

### 1078 Stress-Syndrome Indicators and Insulin Resistance in Patients with Acute Viral Hepatitis and Diarrheal Disease

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**Aim:** To reveal the mechanisms of hormone levels' changes in blood in patients with acute viral hepatitis (AVH) and acute gastrointestinal infections (AGII).

**Patients and Methods:** 117 AVH (33 mild, 76 moderate, 8 severe) and 50 AGII patients were RIA-tested for adrenocortical, thyroid, and pancreatic islet hormones' blood levels. AST and ALT activities and bilirubin in blood were also measured in AVH patients. All the patients didn't have endocrine diseases, their glucosemia was normal.

**Results:** High ACTH, cortisol, T4, TBG, insulin, and glucagon and low TSH, T3, and C-peptide accompanied the AVH and AGII acute phase. The hormone levels approximated the healthy controls' (62 individuals) values during convalescence. As an exception, patients with severe AVH had normocortisolemia. Hypercortisolemia was higher in mild versus moderate AVH. Maximal cortisolemia in each individual AVH patient used to coincide with maximal values of bilirubinemia and AST and ALT activities. Hepatitis exacerbation evoked repeated hypercortisolemia. AVH patients' strong correlation: positive – ALT-ACTH, ALT-TBG, ALT-T4, ACTH-TBG, T4-TBG, negative – cortisol-T3, ALT-TSH, ALT-T3, T3-T4, T3-TBG.

**Discussion:** Severity-cortisolemia irreversible proportion during AVH acute phase indicates towards adrenocortical activation being the main cause of hypercortisolemia (though lowered intrahepatocyte cortisol cleavage cannot be denied) and explain the corticosteroid trend in severe hepatitis treatment. Hyperinsulinemia, normoglucosemia, and low C-peptide in non-diabetic patients with AVH and AGII reflect tissues' temporary insulin resistance.

### 1079 Family History of Malignancies in Patients with Colorectal Cancer

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**Aim** of the study was to determine the frequency of a first degree family history of malignancies in colorectal cancer (CRC) patients and in controls. **Patients and Methods:** the frequency of CRC, gastric, endometrium, breast and lung cancer was investigated in first degree relatives of 275 patients with CRC and in 216 controls in whom a CRC was excluded. Patients with known premalignant conditions (familial adenomatous polyposis-FAP, Lynch syndrome-HNPCC, inflammatory bowel disease) were excluded. Controls and CRC patients were comparable for age and sex. **Results:** the frequency of a first degree family history of CRC and other malignancies is reported in the table.

Family history of cancer

	Colon	Stomach	Endom.	Breast	Lung
CRC	17%	4%	2.5%	3.6%	6.1%
Controls	6.5%	5.8%	3.2%	4.2%	3.7%

The frequency of a positive family history for CRC is significantly higher in CRC patients than in controls ( $P < 0.0001$ ), while no differences were found for a family history of gastric, endometrial, breast and lung cancers. In CRC patients the frequency of a family history of CRC was unaffected by sex and tumor location but was higher in younger patients (<50 yr 22%, 50–70 yr 17.4%, >70 yr 12%). Previously undetected FAP and HNPCC were identified in two patients. **Conclusion:** a positive first degree family history of CRC frequently occurs in sporadic cases of CRC and can be considered a risk factor for this malignancy. Other malignancies occurring in these families are not consistent with any described family cancer, as their frequencies are similar to those reported in control families. The likelihood of a first degree family history of CRC increase with decreasing age. Previously undetected FAP and HNPCC can be identified through a careful analysis of the pedigrees of all incidental CRC cases.

### 1080 Increased Familial Tendency for Metachronous Adenomatous Polyps in First Degree Relatives of Colon Cancer Patients

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**Background.** We have shown that in subjects with even one first degree relative with colon cancer there is an increased risk of adenomatous polyps, characterized by a more proximal location and more severe morphological abnormalities (Gastroenterology 1992; 102:A345). **Aim.** In the present study we sought to determine whether in patients with only one first degree relative with colon cancer there also is an increased tendency for developing metachronous adenomatous polyps after endoscopic polypectomy. **Methods.** The frequency of metachronous adenomatous polyps was evaluated

in 69 patients who underwent a complete colonoscopy with removal of all polyps detected. Patients were selected either on having a positive family history as defined by the presence of only one first degree relative with colon cancer (study group: n. 16 patients; 11 males; 5 females; mean age  $58.9 \pm 2.8$ ) or on having a fully negative cancer family history (control group: n. 53 patients; 35 males; 18 females; mean age  $57.2 \pm 1.6$ ). All subjects had yearly follow up colonoscopy with a mean follow up period of  $35.1 \pm 22.4$  months (study group:  $38.5 \pm 24.2$  months; control group:  $34.1 \pm 21.9$  months;  $p = ns$ ). **Results.** Follow up colonoscopy showed a higher frequency of metachronous adenomas in the study group (25.8%) than in the control group (21.0%). The Mantel-Haenszel Odds ratio estimator (O.R.<sub>M-H</sub>) adjusted for confounding variables (sex and age) was 1.207 with 95% Confidence Interval of (0.406, 3.593). Furthermore the frequency of polypoid lesions located proximally to the descending-sigmoid junction was found to be higher in the study group (87.5%) than in the control group (60.8%). The O.R.<sub>M-H</sub> was 4.5. Recurrence time was similar in both groups. **Conclusions.** There is an increased risk of metachronous adenomatous polyps in patients with even one first degree relative with colon cancer. In these patients the proportion of polyps located proximally to the descending-sigmoid junction is also higher than in patients with negative cancer family history.

### 1081 The Role of Aspiration Cytology in the Diagnosis of Malignant Gastrointestinal Diseases

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In the course of endoscopy authors accomplished the histological sampling with fine needle aspiration in 31 patients. During this procedure the material – gained by means of the sclerotising needle – had been cytologically evaluated. The aim of the study was to determine the usefulness of aspiration cytology in the endoscopy, having mutually applied both methods. During 16 lower and 15 upper examinations 14 malignant processes, 14 inflammations (resp. adenomas) were found, and the result of 3 examinations proved to be negative.

**Results:** In the tumor group one single false negative cytology was found, in three cases only repeated histology could prove carcinoma, although the alteration seemed macroscopically to be malignant. In these cases the cytological examination was unanimously positive. In the 14 inflammatory diseases the results of the cytological examinations were P2-P3.

In the opinion of the authors the aspiration cytology done in the course of endoscopy is a useful method. It can provide results some minutes after the examination, and is highly sensitive in differentiating benign and malignant processes. The wide-spreading adaptation of this method in the diagnosis of malignant gastrointestinal diseases is highly recommended.

### 1082 Blood and Mucosal Activities of Antioxidant Enzymes in Colorectal Adenomas

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It is supposed that about 60% of colorectal cancers, mainly in the left-side colon, arise from the adenoma-carcinoma sequence. Various etiological factors were studied – nutritional, chemical, genetic etc. Increased level of free radicals in the cells are suggested to initiate or promote carcinogenesis in the tissues. The first line of antioxidant defense in the cells is formed by antioxidant defense in the cells is formed by antioxidant enzymes. The purpose of this study was to follow the concentration of malodialdehyde (MDA) and antioxidant enzyme activities in blood and colorectal mucosa of patients with colorectal adenomas (CA) as indirect sign of the level of reactive oxygen species (ROS).

43 patients with CA and 21 control subjects were investigated. Mucosal biopsy specimens were taken during colonoscopy. Antioxidant enzyme activities – superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) – were stated in RBC and colonic mucosa, the concentration of MDA was measured in the serum.

Comparing to the controls, in the group of CA patients following changes of values were observed: (a) increased concentration of MDA, (b) increased activities of CAT and GPx in RBC, (c) increased activities of GPx in colorectal mucosa, (d) no changes in activities of SOD.

It is suggested that changes observed in patients with CA were caused by higher production of ROS in the tissue, mainly by anorganic and organic peroxides (lipoperoxides). Further studies are needed to elucidate the connection of this finding to colorectal carcinogenesis.

### 1083 Gastric Precancerous Conditions: Activity of Antioxidant Defense System

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In gastric carcinogenesis next steps are assumed: superf. and atrophic gastritis (adenoma) – intestinal metaplasia – dysplasia – carcinoma. Phagocytes in inflammatory tissue are source of reactive oxygen species (ROS), they could act as mutagens or promoters of pathological changes. The aim of the present study was to assess antioxidant defense system in the blood and gastric mucosa of patients with precancerous conditions.

94 patients-gastritis superf. (SG), atroph. (AG), after part. gastrectomy (PG), hyperplastic polyp (HP), gastric adenoma (GAD) and 21 controls were examined. Blood and gastric mucosal specimens were analysed. Concentration of malondialdehyde (MDA) and data of antioxidant defense were measured: enzymatic (blood and gastric mucosa) – superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), non-enzymatic (blood) – glutathione (GSH, GSSG), ceruloplasmin (CPL), transferrin, vitamin A, E, C, and Cu, Zn, Se.

In examined groups was observed: (a) increased concentrations of MDA, CPL, in all groups, (b) increased activity of GPx, less frequently SOD, CAT, in the mucosa and blood, mainly in groups PG, AG, GAD, (c) decreased concentrations of GSH, vit C, vit E, and Cu, Se, in groups GAD, HP, AG, SG.

Increased activities of antioxidant enzymes and changed or decreased concentrations of non-enzymatic defense factors indicate that in patients with precancerous conditions is: (1) high generation of ROS in the tissue, and (2) insufficient non-enzymatic antioxidant defense (mainly low level of free radical scavengers).

### 1084 Chemoprevention of Metachronous Adenomas of the Large Bowel: A Double Blind Randomized Trial of Antioxidants

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This study is aimed at investigating a) the efficacy of antioxidant supplementation in reducing the incidence of metachronous adenomas (MA) of the large bowel in pts free from adenomas (AD) after polypectomy and b) the feasibility of long-term chemopreventive trials. Pts are randomized to receive, daily, an active compound (Selenium 200 mcg, Zinc 30 mg, Vit A 6000 IU, Vit C 180 mg and Vit E 30 mg) (arm A) or a placebo (arm B) for 5 years (both provided by Pharma Nord). A 50% reduction in the incidence is hypothesized; 60 events (MA) during the follow-up, are required to test the hypothesis. Pts aged 25–75 yrs, with at least one AD removed and believed to be polyp-free enter the study; pts with FAP, IBD, invasive cancer at any site are excluded. Endoscopy is performed one year after randomization and then every other year. The study started in 1988 and 291 pts were randomized, but 279 were available (144 in arm A and 135 in arm B). Fifty-five pts (38.2%) in arm A and 51 (37.8%) in arm B stopped the treatment: the 4-year actuarial compliance rate was 42.4% and 45.4% respectively. Minor side effects (headache, nausea, dizziness) were reported by 12.7% of pts in arm A and in 11.8% in arm B. At least one endoscopic examination was performed in 150 pts (providing 306 py of follow-up) and 31 MA were detected: 13/178 py in arm A and 18/128 py in arm B, (RR = 0.52, c.i. 0.26–1.02 p = 0.08). Our data show that the main drawbacks in long-term chemopreventive studies are represented by the high rate of drop-outs. However, despite unsatisfactory compliance, the results obtained so far are in support of the original study hypothesis, i.e. a 50% reduction in the incidence of MA.

### 1085 Hepatocellular Carcinoma (HCC) Following Cirrhosis: A Raised Serum Level of Urokinase-Type Plasminogen Activator (u-PA) Measured by an Immunoenzymatic Method (IEM)

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When combined with the alphafetoprotein level (AFP), the plasma u-PA level measured by radioimmunity (RIA) gives an early diagnosis of HCC following cirrhosis. In order to evaluate the usefulness of u-PA as a tumour marker in HCC with an easily reproduced method of measurement, we compared the levels of plasma u-PA measured by a commercial IEM in 2 groups: one

with 46 patients with proven HCC and cirrhosis, and the other group of 46 patients with cirrhosis with no detectable HCC; in all cases the serum AFP was also measured.

**Patients:** (1) "HCC group": 46 patients, (42 men); mean age: 65 years (40–79). HCC confirmed by needle biopsy with cirrhosis (alcoholic: 19 cases); ultrasound formations: unique nodular lesion (UNI): 25 cases; multiple nodular lesions with 2–4 nodules (MNI): 15 cases; diffuse form: 6 cases. (2) "Cirrhosis group" of 46 patients comparable to "HCC group" concerning sex, age, aetiology and degree of cirrhosis.

