomy

Endoscopic polypectomy is the only known effective method of primary prevention for colorectal carcinoma (10–14). In the National Polyp Study, 1,418 patients were followed-up for an average of 5.9 years after colonoscopic clearance of adenomas. These individuals had age- and sex-adjusted rates of colorectal cancer that were 76–90% lower than expected from comparison with reference groups who had not undergone surveillance (14).

Chemoprevention of colorectal cancer: Non-steroidal antiinflammatory drugs

Chemoprevention refers to the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent the evolution into invasive cancer. Non-steroidal antiinflammatory drugs (NSAIDs) are one of the most promising classes of chemopreventive agents, as demonstrated by three well-established lines of evidence – *in vivo* models, human observational studies, and non-randomized human interventional research.

In several different animal models of colon cancer, NSAIDs (e.g. sulindac) inhibit tumour formation (15–17). Patients with familial adenomatous polyposis (FAP), who develop colorectal cancer as a result of a germline mutation in the APC gene, demonstrate regression of rectal adenomas with administration of sulindac (9, 18, 19). A series of observational studies (20–25) have investigated the relationship between aspirin/NSAIDs and sporadic colorectal neoplasia using case-control, nested case-control, and prospective study designs. All but one study suggest that NSAIDs are effective in preventing human colorectal adenoma incidence, carcinoma incidence, and/or cancer-associated mortality, regardless of age, gender, affected colorectal segment, or other underlying risk factors (e.g., diet, history of prior adenomas, socioeconomic status). The preventive effects of aspirin/NSAIDs may require extended periods of exposure, as most investigations reported efficacy only within those using drugs for more than 8–10 years.

Cyclooxygenase-2 and colorectal cancer

Cyclooxygenase is a key enzyme in the formation of prostaglandins. The enzyme is expressed in two forms, COX-1 and COX-2. Overexpression of COX-2 is observed in human and animal colon cancers (17, 26–28). Overexpression of COX-2 in rat intestinal epithelial cells is associated with resistance to apoptosis, an effect that is overcome by treatment with non-selective NSAIDs, such as sulindac (29). This relationship between COX-2 and apoptosis may also be valid *in vivo*, as sulindac induces apoptosis of intestinal epithelial cells of humans with FAP (30). In a murine model of FAP, abnormalities of both proliferation and apoptosis in the pre-neoplastic intestinal epithelium are normalized by administration of non-selective NSAIDs (31). It should be noted, however, that NSAIDs also inhibit carcinogenesis via COX-independent mechanisms. For example, sulindac sulfone, a metabolite of sulindac that does not inhibit COX-1 or COX-2, is chemopreventive in rat models of mammary and colon carcinogenesis (32, 33).

An agent used for prevention of colorectal adenomas in the general population must have very low toxicity. In addition to blocking the activity of COX-2, aspirin and other NSAIDs previously evaluated for colorectal cancer prevention also inhibit COX-1, the constituitively-expressed form of the enzyme. Unlike COX-2, which is induced in response to inflammation or mitogenic stimuli, COX-1 is constituitively present in tissues such as stomach, kidney, and platelets, where prostaglandins are necessary for normal physiologic function (34).

Safety issues with aspirin/NSAIDS/COX-2 inhibitors

The benefit of chemoprevention should largely exceed the potential risks (adverse events under treatment) of therapy. Recently a series of articles has been published describing unexpected adverse cardiovascular effects of COX-2 inhibitors. These

