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World Congress on Gastrointestinal Cancer
AN EFFECTIVE SURVEILLANCE PROGRAMME FOR CLASSICAL BARRETT’S OESOPHAGUS IN A DISTRICT GENERAL HOSPITAL

A Olithselvan
Sjuh-Leeds, Leeds, United Kingdom

Aim: To review the effectiveness of an endoscopic surveillance programme for patients with Barrett’s oesophagus.

Methods: All patients with Barrett’s oesophagus over the period January 1997 to October 2002 were identified from endoscopic and histological records. Surveillance was performed with 2 yearly endoscopies and quadrantic biopsies at 3cm intervals in patients with classical Barrett’s oesophagus (>3cms histologically proven columnar lined oesophagus). Patients with lesser lengths of Barrett’s oesophagus, significant co-morbidity of age over 75 years were excluded. Dysplasia when identified led to repeat endoscopy at 3-6 weeks if high grade or 3-6 months if low grade.

Results: 121 patients (24%) entered the surveillance programme of 505 patients identified with Barrett’s oesophagus from January 1997 to October 2002 (70 months). 205 endoscopies were performed for surveillance with a mean period of surveillance of 3.5 years. The mean age at diagnosis was 60.2 years with Male(69.5%) predominance and a mean length of Barrett’s mucosa at the initial endoscopy of 7.5cms. 5 cases of high-grade dysplasia and 2 cases of adenocarcinoma were detected during the surveillance. One patient with HGD refused surgery and died 2 years latter of carcinoma oesophagus. The repeat biopsies in 3 out of the 4 remaining patients who initially had HGD showed frank adenocarcinoma. Preoperative CT scans were clear of local or metastatic spread. These 6 patients underwent radical oesophagectomy and 5 of the 6 resected specimens showed early (T1,N0) adenocarcinoma with the other showing HGD. All patients remain well and tumour free after 24 months. No interval oesophageal cancers occurred.

Conclusion: Our surveillance programme for Barrett’s oesophagus seems very efficient in detecting early carcinoma and seems to offer successful treatment without an excessive endoscopic workload. It stands in stark contrast to MacDonald’ study.1

Ref. 1 MacDonald CE, Wicks AC, Playford RJ. BMJ 2000; 321: 1252-5

MRNA EXPRESSION SIGNATURES OF COLORECTAL CANCERS WITH MICROSATELITE INSTABILITY DEMONSTRATE DISTINCT IMMUNOGENIC PROFILES

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2 Department of Pharmacogenomics, Bristol Myers Squibb, New Jersey, United States

Purpose of the study: Colorectal cancers displaying high-degree microsatellite instability (MSI-H) have an improved prognosis compared to microsatellite stable (MSS) cancers. The observation of pronounced lymphocytic infiltrates suggests that MSI-H cancers are inherently more immunogenic and the identification of MSI-related tumour associated antigens suggest specific immune responses may be active. Microarray analysis allows gene expression profiling across thousands of genes in a single experiment to produce a global gene expression signature. We aimed to compare the signatures of MSI-H and MSS colorectal cancers using fresh frozen tumour material to identify differences in immunomodulatory gene expression.

Methods: We analysed tissue from 159 colorectal cancer patients with full consent and Local Ethics Committee approval. Genomic DNA was analysed for microsatellite instability in the quasimonomorphic mononucleotide marker BAT-26. High-quality RNA was used for microarray analysis on the Affymetrix® HG-U133A chip (using Affymetrix® protocols) that analyses over 14,000 recognised genes. Data was analysed on GeneSpring software version 6.0. Confirmatory real-time RT-PCR was performed on 28 MSI-H and 26 MSS cancers.

Results and Conclusions: 29 (18.2%) colorectal cancers were identified as MSI-H. A comparison with 104 MSS cancers identified 2070 genes that were differentially expressed between the two groups [P<0.005, Benjamini and Hochberg False Discovery rate]. Discriminatory genes could successfully predict microsatellite status in over 80% of samples in training and test groups. Significantly, several key immunomodulatory genes were up-regulated in MSI-H cancers. These included antigen chaperone molecules (HSP-70, HSP-110, Calreticulin, gp96), pro-inflammatory cytokines (Interleukin (IL)-18, IL-15, IL-8, IL-24, IL-7) and cytotoxic mediators (Granulysin, Granzyme A). Quantitative RT-PCR confirmed up-regulation of HSP-70(1b) [P=0.016], HSP-110 [P=0.002], IL-18 [P=0.004], IL-8 [0.002] and Granulysin [P=0.0001]. The novel observation of Heat Shock Protein up-regulation in MSI-H cancer is highly significant in light of the recognised roles of these proteins in innate and antigen-specific immunogenicity. Increased mRNA levels of pro-inflammatory cytokines and cytotoxic mediators also indicate an activated anti-tumour immune response. This confirms the observation that lymphocytes infiltrating MSI-H colorectal cancer are activated and not anergic. MSI-H colorectal cancer may be a paradigm of an inherent antigen-specific immune response and its study may significantly advance our understanding of tumour immunology and development of immunotherapy strategies.
TUMOR M2-PK IN STOOL: A SCREENING TOOL FOR COLORECTAL CANCER

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2 Asklepios Clinic, Lich, Germany.

Introduction: Proliferating cells, especially tumor cells, express a special isoenzyme of pyruvate kinase, termed M2-PK which can occur in a tetrameric form with a high affinity to its substrate phosphoenolpyruvate (PEP) and in a dimeric form with a low PEP affinity (http://www.metabolic-database.com). In tumor cells the dimeric form is usually predominant and is therefore termed Tumor M2-PK. An ELISA with monoclonal antibodies against Tumor M2-PK in stool has been developed. Until now only non-specific screening tests for blood in the stool could give a hint of events related to colorectal cancer in about 30% of cases. The present study includes 331 patients that underwent complete colonoscopy after the determination of Tumor M2-PK in stool.

Materials and Methods: Stool samples of patients with colorectal cancer and patients without pathologic findings were tested. Tumor M2-PK in stool extracts was determined immunologically with a new quantitative sandwich-type enzyme immunoassay (ScheBo™ Tumor M2-PK™) which is based on two monoclonal antibodies (ScheBo® Biotech AG, Germany).

Results:

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<th>Groups</th>
<th>n</th>
<th>Mean [U/ml]</th>
<th>Median [U/ml]</th>
<th>Range [U/ml]</th>
<th>P vs. controls</th>
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<td>Colorectal Cancer</td>
<td>100</td>
<td>57.7 ± 11.4</td>
<td>16.4</td>
<td>0.7 – 800.0</td>
<td>p &lt; 0.001</td>
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<tr>
<td>Adenoma</td>
<td>107</td>
<td>4.9 ± 0.8</td>
<td>2.1</td>
<td>0.1 – 51.3</td>
<td>p ≥ 0.05</td>
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<tr>
<td>Controls</td>
<td>124</td>
<td>3.4 ± 0.5</td>
<td>1.6</td>
<td>0.1 – 30.6</td>
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Conclusion: The fecal levels of Tumor M2-PK are significantly higher in patients with colorectal cancer than in samples of patients with adenoma or healthy controls (p<0.001). A reference concentration of >4 U/ml corresponds to a sensitivity of 76% for colorectal cancer. Specificity was 78% for the control group. In comparison to a variety of indirect tests that detect blood in stool with a sensitivity less than 30% Tumor M2-PK has a much higher sensitivity. The test directly detects a tumor-specific enzyme that is released by the tumor itself. Tumor M2-PK has the potential as a screening tool for the early detection of colorectal cancer.
A PHASE I STUDY OF RHUMAB VEGF (BEVACIZUMAB) WITH CONCURRENT RADIOThERAPY AND CAPECITABINE IN LOCALLy ADVANCED PANCREATIC CANCER

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Background: Bevacizumab is a humanized monoclonal antibody that prevents the binding of VEGF-α to its receptors, VEGF-R-1 and R-2 (Flt-1 and KDR). Preclinical studies show that VEGF inhibition can increase radiosensitivity. Results from clinical trials of bevacizumab in combination with chemotherapy show promising activity against many different tumor types, including pancreatic cancer. This phase I trial was designed to study the safety of bevacizumab with chemoradiation in locally advanced pancreatic cancer. Correlative functional CT was planned to evaluate tumor blood flow changes.

Methods: Entry criteria included patients with locally advanced (T3N0-T3N1) or medically inoperable (T4N0) pancreatic adenocarcinoma based on CT criteria. Prior chemotherapy was allowed (≤3). Bevacizumab (5 mg/kg IV) was administered to all patients 2 weeks prior to the start of XRT (50.4 Gy treating the primary tumor and gross adenopathy), then every 2 weeks thereafter (2.5 mg/kg, n = 12, then 5 mg/kg n = 12). Capecitabine was administered continuously with radiotherapy on days 1-52 (650 mg/m² PO BID for the first 6 patients, then 825 mg/m² PO BID for the remaining patients. Patients with stable or responding disease were offered maintenance bevacizumab (5 mg/kg IV q 2 wks) until progression. Functional CT was performed on days 0, 14, and at the time of restaging (5 weeks after XRT).

Results: Twenty-four patients have completed treatment, 6 are under treatment. The worst acute gastrointestinal toxicity during chemoradiation was grade 2 (NCI CTC v3) in 9 (38%) and grade 3 in 2 (8%) of patients. Five patients (21%) had G2 hand and foot syndrome. There was one patient each with grade 3 DVT, hypertension and joint pain, and leucopenia, respectively. There have been 3 grade 3 bleeding episodes possibly related to bevacizumab (2 GI and 1 GU, none during chemoradiation. All patients completed radiotherapy (3 with < 5 day interruption), 10/24 (42%) had protocol-mandated 25% dose reductions of capecitabine due to grade 2 toxicity, and one dose of bevacizumab was held in one patient due to bleeding. Only one patient required hospitalization during chemoradiation. One of 12 patients treated at 2.5 mg/kg and 6 of 11 (56%) evaluable patients treated at 5 mg/kg achieved a partial response (50% reduction in maximum axial cross-sectional area). Only 1/23 patients (4%) have experienced objective local tumor progression. Based on functional CT, 3 patients had increased, one decreased, 2 no change in blood flow after the initial dose of bevacizumab. Eight patients’ scans were not interpretable due to artifacts secondary to organ motion, fluid/gas interface or biliary stents.

Conclusion: Treatment with this novel combination of bevacizumab and chemoradiation is well tolerated with encouraging activity at the 5 mg/kg level of bevacizumab in locally advanced pancreatic cancer patients. We plan to continue enrollment on this study at 7.5 mg/kg and 10 mg/kg of bevacizumab. Randomized studies are planned to evaluate this regimen in both the locally advanced and the adjuvant setting.

A RANDOMISED PHASE II MULTICENTER STUDY IN THE PALLIATIVE FIRST LINE TREATMENT OF PATIENTS WITH ADVANCED PANCREATIC CANCER WITH GEMCITABINE PLUS CAPACITABINE VERSUS GEMCITABINE PLUS OXALIPLATIN VERSUS CAPECITABINE PLUS OXALIPLATIN

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Objective: The evaluation of efficacy and toxicity of three different combination therapies, GemCap, GemOx and CapOx in the first line treatment of patients with advanced pancreatic cancer.

Patients and Methods: Of 165 planned patients, 159 pts have been included between June 2002 and February 2003 from 37 centres receiving either gemcitabine 1000mg/m² d 1+8 plus capecitabine 2000mg/ m² d1-14 (GemCap) or gemcitabine 1000mg/m² d 1+8 plus oxaliplatin 130mg/ m² d8 (GemOx) or capecitabine 2000mg/ m² d1-14 plus oxaliplatin 130mg/ m² d1 (CapOx). In each study arm treatment was repeated every three weeks. Progression free survival (PFS) was evaluated as primary study end-point.