**Methods:** the u-PA plasma level was measured by a IEM commercial kit (Tintelize u-PA, Biopool, AB, UMEA, SWEDEN) and the serum AFP by RIA; the Mann whitney non parametric comparison statistic test was used.

**Results:** (1) *Blood levels of u-PA and AFP:* The plasma u-PA level was significantly higher in the "HCC group" than in the "Cirrhosis group" (p = 0.02), the specificity of the u-PA for the diagnosis of HCC was 85% and the sensitivity 28%. (2) *Ultrasound forms of tumours and blood levels of u-PA and AFP:* The plasma u-PA was normal in cases of diffuse HCC, significantly raised only in cases of UNI with a diameter of 4 to 8 cm (p = 0.009) and in cases of MNI (p = 0.003) compared to the cirrhosis group; the serum AFP being quite significantly higher in the "HCC group" independently of the ultrasound forms.

**Conclusion:** this study shows a low sensitivity and specificity of the plasma u-PA for the diagnosis of HCC occurring with cirrhosis. Since the plasma u-PA level is significantly higher in cases of MNI and UNI of 4 to 8 cm diameter. The measurement of the plasma u-PA by MIE would seem of limited usefulness in the detection of HCC.

### 1086 High Dose Rate Brachytherapy (H.D.R.B.T) in Esophageal Cancer

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High dose rate brachytherapy (H.D.R.B.T) is a therapeutic element in non surgical combined treatment to cure esophageal cancer (O.C.). We report the results of thirty patients treated for non metastatic O.C with: external beam radiotherapy (EBRT), chemotherapy and H.D.R.B. between 1990 and 1993.

**Patients:** 30 (29 men); median age: 62 years (45–78); epidermoid carcinoma: 27 cases; site: cervical and upper third: 7 cases, middle third: 13 cases, lower third: 6 cases, two sited: 4 cases; lésions classified (UICC 1987): T1 NO: 6, T2 NO: 9, T3 NO: 3 patients; T1 Nx: 1 case; T1 N1: 1, T2 N1: 4, T3 N1: 6 patients. Contra-indications to surgery: associated complications: 21 cases, previous radiation for head and neck tumors: 8 cases, refusal: 1 case. **Method:** EBRT > 60 Gy followed by 1 or 2 fractions of HDRBT at 7 Gy/surface, three weeks after EBRT, of Savary applicator, in 22 cases; EBRT: 45.50 Gy (cervical oesophagus or previous radiotherapy) with 2 or 3 fractions of HDRBT in 8 cases. 2 cures of concomitant chemotherapy (5FU-CDDP) were associated to radiotherapy in 22 cases (contra-indications to chemotherapy in 8 cases). **Results:** (1) complete local response rate at the end of treatment: 22/30. (2) well tolerated in all cases. (3) complications: 1 vertebral collapse due to osteoporosis in the radiation field; 1 fatal oesophageal fistula (evolutionary disease). (4) survive: 17 patients are alive with non evolutionary disease with a mean follow up of 20 months, more than 24 months in 8 cases (5–45 months).

**Conclusion:** H.D.R.B.T. combined with curative non surgical treatment of esophageal cancer is in the short and mean term well tolerated treatment and seems a promising therapeutic element in non surgical combined treatment of esophageal cancer.

### 1087 Gastric Lymphoma: The Role of Histology and Age

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Gastric lymphoma (GL) often arises from mucosa-associated lymphoid tissue (MALT). Division low-grade (lg, malt-type) versus high-grade (hg) GL has prognostic value. The role of age is unclear. **Methods:** the prognostic value of histology (lg malt-type versus hg) and age were studied in 137 patients with primary GL (1978–1992). Causes of death were divided in NHL and non-NHL-related. Relapses were divided in early (< 12 m), intermediate (12–36 m) and late (> 36 m). **Results:** hg GL occurred more often in elderly patients. Irrespective of underlying histology a CR could be obtained in > 80% of patients. Relapse rates were higher in hg GL, significantly in patients 50–65 yr of age (p < 0.01). Early relapse occurred only in hg-GL: 10/74 pts. Intermediate relapses occurred in 9/74 hg-GL and 8 lg-GL pts. Late relapses were unusual: 3 hg-GL and 4 lg-GL. Death due to NHL (45 pts) occurred more often in hg-GL compared to lg-GL (p < 0.001). Non-NHL related deaths (23 pts) but were mostly confined to patients > 50 y: 7 cardiovascular deaths, 10 malignancies

other than NHL.

	n	CR	Relapse	Died: NHL	Died: nonNHL
Ig GL					
<50 yr	16	100%	19%	2	-
qa50-65 yr	27	96%	19%	1	6
>65 yr	20	67%	25%	8	4
Total	63	90%	21%	11-17%	10-16%
hg GL					
<50 yr	12	75%	17%	4	1
50-65 yr	21	86%	52%	12	3
>65 yr	41	78%	34%	18	9
Total	74	80%	36%	34-46%	13-22%

**Conclusions:** (1) Histological classification in Ig versus hg GL has prognostic value. (2) A high rate of CR was achieved in both Ig and hg GL: 90%/80%. (3) Relapse rate was higher in hg GL, significantly in patients 50-65 yr of age. (4) Early relapse (< 12 months) was only seen in hg GL. (5) Non-NHL death rates were unrelated to NHL-histology and increased with age. Almost 50% was due to another malignancy.

### 1088 Increased Urokinase (uPA) and uPA Receptor Antigen at the Tumor-Host Interface of Colorectal Adenocarcinomas with Poor Prognosis

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The plasminogen activation system, which contributes to extracellular proteolysis and tissue destruction, is suggested to be involved in tumor aggressiveness, invasion, and spread. In the present investigation frozen sections from colorectal adenocarcinomas were studied for the presence of plasminogen activation system components. The location of plasminogen activators (uPA, tPA), uPA receptor (uPAR), and PA inhibitors (PAI-1, PAI-2) was demonstrated by immunohistochemistry. To evaluate any relation between the presence of these components and cancer prognosis, nine patients with good prognosis and 13 patients with poor prognosis were studied. uPA and uPAR at the tumor-host interface was significantly increased in patients with poor prognosis compared to patients with good prognosis ( $p < 0.05$ ). Both patient groups showed an accumulation of uPA, uPAR, PAI-1, and inflammatory cells at the tumor-host interface compared to the tumor tissue ( $p < 0.05$ ). These results point to an imbalance of the plasminogen activation system, with increased uPA and uPAR at the tumor-host interface in poor prognosis tumors. uPAR localizes proteolytic activity to the surface of tumor cells at the interface. uPA and its receptor may, thus, play a role in tumor aggressiveness and invasion. The present study shows that uPA and uPAR may be valuable indicators of prognosis in colorectal cancer.

### 1089 The Contact Activation System in Human Ascites

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Accumulation of ascites is seen in patients with gastrointestinal malignancies, liver failure, and other non-malignant diseases. The cause of this phenomenon is still unknown. Fluid leakage from blood vessels and decreased reabsorption by lymphatics and blood vessels, are probably implicated. Activation of the plasma contact system generates vasoactive mediators, like bradykinin, which may play a role in the accumulation of ascites. This system include the zymogens FXII, FXI, and prekallikrein and the protein cofactor H-kininogen which liberates bradykinin. The inhibitors  $\alpha_2$ -macroglobulin, C1-inhibitor, and  $\alpha_1$ -protease inhibitor regulate the contact system.

We have demonstrated the presence of all the necessary components of the contact system in ascites from patients with gastrointestinal cancer as well as patients with non-malignant liver disease. These studies indicated that the contact system was activated in the malignancy-related ascites, that kallikrein was generated, and that some bradykinin was released *in vivo*. We have also studied the possible activation of the system in ascites by addition of dextran sulphate *in vitro*. It was concluded that malignancy-related ascites allow contact activation to occur, while the benign ascites does not. Our studies also disclosed a high functional level of the contact system inhibitors in malignancy-related ascites. In further studies functional assays for  $\alpha_2$ -macroglobulin, C1-inhibitor, and  $\alpha_1$ -protease inhibitor, and determination of total proteins in ascites, appeared to be very informative tests for the differential diagnosis of ascites.

In malignancy-related ascites the contact system is activated and the permeability increasing peptide bradykinin is released. This may contribute to the accumulation of ascites. Studies of the contact system may give more in-

formation about the mechanisms of ascites accumulation. Furthermore, the contact system inhibitors appear useful for the differential diagnosis of ascites.

### 1090 Familial Adenomatous Polyposis: Establishment of a County Polyposis Register in Romania

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The superior aim of polyposis register is to improve the prognosis of polyposis patients though an early diagnosis and prophylactic treatment. In the early 1991 reviewed the charts of familial adenomatous polyposis recorded at the referral Center of Gastroenterology, Fundeni Hospital, between 1977-1992 and initiated a Polyposis Register. The detailed register comprises: ascertainment of probands, registration of polyposis patients and their family members, construction of pedigrees, identification of family members at risk, surveillance programme, surgical prophylactic treatment option. We used a plentiful methodological arsenal: clinical examination, digestive endoscopy, retinal fluorescein angiography, barium enema, X-ray study of jaw, skull, bones, pathology studies, and cytogenetics studies. Since the initiation of our Polyposis Register we identified 31 probands, 59 "call-up" cases and overall 93 at risk members. Due to screening procedures performed in the at risk persons according with Eurofap programme - 16 polyposis patients were newly diagnosed. Mean age at diagnosis differed significantly between groups being 37 in the group of probands and 18 in the group of at risk patients. Specific follow-up schedules were initiated 11 from 16 patients underwent surgical therapy: 7 proctocolectomy - ileo-anal anastomosis, 3 proctocolectomy - ileostomy, 1 limited resection (disseminated colon cancer - CC). Considering these results we energetic promulgate the need for polyposis registers; the effect of a systematic screening of family members at risk is the low to null incidence of CC, strongly improving the prognosis in this limited but high risk class for CC.

### 1091 Chromosome Sensitivity to Bleomycin-Induced Mutagenesis, in Lymphocytes from Colorectal Cancer Patients Under the Age of 40

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The incidence of colorectal cancer (CRC) in young adults below 40 years of age is rare, these patients may have a genetic background. We studied chromosomal fragility in peripheral blood lymphocytes from patients with CRC, under the age of 40. Lymphocytes were examined from 24 subjects; ten untreated CRC patients under the age of 40 and 14 age matched controls. The mean number of spontaneous chromosomal breaks per cells (b/c) was significantly higher in the right sided CRC patients ( $0.23 \pm 0.12$  b/c) compared to the control group ( $0.09 \pm 0.04$  b/c;  $P < 0.01$ ), but with no significant difference between the left sided CRC patients and the control group. Lymphocytes exposed to the radiomimetic agent-bleomycin, were arrested in metaphase and analyzed for chromosome fragility. Mean chromosome breaks per cell in the left sided CRC patients ( $1.60 \pm 0.49$  b/c) were significantly higher than in either controls ( $0.72 \pm 0.31$  b/c;  $P < 0.001$ ), or the right sided CRC patients ( $0.91 \pm 0.24$  b/c;  $P < 0.01$ ).

The increased spontaneous chromosomal breaks in the right colon as opposed to the increased mutagen-induced chromosomal breaks in the left colon might indicate that in young CRC patients, the occurrence of right sided colon is more likely to be genetically determined, whereas in the left sided CRC environmental carcinogens might play a greater role.

### 1092 Arginase Activity of Normal and Diseased Colorectal Mucosa

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Arginase converts L-arginine to urea and ornithine, the key precursor for putrescine and polyamine biosynthesis.

Endoscopic biopsies were obtained during colonoscopy from 86 subjects. Histology was evaluated in alternate biopsies obtained during the same introduction of the forceps. In additional 15 subjects biopsies from cancer, the adjacent mucosa (AM-up to 2 cm from the tumour margin) and distant mucosa (DM-more than 5 cm from the tumour) were analyzed. Arginase activity was assayed by ornithine determination (ninhhydrin method, 515 nm) after incubation of tissue homogenates with L-arginine for 2 hours at 37°C. Soluble protein was determined by the Lowry method. The activity was expressed

in micromoles of ornithine/min/g protein (U/g). Statistical analysis included logarithmic transformation of data because of their asymmetric distribution.