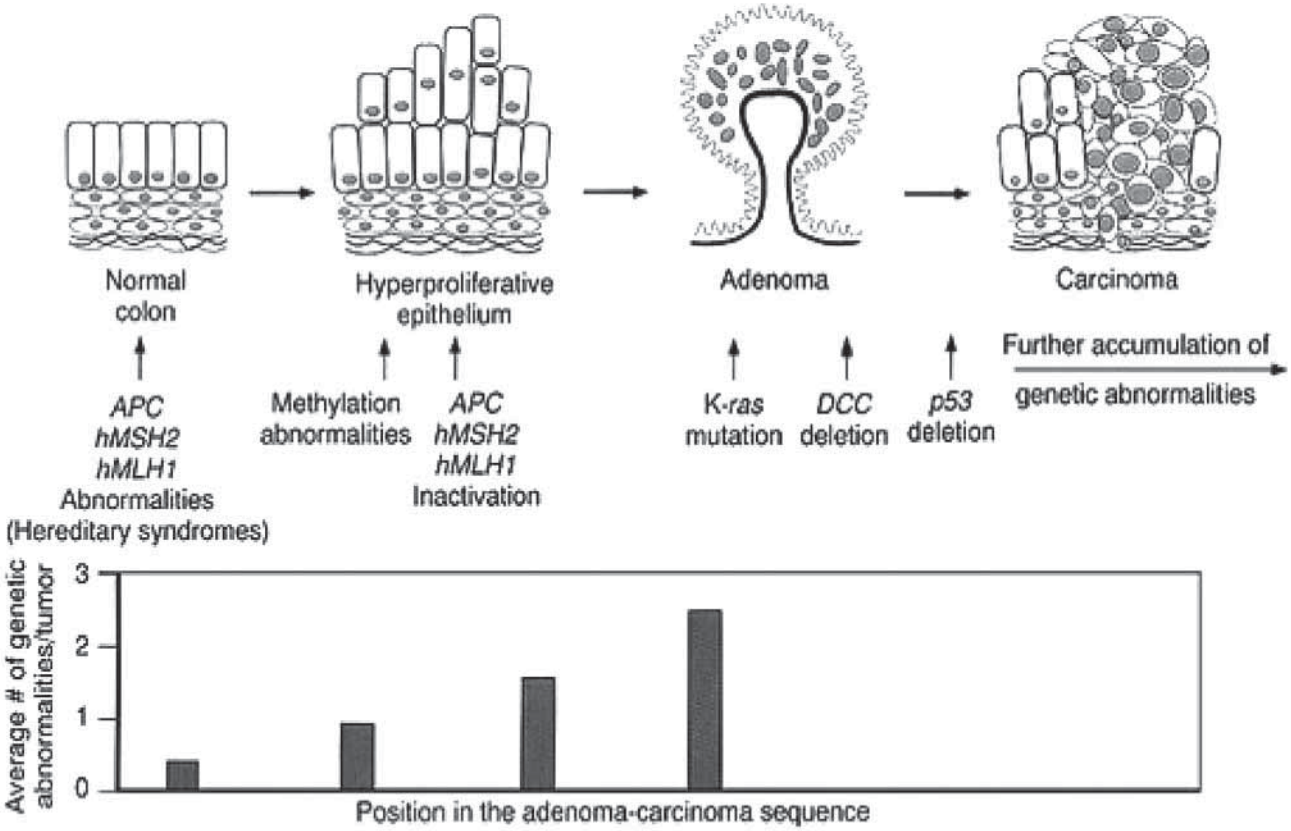

Figure 1. Adenoma-carcinoma sequence (according to Gottlieb, Spokane, USA).

cardiovascular toxicities raise important questions. Because we have a well-established option for the prevention of colorectal cancer (colonoscopy with endoscopic polypectomy), it is not justified to use these agents for the chemoprevention of sporadic colorectal cancer. Chemopreventive treatment should therefore not replace colonoscopic screening and surveillance. Patients who avoid colonoscopic examinations because of chemopreventive treatment may be increasing their colorectal cancer risk. Finally, the risk attached to treatment may outweigh the benefit to a few patients. The place of chemoprevention in colorectal cancer cannot be defined at the present time (35–39).

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Current role of endoscopy and surgery in the management of early cancer of the upper gastrointestinal tract

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Traditionally, early cancer has been defined as those tumours that limit the depths of penetration of the wall of the upper gastrointestinal (GI) tract to the submucosal layer. In that particular situation it is not primarily relevant whether lymph node metastases are present or not. The area where this definition has been most widely used is within the stomach. With the introduction of modern endoscopic magnification tools, vital spraying equipment, high frequence endoscopic ultrasonographic technologies, we have entered en era where more and more cases will be diagnosed with "early neoplastic" lesions in the upper GI tract. At the same time it is obvious that new and more biologically sound concepts will be and have been introduced which clearly delineate the boundaries within which endoscopic, transoral techniques that can and in the future shall ultimately be applied. Similar boundaries have been defined when conventional surgery with radical lymph node dissection should be carried out. However, novel concepts are presently explored when other minimal invasive techniques are used to carry out functional preserving resections combined with local lymph node clearance. In similar situations e.g. the use of sentinel node dissection may become mandatory.

In the field of endoscopic resection of early malignancies the development of mucosal resection technologies expands the mucosal segments that can be incorporated in the respective procedure. Furthermore, the concept of functional preserving resection has now been expanded into a variety of different fields such as: vagus sparing partial or local oesophagectomy, vagal and pylorus sparing gastric resection with local radical lymph node dissection, and – last but not least – pancreas sparing duodenectomy in patients with familial adenomatous polyposis (FAF) with duodenal polyposis and intraepithelial cancer.