Results: In December 2003 at the interim analysis 45, 44, 46 pts had been enrolled in to the respective treatment arms. Median age was 63 yrs (range 40-74), 92% of pts had a KPS>70% and 76% presented with metastatic disease. We performed a stratification with regard to KPS, and stage of disease and we found a good balance between the study arms. At the time of interim analysis, 263 treatment cycles were evaluable for toxicity. The overall bone marrow toxicity with regard to WHO grade 3 or 4 anemia, leukocytopenia and thrombocytopenia was low: 18%, 0%, 0% for GemCap, 0%, 5%, 15% for GemOx and 0%, 0%, 0% for CapOx, respectively. Alopecia WHO grade <2 occurred in 25% (GemCap), 32% (GemOx), 18% (CapOx). Palmar-plantar erythrodysesthesia WHO grade ≥2 was observed in 5% of pts. in the GemCap and CapOx arm.

Conclusion: At the time of interim analysis and at present the three regimens GemCap, GemOx and CapOx show a low profile of toxicity and are well tolerated.
O8
RESECTION OF PREVIOUSLY UNRESECTABLE LIVER METASTASES FROM COLORECTAL CANCER AFTER CHEMOTHERAPY WITH CPT-11/L-OHP/LV5FU: FINAL RESULTS OF A PROSPECTIVE PHASE II TRIAL.
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Purpose of the study. 5 year-survival after LMCRC resection is 30-35%. Folfiri and Folfox are standard regimens in MCRC. The triple combination Folfirinox as induction CT could improve tumor shrinkage and therefore could allow resection of LM in unresectable patients (pts). Summarized description of the project. Based on a multidisciplinary consensus, unresectability is defined as follows: LM in right or left lobe in contact of contralateral liver pedicle; LM in contact of veina cava or involving 2 hepatic veins and in contact with the third; liver remaining mass less than 25-30% of functional liver; no initial forseen optimal resection, but susceptible to become resectable after shrinkage. Biweekly 48h-cycles (Cy): L-OHP 85 mg/m2, CPT-11 180 mg/m2, LV5FU were administered. An Independent Committee (IC) reviewed pts eligibility and RR. The primary endpoint was resectability R0 defined as R0= margin>2mm, R1=margin<2mm, Ra= resection + either cryosurgery or radiofrequency.

Results. Among 34 pts included, 26 were eligible and were assessable for primary endpoint as per IC. Median age=59y [39-69], M/F=16/10, PS 0/1=17/8 (1 missing data), metachronous LM=12 & synchronous LM=14. After a median number of 6 Cy [4-10] before surgery, the overall RR was 73% [CR=1, PR=16, MR=4]. Pathological status after surgery was: R0=9, R1=5, Rv=7. 2 pts had cryosurgery only and 3 pts were not operated upon. Thus 23 pts had complete local treatment and 14 pts could undergo surgical resection R0-R1. Post-surgical complication =3 biliary fistula, 1 hepatic failure and 2 infections leading to hospitalization were reported. After resection, the same CT was pursued in adjuvant setting till 12 Cy in 11 pts. Conclusion. In this population who initially could not undergo optimal resection, 34.6% of assessable pts underwent R0 resection and 88.5% could receive complete local treatment with resection and / or ablation procedures after active CT.

O9
YTTRIUM-90 MICROSPHERES IN THE TREATMENT OF HEPATIC METASTASES FROM COLORECTAL CARCINOMA: INITIAL US EXPERIENCE
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3 Good Samaritan Hospital, Phoenix, United States

Purpose: Review of 243 patients treated with hepatic arterial radioembolization combined with systemic chemotherapy

Methods: Retrospective review of 243 patients (175 men, 68 women) from three institutions with unresectable colorectal hepatic metastases. All had received and failed previous systemic therapy. All patients received intra-arterial embolization of the hepatic artery with yttrium-90 containing microspheres. The patients were followed utilizing both CT and PET scans.

Results: There were 340 infusions of yttrium-90 microspheres; 158 were lobar infusions while the rest were whole liver infusions. Mean radiation dose administered was 147 Gray (range 35-170 Gray). Follow up was 12 months with the median survival not reached. Complications included 7 Grade 3 toxicities (GI ulcers and pancreatitis) and 14 Grade 2 GI ulcers.

Conclusions: Use of yttrium-90 containing microspheres is a viable option for the treatment of unresectable hepatic metastases with promising survival data and complications that are acceptable.
O10 EARLY ONSET COLORECTAL LIVER METASTASES ASSOCIATED WITH A POOR OUTCOME DISPLAY A DISTINCT GENE EXPRESSION SIGNATURE
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Results:
2065 genes were found to be differentially expressed between liver metastases detected within 12 months of the primary and those detected thereafter, using DNA microarrays.

Methods:
31 colorectal liver metastases were snap frozen at operation (18 metastases detected < 12 months and 13 metastases detected > 12 months after the primary) and stored at -70°C. Total RNA was extracted using the RNeasy mini kit (Qiagen) with quantification and quality assessment using the 2100 Bioanalyzer (Agilent Technologies). Microarray experiments were performed using the Affymetrix HG-U133A GeneChip representing 22,283 gene transcripts. Data analyses to identify differentially expressed genes were performed using GeneSpring 6.0 (Silicon Genetics).

Conclusions:
We have identified a highly significant and consistent gene expression signature representing the aggressive behaviour of liver metastases detected within 12 months of the primary. These genes are pivotal in biological pathways associated with metastasis and may be responsible for the observed aggressive phenotype. Further work to evaluate the use of these genes as potential molecular markers or therapeutic targets is required.

World Congress on Gastrointestinal Cancer 16-19 June 2004 Barcelona, Spain
**Background:** FOLFOX4 has shown superiority over LV5FU2 in first line therapy of advanced colorectal cancer. FOLFOX4 combines a simplified (s) LV5FU2 regimen and high-dose oxaliplatin. The limited toxicity of the FOLFOX4 regimen is a cumulative sensory neurotoxicity which imposes to stop therapy in patients still responding.

**Methods:** OPTIMAX study consisted in a phase III trial comparing in first line metastatic colorectal cancer FOLFOX4 (arm A) to FOLFOX7 x 6 cycles followed by simplified LV5FU2 x 12 cycles and FOLFOX7 reintroduction (arm B). 526 patients ≤ 75 years and with Alt Ph <3-time the UNL were enrolled. Patient characteristics (%) are in arm A, 262 pts: M/F = 58/42, PS 0/1-2 = 55/45, median age = 63 yrs (29-75); in arm B, 264 pts: M/F = 62/38, PS 0/1-2 = 56/44, median age = 63 yrs (32-75).

**Results:** Grade 3-4 toxicity (% of pts) was in arm A/B: neutrophils 31.7/21.5, platelets 2.7/10.3, nausea 5.8/10.0, mucositis 2.7/6.1, diarrhea 10.8/12.3, HFS 0.4/3.5, neurotoxicity 18.2/13.0. Response rate (ITT) was 58.5% in arm A and 58.3% in arm B. In arm A and B, median PFS were ... months (n.s.), median OS were respectively 20.0 and 21.2 months (n.s.). The primary endpoint of this study is the time of disease control (TDC). Median TDC was 9.9 months in arm A and 11.3 in arm B (n.s.). With 50% of the patients still alive, median survival was 20.0 months in arm A and 21.2 months in arm B. Oxaliplatin was reintroduced in 40% of the patients in arm B. Responses were observed in 10.4% of the patients and stabilization in 32.0% (ITT). 27 patients had oxaliplatin reintroduced in arm A and 52 received oxaliplatin-based therapy in subsequent lines. Overall 23.8% of patients in arm A and 48.7% in arm B received at least two oxaliplatin-based therapy. Not reintroducing oxaliplatin was protocol violation in 21% of the patients in arm B. In a multivariate analysis, prognostic factors were performance status, number of metastatic sited sites, LDH, alk phosphates and oxaliplatin reintroduction.

**Conclusion:** FOLFOX7 followed by sLV5FU2 has a similar toxicity and efficacy than FOLFOX4 but is more convenient. There was a large variation among centers on oxaliplatin reintroduction which appears as a major prognostic factor. These results allow us to start a new investigational study OPTIMOX2 comparing OPTIMOX1 strategy versus FOLFOX7 x 6 cycles followed by a treatment break and reintroduction of FOLFOX7.
ESOPHAGEAL CARCINOMA AND BRAIN METASTASIS.
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Metastasis from the esophageal carcinoma is an extraordinarily rare occurrence that may account for abnormal neurological findings. In Besat Hospital (Tehran, Iran), among 301 cases of esophageal cancer referred for radiotherapy during a 14-year period (1990-2003), the brain metastasis has been detected in only one case. A 52-years-old man presented with the history of progressive dysphagia from one year ago, which was worsened in previous two months from admission time. The diagnosis of esophageal cancer was suggested, when the barium swallow X-ray showed narrow area at mid and lower part of esophagus with irregular mucosal pattern, and Endoscopic study detected esophageal mucosal lesion, 30 cm far from incisura. The diagnosis of squamous cell carcinoma was confirmed by pathologic study of Endoscopic guided biopsy specimen. External radiotherapy to anterior and posterior of neck and mediastine and also seven-month period chemotherapy were given for the patient. In that time the patient complained from severe and progressively increasing headache in the frontal area. The CT-scan showed lobulated enhancing mass lesion of left frontal lobe seen with severe surrounding edema and collapse of ipsilateral ventricular system most likely was metastasis. In this phase two opposite field whole brain radiotherapy with the tumor dose of 4000 cGy delivered in 16 fractions over a 3-week period. He was discharged with an acceptable condition, and improvement of headaches in August 2003. The infrequent dissemination of the brain of this neoplasm has been described but the mechanism is unclear. The short-course, and high-dose-per-fraction treatment for brain metastases from esophageal cancer should be selected from the viewpoint of quality of life.