The following mean values of arginase activity (U/g) were found: normal mucosa (NM) 95.6, anastomosis after curative colon resection for cancer (AN) 128.8, adenoma (AD) 209.8, carcinoma (CA) 812.2, idiopathic proctocolitis (IPC) 400.6, Crohn's disease of the colon (CD) 1302.8. The mean values of the following groups were significantly different ( $p < 0.05$ ): (1) AD-NM, (2) CA-AD-AN-NM, (3) IPC-AN-NM, (4) CD-IPC-AD-AN-NM. Determination of arginase in cancer and surrounding mucosa revealed the following mean values: CA 541.4, AM 162.9, DM 94.7. The mean value of CA was significantly different ( $p < 0.05$ ) both from AM and DM.

This is the first description of distinctly increased arginase activity of the colorectal mucosa in inflammatory bowel disease. Arginase may well reflect the proliferative activity in neoplastic as well as inflammatory conditions of the bowel mucosa. The gradient of arginase activity in bowel cancer and the surrounding mucosa requires further investigation.

### 1093 Significance of Strip Biopsy in Cases of Colorectal Flat Lesions

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Small colorectal neoplasms with slightly depressed or flat appearance are often found by means of endoscopic examination. Seventy-nine lesions were observed by colonoscopy using indigocarmine contrast method. The colonoscopic findings of these lesions were Ila + IIc type in 7 cases, Ila type in 34 cases, I + Ila type in 2 cases, I type in 1 case, Is (sessile) type in 32 cases and crepey type in 3 cases. The diameter of these lesions ranged from 3 to 22 mm. They were resected by strip biopsy without any technical hazards. Resected specimens were observed under dissecting stereomicroscope and were cut along the maximal diameter line to get correct histological diagnosis. Histological diagnosis of these lesions was carcinoma, adenoma or hyperplastic polyp. Incidence of carcinoma was 57% (4/7) in Ila + IIc type, 15% (5/34) in Ila type, 50% (1/2) in I + Ila type, 100% (1/1) in I type, 0% (0/32) in Is type and 0% (0/3) in crepey type.

These results indicate that colorectal neoplasms with slightly depressed appearance, which correspond to IIc in endoscopic appearance, have a high potential of malignancy even in minute size. Therefore strip biopsy is recommended for such colorectal small depressed lesion as soon as possible.

### 1094 Colon Cancer Screening in Germany – Six Year Review

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Screening for colon cancer by fecal occult blood testing (Hemoccult) was started in Germany 1977 as part of an annual cancer checkup. This checkup is offered free of charge to all adults covered by statutory health insurance. For the 6 years 1985–1990 the results are now available. On average, 10% of the men and 22% of the women age >45 years eligible participate. Women screen much more regularly and most often in the age group 45–54. Men participate mainly in the age group 55–64. The fecal occult blood test is positive in 0.9% of women and 1.9% of men, rising gradually with age in both sexes. About 75% of the positive screenees have an appropriate diagnostic workup. A total of ~1,500 colorectal cancers are found annually, 0.1/1000 female and 0.8/1000 male screenees; positive predictive value for cancer 1.4% in women and 4.2% in men. Polyps are not registered. Stage of cancers traced and the effect of this screening on mortality are not known, since there is no cancer registry and strict data protection rules prevent such analysis. However, the effectiveness of this screening can be assessed indirectly from a characteristic dependance of positivity and case detection rates on the screening interval. In all age groups these rates are highest on the first screening. There is a sharp drop when rescreening is done after 1 year (and treatment of initial bleeding sources). Rescreening after a 2 year interval shows a rise and rescreening after 3 years has detection rates as in initial screening. Also, the total number of cancers found has decreased gradually over the 6 years in this repeatedly screened population.

**Conclusion:** Repeated fecal occult blood screening is effective in successively removing colorectal cancer from a participating population. Annually repeated screening appears to be necessary to achieve this result.

### 1095 Hepatic Resection for Colorectal Liver Metastases

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The lack of other effective treatment for colorectal liver metastases makes hepatic resection a primary treatment consideration in appropriate cases. Between January 1980 and December 1990, 26 selected patients with liver

colorectal metastases who underwent hepatic resection were reviewed. The age, sex, site of primary lesion, histological grade, lymph node involvement, location, size, and number of hepatic metastases, type of hepatic resection, and preoperative CEA blood levels were documented. Complete removal with histologically negative resection margins was accomplished in 24 patients. The extent of resection performed was hepatic lobectomy in 12 patients, segmentectomy in 8 patients and wedge resection in 4 patients. The 5 year survival rate was 30.5 percent. Patients with metachronous metastases showed a better survival rate than those with synchronous lesions – 46.6 percent versus 13.6 percent respectively ( $p = 0.08$ ). None of the other factors studied showed a significant effect on survival. All patients were followed from the time of hepatic resection to the time of this study or death. During a median follow-up of 30.9 months, 20 patients developed recurrence of their disease. Patterns of recurrence included liver (8), liver and extrahepatic sites (4), lungs (4), and periaortic lymph nodes (1). In 3 patients who died from their disease there was no available data. There was no perioperative mortality. Morbidity arose in 66.6 percent of patients with a majority of the complications being minor. Even after "curative" hepatic resection, the liver remains the principal site of recurrence (60% in our series) which indicates the systemic nature of the disease in most of our patients. We conclude that hepatic resection can be performed safely enough to be recommended in selected patients.

### 1096 Malignant Potential of Colorectal Adenomas with a Diameter of Less Than 5 mm

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It is widely accepted that most colorectal carcinomas develop within pre-existing adenomas. Nevertheless there is at present no general agreement concerning the premalignant properties of small adenomas. Because of their high prevalence in western populations exact data on their malignant potential are of great importance to evaluate the merits of programs for prevention of colorectal cancer.

To assess the malignant potential of colorectal adenomas 7,963 polyps removed during 27,602 consecutive colonoscopies at our department from 1978 to 1992 were included in this study. From 7,552 polyps examined histologically 5,796 (76.7%) were classified as adenomas. For statistical evaluation adenomas were divided into the following classes: Adenoma size was classified as small (<5 mm), medium (5–10 mm) or large (>10 mm). Using the system of Morson dysplasia was categorized as mild, moderate or severe.

The overall prevalence of severe dysplasia or invasive carcinoma in adenomas <10 mm was 7.8%. In the class of adenomas <5 mm severe dysplasia was detected in 3.4%.

Facing the considerable percentage of severe dysplasia occurring in small adenomas we conclude that removal of small adenomas may reduce the risk of colorectal cancer.

### 1097 The Combined Chemotherapy in Colorectal and Pancreatic Carcinoma (5-FU, Folinic Acid and Interferon)

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**Objective:** The treatment of advanced colorectal cancer has improved in the last years. Clinical trials attempting to modulate 5-FU by folinic acid (FA) and interferon (IF) have demonstrated improvements in objective response rates compared with single-agent 5-FU). This combined modality therapy has also activity in pancreatic cancer.

**Materials and Methods:** 32 patients with colorectal cancer and 21 patients with pancreatic cancer received 6 cycles of combined chemotherapy (5-FU, FA, IF).

**Results:** Of the 32 patients with colorectal cancer, one had a complete response, and 10 had partial responses. The overall response rate was 34.3%. The median length of survival of all patients with colorectal cancer enrolled in this study was 10.5 months.

Of the 21 patients with pancreatic carcinoma no complete/partial response was registered. 12 patients (57.1%) had a stable tumour disease, one had a minor response. The median length of survival of all patients with pancreatic cancer was 6.9 months.

The superiority of the 5-FU/FA/IFN-combination is reflected by interval-to-progression, tumor response, weight gain (50% and 42.8%), relief of symptoms (pain) (37.5% and 47.6%) and improvement in performance status (46.8% and 28.5%).

**Conclusion:** As a single agent, 5-FU has produced response rates of approximately 20%. Based on initial encouraging results of the combination of 5-FU with FA and IF in the treatment of advanced colorectal cancer, the combined therapy was used 21 patients with pancreatic cancer and showed good therapeutic activity.

### 1098 Diagnosis of Periapillary Carcinoma: Evaluation of Ultrasound, Computed Tomography and ERC/PTC

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**Aim of the study:** Resectability of periapillary carcinomas depends mainly on the extension of the tumour mass. We compared the value of ultrasonography, computed tomography and ERC/PTC in demonstrating the tumour itself.

**Method:** In 50 patients with periapillary carcinomas Ultrasound (US), Computed Tomography (CT) and ERC or PTC was performed. Diagnosis was verified by biopsy, surgery, autopsy or observation of the clinical course.

**Results:** The level of biliary obstruction correctly was indicated by US and CT in 93% of the cases. The pancreatic duct was dilated in 77% of patients, in all of whom both methods had a diagnostic accuracy of 100%. ERC/PTC was used as gold standard. Correct visualisation of the tumour itself was possible in 36% by US and 48% by CT. ERC/PTC identified intraductal tumour growth in all patients.

**Conclusion:** Although the level of obstruction of the main biliary and pancreatic duct accurately can be identified by US and CT, the tumour itself cannot be visualized in 52% of the cases.

### 1099 Prognostic Parameters in Patients with Periapillary Carcinoma

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**Purpose of the study:** In patients with periapillary carcinoma the decision between surgical and endoscopic therapy must consider the individual prognosis of the patient. We studied the prognostic value of some easily available parameters.

**Method:** Retrospective evaluation of the results of ERCP, clinical and chemical data in 50 patients with localized disease (i.e. without metastases) (age 44–89). Diagnosis was based on ERCP and verified by surgery, autopsy or observation of the clinical course.

**Results:** Loss of weight impaired three-years-survival-rate significantly from 23% to 3% ( $p = 0.04$ ). Bilirubin  $>15$  mg/dl on admission influenced prognosis significantly: Two-years-survival-rate 0% vs 32% ( $p < 0.04$ ). Complete obstruction of the main biliary duct (MBD) found by ERCP correlated with significant decrease of one-year-survival-rate compared with stenosis of the MBD: 0% vs 55% ( $p < 0.04$ ).

**Conclusion:** Loss of weight, bilirubin  $>15$  mg/dl on admission and complete obstruction of the main biliary duct in ERCP are criteria of bad prognosis in patients with localised periapillary carcinoma and therefore should be considered in deciding between surgical and endoscopic therapy.

### 1100 Efficacy of Sulindac in the Colon of Genetically Proven Familial Adenomatous Polyposis (FAP)

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According to some recent publications, Sulindac (a NSAID-preparation) induces a marked regression of polyps in the distal colon or rectum of FAP-patients. However, only few data exist regarding polyp regression in the entire colon, because efficacy of therapy is monitored mainly by rectosigmoidoscopy.

**Methods:** In a prospective trial 10 FAP-patients (6 m; 15 to 73 yrs) received Sulindac  $3 \times 100$  mg/d for 4 months. 8 patients had an intact colon and 2 patients had a right-sided hemicolectomy. Before and after treatment all patients underwent colonoscopy which was recorded on videotape for blinded control. The number and size of polyps were assessed. Biopsy samples were taken for histology in particular for grading of dysplasia (I–III). So far 8 patients have been analyzed for the adenomatous polyposis coli- (APC-) gene by linkage analysis and/or direct testing for the mutation.

**Results:** The mean number of polyps per patient in the entire colon decreased significantly from 158.5 to 19.1 (i.e. by  $87.8\% \pm 9.0$ ) ( $p = 0.001$ ). In the subgroup of 8 patients with intact colon, the mean number of polyps in the right-side colon decreased from 116.3 to 0.1 (i.e. by  $98.8\% \pm 3.3$ ) ( $p = 0.001$ ) compared to the left-side colon from 77.5 to 21.5 (i.e. by  $76.1\% \pm 18.2$ ) ( $p = 0.001$ ). There was only 1 polyp left in the right-side colon in 1 out of 8 patients after treatment. In the entire series the mean diameter of the largest polyps was reduced significantly from 5.4 to 3.2 mm (i.e. by  $36.5\% \pm 20.6$ ) ( $p = 0.001$ ). The histology of polyp specimens showed a lesser degree of dysplasia in 50% (5/10) of patients after treatment.

**Conclusions:** Sulindac is very effective in inducing polyp regression in genetically proven FAP-patients regarding the number, size and histological staging of the adenomas. The most significant effect was observed in the proximal colon.