Definitely, the minimal invasive surgical approach to the management of patients with early neoplastic lesions of the GI tract has opened up novel oppor-

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tunities and therapeutic concepts, which have potential benefits for the patients. However, there are also associated pitfalls and hazards mainly based on the very important prerequisite, namely that all these lesions, if adequately treated, basically should not expose the patients to an enhanced risk of succumbing due to recurrent and progressive disease. This very important presumption rests on the basic concept that "adequate" treatment is offered even in situations where the tumour may have spread to the local lymph nodes. If, for instance, a patient with a T1sm1-tumour exhibits signs of N_1 disease and is not submitted to adequate radical operation, that patient has been exposed to an unacceptable risk of having had a suboptimal therapy, which might have the flavour of being fancy but not evidence-based. Accordingly, if currently minimal invasive technology is applied in the management of patients with early cancers, it is seriously recommended that it is done within the framework of controlled clinical trial protocols.

Tentative management algorithm for early neoplastic lesions

Although construction of management algorithms have a »best before date label«, it still seems relevant to present such algorithms focusing on three major areas of the upper GI tract: the distal oesophagus, stomach and duodenum.

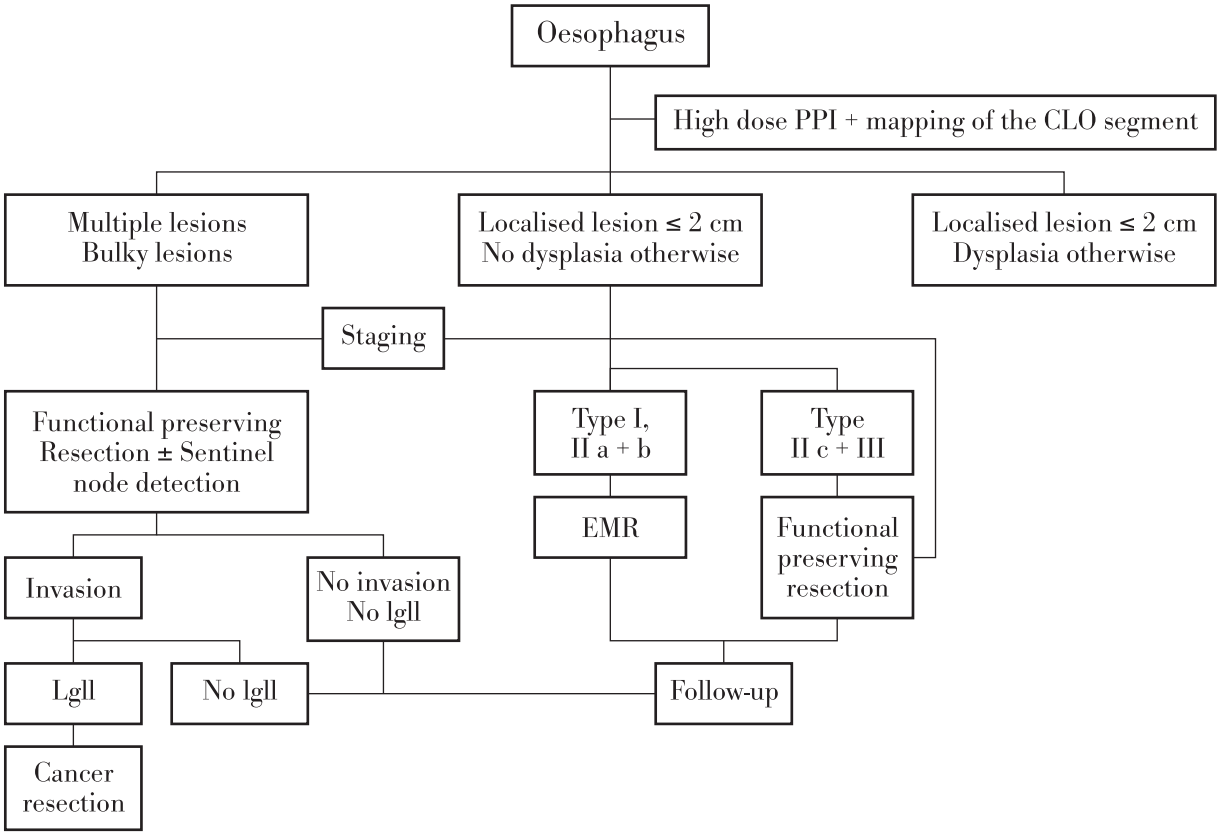

Figure 1. Tentative algorithm for the management of early oesophageal cancer.
Legend: CLO – columnar lined oesophagus, EMR – endoscopic mucosal resection, Lgll – lymph nodes, PPI – proton pump inhibitor.