REBAMIPIDE INHIBITS GROWTH OF HUMAN GASTRIC CANCER CELLS: SURVIVIN AS THE MAJOR TARGET
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BACKGROUND: Rebamipide, an amino acid analog of 2(1H)-quinolinone - a novel drug developed in Japan - is clinically effective for treatment of gastritis and healing of gastroduodenal ulcers. Rebamipide’s effect on gastric cancer cell proliferation and growth remains unexplored. Survivin is a 16.5 kDa anti-apoptosis/cell cycle regulatory protein that suppresses apoptosis by inhibiting caspases and facilitates normal cell division in G2/M cell cycle. Survivin is overexpressed in embryonic tissues and in human cancers, including gastric cancers. Our previous studies demonstrated that survivin is expressed in normal human gastric mucosa and is temporarily overexpressed in the epithelial cells of gastric ulcer margin, where it likely plays protective and healing-promoting roles. In contrast, a sustained overexpression of survivin mRNA and protein is a characteristic feature of gastric cancer, where by inhibiting apoptosis, survivin promotes cancer cells growth and survival. PURPOSE: This study was aimed to determine: 1) Survivin expression in human gastric cancer AGS cells, 2) whether downregulation of survivin affects cancer cell growth and viability, and 3) the effect of rebamipide treatment of gastric cancer AGS cell on expression of survivin and proliferation. METHODS: Cultured human gastric cancer AGS cells were treated with either vehicle or rebamipide 0.5-5 mg/ml for 3 - 48 hrs. STUDIES: 1) expression of survivin by Western blotting, 2) immunostaining for survivin and signal intensity quantification using video image system, and 3) cell proliferation using 3H thymidine-uptake. 4) To determine the role of survivin in gastric cancer cell growth, we down-regulated survivin expression in AGS cells using specific siRNA. RESULTS: Survivin is strongly expressed in human gastric cancer AGS cells, as demonstrated by Western blotting and immunostaining. Treatment of AGS cells with survivin siRNA significantly reduced AGS viability and growth by ~2.4-fold (p<0.001). Treatment of AGS cells with rebamipide significantly reduced survivin expression by ~3-fold (p<0.002) at 8 – 24hrs. This rebamipide-induced downregulation of survivin preceded, a significant 3.6-fold inhibition of AGS cell proliferation (p<0.001) at 24 and 48 hrs. CONCLUSIONS: 1) Survivin is strongly overexpressed in gastric cancer cells. 2) Survivin downregulation with siRNA inhibits gastric cancer cells viability and growth. 3) This is the first demonstration that rebamipide arrests growth of human gastric cancer cells by reducing survivin expression and inhibiting cell proliferation. 4) These data indicate potential new application of rebamipide for chemoprevention and/or as an adjuvant therapy for gastric cancer.
BACKGROUND: Survivin is a member of the Inhibitor of Apoptosis Protein (IAP) family, which suppresses apoptosis and regulates cell cycle. Survivin is overexpressed in fetal tissue, rapidly dividing cells and in a variety of human malignancies. It inhibits pro-apoptotic caspases -3 and -7 and by attaching to the mitotic spindle also acts as a microtubule stabilizer during mitosis. These actions give cells overexpressing survivin a significant growth and survival advantage. Survivin is strongly and sustained overexpressed in human gastrointestinal cancers, especially in gastric, esophageal and colonic cancers. Limited studies demonstrated that in gastric cancer expression of survivin plays a role in tumor progression and chemo resistance of malignant cells to anticancer drugs. PURPOSE: this study was aimed to determine: (1) expression and cellular localization of survivin and the total and active caspase-3 in: (a) surgical specimens of gastric cancers (n=36), (b) in human gastric cancer AGS cells, and (2) to examine in gastric cancer AGS cells the effect of treatment with rebamipide (novel, free radical scavenging drug) on survivin expression and cell proliferation. STUDIES: (1) Survivin expression by Western blotting, (2) localization by immunostaining and (3) cell proliferation using immunostaining for proliferating cell nuclear antigen (PCNA) in surgical specimens and 3H-thymidine uptake for AGS cells. RESULTS: In normal gastric mucosa survivin expression was predominantly localized to the nuclei of progenitor cells in neck area and to some surface epithelial cells. Gastric cancer specimens demonstrated strong overexpression of survivin in cancer cells vs. non-malignant epithelial cells (>10-fold increase; p<0.001). In gastric cancer cells survivin expression was localized to both nuclei and the cytoplasm and was closely correlated with increased cell proliferation (p<0.001). Expression of active caspase-3 in gastric cancer specimens was minimal or undetectable in areas of survivin overexpression. Survivin was strongly expressed in AGS human gastric cancer cells. Treatment of gastric cancer AGS cells with rebamipide (clinically relevant concentrations) significantly reduced survivin expression by ~3 fold at 8 - 24 hrs (p<0.002) and inhibited gastric cancer cell proliferation by >3.5 fold at 24 and 48 hrs (p<0.001 vs. baseline). CONCLUSIONS: 1) In human gastric cancer tissue survivin is strongly overexpressed while active caspase-3 (that executes apoptosis) is undetectable. 2) Overexpression of survivin gives gastric cancer cells a significant growth and survival advantage. 3) Rebamipide treatment significantly reduces survivin expression and inhibits gastric cancer AGS cell proliferation, reflecting its strong anticancer property. 4) This study identified rebamipide as drug targeting survivin in gastric cancer cells and thus indicating new potential clinical applications for this drug.
ADJUVANT CHEMOTHERAPY FOR HIGH RISK GASTRIC CANCER

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Introduction: Although many trials exist in which adjuvant chemotherapy in gastric cancer is compared with surgery alone, the results are controversial and the real role of chemotherapy remains debatable. Nevertheless, according to survival analyses the extensive surgery have to be appended with systemic therapy in high risk cases.

Objective: To evaluate the effectiveness of adjuvant chemotherapy retrospective analysis was performed on high risk (N+, low differentiation) gastric cancer patients who received adjuvant chemotherapy after radical surgery.

Patients and Methods: 68 patients were followed between 1997 and 2004. Median age was 59,4 years (range 29-84). 43pt 63,3% of patients were male and 25pt 36,7% were female. Total or subtotal gastrectomy with D2-3 lymphadenectomy was carried out in 62 pts (91,1%) and in 6 pts (8,9%) respectively.

TNM staging was: stage I: 2 pts, II: 18 pts, III: 32 pts, IV(T4N2M0): 16pts. 58 pts (85,2%) had poorly or undifferentiated carcinomas.

The most often used regimens were FAM: 28 pts (%); MMC 20 mg/sqm i.v.-bolus every 6 week: 27pts (%); ELF: 2 pts (5,8%); 5FU 1000 mg/sqm i.v.-bolus and MMC 15mg/sqm i.v.-bolus every 3 week: 3 pts (5,8%).

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Results: We compared two leading regimen. Follow-up time of FAM was maximum 6 years, of MMC 3,5 years. according to rate by stages: I st: all 2 pts received FAM, no deaths recorded; II st: FAM 5 pts, 4 of them died, MMC 11 pts, 5 of them died; III st: FAM 14 pts, 10 deaths (%), MMC 12 pts, 8 died; IV st: 8 pts received FAM, 6 of them died (66,6%); 4 received MMC, 1 died. Median time from last treatment cycle to death with FAM regimen was 17.4 months (range 1-51), with MMC 9.3 months (range 2-26). Two year survival with FAM 48%, with MMC only 22,3%

Conclusions: Both, the historical FAM regimen and MMC monotherapy showing effect in some single institutional studies, did not prolong survival in gastric cancer patients. Therefore, other regimen have to be find for adjuvant therapy for high risk gastric cancer.
P8
CAN BE SURGERY FOR GASTRIC CANCER LESS INVASIVE WITH SENTINEL NODE DETECTION – PRELIMINARY RESULTS
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The adaptation of intraoperative lymphatic mapping (ILM) and selective lymphadenectomy for the staging of solid neoplasms has resulted in many new application of these methods. Identification of the sentinel nodes (SNs) that drain the gastric cancer may significantly improve staging and alter the extent of lymphadenectomy.

THE AIM of the study was to test feasibility and accuracy of ILM among patients with gastric cancer.

MATERIAL AND METHOD: 18 consecutive patients with not advance gastric cancer (T1-3, N0, M0) were included in the study. The human albumin labeled with technetium 99m was endoscopically injected in the base of the tumor one day before surgery in 4 patients. In all cases ILM was performed with the use of blue dye injected intraoperatoritively in the tumor area under the gastric serous. Standard radical gastrectomy with adequate lymphadenectomy was performed in all patients. After localization of SNs with the gamma probe (Navigator) or by the visual inspection of the epigastric area the nodules were removed and histologically examined.

RESULTS: in all studied patients we localized SNs with both methods. The number of stained nodules was between 1 – 4 (average 2.7). The authors present correlation between primary localization of the tumor and localization of SNs. In case of 4 patients in mapped nodules there were neoplasm cell as well as in other removed nodules. In two cases we observed skip metastases. In all other cases, negative SNs correlated with N0 stage.

CONCLUSION: The preliminary results of the study show, that sentinel node navigator surgery for gastric cancer is a promising technique although the lymphatic streams from the stomach is very complex, resulting in few sentinel lymph nodes. To final evaluation of its clinical value and influence on the extent of lymph node dissection in gastric cancer the prospective study including more patients is needed but with the use of laparoscopic gamma probe it is a new perspective for laparoscopic gastrectomies.

P9
PROGNOSTIC VALUE OF IMMUNOCYTOCHEMICALLY DETECTED TUMOR CELLS IN THE PERITONEAL LAVAGE OF CURATIVELY RESECTED GASTRIC CANCER UICC STAGE I
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Purpose of the study: We evaluated the prognostic significance of immunocytochemically detected free peritoneal tumor cells of patients with gastric cancer due to the fact that its value in early stage tumors is not evaluated sufficiently.

Summarized description of the study: Peritoneal lavage was performed in 346 patients before tumor resection of a gastric carcinoma between 1987 – 2001. The study group contained 75% pT1 / pT2 tumors and 51% were pN0. Free peritoneal tumor cells were detected immunocytochemically. The median follow time was 70 months.

Results: 21% had free peritoneal tumor cells (FPTC) at the time of operation. The 10 year survival of patients with FPTC was 35% and significantly worse than the survival of patients without FPTC (68%) (p<0.0001). FPTC were an independent prognostic factor with a relative risk of 2.1 to die cancer-related. FPTC were present in 9% of UICC stage I tumors. Patients with gastric cancer stage I or stage II and presence of FPTC had identical 10-year survival rates of 58%, respectively 59%. Subgroup analysis identified FPTC as an independent prognostic factor in UICC stage I cancer.

Conclusions: Free peritoneal tumor cells were present even in early stage gastric cancer and were correlated with poor prognosis.
P11
PACLITAXEL, CARBOPLATIN AND ORAL ETOPOSIDE IN ADVANCED GASTRIC ADENOCARCINOMA: ASSOCIATION WITH SEVERE MYELOTOXICITY
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Introduction: The prognosis of locally advanced or metastatic adenocarcinoma of the stomach is poor. In an attempt to improve therapeutic results, we undertook a phase II trial to investigate a combination of paclitaxel, carboplatin and oral etoposide, all active drugs in this malignancy, and with a synergistic effect in combination.

Patients and methods: Fourteen patients with advanced gastric adenocarcinoma were treated with paclitaxel 200 mg/m² IV, carboplatin AUC 6 IV on day 1, and oral etoposide 50 mg/day alternating with 100 mg/day on days 1 through 10. Cycles were repeated every three weeks.

Results: Of the 14 patients treated, partial response was observed in 3/12 (25%) evaluable patients. Median survival for the entire group was 7 months. The treatment was associated with severe myelotoxicity. Neutropenic fever that required hospitalization developed in 7/14 (50%) of patients, and symptomatic anemia that required blood transfusion was noted in 8/14 (57%). There was one drug-related death associated with neutropenic fever, gram-negative sepsis, grade 4 thrombocytopenia and gastrointestinal bleeding. Non-hematological toxicity was moderate.

Conclusions: We conclude that the current regimen of paclitaxel, carboplatin and oral etoposide is not recommended in advanced gastric carcinoma due to unacceptable myelotoxicity.

P12
SURGICAL TREATMENT OF GASTRIC CANCER
A FIVE - YEAR EXPERIENCE
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This is a review of our own experience in the surgical treatment of gastric cancer during the period from January 1997 to December 2001.
During this time 182 patients underwent surgical treatment for gastric cancer with a median age 55.3 years (18 – 81 years) and with a male to female ratio 1.83 / 1 (118 male and 64 female).
The median pretreatment delay was 126 days (1 – 14 months). The most common sign was epigastric discomfort (88 %) 160, anorexia (56%) 102 and weight loss (48%) 87. Obstructive signs and symptoms were present in 23 % 42of cases and digestive hemorrhage in 10 % 18of cases.
Diagnosis was confirmed in 78% 142 of cases by preoperative biopsy.
In 61.5 % 112of patients the disease was located on inferior stomach, in 11.6 % 21on middle stomach, in 22.5 % 41on proximal stomach and in 4.4% 8on total.
According to TNM staging system, were 8% on stage 1, 39% on stage 2, 20% on stage 3 and 33% on stage 4.
The surgery was curative in 58.1% of cases, palliative in 13.4% and by – pass and exploratory laparotomy in 28.5 % of cases.
The postoperative morbidity and morality rates were 14.6% and 2.9% respectively.
Conclusion. In this study is demonstrated the increasing incidence of proximal gastric cancer with a high occurrence in advanced stage and the decreasing incidence of distal gastric cancer with a high occurrence of early stages. An increasing early diagnosis reflected in a better control of the disease, low morbidity and mortality rates, and a better survival.
Introduction: Gastric cancer continues to be a major worldwide health problem. The prognosis of these patients is primarily related to the stage of disease but even for limited cases they usually have recurrences after surgery alone. For this reason both adjuvant radiotherapy and chemotherapy have major impact on treatment outcomes.