### 1101 Early Detection of Cancer in Ulcerative Colitis Based on Colonoscopic Surveillance

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The aim of this study was to evaluate risk factors, management and diagnostic problems of colon cancer in U.C. based on a long-term prospective follow-up. **Methods:** 189 patients with U.C. (103 males, 86 females, mean age at onset 34, at presentation 38) entered a long-term follow-up (mean 12.5, range 8.0–24.5 years) including colonoscopies with multiple biopsies every 2–3 years after duration shorter than 10 years, every year after 10–20 years or more, individually with sigmoidoscopies during intervals. In cases of dysplasia colonoscopy was repeated after 6–9 months in mild, 3–6 months in moderate and within 3 months in severe findings. **Results:** During the follow-up colon cancer was diagnosed in 9 patients: none in distal colitis (60), 3 in left-sided (68) and 6 total colitis (60 cases); in one case after less than 10 years (62), in 5 at 10–20 years (62) and 3 after more than 20 years (28 cases). The cumulative risk was highest in total colitis after more than 20 years. Actuarial analysis showed a significantly higher risk at 10–20 and particularly after 20 years than in corresponding populations. In all the cancer cases dysplasia of various degrees was found; the diagnosis of cancer before surgery was clear-cut in 3 cases, in the remaining 6 indication for surgery was based on repeatedly found marked dysplasia and/or associated macroscopic lesions. The cancers were type Dukes A or B in 8 cases and C in one case. A cumulative risk of dysplasia with duration occurred in the patients without cancer. **Conclusions:** The risk of cancer in U.C. increases with duration and extent; colonoscopic surveillance with careful evaluation of macro- and microscopic findings is justified to achieve an early diagnosis.

### 1102 Importance of Colonoscopic Screening in Hereditary Non-Polyposis Colon Cancer /HNPCC/

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The identification of Lynch syndromes (Hereditary non-polyposis colon cancer – HNPCC) offers the possibility of early detection of colon cancer based on colonoscopic screening. **The aim of the study** was to evaluate results of colonoscopic screening in HNPCC in comparison with colonoscopic findings in symptomatic subjects with genetic characteristics of this syndrome. **Methods:** Colonoscopic screening was started in 339 asymptomatic subjects (mean age 47) conforming with criteria of HNPCC and colonoscopic surveillance continued for 11 years. During this time colonoscopy was performed in 239 symptomatic subjects (age 59) in whom characteristics of HNPCC were detected at presentation. **Results:** In the screened group initial colonoscopy revealed cancer in 16.2% and adenomas in 32.1%, in the symptomatic group cancers in 61% (8% of them multicentric) and adenomas in 30% (villous structures twice as frequent as in the screened group). In the screened group 78% of the cancers and 73% of the adenomas were in the right colon, in the symptomatic group 58% and 52%, resp. The distribution of the individual risk – according to the number of direct cancer relatives – was similar in both groups, however, only slightly decreasing with a declining risk. Staging of cancers showed type Dukes A or B in 82% and C in 18% in the screened group; Dukes A or B in 67%, C in 18% and D in 15% in the symptomatic group. Surgery was palliative in 22% of the symptomatic and in no case of the screened group. 65% of the symptomatic and all of the screened group showed 5 year survival. **Conclusions:** Colonoscopic screening in HNPCC with detection of lesions prior to symptoms appears to be fully justified to achieve an early diagnosis of colon tumours.

### 1103 Interferon and Embolization in Mid-Gut Carcinoid

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To study the effect of interferon and embolization of liver metastases on tumour markers and survival, 42 patients (pts) with midgut carcinoid tumour and liver metastases were embolized when technically possible. Subsequently, all patients received  $\alpha$ -2b-Interferon.

During the first year three patients died, five interrupted the treatment due to side effects. Mean 5-HIAA was significantly reduced in the embolized patients (501 to 206 vs. 393 to 307) mmol/24 h and grouped by this variable, 15 pt (36%) showed objective response. Grouped by CT measurement of the largest liver metastasis only embolized pts were responders. To elucidate the contribution of each treatment, patients who were responders or had stable disease by 5-HIAA were randomly assigned to continue or stop interferon. Only pts who continued, maintained low 5-HIAA values: mean (95% confidence interval (CI): 212 (110–604) vs. 419 (140–1693) mmol/24 h. At 1/5-93

when all pts had been observed for at least two years Kaplan-Meier curves for these two groups showed significantly prolonged survival in the interferon treated pts. From diagnosis mean survival in those who continued was  $178 \pm SE28.5$  months and in those who stopped  $76 \pm SE16.8$  months ( $p < 0.05$ ). Mean survival for all pts with the carcinoid syndrome from diagnosis was  $107 \pm SE15.6$  months.

Our study show that embolization induces objective reduction in tumour size, however, no certain effect on survival was demonstrable. Also, in pts who tolerate and continue interferon therapy, response by tumour markers and survival, is superior compared to pts who were assigned to stop this treatment.

### 1104 Carcinoid Heart Disease

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To study carcinoid heart disease, 42 consecutive patients (pts), 30 females and 12 males, median age 63 years (23–75) years with histologically verified midgut tumour, liver metastases and urinary 24-h 5-hydroxy indol acetic acid (5-HIAA) above 50 mmol were screened with M-mode, 2D and Doppler echocardiography.

All pts. had a left ventricular fractions exceeding 50%. Moderate to severe tricuspidal regurgitation (TR) was diagnosed in 22 pts (61%). Mitral or aortic regurgitation occurred in nine (24%) and seven (19%) respectively. The mitral flow peak early (E) and late (A) velocity ratio was significantly decreased compared to age matched normal subjects. The group of pts. with 5-HIAA exceeding 1000 mmol/24 hours were characterized by significantly more patients with severe TR.

Our finding of frequent TR in carcinoid pts is in line with previous reports. However, a reduced left ventricular compliance as shown by the decrease in E/A-ratio, may indicate that the fibrosis known to occur in carcinoid disease with a preponderance for the right heart, even involve the left side. As serotonin is degraded in the lung circulation, other mediators like substance P and PDGF may be involved.

### 1105 Biennial Versus Quadrennial Colonoscopic Surveillance of Patients with Pedunculated and Small Sessile Tubular and Tubulovillous Adenomas

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It is unknown to what degree adenoma patients may benefit from any type of follow-up, but mortality from colorectal cancer will probably be reduced.

The present study was designed to demonstrate whether follow-up intervals could be extended from 2 to 4 years without increasing the risk of new significant neoplasia in patients with previous pedunculated and small sessile tubular and tubulovillous adenomas. Patients with villous adenomas and with sessile adenomas larger than 5 mm were excluded from the present study.

Six hundred and seventy-three patients have been included from 1981 to 1993 and randomised to either type of follow-up, so far accounting for 2,404 person-years of follow-up. More patients with new adenomas have been detected, using intervals of 2 years (81/332) instead of 4 years (61/341), (RR = 1.4, 1.0–1.8). However, the number of patients developing significant neoplasia (cancer, severe dysplasia, villous adenoma, adenomas larger than 10 mm) was not different (14/332 versus 14/341, RR = 1.0, 0.5–2.1). The last number included one cancer Dukes' A in the group with biennial examinations and two cancers, Dukes' B, in the group with quadrennial examinations. Perforation from colonoscopy occurred twice during biennial examinations and once during quadrennial examinations.

The present figures suggest that it is justified to prolong the intervals from 2 to 4 years between follow-up examinations during the initial 8 years after removal of pedunculated and small sessile tubular and tubulovillous adenomas.

### 1106 Alcohol, Cigarette and Coffee Consumption in Patients with Colorectal Adenomatous Polyps

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The relation between alcohol, cigarette, coffee consumption and Colorectal Adenomatous Polyps (CAP) is not well established. Aim of this study is to investigate the above relation in our patients.

**Patients-Methods:** We studied 89 consecutive patients (40 men, 49 women, mean age 66.3 years) with CAP without family history of polyposis, been diagnosed by colonoscopy and histology (group A) and 75 controls (42 men, 33 women, mean age 60.3 years) without evidence of polyps on colonoscopy (group B). We compare the average weekly consumption of al-

cohol and the daily consumption of cigarettes and coffee during the last two years in both groups by the Mann-Whitney U method correcting for the age and sex ratio.

**Results:** We found out that the consumption of alcohol was greater in group A (average 4.8 units\*) compared to group B (average 2.8 units,  $p < 0.005$ ). The consumption of cigarettes was moderately higher in group A ( $p < 0.05$ ) and the consumption of coffee was only slightly higher in group A. The relative risk of CAP for group A was approximately three times greater for alcohol consumption of 1–10 units and six times greater for consumption of more than 10 units, compared to controls. Concerning cigarette consumption the relative risk of CAP was almost double, compared to controls.

**Conclusion:** Alcohol and to a lesser extent, cigarette consumption possibly constitute significant factors for the presence of CAP and may be related to their pathogenesis. Coffee consumption was not found significant for CAP risk.

\*1 unit = 10 gr. Alcohol.

### 1107 Are Tumor Markers CEA, CA19-9 and CA72-4 Useful in the Follow-Up Patients with Cancer of Stomach?

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CA19-9 and CEA are reputed as tumor markers used in the diagnosis of stomach cancers. Tumor-associated glycoprotein CA72-4 is a high molecular weight glycoprotein found in the sera of patients diagnosed with gastrointestinal malignancies.

The aim of this study was to assess their individual and combined sensitivities and usefulness. Our studies were performed 67 patients (49 men and 18 women aged 27 to 80 years), with histologically diagnosed adenocarcinoma of the stomach.

Blood samples for tumor markers were collected from all patients 3 days before the surgery, 14 days after the surgery and every 1 month thereafter during clinical follow-up. Serum CEA, CA19-9 and CA125 were determined by EIA assay using kits Hoffmann-la-Roche (Austria), CA72-4 using EIA kits CIS Biointernational (France).

We have observed elevated levels of CEA (>5 ng/ml) in 31% patients, elevated levels of CA19-9 (>37 U/ml) in 42% patients and elevated levels of CA72-4 (>6 U/ml) in 40% patients.

Sensitivity of:	CEA and CA19-9	- 46%
	CEA and CA72-4	- 54%
	CA19-9 and CA72-4	- 49%
	CEA, CA19-9 and CA72-4	- 67%

We have observed that CA19-9 and CA72-4 elevated levels has been predicted clinical recurrent of the disease from 3 to 5 months.

**Conclusions:** (1) Serum levels of CEA, CA19-9 and CA72-4 are useful for follow-up patients with cancer of stomach.

(2) Serum elevated levels of high specific CA72-4 can provide an important and clinically useful information for the early appearance of the recurrent disease.

### 1108 Increased Urinary Copper Excretion in Cancer of the Digestive Tract

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Elevated urinary copper excretion is thought to represent a relatively specific laboratory marker of Wilson disease. However, in an experimental model of renal tubular necrosis an increase in urinary copper was demonstrated to accompany hyperzincuria. Hyperzincuria is known to be associated with a variety of pathological conditions, including cancer.

We have measured by atomic absorption spectrophotometry urinary zinc and copper concentrations in 31 patients with cancer of the digestive tract as well as 9 healthy controls. Urinary zinc and copper concentrations were expressed as zinc/creatinine and copper/creatinine ratios. Both urinary zinc and copper were significantly elevated in cancer patients compared to controls ( $2.08 \pm 1.47$  vs  $0.65 \pm 0.53$  mmol/mol creatinine and  $125 \pm 137$  vs  $32 \pm 10$  umol/mol creatinine; Mann-Whitney U test,  $P < 0.0005$  and  $P < 0.01$ , respectively). Urinary copper correlated with urinary zinc (Spearman rank correlation coefficient,  $r_s = 0.6049$ ,  $P < 0.005$ ).

We conclude that an increase in urinary copper excretion is not restricted to Wilson disease and appears to be present in a significant portion of cancer patients as well. Elevated urinary zinc and copper excretion may reflect renal tubular dysfunction associated with cancer.

### 1109 Different Renal Zinc Handling in Crohn's Disease and Colorectal Cancer

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Urinary zinc excretion is known to be elevated in cancer patients, but the mechanism involved is still a matter of discussion. Although urinary zinc is increased in many different disorders associated with systemic inflammatory response, it was reported to be normal in patients with Crohn's disease.