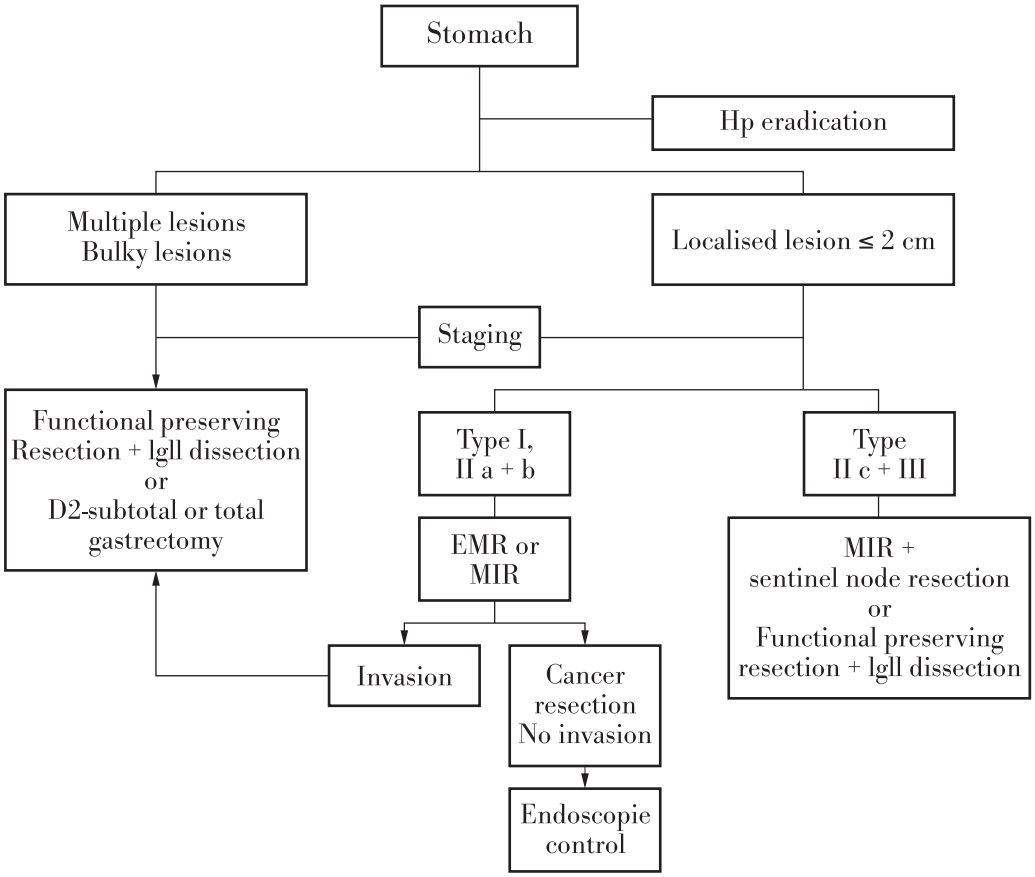

Figure 2. Tentative algorithm for the management of early gastric cancer.
Legend: EMR – endoscopic mucosal resection, Hp – Helicobacter pylori, Lgll – lymph nodes, MIR – minimal invasive resection.

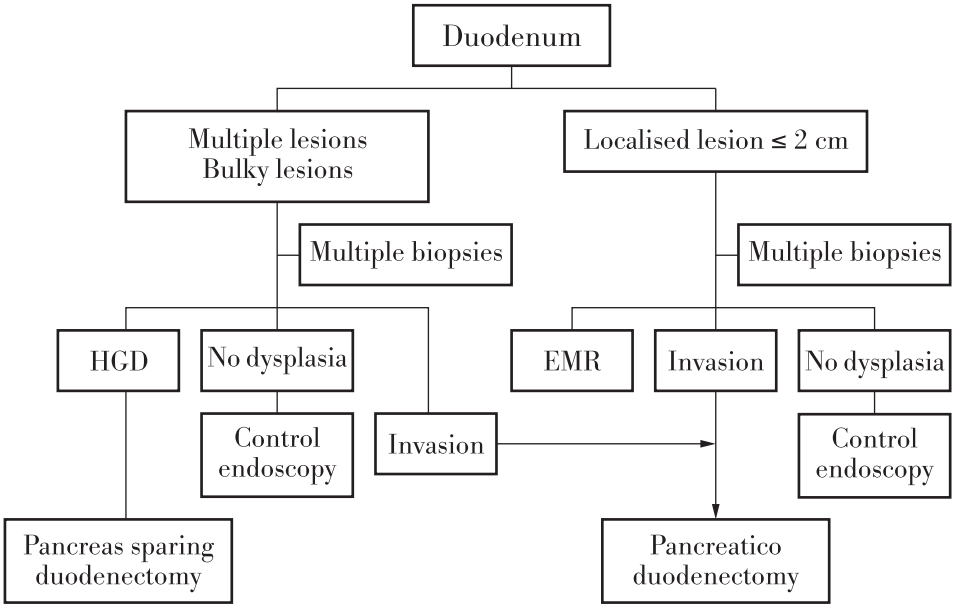

Figure 3. Tentative algorithm for the management of early duodenal cancer.
Legend: EMR – endoscopic mucosal resection, HGD – high grade dysplasia.

Instructions to the authors

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