Aims: We investigated the impact of adjuvant chemoradiotherapy versus adjuvant chemotherapy alone on overall survival rate for gastric cancer patients.

Material and methods: A number of 35 patients with gastric resection for adenocarcinoma were included between February 1998 and March 2000. 17 of them received adjuvant chemoradiotherapy and 18 patients received only adjuvant chemotherapy. Patients characteristics: 12 females, 23 males; median age 52 years (range 38 – 63 years); histologically confirmed adenocarcinoma of the stomach; stage IB – IVM0 disease; radical surgery; performance status ECOG 0-2; no other comorbidities. Treatment schedule: Arm A: 45 Gy external beam conventional radiotherapy (1.8 Gy/day, 5 days/week) associated with concurrent chemotherapy – Leucovorine 20 mg/m2/day bolus iv and 5 Fluorouracil 425 mg/m2/day bolus iv on day 1-5 and 29-32. Patients received two more chemotherapy cycles, consisting of Leucovorine 20 mg/m2/day bolus iv and 5 Fluorouracil 425 mg/m2/day bolus iv on day 1-5, repeated q 4 weeks. Arm B: 6 chemotherapy cycles, consisting of Leucovorine 20 mg/m2/day bolus iv and 5 Fluorouracil 425 mg/m2/day bolus iv on day 1-5, repeated q 4 weeks. Follow-up visits were performed every 3 month for two years, and every 6 month subsequently. Clinical examination, complete blood count, blood chemistry, chest X rays and computer tomography were done.

Results: Median follow-up period was 46 month. The median overall survival was 36 month for chemoradiotherapy group and 29 month for chemotherapy group (p=0.047). 12 patients are still alive. The toxicity was manageable. Grade 3-4 gastrointestinal toxicity occurred in 41.18% and 29.41% cases respectively for arm A. Grade 3 gastrointestinal toxicity occurred in 22.22% cases for arm B. There were no treatment related deaths.

Conclusion: Adjuvant radiochemotherapy increased overall survival compared to chemotherapy alone. The regimen was well tolerated. 5FU modulated with Leucovorine and external beam radiotherapy should be considered for all high risk gastric cancer patients.

Oxaliplatin(OHP) and 5Fluourouracil(5FU) efficacy and toxicity strictly depend on circadian rhythms in cell cycle regulation, reduced glutathione content, dehydropyrimidine and thymidilate synthase activities, topoisomerase I activity, membrane permeability as well as liver and renal blood flow. From August 2002 to August 2003 (Tab.1) 11 untreated gastric cancer patients(pt) were treated with OHP based chronomodulated delivery schedule using Melodie® infusion system: OHP 25 mg / m² /d1-4q14 ( sinusoidal 12 hour infusion with flow rate peak at 4:00pm); 5FU 900 mg/m² and L-Folinic Acid (LFA) 150 mg/m² d1-4q14 (sinusoidal 12 hour infusion with flow rate peak at 4:00am).69 cycles (7,2 average per pt.) were performed: average dose intensity was 49,05 mg/sqm/w, 288,11 mg/sqm/w 1765,00 mg/sqm/w for OHP, LFA and 5FU respectively(Tab 3). Average dose according to body surface was 640,08 mg/sqm, 3.758,02 mg/sqm, 23.030,69 mg/sqm respectively.

No cycle was delayed due to toxicity. Haematological and hepatic toxicity weren’t observed, neither was any gr. 4(WHO) toxicity. Radiological Objective Response evaluation has been performed in all pts (Tab.2). ORR(CR+PR) was 22,2% but Clinical Benefit (RC+RP+SD) was obtained in 77,7%. Median TTP is 7,2 months, median survival is 8,3 months and median follow up is 8,6 months. These data confirm that FFL4/10 schedule has very interesting activity in metastatic gastric cancer. Moreover, chronomodulated infusion is considerably less toxic than conventional flat and bolus infusions. Due to this pilot experience have been activated by Italian Group of Chronotherapy a perspective national multicentric phase 2 study with an expected accrual of 50 pts in 2 years (2004-2005).

Tab.1 | Age | n° pts | 11 | Tab.2 | ORR
--- | --- | --- | --- | --- | ---
min | 35 | TTP(med) | 7,2 | RP+RC | 22,22%
max | 70 | Surv(med) | 8,3 | RM | 33,33%
mean | 60 | Cycles | 69 | SD | 22,22%
mediana | 66 | mean | 7,20 | PD | 22,22%
Background:
Esophageal cancer is a relatively uncommon but extremely lethal malignancy in the world. Very high annual incidence is reported in northern region of Iran. Epidemiological studies implicate dietary and environmental factors in risk of it, especially in high prevalence area, but more data is needed.

Materials and method:
In setting of multi centric case-control study during 1998-2002 in northwest of Iran (west azerbaiyan province), 180 patients with histological diagnosis of esophageal cancer and 200 healthy individuals as control group were enrolled. All case and control subjects were matched for age, sex and alcohol drinking and evaluated for smoking, hot tea drinking, dietary habits of pickled vegetables and preserved bread consumption and low intake of fruit&fresh vegetables, family history of esophageal cancer and dental hygiene. Mantel Haenszel Odds Ratio (OR) were used for measuring probable risk factors.

Results:
Smoking with OR 6.8 and 95% confidence interval (CI) 4.6-9, hot tea: (OR 5.84, 95% CI 3.15-10.83), high pickled vegetables intake (OR 4.68, 95% CI 2.05-10.72), poor dental hygiene: (OR 4.65, 95% CI 1.99-10.84), preserved bread consumption: (OR 3.7, 95% CI 2.1-5.3), low fruit & fresh vegetables intake: (OR 2.3, 95% CI 1.1-3.5), were major risk factors in this area.

Conclusion:
In addition to well known risk factors for esophageal cancer such as drinking, smoking, hot tea, pickled vegetables, preserved bread and low fruit & fresh vegetables intake, Poor dental hygiene should be considered as a potential preventable risk factor.

Introduction:
Esophageal cancer expressing bcl-2, MMP-9 and MDR-1 is incurable due to potent radio- and chemoresistance caused by drug efflux and inhibition of apoptosis.

Methods:
Radio- and chemoresistant esophageal Ca overexpressing MDR-1, MMP-9 and bcl-2 was treated with VRL and SnEt2 entrapped into the lipophilic core of LDL targeting the tumor proliferating cell surface which possess an enhanced number of LDL receptors. A patient’s esophageal Ca was treated photodynamically with laser light. With high density cDNA array technology, we detected expression changes of various genes pre and post-treatment.

Results:
Post treatment, LDL facilitated SnET2 access into tumor cells via receptor mechanisms. Laser irradiation induced microtubule (MT) depolymerization in tumor and endothelial cells according to immunofluorescence microscopy using b-tubulin antibody. Enhancement in intracellular calcium resulted in MT depolymerization which acted synergistically with the MT depolymerizing action of PDT. Flow cytometry exhibited cell cycle arrest at G2/M phase. After PDT there was overexpression of bcl-2, VRL caused downregulation of bcl-2 by phosphorylation and upregulated Bax circumventing resistance to chemotherapy and photocytotoxicity. Irradiation generated reactive oxygen species with electron transfer event as type-I photoinduced damage and singlet oxygen with type-II biological damage causing tumoral cell death. PDT induced c-fos and c-jun and activated p38 which phosphorylated ATF-2 and Elk-1 and downregulated MDR-1, MMP-9 and VEGF while it induced c-myc and WAF1/CIP1/p21 causing arrest of cell cycle in tumor cells through inhibition of cdk2, cdk6, cyclin D1 and cyclin E. We detected a drop in mitochondrial potential and ATP level reducing cell respiration. Release of cyt-c from mitochondria into the cytosol initiates mitochondria associated apoptotic events in tumor cells. Caspase assays revealed activation of procaspase-3 activity via complex formation with dATP, APAF-1 and cleavage of procaspase-9. Caspase-3 induces apoptosis causing cleavage of a number of proteins including DFF, PARP, DNA ladder formation, TUNEL and DEV/Case activity. Apoptosis was also confirmed with TdT and DNA elution assay. The majority of tumor cells were eradicated by apoptosis according to counting DAP1 stained nuclei and FITC(+) cells by fluorescence microscopy. Furthermore, PCD was evaluated with propidium iodide staining and flow cytometry with annexin-V. Irreversible morphological apoptotic signs of D2 phase were exhibited with electron microscopy. Exposure of PS on the plasma membrane of apoptotic cells activated their phagocytosis by adjacent tumor cells indicating a bystander killing effect. Cytotoxicity was revealed by MTT and BrdU assays measuring metabolic activity and DNA synthesis of tumor and endothelial cells which inhibited angiogenesis.

Conclusion:
We induced irreversible D2 apoptosis in radio- and chemoresistant esophageal Ca by combined PDT and chemotherapy after phosphorylating bcl-2 and downregulating MDR-1, MMP-9 and VEGF circumventing chemoresistance and radiation resistance and inhibiting angiogenesis and metastatic potential.

World Congress on Gastrointestinal Cancer 16-19 June 2004 Barcelona, Spain
PHOTODYNAMIC THERAPY (PDT) VERSUS ARGON – PLASMA COAGULATION (APC) IN\nNEOPLASTIC AND NON-NEOPLASTIC BARRETT’S ESOPHAGUS\nAli M Kassem1, Lofty H. Abu-Dahab1, Mohamed A. Alsenbesy1, Thomas Zoepf2, Axel Eickhoff2,\nRalf Jakobs3, Juergen F. Riemann3\n1 Internal Medicine Department, Sohag, Egypt\n2 Medical Clinic (C), Ludwigshafen, Germany\n
Introduction: Barrett’s esophagus is associated with an increased incidence of\nintraepithelial neoplasia (IPN) and adenocarcinoma in the specialized glandular\ncolumnar epithelium with a 30-52 fold increase compared to the normal population.\nAlongside surgical treatment for high grade dysplasia and early carcinoma, endoscopic\ntreatment procedures play a potentially important role as they showed satisfactory\nresults in preliminary studies. Endoscopic mucosal resection (EMR), photodynamic\ntherapy (PDT) and argon plasma coagulation (APC) are particularly promising. The aim\nof this work is to compare the effectiveness of photodynamic therapy (PDT) as a recent\nalternative method versus Argon-Plasma coagulation (APC) in ablation of neoplastic Barrett’s\nesophagus.

Methods: Forty-five patients with age ranging from 44 to 73 were included in our\nstudy. 23 patients received photodynamic therapy (PDT), while 22 patients were\ntreated with argon plasma coagulation (APC) representing group A and B respectively.\n5-aminolevulenic acid (5-ALA) was used as a photosensitizer for Barrett's lesions £ 2\nmm in depth as shown by the miniprobe ultrasound (MEUS), and photosan-3(Ps-3) was\napplied for lesions between 2-5 mm in depth in group A. APC with 70 Watt was\nperformed for neoplastic Barrett's lesion in group (B), while 40 Watt was used for non-\nneoplastic Barrett. Acid suppression was maintained in all patients (Omeprazole, 40 mg\ntwice daily).