We have investigated urinary excretion of zinc and neopterin, an index of systemic immune activation, in 31 patients with colorectal cancer and 25 patients with Crohn's disease. Zinc was determined by atomic absorption spectrophotometry and neopterin was measured by high performance liquid chromatography; the resulting concentrations were expressed as zinc/creatinine and neopterin/creatinine ratio.

Urinary zinc excretion was significantly higher in colorectal cancer compared to both patients with Crohn's disease and 8 healthy controls ( $1.91 \pm 1.04$  vs  $0.66 \pm 0.38$  and  $0.52 \pm 0.31$  mmol/mol creatinine; Mann-Whitney U test,  $P < 0.0001$ ). On the other hand, the difference between the patients with Crohn's disease and the controls was not statistically significant. As expected, neopterin was elevated in both colorectal cancer and Crohn's disease ( $343 \pm 328$  and  $252 \pm 128$  vs  $157 \pm 45$  umol/mol creatinine;  $P < 0.005$  and  $P < 0.02$ , respectively). A significant correlation between urine zinc and neopterin was observed in colorectal cancer (Spearman rank correlation coefficient,  $r_s = 0.415$ ,  $P < 0.05$ ), but not in Crohn's disease.

Urinary zinc excretion is significantly elevated in colorectal cancer and this phenomenon may be linked to immune activation. The difference in renal zinc excretion between colorectal cancer and Crohn's disease could be explained by high prevalence of zinc deficiency in the latter. Measurement of urinary zinc may be, in certain circumstances, helpful diagnostically.

### 1110 Prevalence of Helicobacter Pylori (HP) in Gastric and in Non-Gastric Carcinoma Patients

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Aim of this study was to compare the seroprevalence of HP infection in gastric carcinoma (GC) versus non-gastric carcinoma (NGC) patients.

**Methods:** During a period of 28 months 228 GC (M/F: 136/92, age range 19–94; mean 69 yrs) were screened for HP. One hundred thirty five were in the antrum, 71 in the corpus and 22 in the fundus. The serological response to HP was assessed by measuring the IgG by ELISA. We also assess the seroprevalence of HP infection in 150 NGC patients (lung n = 36, breast n = 42, genitourinary n = 42, GI tract n = 12, others 18) (M/F: 76/74, age range 31–81; mean 56 yrs).

**Results:** The overall seroprevalence of HP infection in GC and in NGC was 76% and 56% respectively ( $P < 0.001$ ). The Table is showing the results according to age.

	GC	NGC	P
HP +ve < 60 years	44 (81%)	54 (58%)	0.001
HP +ve > 60 years	130 (75%)	30 (53%)	0.001

No difference was found between HP status and cancer site (78%, 73% and 73%: antrum, corpus and fundus respectively). 163 GC (123 HP+ve) were found to have an intestinal type, 56 (43 HP+ve) a diffuse and 9 (8 HP+ve) a lymphoma (NS).

**Conclusion:** 1. The overall seroprevalence of HP infection in GC patients is statistically higher compared to NGC patients.

2. According to age the higher seroprevalence was found in the younger GC patients.

3. No difference was found regarding HP status and cancer site and/or histological type.

### 1111 Intraoperative Peritoneal Lavage Cytology (IPLC) and Continuous Chemo-Hyperthermic Peritoneal Perfusion (CCHPP) Therapy for Advanced Gastric Cancer

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**Aim:** To evaluate the detectability of free cancer cells by IPLC and the effect of CCHPP for the prevention of peritoneal recurrence after surgery for gastric cancer penetrating the entire wall (serosal invasion). **Methods:** (1) IPLC: The Douglas' pouch was irrigated with 50 ml of warm saline immediately following laparotomy. The saline was collected, centrifuged (5 min at 1500 rpm). The sediment was prepared to slides and was stained with Papanicolou's. Either positive or negative cytology for free cancer cells was determined during surgery. (2) CCHPP: For IPLC positive patients, peritoneal irrigation was commenced immediately after the surgery. First, the peritoneal cavity was irrigated with warmed saline (43.5°C) at a rate of 1000 ml/min for 20 min. Then, the peritoneum was exposed for 60 min to warmed (43.5°C) circulating saline (total volume 4000 ml) containing 50 mg/l of CDDP and 10 mg/l of MMC. The temperature of the irrigating solution was continuously monitored at 3 sites in the intraperitoneal cavity and in the vicinity of the reconstructed (substituted) stomach. CCHPP was also performed, irrespective of the result of IPLC, for patients with a macroscopic serosal invasion larger than 4 cm in diameter. **Results:** (1) IPLC was performed in 233 patients with gastric cancer penetrating up to the serosa. The rate of occurrence of free cancer cells (positive IPLC) was 10.7% for the entire patients, 7.2% for the 172 resected patients and 13.1% for the 61 non-resected patients. Positive IPLC was seen in 11.9% of the 198 patients who had no macroscopic peritoneal dissemination and in 20% of the 100 patients who had histological serosal invasion. (2) CCHPP was adopted for 16 patients with either macroscopic or microscopic gastric serosal invasion. The cumulative survival rate for the patients with histological gastric serosal invasion was not related to positive/negative IPLC ( $p = 0.52$ ). CCHPP could not significantly prolong the survival for those with positive IPLC. **Conclusion:** We introduced CCHPP combined with IPLC as a prophylactic measure for peritoneal recurrence after surgery for gastric cancer. This modality, however, yielded only an equivocal result. Modification or combination of CCHPP with other methods should be investigated.

### 1112 Epidemiology of Gastric Cancer in Patients Diagnosed in Large Hospital in North-Western Part of Poland

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The aim of this study was to analyse the potential changes in gastric cancer (G.C.) localisation and G.C. dependence on patients' sex.

During the period of 1988–1992 at our hospital 13.088 endoscopies of upper digestive tract were performed. On the ground of macroscopic views confirmed by histopathology and in majority of cases cytology examinations 175 cases of G.C. were detected. 74% were recognized as adenocarcinoma and the rest as carcinoma solidum or planocellulare. The diagnosis was mostly established in patients who were in their fifties and sixties and there was no dependence on sex.

It was noticed that during above period the incidence of G.C. in females has been increasing and it was almost doubled in the last year of study (1992) compared to the first year (1988).

Considering the distribution of G.C. a strong tendency of "moving" cancer from the lower to the middle part of the stomach was observed. The number of G.C. located in corpus area was 2.3 times higher in 1992 in comparison with 1988, whereas constant decreasing of prepyloric and pyloric localisation was noticed.

The results of our study, especially these connected with G.C. distribution may suggest possible changes of aetiological factors in this cancer.

### 1113 Decreased Expression of Gap Junction Proteins in the Human Gastric Adenocarcinoma: An Immunohistochemical Study

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Most cells carry on their vital activities such as differentiation and proliferation by maintaining homeostasis through intercellular communications via the gap junction (GJ). Reduced gap junctional intercellular communication has been postulated to play a role in carcinogenesis. An immunohistochemical method was used to determine whether GJ in human gastric surface mucous cells play a role in the development of gastric adenocarcinoma.

**Materials and Methods:** We studied 7 patients with gastric adenocarcinoma (M/F: 6/1, age  $62 \pm 9$ ). Biopsy specimens were obtained endoscopically

from the cancer tissue, as well as the gastric mucosa of the greater curvature of the upper body and the antrum distant from the cancer. Specimens were immediately frozen by N<sub>2</sub>. Fresh frozen sections were examined for the presence of GJ by the ABC method using an anti-connexin 32 monoclonal antibody.

**Results:** GJ was not detected in the cancer tissue of all cases (0%), while it was detected in all the specimens in the non-cancerous distal sites of the body (100%) and also detected in 4 of the 7 specimens (43%) in the non-cancerous distal sites of the antrum.

	Cancer	Body	Antrum
+	0	7	3
GJ			
-	7	0	4
%	0	100	43

From these findings, one may hypothesize that a loss of intercellular communication via the GJ leads to the development of gastric adenocarcinoma.

### 1114 Diagnostic Difficulties in Gastric Cancer in the Era of Endoscopy

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A retrospective analysis was performed by the authors to study the possible correlation between the endoscopic appearance and histological type of gastric cancers diagnosed between 1983 and 1992 as well as the rate and type of false negative diagnoses and distribution of different histological types in stump cancer cases.

Data sheets of patients, detailed endoscopic and histologic descriptions were used for evaluation.

Out of 273 tumor cases (1.17% of all examinations) 261 proved to be carcinoma, 149 belonged to the intestinal, 84 to the diffuse and 28 to the unclassifiable type of cancers (Laurén's classification). Mean age was 61.1 yrs in the diffuse and 67.1 yrs in the intestinal histological groups. Endoscopic appearance was evaluated according to Mařatka's classification. In the groups of intestinal and unclassifiable tumors fungating type (III) was the dominant one (54.3% and 60.7%), ulceriform (II) and infiltrating (IV) appearance proved to be more typical to the diffuse histological type (40.5% and 25%).

After the first examination 28 out of 261 (10.7%) lesions were diagnosed macroscopically as benign ones. Benign ulcers and scars were the main endoscopic diagnoses in these cases. Primarily false endoscopic diagnosis was more frequent among cases with diffuse type tumors (17.85%), its occurrence was 7.4% and 7.1% in the two other groups. 9.6% of all cancers developed in the resected stomach of 18 male and 7 female patients. Cause of resection was ulcer disease in 68 and malignancy in 32 per cent of these cases. Histological type of cancer was dominantly intestinal in the "ulcer" group (11 out of 17).

It has been concluded that 1. in spite of the rapid technical improvements in GI endoscopy gastric cancers even in their advanced forms may cause diagnostic problems. The variability of their macroscopic appearance often misleads the investigator especially in cases of diffuse type tumors which often mimic the appearance of benign ulcers or by spreading under the mucosa can hardly be confirmed histologically. 2. beside careful evaluation of the clinical data repeated examination and use of complementary methods are often needed for the correct diagnosis.

### 1115 Clinical Features of Colorectal Cancers

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Cancer of the large bowel is very common particularly in developed countries. The clinical features are depended on the biological growth characteristics and by the location and stage of the cancer.

The aim of this study was to evaluate the frequency of each symptom in relation to the location of the tumor and to investigate whether there are changes between the decades 1965–1974 (group A) and 1975–1984 (group B). We also have investigated if there are any changes at tumor stages at the time of diagnosis between groups A and B. The total number of patients are 297 (group A 101, group B 196).

The results are shown in the following tables which described the most common symptoms and the tumor stages at the time of diagnosis.

Location	Symptoms			
	Anemia	Bleeding	Change in bowel habits	Weight loss
Cecum	26 (8.7%)		23 (7.7%)	18 (3%)
Ascending	23 (7.7%)	9 (3%)	20 (6.7%)	
Transverse & Descending	18 (6%)	14 (4.7%)	18 (6%)	
Sigmoid	34 (11.4%)	45 (15.1%)	46 (15.4%)	
Rectum	56 (18.8%)	101 (34%)	71 (23.9%)	

Stages	Group A	Group B
DUKES A	1 (0.1%)	15 (7.6%)
DUKES B	61 (60.6%)	108 (55%)
DUKES C	16 (16%)	28 (14.2%)
DUKES D	23 (22.0%)	45 (23%)

We conclude that the most common symptom for the Rectum and Sigmoid is the bleeding and for the Transverse-Descending, the ascending and the Cecum the Anemia. The second symptom is the change in bowel habits for all the large intestine. No statistical difference in tumor stage was noticed between the two groups. A disappointing fact is the high percentage of advanced stages in both groups, at the time of diagnosis.

### 1116 Which is the Role of Fibronectin and Alpha1 Antitrypsin in the Differential Diagnosis of Peritoneal Carcinomatosis?

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Differential diagnosis of ascites remains a challenge for physicians, and new diagnostic tests are investigated in order to evaluate it. Ascitic fluid Fibronectin is released as a product of tumour growth from neoplastic peritoneal macrophages. So is alpha1 antitrypsin as a major antiprotease able to inhibit the protease enzymes of transformed cells. Both have been evaluated as useful tests in the diagnosis of malignant ascites. Our study is proposed to assess the value of measuring Fibronectin (FN), and alpha1 antitrypsin (AAT) in ascitic fluid in the diagnosis of peritoneal carcinomatosis.