Results: The mean follow-up period was 16.83 (SD10.8) and 12.66 (SD 10.05)\nmonths after PDT and APC respectively. 100% of intraepithelial neoplasia (IPN) were\neradicated after APC versus 92% after PDT. After PDT, all patients with grade 3 IPN\n(according to Vienna classification) were eradicated, while 8% of grade 4 IPN\nprogressed into grade 5 and were referred to curative esophagectomy. The length of\nBarrett's mucosa decreased by a mean of 79.5% (SD 22.38%) and 84.4% (SD 18.18%)\nof the initial length after PDT and APC, respectively. The initial rate of complete\neradication of Barrett's mucosa after PDT was noticed in 17% of cases. This rate has\nbeen raised to 60% after using supplementary APC and EMR.

Conclusion: PDT with supplemental APC and EMR reduces the length of Barrett and\neradicates grade 4 IPN (early cancer). APC is effective for Barrett patients with grade 3\nIPN (low grade dysplasia). Long term follow up is required to prove the effectiveness of\nablation therapy in reducing the rate of esophageal adenocarcinoma.
NEOADJUVANT CHEMOTHERAPY IN ADVANCED GASTRIC CANCER WITH MICRODISSEMINATION
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The purpose of the study was to develop an effective method of the combined modality treatment of the IV-th stage gastric cancer by applying chemotherapy (CT) and palliative surgery.

Patients and methods: A total of 28 patients were enrolled into this trial. 18 patients received treatment continuously according to the schedule, 9 patients were excluded from the study due to disease progression, 1 patient died because of CT-related complications. The test group included 21 men (75%) and 7 women (25%), with the average age of 57 years. All patients were subjected to cytoreductive or symptomatic surgery. Cisplatin, at dose of 30 mg/m2, was injected intraperitoneally at the 1-st and 4-th day after having performed the surgery. Chemotherapy with xeloda, at dose of 2500 mg/m2, and cisplatin, at dose of 50 mg/m2 (intravenously), was administered at the 10-courses every 4 weeks. Patients were operated 2 weeks after the second chemotherapy course. After chemotherapy was completed, second blood/ bone marrow examination was performed. Results: of 79 patients with advanced gastric cancer evaluated, 53.1% had detectable cancer cells in peripheral blood or bone marrow (42 patients). From this group 28 received preoperative chemotherapy. In 5 patient clinical and/or endoscopical signs of tumour regression were observed, and two patient progressed with the disease.

In 14 patients second evaluation of blood or bone marrow revealed no cancer cells. In patients who responded to chemotherapy with bone marrow R0 resection was possible in 9/14 patients vs 6/14 patients in non responders group and 5/14 in no chemotherapy group.

The toxicity observed was mild to moderate. The average surgery delay was 54 days. Conclusion: Circulating cancer cells can be detected in the peripheral blood or bone marrow in more than 50% of patients with advanced gastric cancer. Preoperative chemotherapy can eradicate these cells in about 50% of these patients. The effect of eradication on the course of the disease and survival may be beneficial due to the increase of R0 resections rate, but requires further evaluation.

PALLIATIVE COMBINED TREATMENT OF THE IV STAGE GASTRIC CANCER
Dmitry N. Popov
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The purpose of the study was to develop an effective method of the combined modality treatment of the IV-th stage gastric cancer by applying chemotherapy (CT) and palliative surgery.

Patients and methods: A total of 28 patients were enrolled into this trial. 18 patients received treatment continuously according to the schedule, 9 patients were excluded from the study due to disease progression, 1 patient died because of CT-related complications. The test group included 21 men (75%) and 7 women (25%), with the average age of 57 years. All patients were subjected to cytoreductive or symptomatic surgery. Cisplatin, at dose of 30 mg/m2, was injected intraperitoneally at the 1-st and 4-th day after having performed the surgery. Chemotherapy with xeloda, at dose of 2500 mg/m2, and cisplatin, at dose of 50 mg/m2 (intravenously), was administered at the 10-14th day after the surgery with a three-week interval between the courses until disease progression took place. The influence of cytostatic drugs on the values of peripheral blood and bone marrow haemopoiesis was assessed along with applying chemotherapy. The life quality parameters were evaluated by using the EORTC QLQ-C30 & STO22 module.

Results: 12 cytoreductive (43%), 10 symptomatic (35.7%) and 6 explorative (26%) surgical operations were carried out. The resectability proved to be 42.8%. The postoperative lethality rate was 0%, 56 intraperitoneal injections of cisplatin and 93 courses of CT (xeloda, cisplatin) were performed. Gastrointestinal, hematological and renal toxicities were assessed according to the CTC-NCIC scale. The first estimate of the treatment efficiency was obtained after having completed the first two courses of CT. Disease regression and disease stabilization were recorded in 10 cases (35.7%) and 12 cases (42.8%) respectively, while disease progression was observed only in 6 cases (21.4%).

The observed regression time was from 3 to 23 months with stabilization duration being from 3 to 12 months. The observation period was from 2 to 23 months.

Conclusion: The method of the combined treatment of stage IV gastric cancer has been developed. Palliative surgeries provide the conditions for performing chemotherapy on patients with unfavorable prognosis. The toxicity induced by the above-mentioned CT regimen has proved to be mild. The chemotherapy carried out at early time after the surgery has no significant influence on the adaptive period and compensatory potentialities of patient organism.
P22
FEATURES OF METABOLISM OF DNA IN A TUMOUR AND HEALTHY TISSUES OF PATIENTS WITH A STOMACH CANCER
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Introduction: Proliferative processes, amplified in tumour are connected to disturbance of DNA metabolism. In fast-growing tumoral tissues intensity of biosynthesis of DNA on a “spare” way which key enzyme is Thymidine kinase is increased. It is established also, that speed of degradation of DNA in tumours is reduced, probably, because of decrease in activity of catabolic enzyme-DNA-ase.

Aims: To define comparative activity of Thymidine kinase and DNA-ase in primary tumour of human liver and liver, which has been not touched by metastasis, patients with a stomach cancer with various degree of severity of disease.

Materials and methods: Are investigated bioptate of liver of healthy persons who have died from accidents, 7 preparations of tumour of liver and bioptic material of 25 patients with stomach cancer of various degree of severity. Activity of TP defined in nuclear juice (nucleus allocated differential centrifugation) a radioisotope method, with use of radioactive Thymidine C$^{14}$. The activity of DNA-ase defined in chromatin of cellular nucleus by spectrophotometrically method. Activity of enzyme expressed in nmol/min/mg.

Results: Activity of TK in bioptate of a primary tumour of liver in 6 times was higher than norm (2.5±0.4 nmol/min/mg) and has made 19.0±1.6 nmol/min/mg. The activity of DNA-ase in these preparations 0.90±0.8 nmol/min/mg, i.e. is sharply reduced in comparison with norm –3.21±0.19 nmol/min/mg. At research activity of enzymes in a liver of patient the stomach cancer at stage T3N1M0 observes infringement of activity of enzymes of metabolism of DNA, and the tendency of change is similar to dynamics of change of activity of enzymes in a tumour. Probably, takes place “system” influence of tumour on an organism. The revealed sharp change of activity of TK (substantial growth) and activity of DNA-ase (authentic decrease), observable and in the tumour, and in healthy tissues of an organism tumour carrier can be used at diagnostics of malignant tumours.

P23
SURGICAL TREATMENT OF ADVANCED RECTUM CARCINOMA
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Introduction: Surgery plays the most important role in treatment of advanced rectum carcinoma. The appropriate surgical operation gives the best chances for longer survival and it can obtain better conditions for adjuvant therapy – radio and/or chemotherapy.

Aim: The objective of this overview is to show that applied surgical method depends on tumor distance from ano-cutan line and on T factor.

Methods: Examined and evaluated patients were under surgical treatment in last years at the Institute and they all had advanced rectum carcinoma (T3 and T4 grade). 50 patients had advanced disease (T3 and T4 grade). Positive lymph nodes had 21 patient and distance metastasis 16 patients.

Results: The results showed that in advanced rectum carcinoma the most often surgical approach was Milles operation – 27 patients (54%), Anus praeter naturalis – 16 patients (32%), Dixon operation – 4 patients (8%) and others. 34 patients (68%) had tumor located 2-6cm from ano-cutan line (rectoscopic measured). In all cases resection edges were without malignancy marks. In treatment was respected the Institutes protocol for treatment of malignant patients.

Conclusion: From our results comes that in advanced rectum carcinoma the most important factor for selection of operation type is tumor distance from ano-cutan line.

KEY WORDS:
1. Rectal carcinoma
2. Milles operation
3. Rectal carcinoma surgery
THE USE OF MECHANICAL LINEAR STAPLER IN MESORECTUM RESECTION
Filippo Scevola, Sergio Sandrucci, M.Baudolino, Matteo Goss, Antonio Mussa
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We have studied a new mesorectum resection by using linear mechanical stapler of last generation. Our aim is to perform surgical and operating room timing, and to obtain a good surgical resection with an accurate haemostasis. We have studied two groups of patients composed by 10 patients each randomized, affected by rectum middle-low carcinoma, using in a group the linear stapler (Versafire™), and in the other group proceeding with the classical intervention, with haemostasis handled with free noose or with a Vicryl stitch. Analyzing data we have observed an average difference in the duration of intervention from abdominal incision to mesorectum time of 58±12 minutes. The anastomosis was conducted with the use of a circular mechanical stapler, previous the confection of a hand made tobacco bag, with a monofilament wire reabsorbable. All the 20 interventions were performed by the same surgeon. We have not observed statistically significant differences looking the following post operatives complications: number of days of bed stay, duration of antibiotics therapy, beginning of canalization, quantity of liquid removed form the drains and time of stay of the drain. In conclusion, the use of mechanical linear stapler in mesorectum carcinoma, let a reduction of operating time, keeping although an optimal intervention and postoperative quality of live.

SENTINEL NODE BIOPSY IN ANAL CANCER; STAGING: RECENT ADVANCES
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Anal carcinoma is a rare cancer, representing 1-2% of all large bowel cancers. Surgical excision by abdominoperineal resection has been the standard treatment. In the 1920s and 1930s inguinal node dissection was included in the surgical management of these patients. In the 1950s it was evident that the morbidity associated with lymph-node dissection was much greater than any survival benefit and this procedure was abandoned. Since 1974 “multimodality treatment” with a combination of radiation and chemotherapy has become the standard treatment. Inguinal lymph node status is an important prognostic factor and the presence of inguinal nodes is an independent prognostic factor for local failure and overall mortality. Metastases to the superficial inguinal lymph nodes occur in 15-25% of cases. The sentinel node concept can be applied to the management of patients with anal carcinoma. We applied this technique in three patients. They were treated as a day surgery procedure. No mortality and no morbility were observed. Postoperative histology evidenced the presence of inguinal bilateral lymph node metastasis in the patients. These cases demonstrate that the sentinel node in anal cancer is a feasible procedure. It doesn't require beds for recovery, considering its feasibility in local anesthesia as a day surgery procedure. It is significant and also permits the detection of nodes negative to clinical examination. Considering the strong correlation between prognosis and node involvement, we consider this technique an important and simple method for detecting lymph node status and for an adequate pre-treatment staging of anal carcinoma, fundamental for the choice of radiation plan. Further studies are needed to confirm these results.
INTRAVENOUS 5 FLUOROURACIL VERSUS ORAL UFT AS PREOPERATIVE CONCURRENT CHEMORADIATION FOR RECTAL CANCER
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Purpose:
Neoadjuvant chemoradiation is widely used in the treatment of rectal cancer. The aim of this study was to compare tumor response (down-staging) and toxicity obtained with preoperative radiotherapy and two different concomitant chemotherapy schedules: intravenous 5-FU (5 Fluorouracil) and oral UFT (Tegafur:Uracil).

Methods:
From June 2001 to September 2003, 58 consecutive patients with rectal adenocarcinoma were treated in our institute with external pelvic radiotherapy, to a dose of 45 Gy over 5 weeks and concomitant chemotherapy: group A) 32 patients were treated with oral UFT 240 mg/m²/day and 30 mg/day leucovorin for 28 consecutive days during the first 4 weeks of radiotherapy; group B) 26 patients were treated with bolus 5FU 500 mg/m²/weekly x 5 (patients who refused UFT protocol) or with bolus 5FU during the 3-5 days of first and fifth weeks of radiation therapy (patients from Asaf Harofeh hospital). Pretreatment TRUS was performed in all patients in group A (6 T2No, 18 T3No, 7 T3N1, 1 T4N1) and for 17 of 26 patients in the group B (7 T2No, 9 T3N1, 1T3N1). The interval between the end of radiotherapy and surgery ranged from 4 to 8 weeks. Tumor response was classified into pCR (pathological complete response), pDS (pathological down-staging), cDS (clinical down-staging), SD (stable disease), LP (local progression), DP (distant progression).

Results:
Overall toxicity was comparable among groups A and B. Grade 1-2 diarrhea was the most frequent acute toxicity, 34.4% in group A and 30.7 % in group B. Grade 3 diarrhea was observed in 1 patients (3%) in group A and in 1 patient (4%) in group B. Tumor response was pCR - 3/32 (9.3%), pDS - 10/32 (31.2%), cDS - 1/32 (3.1%), SD - 14/32 (43.7%), LP - 2/32 (6.2%) , DP- 2/32 (6.2%) in group A versus pCR - 2/26 (7.6 %), pDS - 3/17 (17.6%), SD - 6/17 (35.2%), LP - 6/17 (35.2%) in group B. The overall response to chemoradiation therapy in group A was 13/32 (40.6%), in group B - 5/17 (29.4%) (p=0.64). Local tumor progression during the treatment was more common in group B (p= 0.027).

Conclusion:
There was a trend to increased response in the oral UFT group compared to the 5FU group. Oral UFT preoperative regimen was well tolerated and appears to be at least as active as IV. Thus and because of its convenience to patients it seems that oral fluoropyrimidine should supersede intravenous 5FU for the neoadjuvant chemoradiotherapy of rectal cancer.
**P28**

**PREOPERATIVE CHEMORADIOThERAPY IN RECTAL CANCER-EFFECT ON DOWNSTAGING AND POSSIBILITY OF SPHINCTER SPARING SURGERY**

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Minia Oncology Centre, Assuit, Egypt

**Objectives:** To evaluate the influence of pre-operative chemo-radiation on resectability of locally advanced rectal cancer and the possibility of performing sphincter-sparing surgery in cases not suitable for this procedures. **Methods:** 30 patients with rectal carcinoma either border line resectability or not suitable for primary sphincter sparing surgery. Performance status ≥60, adequate bone marrow reserve and adequate hepatic and renal functions. All patients had been staged by radiological studies and endoscopies. **Treatment:** All patients were treated by combined chemotherapy. Radiotherapy with dose of 45 Gray in 25 fractions over 5 weeks. Chemotherapy with 5-fluorouracil 500 mg/m² I.V infusion over 2 hours and leucovorin immediately before radiation setting for first 3 days of the first week and the first 3 days of the last week of radiation. Patients were evaluated 4-6 weeks after treatment. Operable patients were subjected to abdominoperineal resection (APR) or low anterior resection (AR). Toxicity was evaluated using WHO Common Toxicity Criteria. **Results:** 30 patients were included; the median age was 48 years. Partial response was reported in 63.4% of patients and stable disease was reported in 33.3% of patients while progressive disease was reported in only one patient. Low anterior resection (AR) had been performed in 8 patients out of 12 (66.2%) who had initially not suitable for primary sphincter preservation, while abdominoperineal resection (APR) had been performed in 11 patients out of 18 patients (61.1%) who had initially border line resectability. Tumor down staging was achieved in 66% of patients. Tumor stage was identified as the only significant prognostic factors in response. Local control rate at 18 months were 85%. Actuarial overall survival for patient with curative resection at 18 months, were 85% respectively. Toxicities included G3 leucopenia in 10% of patients, Diarrhea G3 in 13.3% of patients. **Conclusion:** Preoperative chemo-radiotherapy is an effective treatment in inducing down-staging of locally advanced rectal cancer patients and enhance curvative resection and sphincter preserving procedures.

**Keyword:** Colorectal cancer; Chemoradiotherapy

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**P29**

**EPIDERMAL GROWTH FACTOR RECEPTOR EXPRESSION IN ANAL CANAL CARCINOMA**

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² Department of Pathology - Princess Margaret Hospital, Toronto, ON, Canada

**Purpose:** Molecularly targeted therapies have expanded the possibilities for treatment of various cancers. Squamous cell carcinomas have been shown to express high levels of epidermal growth factor receptors (EGFR). The aim of this study was to determine the frequency and intensity of expression of EGFR in squamous cell anal canal cancer specimens. A number of other cell surface and cell cycle markers that are potential therapeutic targets were also examined.

**Methods:** Archived paraffin-embedded tissue specimens from patients with anal canal carcinoma treated at Princess Margaret Hospital between 1993 and 1997 were collected. They were evaluated for EGFR, HER2/neu, p53, Bcl-2, and Cyclin-D1 expression by immunohistochemistry. Clinical data was collected by chart review.

**Results:** Twenty-one specimens were collected and showed the following:

<table>
<thead>
<tr>
<th>Marker</th>
<th>EGFR</th>
<th>HER2/neu</th>
<th>p53</th>
<th>Bcl-2</th>
<th>Cyclin-D1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of expression</td>
<td>+</td>
<td>±</td>
<td>°</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>1+</td>
<td>21</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>2+</td>
<td>6</td>
<td>28.6</td>
<td>2</td>
<td>9.5</td>
<td>4</td>
</tr>
<tr>
<td>3+</td>
<td>3</td>
<td>14.3</td>
<td>0</td>
<td>0</td>
<td>4</td>
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<tr>
<td>4+</td>
<td>7</td>
<td>33.3</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

+: number of positively staining specimens

The patterns of protein expression did not appear to correlate with the degree of histologic differentiation nor with clinical outcomes such as lymph node involvement or disease recurrence.

**Conclusions:** Anal canal cancers universally strongly express EGFR and are negative for HER2/neu. Clinical trials using EGFR inhibitors or antibodies are warranted.
Objective: To examine the efficacy and safety of the combination of oxaliplatin, capecitabine and radiotherapy as preoperative therapy in locally advanced cancers of the rectum.

Material and Method: 18 patients either with low lying tumor, needing APR or with inoperable disease were recruited. All patients had preoperative investigations including MRI pelvis. All received chemoirradiation. Chemotherapy consisted of capecitabine 750mg/m^2 BD given daily 10 dose per week, oxaliplatin 60 mg/m^2 given 2 hour intravenous infusion every week for 5-6 weeks and pelvic irradiation with 1.8 Gy/Fr daily 5 Fr/wk to 45-50.4 Gy. Post-chemoradiotherapy imaging with MRI or CT were done before subsequent resection followed by adjuvant chemotherapy (5 Fu/Lev).

Results: As of Mar 2004, all 18 had preoperative therapy as well as were also available for toxicities, 15 were evaluable for imaging response (2 other under process at the time of writing) and 18 for pathological response. 17 patients had complete resection (R0): 9 APR (abdominoperineal resection), 6 LAR (low anterior resection) and 2 PE (pelvic exenteration) and 1 patient had microscopically involved resection margin (R1). For tumours at 0-2cm from anal verge: 4 APR and 1 PE were performed. For tumour >2cm from anal verge: 5 APR, 7 LAR and 1 PE were performed. For the 11 patients with radiologically evaluable disease: 40.15% mean reduction in 3 dimensional tumour-volume was noted. The WHO response on MR: 25-50%: 4 (36.4%), 50-75%: 1 (9.09%), >75%: 6 (54.55%) yielding a radiological response rate of 63.64%. There were 4 pathological complete response, 9 pathological partial response yielding an overall response rate of 72.2%. Toxicities were mild: neutropenia: G1/2: 22.2%/11.1; sensory neuropathy: G1/2: 50.0%/5.6%; radiation dermatitis: G1/2: 55.6%/33.3%; Diarrhea: G1/2/3: 44.4%/33.3%/5.6%. Tenesmus: G1/2/3: 72.2%/38.9%/16.7%. No other G3 or G4 toxicities were observed. There was 1 anaphylactic reaction and 1 rash/fever associated with oxaliplatin infusion; and 1 poor wound healing.

Conclusion: Preoperative chemoradiation with oxaliplatin and capecitabine is well tolerated and significant downstaging is observed in both the primary lesion and peritumoral nodes of locally advanced rectal cancer. The MRI data will be updated in the meeting.

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MR IMAGING OF THE EFFECTS OF NEO-ADJUVANT THERAPY ON RECTAL CARCINOMA
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INTRODUCTION

Neo-adjuvant radiotherapy reduces local recurrence in rectal cancer patients. MRI has been used after neo-adjuvant therapy to stage the tumour and aid surgical planning. Our aim was to document the effect of this therapy in particular short course radiotherapy on rectal carcinoma using MRI, which has not previously been described.

METHODS

MRI was performed before and after neo-adjuvant therapy in 12 patients. Nine patients had short course radiotherapy and 3 had long course chemoradiotherapy. Axial and sagittal T2W images were supplemented with high-resolution oblique T2W images axial to the tumour. We assessed radiological stage and maximum tumour thickness, before and after neo-adjuvant therapy. MRI of the rectal tumour specimen was used to help correlate the tumour appearance with histology, the gold standard.

RESULTS

Ten patients were radiological stage T3 and 2 were stage T4 prior to neo-adjuvant therapy. The T stage accuracy was 85%. Two patients were overstaged from T3 to T4 and none were understaged. Overall there was a 17% reduction in tumour thickness (cm) post neo-adjuvant therapy, which was statistically significant (p<0.01). Following short course radiotherapy, 2 tumours were downstaged: one from stage T3 to T2; the other from stage T3 to T1. Also the average tumour thickness was significantly reduced (p<0.05) following short course radiation treatment. Further, the overall lymph node staging accuracy was 75% with no significant change in the size or number of nodes following neo-adjuvant treatment.

CONCLUSION

We have shown that both neo-adjuvant chemoradiotherapy and short course radiotherapy result in a significant reduction in the size of rectal tumours prior to surgery. Short course radiotherapy resulted in downstaging of tumour in two patients, one of whom would have benefited from local excision surgery alone. The latter feature has not been previously documented and may aid in the planning of the most appropriate surgical procedure for individual patients.

VASCULAR SUTURE IN ABDOMINOANAL RESECTION OF THE RECTUM
Rasulov Rodion1, Minakin Nikolay2, Plenkin Sergey2
1 Irkutsk Institute For Postgraduate Medical Studies, Irkutsk, Russia
2 Regional Oncological Hospital, Russia

Introduction: To develop the technique allowing bringing the initially short sigmoid colon downwards into the anal canal following the abdominoanal rectum resection.

Method: In the course of January, 2002 – April, 2003, we have performed 43 abdominoanal resections of the rectum. In 10 cases, the sigmoid colon was initially short, and the attempt of bringing it downwards into the anal canal after the abdominoanal resection required the additional mobilization of the left colon half with crossing the great vessels. Due to the severity of patients’ state and concomitant pathologies in group A (n=5), the operation was finished with the end colostomy. In group B (n=5), to form the sufficient length of the intestine brought downwards, mobilization of the left colon was performed, as well as crossing the inferior mesenteric artery at the site of its deviation from the abdominal aorta. Besides, in every patient in group B the obvious ischemia of the distal part (15-18 cm) of the intestine prepared for bringing downwards was observed. In that group, the blood flow via the great vessels was restored by placing the inner ileo-inferiormesenteric anastomosis. Subsequently, bringing the sigmoid colon downwards into the anal canal with the excess was performed.