**Materials and methods:** A total of 111 consecutive ascitic patients admitted for the first time to the gastroenterology unit were studied. Patients were allocated to two groups: *Group I* consisted in 21 metastatic neoplasms to the peritoneum, confirmed by peritoneoscopy or histologic examination of peritoneal biopsies and/or a positive cytological examination in each. A second group (*Group II*) included 90 patients without peritoneal carcinomatosis, consisting of 56 uncomplicated cirrhosis, 10 cirrhosis with hepatocarcinoma, 21 spontaneous or secondary bacterial peritonitis, and 3 miscellaneous patients. We did not have any tuberculous peritonitis. Plasma and ascitic fibronectin levels were measured by automated Immunonephelometric test (Hoechst Ibérica, Marburg, Germany). The results of plasma and ascitic fluid FN, and AAT values were expressed in mg/dl as (mean  $\pm$  SD and range). **Results:** The cytological examination were positive for malignancy in 7/21 patients. Plasma fibronectin levels were  $42.9 \pm 31$  (range 1.9–142) in group I and  $26.4 \pm 23.9$  (range 4.7–215) for Group II. These differences are significant ( $p < 0.05$ ) in the ascitic fluid fibronectin values were *In Group 1*  $20.2 \pm 22$  (range 1.9–97), and in *Group 2*  $6.9 \pm 9.7$  (range 1.8–61), and these difference are also significant ( $p < 0.001$ ). Setting a cut-off point of more than 15 mcg/ml the *sensitivity* is 55.5%, the *specificity* 94.1%; the *positive predictive value* 66.6% and the *negative predictive value* of 90.9%. The results for *alpha1 antitrypsin* were: *Group 1:* serum AAT levels  $449 \pm 186$  (range 218–923) and  $316 \pm 105$  (range 119–652) in *Group 2*. These differences were significant ( $p < 0.05$ ). *Group 1:* In the ascitic study the AAT values were  $263 \pm 108$  (range 95–441), and in the *Group 2:*  $92 \pm 76$  (range 15–465), and also the difference were significant ( $p < 0.001$ ). Setting a cut-off point of more than 150 mg/dl the *sensitivity* were 78.5%, the *specificity* 86.3%, the *positive predictive value* 52.3% and the *negative predictive value* of 95.4%. If we used together both tests in the ascites study and classified as peritoneal carcinomatosis the patients with AAT > 150 and Fibronectin > 15 mg/dl, then *sensitivity* were 75%, the *specificity* 96.7%, the *predictive positive value* 81.8%, and the *predictive negative value* 95.1%. **Conclusions:** (1) The ascitic fluid Fibronectin is a simple test, with high specificity for early diagnosis of malignant ascites. (2) The ascitic fluid Alpha1 antitrypsin is also an easy to perform test, with higher rates of sensibility but lower specificity than ascitic fluid fibronectin for neoplastic ascites. (3) If we use both tests together the specificity and predictive negative values are improved for the proposal diagnosis. In our opinion these parameters may be reported to offer practical discrimination between malignant ascites and not so ones.



### 1117 5-Aminolaevulinic Acid as a New Photosensitiser for Photodynamic Therapy of Oesophageal, Duodenal and Colorectal Tumours

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5-aminolaevulinic acid (ALA) is a naturally occurring intermediary in the haem synthetic pathway. After systemic administration it induces transient endogenous accumulation of protoporphyrin IX (PPIX) predominantly in tumour and normal mucosa and has recently been exploited as a new photosensitising agent for photodynamic therapy. Eighteen patients with colorectal (8), duodenal (6) or oesophageal tumours (4) were studied. After 30–60 mg/kg of ALA administered orally biopsies of tumour and normal mucosa were taken 1–72 hours later. Patients stayed in subdued lighting for 24 hours after ALA. The specimens examined by fluorescence microscopy with digital quantification gave tissue levels of photosensitiser. Ten patients were given a second dose of ALA a few weeks later and their tumours were treated with red laser light from a gold vapour laser (50–100 J). The peak fluorescence of PPIX could be detected 4 to 6 hours after administration of ALA. In oesophageal and duodenal patients the tumour and normal mucosa fluorescences were similar and high in both localisations. In the large bowel the dose of 60 mg/kg was needed to obtain similar sensitisation. It also improved the tumour:normal mucosa ratio to 5:1. Of ten treated patients eight showed superficial mucosal necrosis in the areas exposed to laser light. Macroscopically tumours were covered with whitish necrosed material and histologically clear necrosis with fibrin exudate could be found. Six patients had transient rises in serum aspartate aminotransferases, 2 mild skin photosensitivity reactions and 5 mild nausea and vomiting. We conclude that photodynamic therapy with ALA may be a promising technique for the treatment of small tumours and areas of dysplasia.

### 1118 Prevalence of Hereditary Non Polyposis Colon Cancer: Prospective of Prevention

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The lack of colorectal cancer registry and disagreement of definition criteria interfere with evaluation of HNPCC prevalence. According to the criteria proposed by International Collaborative Group of Amsterdam, only two out of a series of 115 consecutive colorectal firstly diagnosed cancer patients (1.74%) had the minimum requisites: at least three family members with colorectal carcinoma; two of these mutual first-degree relatives in two different generations; at least one diagnosed before the age of 50 years.

Lynch however originally proposed the following criteria: vertical transmission; aggregation in sibling; early age at onset (<51 years); location in the right colon; multiple primary tumors; mucinous carcinoma. In our experience six criteria were verified in 1/115 patients; five and four in none; three in 1; two in 7; one in 36; none in 70 patients.

The poor HNPCC prevalence in our series, which is also confirmed by other few reports, could encourage protocols of secondary prevention, even in view of recently identified genetic markers.

### 1119 Selenium in Patients with Colorectal Cancer and Neoplastic Polyp

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Whether selenium deficiency is a primary aetiological factor or a paraneoplastic phenomenon is widely discussed. In the cases of patients with early cancer or/and precancerous lesion paraneoplastic effects can be negligible. The aim of this study was to select patients with colorectal cancers and colorectal polyps comparing their blood selenium concentrations, to examine the correlation between the blood selenium levels and histological types including the severity of dysplasia of polyps removed.

Subjects were examined colonoscopically and the final diagnosis was based on histology. All of the polyps were removed endoscopically. 51 patients with newly diagnosed colorectal cancer, 76 patients with colorectal polyp were examined. According to the histology of removed adenomatous polyps four groups were studied; comprising: a, 18 patients without any evidence of dysplasia or with moderate dysplasia, b, 20 patients with mean grade of the dysplasia, c, 21 patients with serious dysplasia or carcinoma in situ, d, 17 patients with villous adenoma. The control group consisted of 30 healthy donors of the local blood bank.

Selenium was determined by the fluorimetric method. The whole blood selenium levels were found to be significantly ( $p < 0.001$ ) lower in patients with colorectal cancer (mean:  $49 \pm 18$  ng/ml) and with villous adenoma (mean:  $45 \pm 19$  ng/ml) then those of blood donors (mean:  $64 \pm 19$  ng/ml).

There was no correlation between the blood selenium levels of patients with adenomatous polyp and the severity of dysplasia in removed polyps.

These findings suggest that selenium deficiency may play a role in the development of colorectal cancer arising from villous adenomas.

### 1120 Evolutivity of Digestive Endocrine Tumors (DET) and Their Metastases

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Treatment of DET depends on their evolutivity, which is claimed to be slow but has not been extensively studied. *Patients (pts) and methods.* 20 pts (12 M, 8 F, median age 49 years (20–75)) with a DET and followed at least 6 months were studied. Primaries were carcinoid tumors ( $n = 8$ ), gastrinomas ( $n = 6$ ), calcitoninoma ( $n = 1$ ) and non-secreting tumors ( $n = 5$ ); they were located in the pancreas ( $n = 11$ ), small bowel ( $n = 7$ ), rectum ( $n = 1$ ) and in a peripancreatic lymph node ( $n = 1$ ). 12/20 pts underwent surgical resection. Metastases were present in 19/20 pts, located in the liver (LM) in 18, peritoneum in 4, lymph-nodes in 2, bone in 1. LM were metachronous in 6 cases (median time from diagnosis: 36 months). Median follow-up was 25 (6–72) months; imaging techniques (CT scan 13, ultrasonography 3, endoscopic ultrasonography 1, MRI 3) were performed at the beginning and at the end of the follow-up period. 12 pts received antitumoral treatment: chemotherapy with streptozotocin-5 fluoro uracile in 9, chemoembolization for liver metastases in 6, somatostatin analogues in 6. Tumoral evolution was assessed according to WHO criteria.

*Results.* (1) *Liver metastases:* progression >25% (PROG), no change (NC) and objective responses (RO, >50%) were recorded in 78, 11 and 11% of the pts, respectively. PROG was observed in 75% of the 12 pts receiving antitumoral treatment after 24 (6–72) months, and in 83% of the 8 non-treated pts after 16.5 (6–72) months. (2) *Primary tumors* were evaluable in 8 pts not operated on: 5 NC (62%); 3 PROG. Four pts with LM had NC in the size of the primary tumor: LM progressed in all. (3) *Survival:* 1 pt died 24 months after LM diagnosis.

*Conclusion:* In this series of 20 consecutive pts, malignancy (= metastases) of DET is extremely frequent. Liver metastases increase in size in 3/4 pts after a 2-year follow-up. Such an increase is not influenced by cytotoxic treatment and is not paralleled by progression of the primary tumor.

### 1121 A Case-Control Study for Evaluating Occult Blood Screening for Colorectal Cancer Using Immunochemical Hemagglutination Test

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The efficacy of screening for colorectal cancer by Hemoccult test has been shown by means of a randomized controlled trial. The aim of this study is to evaluate the screening using immunochemical hemagglutination test (Hem-Sp®, Fujirebio Inc, Japan) which was shown to be better than Hemoccult test in both sensitivity and specificity (St. John, et al). *Methods:* A case-control study was conducted in the local municipalities where annual colon cancer screening by Hem-Sp had been performed since 1986 without previous colon cancer screening before 1986. A case was defined as a person died of colorectal cancer during 1986–1992 in the persons who had been living in the town and was diagnosed after the screening had been started. Three controls were selected randomly from the registry file of the inhabitants of 1986, matched by sex, by year of birth and by residential area for each case. Screening histories were compared between a case and the controls within 1, 2, 3, 4 and 5 years before the date of diagnosis of the case. Odds ratios of dying of colorectal cancer for screened versus non-screened individuals were calculated using conditional logistic regression analysis (SAS, PROC PHREG). *Results:* There were 179 cases and 537 controls. The odds ratios of dying of colorectal cancer for those having had screening history within 1, 2, 3, 4 and 5 years before case diagnosis were 0.46 (95% CI: 0.21–1.02), 0.45 (0.23–0.89), 0.50 (0.26–0.95), 0.72 (0.36–1.44) and 0.82 (0.37–1.81), respectively. A statistically significant reduction of odds ratios less than 1.0 were observed within 2 and 3 years before case diagnosis. The odds ratios increased towards 1.0 as extension of the duration during which screening histories were compared. Odds ratios also increased towards 1.0 as the number of years since most recent screening increased. *Conclusion:* Screening using immunochemical hemagglutination test is suggested to reduce colorectal cancer mortality by about 55%.

## 1122 Functional Gastric Impairment in Carcinoma Pancreas

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Controversy continues concerning the role of prophylactic gastric bypass in advanced carcinoma pancreas. Recent reports have questioned its role, since it is associated with significant morbidity – mainly delayed gastric emptying (DGE). The study was designed to objectively document gastric emptying (GE) patterns by radiolabelled solid meal, a) preoperatively in patients with carcinoma pancreas, and b) to compare the GE patterns in patients with carcinoma pancreas before and after a gastric bypass.

Gastric emptying studies were performed using indigenously prepared  $^{99m}\text{Tc}$  radiolabelled meal. The method was standardised and reproduced in 30 healthy volunteers. 18 patients with carcinoma pancreas were studied preoperatively and 8 of these were studied on day 7th postoperatively after gastric bypass surgery. Postoperative evaluation was also done for morbidity, mortality and for the time period for resumption of oral feeds.

The standard normal, gastric emptying  $t_{1/2}$  was  $84 \pm 13$  min in the healthy volunteers. 10/18 patients (55%) with carcinoma pancreas had a DGE,  $t_{1/2}$  range 116–400 min ( $199 \pm 85$  min). 8 patients with advanced carcinoma pancreas had the study performed pre and postoperatively. 5/8 had DGE preoperatively. There was no significant difference in GE patterns of these patients before and after a gastric bypass. Clinically, all patients resumed oral feeds on a mean 4.6 days (range 3–8 days). One patient (12.5%) had a clinically evident DGE.