Results: Operation was completed with the end colostomy in group A. In group B, bringing the sigmoid colon downwards into the anal canal was made in every case. In doing so, the adequate blood supply of the intestine brought down was achieved by applying the inner ileo-inferiormesenteric anastomosis.

Conclusions: Additional mobilization of the left colon parts and inner ileo-inferiormesenteric anastomosis allow formation of sufficient length of the intestine brought downwards with the adequate blood supply.
P34
RESULTS AFTER PRE-OPERATIVE AND INTRA-OPERATIVE RADIOTHERAPY FOLLOWED BY SURGERY FOR PRIMARY LOCALLY ADVANCED AND RECURRENT RECTAL CANCER PATIENTS
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¹ Erasmus MC – Daniel Den Hoed Cancer Center: Surgical Oncology, Rotterdam, Netherlands
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³ Erasmus MC – Daniel Den Hoed Cancer Center: Statistics, Rotterdam, Netherlands

Purpose of the study
Primary locally advanced and recurrent rectal cancers are challenging problems in colorectal cancer treatment. Multi-modality treatment such as pre-operative radiation therapy, intra-operative radiotherapy (IORT), extensive surgery and chemotherapy are all factors that might improve outcome. The purpose of this study was to analyse the results of pre-operative and intra-operative hyper-fractionated radiotherapy followed by surgery for patients treated in our tertiary referral cancer center.

Methods:
Between 1985 and 2003, 208 patients with primary locally advanced and recurrent rectal cancer were prospectively entered in our database. All 116 patients with locally advanced rectal cancer were treated with pre-operative radiotherapy. Pre-operative radiation was performed in 59 patients with recurrent rectal cancer, 33 patients did not receive pre-operative radiotherapy. Pre-operative radiotherapy was delivered with a median dose of 50 Gy. Starting in 1997, IORT was delivered in those patients with marginal or incomplete resection margins, judged on frozen section specimen taken during surgery. Local failure free survival and overall survival were calculated using Kaplan Meier methods. Prognostic factors for local failure or survival were calculated using the log-rank test and the Cox proportional hazard analysis.

Results:
Mean age of all patients with primary locally advanced and recurrent rectal cancer was 65 (26-84) years. A complete resection of the tumor (R0) was possible in 98 (84%) of patients with a primary locally advanced rectal cancer. A R0 resection was performed in 64% of the patients with a recurrence who received pre-operative radiation and 45% of the non-irradiated patients. A complete response after radiotherapy was found in 2% of the patients with a primary locally advanced rectal cancer. Postoperative mortality was 3%.

The overall 3- and 5-year local control rate was respectively 75 and 63% for patients with locally advanced rectal cancer. Overall survival after 3 and 5 year was 51 and 43% in this group of patients. IORT was given in 23 patients and improved local control significantly for patients with narrow or incomplete resection margins (p<0.001). Five year overall survival was statistically significantly improved for R0 compared to R1/2 resections (p=0.001) and for negative compared to involved lymph nodes (p=0.007).

The overall results of patients treated for recurrent cancer were significantly worse with local control rates of 25 and 16% and overall survival of 32 and 13% after respectively 3 and 5 years. Preoperative radiotherapy compared to surgery alone improved local control rates statistically significantly after 3 and 5 years (p=0.036). Complete response after pre-operative radiotherapy was an important prognostic factor for an improved survival for patients with recurrent rectal cancer.

Conclusions:
Patients with primary locally advanced rectal cancer have an improved outcome compared to patients with recurrent rectal cancer. Pre-operative radiotherapy should be standard treatment for patients with locally advanced and recurrent rectal cancer. Intra-operative radiotherapy should be considered for patients when narrow or incomplete margins are expected during surgery. Neo-adjuvant chemo-radiation therapy might further improve complete response and resection (R0) rates and as a result improve patient outcome.

P35
IS THERE IS A ROLE FOR PREOPERATIVE CHEMOTHERAPY IN LOCALLY ADVANCED UNRESECTABLE RECTAL CANCER
Samir Eid
Assiut University Hospital, Assiut, Egypt

Background and purpose:
To evaluate the role and efficacy of preoperative systemic chemotherapy alone in improving tumour response, sphincter preservation in patients with locally advanced cancer rectum.

Patients and methods:
29 patients diagnosed with locally advanced unresectable rectal cancer received preoperative 5FU by intravenous infusion 600 mg/m² D1-5, leucovorin 20 mg/m² D1-5 and cisplatin 80mg/m² D1 every 3 weeks for 3 cycles followed by surgical resection within median time 8 weeks. All patients received local radiotherapy after surgery. All patients assessed for tumour response as regards down staging and resectability and treatment toxicity and median disease free survival.

Results:
Study include 29 patients, with locally advanced rectal cancer most of them presented by T3 (18) patients and T4 (9) patients. After chemotherapy treatment 6 patients developed disease progression and secondries and 3 patients were unfit for surgery, 20 patients subjected to surgical interference aiming for cure 11 by anterior resection and 9 by A P. As regard response about 13 patients showed PR while no one showed CR. After one year follow up 12 patients were disease free. Toxicity of treatment were mild & will tolerated

Conclusion:
Pre operative chemotherapy alone can be effective in the management of locally advanced cancer rectum and sphincter preservation surgery through tumour down staging can be occurred. Radiotherapy is reserved for local control to minimize local recurrence after surgery.
TREND TO IMPROVED PATHOLOGICAL CR RATE WITH DOSE ESCALATION OF PREOPERATIVE CHEMORADIATION FOR RECTAL CANCER.

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2 University Toronto, Toronto, Canada
3 Princess Margaret Hospital, Department Medical Oncology, Toronto, Canada
4 Princess Margaret Hospital, Department Medical Oncology, Toronto, Canada
5 Princess Medical Hospital, Department Biostatistics, Toronto, Canada

Purpose of Study
Three consecutive phase II studies of preoperative radiation therapy and concurrent continuous infusion 5-Fluorouracil (5FU) with increasing dose were undertaken to assess acute toxicity and pathological complete response rate (pCR).

Methods
One hundred and thirty six patients with biopsy proven adenocarcinoma of the rectum, and radiological evidence (CT, MRI or TRUS) of tumor extension beyond the muscularis propria (T3/T4), or node involvement (N1/N2) were treated between January 31st 1998 and January 31st 2002. An initial cohort of patients received 40Gy in 20 fractions, a second 46Gy in 23 fractions, and a third 50Gy in 25 fractions. 5FU was given by continuous intravenous infusion (225mg/m²/day) 7 days a week, throughout the radiation. Patients were treated with a three or four field technique, radiation fields encompassing the gross tumor volume with a 3 to 5 cm margin. Surgery was planned for 4 to 6 weeks after completion and followed by 4 cycles of adjuvant 5FU and folinic acid.

Results
The mean age of patients was 62.4 years (range 34-83) and 81 (59.6%) were male. There was no statistical difference in patient demographics or tumour characteristics with the exception of fewer N1 patients in the third cohort.

<table>
<thead>
<tr>
<th>Radiation Dose</th>
<th>40Gy (n=47)</th>
<th>46Gy (n=53)</th>
<th>50Gy (n=36)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>T Stage (%)</td>
<td></td>
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<tr>
<td>2 (4.3)</td>
<td>2 (3.9)</td>
<td>1 (2.8)</td>
<td>0.76</td>
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<tr>
<td>40 (85.1)</td>
<td>48 (92.3)</td>
<td>32 (88.9)</td>
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<tr>
<td>10 (6.6)</td>
<td>2 (3.9)</td>
<td>3 (8.3)</td>
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<tr>
<td>N Stage</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>25 (53.2)</td>
<td>24 (45.3)</td>
<td>27 (75.0)</td>
<td>0.030</td>
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</tr>
<tr>
<td>18 (38.3)</td>
<td>25 (47.2)</td>
<td>5 (13.9)</td>
<td></td>
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<tr>
<td>4 (10.6)</td>
<td>4 (7.6)</td>
<td>4 (11.1)</td>
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<tr>
<td>M Stage*</td>
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<tr>
<td>43 (91.5)</td>
<td>50 (94.3)</td>
<td>35 (97.2)</td>
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</tr>
<tr>
<td>4 (8.5)</td>
<td>3 (5.7)</td>
<td>1 (2.6)</td>
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<td>Any toxicity (%)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>39 (83)</td>
<td>42 (79.3)</td>
<td>32 (88.9)</td>
<td>0.49</td>
<td></td>
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<tr>
<td>Pathological CR (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>7 (14.9)</td>
<td>10 (18.9)</td>
<td>11 (30.6)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>n (%) with APR** surgery</td>
<td>12 (25.5)</td>
<td>25 (47.2)</td>
<td>16 (44.4)</td>
<td>0.063</td>
</tr>
<tr>
<td>n (%) with wound complications</td>
<td>5 (10.6)</td>
<td>12 (22.6)</td>
<td>13 (36.1)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Liver lesions suitable for resection
** Abdominoperineal resection

Conclusion
Preoperative radiation with concurrent chemotherapy is well tolerated. The pCR for the entire cohort was 21. We did not demonstrate a dose response, although there was a trend towards improved pCR with increasing dose. An increase in wound complications with dose escalation was observed but when corrected for whether an APR was performed or not, this was not statistically significant. 50Gy in 25 fractions over 5 weeks with concurrent SFU infusion remains our standard.
P38
TWO YEARS’ FOLLOW UP RESULTS OF NEOADJUVANT CAPECITABINE AND RADIOTHERAPY IN LOCALLY ADVANCED RECTAL CANCER
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**Purpose:** 5-Fluorouracil (5-FU) is the most common chemotherapeutic agent used in the treatment of colorectal cancer, as either palliative treatment or adjuvant treatment with pelvic radiation for Dukes stage B and C rectal cancer. Radiation is used also as neo-adjuvant treatment to downstage a tumor before surgical resection to facilitate operability or sphincter-sparing surgery, and the use of 5-FU as a radiosensitizer is now widely accepted. Recently, two phase III clinical trials demonstrated equivalent response rate (RR), time to disease progression (TTP) and overall survival of capecitabine (Xeloda) to 5-FU/leucovorin (Mayo Clinic regimen) in patients with metastatic colorectal cancer. Xeloda has a tumor selective mechanism of action and was developed as an oral fluoropyrimidine carbamate capable of mimicking continuous 5-FU infusion.

**Methods:** We designed the protocol combining capecitabine and concurrent radiotherapy in locally advanced rectal cancer in neoadjuvant setting. The eligibility criteria were as follows: histologically verified rectal adenocarcinoma, locally advanced tumor (cT3-4, and/or N+), age 18-75 years, ECOG PS 0-2, normal hematological, biochemical parameters. The N status was evaluated by transrectal sonography. Capecitabine in a dose 825 mg/m^2 twice daily was given on days 1-38 concomitantly with pelvic radiotherapy 1.8 Gy daily up to 45 Gy followed by a 3-fraction boost up to the overall dose of 50.4 Gy. Radiation lasting 5-6 weeks was interrupted for weekends but capecitabine had been continued on weekend. The surgery was performed within 6 weeks after the completion of chemoradiotherapy.