The study objectively documents a preexisting gastric functional impairment in 55% of patients with carcinoma pancreas. This functional impairment persists inspite of a gastric drainage procedure. Routine prophylactic gastric drainage in carcinoma pancreas thus is not recommended.

## 1123 Prognostic Indicators in Malignant Large Bowel Obstruction

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**Purpose:** The outcome of patients undergoing curative surgery for obstructed colorectal cancer is poor, even in those surviving the postoperative period. Obstructing cancers behave in an aggressive manner, and the factors which influence tumour recurrence and death in these patients is unknown. The aim of this study was to identify clinical and pathological features associated with long term survival in obstructing colorectal cancers. **Methods:** Of 736 consecutive patients with colorectal cancer admitted to a single institution (1983–1991), 155 (21%) presented with bowel obstruction. 57 of these (37%) underwent palliative procedures or died in the postoperative period, and were excluded from study. The remaining 98 cases were included (M:F 52:46, mean age 69; range 44–87). Follow-up was complete to July 1993. 21 discrete clinical, operative, morphological and histological variables were studied. Clinical data were obtained from a prospective database. All histological slides were retrieved and examined by a pathologist blinded to clinical features and outcome. **Results:** 5 year cancer specific survival was 32% overall. Variables significantly related to poor outcome included tumour stage (Logrank analysis;  $p = 0.0001$ ) tumour necrosis ( $p = 0.0003$ ), poor tumour differentiation ( $p = 0.003$ ), mucin production ( $p = 0.008$ ), vascular invasion ( $p = 0.009$ ), perineural invasion ( $p = 0.009$ ), absence of a lymphocytic infiltrate ( $p = 0.02$ ) and the presence of concomitant bowel perforation (0.04). No other variables were significantly associated with survival. Regression analysis identified tumour stage (Relative risk (RR), 3.1;  $p = 0.0005$ ), bowel perforation (RR 3.4;  $p = 0.001$ ), mucin production (RR 2.8;  $p = 0.003$ ) and tumour differentiation (RR 2.0;  $p = 0.04$ ) as independent predictors of prognosis. From this analysis two groups emerged. Group 1 included 34 patients without poor prognostic features (5 year survival, 58%). Group 2 contained the remaining 64 patients with at least one poor prognostic feature (5 year survival, 16%) (logrank analysis;  $p < 0.00001$ ). **Conclusion:** Conventional prognostic indicators can identify the majority of patients with malignant large bowel obstruction who are at high risk of tumour recurrence and death. Such patients might reasonably be included into trials of adjuvant therapy in the future.

## 1124 Endosonographic (ENS) Evaluation of the Down-Staging Effect of Preoperative Radiotherapy on the N Stage in Rectal Carcinoma

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Preoperative radiotherapy in rectal carcinoma, reduces the T stage as previously shown by using ENS<sup>1</sup>. At that time, its effect on the N stage could not be demonstrated due to the limited number of patients. Here, ENS was used

again to evaluate the effect of radiotherapy on the N stage in a larger series of patients.

Comparison between ENS before and after radiotherapy could not be used as ENS staging after radiotherapy is poor. Thus initial ENS was compared to the pathology of the resected specimen for TN stage in patients treated with or without preoperative radiotherapy. From 1987 to 1993, 69 patients (all with uT2-UT4 tumor) were operated on for rectal carcinoma after radiotherapy (mean 35 Gy). During the same period, 40 patients (excluding uT1 tumor) were operated on without radiotherapy according to the choice of the referring physicians. The 2 groups were similar for age, sex, location of the tumor, but metastatic nodes were more frequently found in the radiotherapy group.

In controls, ENS accuracy was 75% for T and 77% for N. In the treated group, it was significantly inferior with 52% and 62% respectively. The discrepancy was explained by a higher rate of overstaging in the treated versus the control group: for T, 43.5 vs 17.5% and for N, 36.2 vs 12.5%. As the 2 groups were comparable, only a down-staging effect of radiotherapy, present in about 25% of patients could explain the results. Of several factors studied (age, gender, tumor location, delay between surgery and radiotherapy, initial T status), none affected clearly the frequency of the N down-staging.

Thus this study confirmed the down-staging effect of preoperative radiotherapy in rectal carcinoma for the T stage and demonstrated it for the N stage. Down-staging was found in about 25% of patients. Controlled studies are now needed to determine the survival and the rate of local recurrence in patients with and without a down-staging effect.

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## 1125 Chemo- and Radiotherapy in Esophageal Squamous Cell Carcinoma Invading the Tracheobronchial Tree

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In esophageal squamous cell carcinoma, invasion of the tracheobronchial tree induces a risk of fistula during treatment (endoscopy, chemotherapy or above all radiotherapy). Here was studied the survival and the risk of fistula in a series of patients with suspected invasion of the tracheobronchial tree, treated by non surgical multimodal protocols including radiotherapy.

From June 88 to March 93, 41 patients (mean age 53 yr) with an esophageal squamous cell carcinoma (upper,  $n = 20$ ; mid,  $n = 21$ ) were staged T4 (UJCC 1987) for invasion of the tracheobronchial tree. Invasion was demonstrated by endoscopic biopsies ( $n = 9$ ), or suspected at bronchoscopy (rigidity of the airway wall) ( $n = 18$ ), echoendoscopy ( $n = 9$ ) or CT scan ( $n = 5$ ). 34 patients were N1 and 7 M1 at initial staging. Multimodal protocol included endoscopic dilation if needed, chemotherapy (5 FU-CCDP) and Nd:YAG laser for 2 or 3 sessions and in case of tumor response, radiotherapy in split course associated with chemotherapy.

At the date point (October 93), only 4 patients, all with radiotherapy, were alive (follow-up: 7 to 27 months). A patient had only endoscopic dilation (immediate fistula). Only 40 patients received chemotherapy (1–10 sessions) and 21 radiotherapy. The reason for not giving radiotherapy in 19 was: fistula during chemotherapy in 5, no regression of secondaries in 6, of bronchial invasion in 7 and infection in 1. Mean survival of the 21 patients with radiotherapy was 9.5 months vs 3.5 in others. There were 2 late fistulas (9%). Thus radiotherapy was given in 1/9 (11%), 10/18 (56%) and 10/12 (71%), when invasion was diagnosed respectively by biopsies, by the wall pattern at bronchoscopy, and by imaging methods. Fistula were found respectively in 3 (33%), 4 (22%) and 1 (7%) in these 3 groups.

For cancer invading the tracheobronchial tree, chemotherapy followed when possible by radiotherapy can be used with an acceptable risk of fistula (20%) especially if bronchial biopsies are negative. This treatment is the only hope for a long survival.

## 1126 Assessment of Sucralfate Coating by Sequential Radionuclide Imaging in Radiation Induced Oesophageal Lesions

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The value of mucosal protection with sucralfate in patients with gastric ulceration is well documented. Although advocated as an effective treatment of oesophageal lesions as well, we found it to be of only limited value in dealing with radiation induced oesophagitis. Assuming that this might be due to inadequate mucosal "coating" we administered technetium-99m labelled sucralfate to 26 patients (18 M, 8 F); median age 67 yrs, with endoscopically proven ulcerative oesophagitis secondary to irradiation for oesophageal car-

cinoma (15 squamous cell carcinoma, 11 adenocarcinoma). Patients usually suffered from retrosternal pain ( $n = 17$ ), with the need for analgetics in 10 of them (38%). Some dysphagia was present in 18, but severe (liquids only) in 7 (27%).

The degree of sucralfate coating was evaluated on basis of the persistence of the radionuclide in the affected oesophageal segment. Scans were performed at regular intervals up till 120 minutes following administration of 150 MBq  $^{99m}\text{Tc}$  labelled sucralfate. Subsequently, additional oesophageal scanning using  $^{99}\text{Tc}$  colloid was performed in order to evaluate concomitant motility disorders or stenosis.

Abnormal scans were found in 24/26 patients (92%), although only for a limited period of time. In 11 patients (42%) residual radioactivity was observed for more than 30 minutes, and in only 4 (15%) for 1–2 hours. In 16 patients with a positive sucralfate test, the colloid scan was positive as well, indicating concomitant stenosis. The clinical response to sucralfate was minimal: only 8 patients (31%) noticed some, but not sufficient relief of retrosternal pain.

Our findings suggest that the inability of sucralfate to alleviate irradiation-induced odynophagia may be related to insufficiently lasting adherence of this compound to damaged oesophageal mucosa.

### 1127 High-Dose Rate (HDR) Intraluminal Irradiation for Esophageal Cancer in Clinical Practice

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In esophageal cancer intraluminal irradiation has been applied prior to or even without external radiotherapy for rapid tumor reduction and relief of dysphagia. Since the new High Dose Rate source (HDR) has become available the irradiation time could be reduced from several hours to 10 minutes resulting in a much more tolerable procedure from the patients point of view. To evaluate the palliative effect of HDR intraluminal irradiation we performed a prospective study in two groups of patients with esophageal obstruction. *Group A*: 45 pt with only locally advanced disease, no metastasis: 33 M, 12 F, median age 67 yrs; adenocarcinoma 20 pt; squamous cell carcinoma 24 pt. Treatment: 10 Gy HDR with  $^{192}\text{Ir}$ idium, 2 weeks rest followed by external beam irradiation of 40 Gy/4 weeks. *Group B*: 34 elderly pt in poor general condition and/or with distant metastasis: 19 M, 15 F, median age 74 yrs; adenocarcinoma 21 pt; squamous cell carcinoma 13 pt. Treatment: one session of 10 ( $n = 23$ ) or 12  $\frac{1}{2}$  Gy ( $n = 11$ ) HDR.

**Results:** *Group A*: tumor response as demonstrated by barium meal and/or endoscopy: 12 partial and 10 near-complete and 10 complete remissions (overall 71%). Improvement of dysphagia: 30 (67%). Side-effects: minor acute esophagitis 9, fistula 3. *Group B*: tumor response: 1 complete, 1 near-complete, 2 partial and 8 minor responses (35%). Subjective improvement: 53%. Side-effects: none. Duration of response: 3–4 months, almost equal to life expectancy.

**Conclusions:** 1. HDR is a safe and well tolerated procedure in patients with esophageal cancer. 2. Adequate palliation can be achieved by HDR alone in patients with a poor diagnosis. 3. HDR in combination with external beam irradiation results in effective tumor reduction and relief of dysphagia in patients with a more favorable prognosis due to only locally advanced disease.

### 1128 Expression of Epidermal Growth Factor (EGF) and Laminin (LN) in Colorectal Cancer with Liver Metastasis

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To evaluate biological activity of colorectal cancer, especially with liver metastasis, we investigate the expression of EGF for a marker of malignant character of cancer cell, and LN as one of the major component of basement membrane of cancer cell. Surgical specimens from primary lesions were examined using immunohistochemical techniques. Total number of the patients analyzed for this study is 98 free of liver metastasis at the time of operation. Among 98 patients, 24 patients were diagnosed liver metastasis during the follow-up. Immunoreactivity for EGF and LN were as follows; EGF(-)LN(-): 30 cases, EGF(-)LN(+): 16 cases, EGF(+ )LN(-): 35 cases and EGF(+ )LN(+): 17 cases. The incidence of liver metastasis in these cases were 23.3% (7/30), 6.3% (1/16), 31.4% (11/35), 29.4% (5/17) respectively. These results show the incidence of liver metastasis were significantly high in the cases of EGF(+ )LN(-) compared with the cases of EGF(-)LN(+). Then, how these immunoreagents are expressed in synchronous liver metastasis were examined in 49 patients. The results were as follows; EGF(-)LN(-): 22.4% (11/49), EGF(-)LN(+): 10.2% (5/49), EGF(+ )LN(-): 38.8% (19/49) and EGF(+ )LN(+): 28.6% (14/49). These are the same immunoreactivity as above asynchronous

liver metastasis cases. These results suggest the cases of EGF(+ )LN(-) are high risk group of liver metastasis. Liver metastasis is one of the most important prognostic factor of the patients with colorectal cancer. In order to improve survival rate, the cases of EGF(+ )LN(-) are necessary to make strict follow-up periodically.

### 1129 Detection of K-ras Gene Mutations in the Stool Sample of Patients with Colorectal Tumors

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**[Purpose]** The present study was made to inquire whether or not an examination of stool for K-ras mutation is clinically useful.

**Methods** The subjects were 36 patients with colorectal tumors (20 with adenoma and 16 with cancer). About 100 mg of stool was treated to digest protein. It was subsequently treated with Hexadecyl Trimethyl Ammonium Bromide. Using the purified DNA, K-ras Codon 12 mutation was detected, according to the Mutant-Allele-Specific Amplification technique (S Takeda et al., 1993). Stool samples showing positive mutation were subjected to dot-blot hybridization to determine the type of mutation. Stool collected after tumor resection and excised tumor tissues were subjected to dot-blot hybridization.

**Results** (1) Mutation in tumor tissue was detected in 6 (30.0%) of 20 adenoma patients. Of these 6 cases, 3 (50.0%) showed mutation in stool. (2) Mutation in tumor tissue was detected in 5 (31.3%) of 16 cancer patients. Of these 5 cases, 4 (80.0%) showed mutation in stool. (3) There were no false positive cases (cases in which only stool showed positive mutation). (4) In 6 of 7 cases in which mutation was detected in both tissue and stool, the type of mutation was the same. None of the stool samples, collected after tumor resection, showed mutation.

**Conclusion** (1) No stool samples after tumor resection showed K-ras mutation, indicating a high correlation between this test and tumor. (2) There were no false positive cases, indicating a high specificity of this test.

### 1130 Photodynamic Therapy of Gastrointestinal Cancer

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Photodynamic therapy (PDT) is an investigational cancer treatment modality. The basis of this therapy involves the *in situ* activation by light of a photosensitizer accumulated in tumour and normal tissue causing cell death. The specificity of the PDT-effect correlates to the distribution of photosensitizer. Photofrin, the most widely used photosensitizer, offers limited tumour selectivity and causes cutaneous photosensitivity of 4–8 weeks duration. 5-aminolevulinic acid (ALA) is a natural precursor in the biosynthesis of haem, where both the conversion of glycine and succinyl co-enzyme A into ALA and the conversion of Protoporphyrin IX (PpIX) into haem are rate limiting steps. Exogenous ALA administered in excess overloads the natural regulatory mechanisms and the induced photosensitive PpIX accumulates with high specificity in epithelial tumour cells.

More than 1000 skin cancers, essentially basal cell carcinomas, have been treated with excellent result. Animal studies have shown that carcinomas deriving from both squamous, serosal and glandular epithelium are sensitive to this treatment modality. In view of these results we have explored the potential of PDT in three different types of gastrointestinal cancer.

Patients with oesofagial, gastric and colorectal tumours to whom surgery was contraindicated were endoscopically treated with either ALA- or Photofrin-based PDT. The light source was a copper vapour pumped dye laser and monochromatic light was transmitted by a quartz fiber. Complete response was observed in all three tumour types, some tumours recurred which was expected since neither light dosimetry nor ALA-dose were optimized. The observed destruction of adjacent normal tissue was limited due to the high specificity for tumour tissue, allowing this treatment to be repeated in case of partial response or recurrence. ALA given systemically was well tolerated, the patients presented a low transient increase of hepatic enzymes and a cutaneous photosensitivity of less than 24 hours.

Endoscopic photodynamic tumour treatment is in rapid development and has a potential in gastrointestinal oncology.

### 1131 Regional Chemotherapy for Liver Malignancies at Patients with Primary Gastrointestinal Neoplasms

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Most of the patients undergoing surgery for gastrointestinal malignancies

show regional and/or distant metastasis. In the Year 1992 734 patients were admitted for gastrointestinal malignant neoplasms, 53 of them for primary liver tumor. 24 of these patients underwent hepatic resection. 170 of the 734 patients also had liver metastasis. The patients having multi-organ distant spread of the disease are candidates for systemic chemotherapy. The patients having liver metastasis only are treated by means of locoregional arterial cytotoxic infusion. In all cases the diagnosis was confirmed by histological examination. The vented B. Braun Implantofix arterial cannula with port was inserted via the pancreaticoduodenal artery at the time of the primary operation or during separate surgery. For some of the patients angiographic method was used with or without subcutaneous port. In the period from 1985 to 1994 84 patients were treated via intra-arterial cannula. According to our analysis using the Kaplan Meyer formula the best survival i.e. 29 month could have been achieved at patients undergoing hepatic resection plus locoregional chemotherapy. The cumulative survival rate following any other method of treatment was less favorable, that means 11 to 18 months according to the method used.

### 1132 PCNA/Cyclin Defined Proliferative Activity in Colorectal Adenomatous Polyps

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Proliferative activity in 45 colorectal adenomatous polyps was evaluated with the use of immunochemistry and PCNA/cyclin monoclonal antibodies in alcohol fixed paraffin embedded sections. The size of polyps between various histologically classified groups of adenomas was also compared. All examined polyps were resected endoscopically from 40 patients. Proliferative activity was measured by the proliferation index.

No statistically significant differences in proliferation index between histologically classified groups of adenomas and between selected size groups of polyps were found.

Method using monoclonal antibodies to PCNA/cyclin in investigation of the proliferation activity in paraffin sections is recommended because of its technical and economical advantages.

### 1133 5-FU Modified Chemotherapy Following Surgical Resection for Large Bowel Cancer

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From 1982 to 1986, a randomized control study has been performed to investigate the chemotherapeutic effect of 5-fluorouracil (5-FU) regimen on resected colorectal carcinoma. 218 patients were randomly assigned to either 5-FU modified chemotherapy group or contral. 110 patients received modified chemotherapy of 5-FU "3.2.1" regimen. Totally the patients received 6 courses of treatment. The first course started on 14th day after operation. During the first year, 3 courses were given at an interval of 12 weeks. During the second year, 2 courses were given at an interval of 6 months. In the third year only one course was given. The patient's 5-year survival rate in this group was 80.6% with the rate in the stage B and C being 86.0% and 64.7% respectively, which were significantly higher than those in surgery alone ( $P < 0.01$ ), and other surgery plus routine chemotherapy regimens (including 5-fluorouracil routine regimen, combination of chemotherapy with 5-fluorouracil and chemoimmunotherapy with 5-fluorouracil plus levamisole) with P value being less than 0.05. We conclude that the modified chemotherapeutic regimen of 5-FU "3.2.1" has good efficacy and safety in the treatment of patients with colorectal cancer in clinical practice. The results also strongly suggest that the 5-FU modified chemotherapy is the best one at present.

### 1134 Fedotazine Versus Metoclopramide in Functional Dyspepsia: Results of a 6 Week Multicenter Therapeutic Trial

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Efficacy and safety of fedotazine (FZ), a peripheral  $\kappa$  agonist, were compared to those of metoclopramide (MC) in patients with functional dyspepsia. *Methods.* 381 patients were entered into a phase III, double blind, parallel group, multicenter trial and fulfilled the following criteria: presence in the last 3 months, and at least 3 times a week, of 2 or more post-prandial dyspeptic symptoms: epigastric pain, early satiety, fullness or epigastric distension, nausea or vomiting, feeling of slow digestion. An underlying organic disease was ruled out through medical examination, gastroduodenoscopy, upper abdominal ultrasound and routine blood tests. Patients completed a diary card daily and rated the overall intensity of their symptoms (main end-point) as well as the intensity of each dyspeptic symptom using a 0 to 4 verbal scale. A quality of life (QoL) questionnaire [1] was completed before and after the

treatment period. At the end of a run-in period lasting 7 to 14 days, patients no longer meeting the inclusion criteria were excluded. 302 patients (172 females, 130 males, aged  $45 \pm 14$  yrs,  $m \pm SD$ ) were randomized to receive either oral FZ, 30 mg tid ( $n = 152$ ) or oral MC, 10 mg tid ( $n = 150$ ) during 6 weeks. Intent-to-treat analysis was performed. In the absence of a significant difference (ancova), an equivalence test was carried out. *Results.* FZ and MC treatment groups were comparable before treatment. The overall symptom intensity score was similarly improved with MC ( $1.80 \pm 0.56$  to  $1.28 \pm 0.64$ ) and FZ ( $1.79 \pm 0.70$  to  $1.30 \pm 0.71$ );  $p$  equivalence  $< 0.01$ . Score improvements for each dyspeptic symptom were also equivalent in both groups. Drug-related adverse events were significantly less common in the FZ group ( $12.0$  vs  $19.2\%$ ,  $p = 0.03$ ), notably for CNS adverse effects (somnia:  $2.6$  vs  $8.7\%$ , odd ratio:  $3.5$ ,  $p = 0.05$ ). There were significantly fewer treatment discontinuations for adverse events in the FZ group ( $4.6$  vs  $12.7\%$ ,  $p = 0.01$ ). Several items of the QoL questionnaire and multivariate analyses on all items showed a significantly greater improvement in the FZ group compared with the MC group ( $p < 0.05$ ). *Conclusion.* After a 6 week treatment, efficacy of fedotazine is equivalent to that of metoclopramide in the symptomatic relief of functional dyspepsia complaints. Fedotazine is better tolerated than metoclopramide and has a better effect on patients' quality of life.

[1] Gerin P et al. *Fundam Clin Pharmacol* 1992; 6: 263–276

### 1135 Is Combination of Neodym-Yag-Laser and Endocavitary Brachyradiation in Stenosing Esophageal Carcinoma Superior to Both Methods Uncombined?

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*Introduction:* Aim of all palliative therapy of inoperable esophageal carcinoma is to increase the quality of life by restoration or improvement of passage for oral nutrition. For this goal there exist different palliative procedures. Our work refers to the comparison of Nd-YAG-laser therapy and endocavitary afterloading respective the combination of both methods.

*Methods:* From 07/91 to 09/93 we divided randomly our patients with stenosing esophageal carcinoma in three groups. The indication for therapy was dysphagia, as consequence of which the caloric requirement could not be covered up. The patients with failure of the afterloading therapy were treated with combined therapy. Eighty four pts. (436 applications, mean 5.1, min 2 to max 9) were primarily treated with laser, 139 pts (488 applications, mean 3.5, min. 1 to max. 11) treated with afterloading and 52 pts. (122 applications, mean 2.3, min. 1 to max. 9) with the combination of both. 31% of the pts. were female, 69% male, the mean age was 68 years (37–89).

*Results:* The 52 pts. who were primarily assigned to afterloading but were treated further on in combination with laser therapy can be seen as therapy failures of the only afterloading therapy (37.4%). With comparable survival times of the three therapy groups (laser: 10.6 months, afterloading: 10.2 months, combination: 10.9 months) there was achieved a longer therapy interval with the combination of laser and afterloading (interval of laser application: 2.7 weeks, of afterloading 2 weeks and of the combination: 4.1 weeks). The complication of fistulation with lasertherapy was 2/84 pts. (2.38%), with afterloading 12/87 pts.: 13.80%.

*Conclusions:* In 37.4% of the patients where primarily an afterloading therapy failed a recanalisation was achieved with further laser application. In the group with the only lasertherapy all tumor stenoses could be opened primarily and permanently. Furthermore with the only afterloading therapy there was a six fold higher complication rate of fistula. The advantage of the combination therapy was the longer therapy interval.

### 1136 C3 Phenotypes and Cigarette Smoking in Patients with Duodenal Ulcer; Preliminary Results

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It has been reported an increased risk of Peptic Ulcer in people phenotypically C3FS and C3F [1]. In addition, the association of cigarette smoking with Duodenal Ulcer (DU) is known. In this study we looked for any relationship between cigarette smoking and C3 phenotypes in patients with DU in comparison with Healthy Controls (HC). 101 consecutive unrelated patients with DU (M: 74, W: 27, Mean age  $\pm SD$ :  $48.3 \pm 15$  years) and 95 unrelated HC (M: 60, W: 35, Mean age  $\pm SD$ :  $48.4 \pm 16$  years) well matched for socioeconomic status and area of origin were studied. Patients and controls were divided according to their smoking Habits in 4 groups: never smoked, ex-smokers (at least a year before), current smokers of 10–20 cigarettes/d, current smokers of more than 20 cigarettes/d. C3 phenotypes were determined as it was described [1]. "Statgraphics" was used for statistics. *Results:* C3 phenotypes