**Results:** Since X/2001 58 patients were recruited for the therapy out of those 41 patients (pts) have been operated and their median follow up has reached 20 months so far. Median age reached 59 years, there were 29 males, 12 females. Radical resection of residual cancer has been done in 40 pts. Rectal amputation was performed in 17 pts, abdominoperineal resection in 14 pts and sphincter-saving resection in 15 pts. Pathological examination showed a pT0-T1 rate of 47.4%. Positive distal resection margin occurred after low anterior resection in the third patient who refused reoperation that would imply rectal amputation. Conclusions: The concomitant radiotherapy with capecitabine for locally advanced rectal adenocarcinoma demonstrated promising efficacy. The combination appears to be a safe therapeutic choice improving the possibility for the rectum sparing surgical procedure.

P39
DOWNSTAGING IN RECTAL CANCER TREATED WITH NEOADJUVANT FOLFOX-4 FOLLOWED BY CHEMORADIATION: ULTRASOUND ASSESSEMENT
G Pérez Manga, R García, FA Calvo, E Del Valle, JA Arranz, M Gómez-Espi, P García Alfonso
Hospital General Universitario Gregorio Marañón, Madrid, Spain

**Purpose:** To assess by endorectal ultrasound the effects of neoadjuvant treatment in locally advanced rectal cancer (LARC) using two consecutive modalities: induction chemotherapy alone followed by preoperative chemoradiation.

**Patients and Methods:** From February/2001 to October/2001 20 consecutive LARC patients were treated with induction FOLFOX-4 (x 2 cycles), followed by chemoradiation (45-50 Gy + oral Tegafur 1200 mg/day). Surgery was planned 4-6 weeks after the completion of chemoradiation. Endorectal ultrasound to assess neoadjuvant treatment effects were practised at initial staging (U1) and restaging after FOLFOX-4 (U2) and before surgery (U3).

**Results:** Ninety-five percent of patients were pT3-T4 staged by rectal ultrasound at diagnosis. Eight out of 20 patients (40%) had high rectal tumors (distant ≥ 8 cm from the anal margin).

<table>
<thead>
<tr>
<th>uT1</th>
<th>uT2</th>
<th>uT3</th>
<th>pT</th>
</tr>
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<tbody>
<tr>
<td>T0-1</td>
<td>4/17</td>
<td>9/20</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>2/16</td>
<td>5/17</td>
<td>2/20</td>
</tr>
<tr>
<td>T3</td>
<td>14/16</td>
<td>5/17</td>
<td>8/20</td>
</tr>
<tr>
<td>T4</td>
<td>0/16</td>
<td>0/17</td>
<td>0/20</td>
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<tr>
<td>TX</td>
<td>3/17</td>
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<tr>
<th>uN1</th>
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<th>uN3</th>
<th>pN</th>
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<tbody>
<tr>
<td>N-</td>
<td>8/20</td>
<td>9/17</td>
<td>14/19</td>
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<tr>
<td>N+</td>
<td>8/20</td>
<td>5/17</td>
<td>1/19</td>
</tr>
</tbody>
</table>

pT vs. uT1: $p = 0.006$ (McNemar test)
pN vs. uN1: $p = ns$

pT vs. uT3: Kappa = -0.340 (p = ns)
pN vs. uN3: kappa = 0.316 (p = ns)

**Conclusions:** In this serie, we showed a statistically significant downstaging T with neoadjuvant FOLFOX 4 followed by chemoradiation. However, a significant downstaging N could not be demonstrated. There was not a statistically significant concordance between the final T and N values predicted by endorectal ultrasound examination before surgery, and the T and N values observed in the histological examination, particularly in high rectal tumors.
P40
EFFECTIVENESS OF PREOPERATIVE DOWNSTAGING/DOWNSIZING NEOADJUVANT CHEMOTHERAPY AND CHEMORADIOThERAPY IN LOCALLY ADVANCED RECTAL CANCER.
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1 Kent Oncology Centre, Maidstone Hospital, Kent, United Kingdom
2 Royal College Of Physicians, London, United Kingdom
3 Royal College of Radiologists, London, United Kingdom
4 Royal College of Surgeons, London, United Kingdom
5 Medway Hospital, Kent, United Kingdom
6 University of London, London, London, United Kingdom

Introduction: Recognition of the importance of achieving a negative circumferential resection margin CRM, has established this as an important endpoint in the management of patients with rectal cancer. Patients with locally advanced (T3, T4, N+) and low rectal cancers have a higher risk of an involved CRM. Studies have demonstrated a positive CRM to be associated with a greater risk of local recurrence and poor survival. MRI has become an important imaging modality in accurately staging patients preoperatively, enabling detection of patients with locally advanced and low rectal cancers, who are therefore not candidates for immediate surgery. Preoperative neoadjuvant chemotherapy and chemoradiotherapy is now recognised as an effective strategy in downstaging/downsizing these tumours, and thus achieving a negative CRM. Cancer Unit Colorectal MDTs offer patients the most effective approach to achieve this important surgical endpoint. Neoadjuvant combination chemotherapy prior to chemoradiotherapy, can lead to a rapid symptomatic response, may reduce the requirement for defunctioning procedures and improve tolerance to chemoradiotherapy due to enhanced radiosensitivity.

Method: 50 consecutive patients, from January 2000 to date, selected for preoperative downstaging neoadjuvant combination chemotherapy and chemoradiotherapy, were identified from a prospective database. These patients were managed by two MDTs, linked to a single Cancer Centre and Oncology Team, following a single treatment protocol. Patients received combination neoadjuvant chemotherapy followed by a standard chemoradiotherapy schedule. Surgery was performed approximately 6 weeks after completion of the chemoradiotherapy. We present the histopathology results of this cohort following the definitive resection.

Results: This remains an ongoing prospective analysis. Of 35 patients analysed to date, 32 patients (91.4%) have undergone definitive resection with apparently curative resection ACR, 1 patient was considered to have a palliative resection and 2 patients (5.7%) were inoperable. Of the patients undergoing ACR, histological data demonstrated that 3 patients (9.4%) achieved pCR, 26 patients (81.2%) had residual tumour with a negative CRM and 3 patients (9.4%) had a positive CRM. To date 1 patient having an ACR has suffered a local recurrence and this patient has developed metastatic disease. The mean follow up for the patients analysed to date is 13 months from the time of definitive surgery.

Discussion: The prime objective of preoperative downstaging chemotherapy and chemoradiotherapy is to maximize the potential for an ACR and a negative CRM, and consequently reduce the risk of local recurrence and metastatic spread following definitive surgery. The ability to achieve a pCR is well recognised – 9.4% in our series. The pCR rate appears to relate to the use of combination chemotherapy and there is a radiotherapy dose response effect. The use of neoadjuvant chemotherapy prior to chemoradiotherapy has advantages and we have demonstrated that this approach is deliverable in a patterns of care study.

World Congress on Gastrointestinal Cancer 16-19 June 2004 Barcelona, Spain
Preoperative chemoradiation in LARC may produces downstaging and downsizing of the tumor, and offers patients (pts) the opportunity of a better local control and, in selected cases, sphincter sparing procedures. Oxaliplatin displayed radiosensitizing properties and significantly enhanced the antitumour activity of TS inhibitor, 5-FU and raltitrexed. In a previous dose-finding study we showed that Oxa (100 mg/m²) + TOM (2,5 mg/m²) + 5 FU (900 mg/m²) + LFA (250 mg/m²) given concomitantly to radiotherapy is a feasible approach for LARC in a preoperative setting (Avallone A, ASCO 2003). Therefore, a phase II study was started to determine the activity of this treatment in newly diagnosed patients with EUS- and MRI-defined LARC.

Methods and Patients: Eligible pts received three biweekly courses of OXA + TOM on day 1 and 5-FU + LFA on day 2 in combination with pelvic RT (45 Gy, 1,8 Gy/fraction x 25 fractions) Chemotherapy was always administered prior to radiotherapy and toxicity was evaluated weekly with NCI-CTC version 2. Total Mesorectal Excision was planned 6-8 weeks after chemoradiation. EUS and MRI was repeated after chemoradiotherapy. Pts with cT4, pN+ and clinical circumferential resection margin (CRM) also were evaluated 4 months of adjuvant 5-FU/LFA.

Results: 22 pts (12 female, 10 male) were recruited. Median age was 60, with PS (ECOG) 0-1. Clinical staging revealed T4, N+ and clinical CRM+ (< 5 mm defined with MRI ) respectively, in 3 pts, 17 pts (11 N1;6 N2) and 15 pts. So far, 22 pts were evaluable for EUS and MRI response and 21 pts have proceeded to TME. Downsizing of the tumor was detected in all pts. At pathological evaluation tumor regression away from CRM occurred in all but one pts, 9 pts showed a complete response (TRG 1), 11 pts a downstaging ( 8 TRG 2 and 3 TRG 3) and 2 pts a no stage variation ( 1 TRG 3 and 1 TRG 4). Safety findings were concordant to the phase I results with incidence of hematological NCI grade 4 in only 5 pts ( 5 Neutropenia) and non-hematological NCI grade 3 in 4 pts ( 3 diarrea and 1 stomatitis). These preliminary results show the extreme safety profile and efficacy of the used combination but a larger number of pts is needed. Updated results will be presented at the meeting.
RADIO CHEMOTHERAPY (RT-CT) IN CANCER OF THE RECTUM, ADMINISTERED DURING THE PRE OR POST OPERATIVE PEIOD, OUR RESULTS

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1 SSK Okmeydani Training Hospital, Department Of Radiation Oncology, Istanbul, Turkey
2 Servei D'Oncologia Radioteràpica, Barcelona, Spain
3 Servei De Cirurgia General I Digestiva, Barcelona, Spain

Between 1996 and 1999, 337 patients affected with cancer of the rectum were treated in our department. RT-CT was administered in 100 patients during the preoperative period and it was performed on 237 patients during the postoperative period.

The chemotherapy consisted of:

1. In the preoperative treatment 5FU 300mg/m2/day was administered in continuous infusion, 5 days a week for 5 weeks; after surgery: 5FU and LV (425/20) in bolus, 5 days a week, every 4 weeks for 4 cycles.

2. In the patients operated on: 5FU and LV (425/20), 5 days a week, for 6 cycles during radiotherapy. 5FU was administered in continuous infusion 225mg/m2/day, during the entire radiotherapy.

The distribution by stages is unfavourable to the RT-CT preoperative group, with 14 patients with non resectable disease and 73% of the cases were classified as T3N+. In the RT-CT postoperative group 35% were classified as pT3N+. However, the different method of staging use between the two groups must be taken into account.

The global survival at 5 years is 74.09% in the group of patients treated with post operative RT-CT and 74.86% when it is administered in the preoperative period (p=0.0623).

The global survival of patients treated with pre or postoperative RT-CT is not different when analysed with respect to the stages.

Survival free of disease at 5 years: 64.23% when RT-CT was administered in the postoperative period and 68.32% when it was performed in the preoperative period (p=0.4065).

The toxicity as regards late radical enteritis has been low: up until now and for the entire group of 337 patients, only 8 had to be intervened again because of this cause (2.4 %) and another 18 patients came to the hospital due to radical enteritis which was solved by conservative means (5.3 %).

In the group of patients treated with preoperative RT-CT, we have analysed survival according to the response to treatment prior to surgery. The global survival at 5 years is 83.55 % in the group that responded to the treatment and 52.87 % among those who did not respond (p=0.0007).

CONCLUSIONS:

1. We did not manage to see differences in survival in the patients treated with pre or postoperative RT-CT, which is in concordance with what has been published up until now.

2. The late toxicity in our series has been low, with a late toxicity G IV of 2.4 % and 5.3 % as G III.

3. The differences observed in the survival of patients treated with pre-operative RT-CT among those that respond and those who do not, obliges us to study genetic response markers so that we can design better plans of treatment.

ANALYSIS OF OUR HEPATOCELLULAR CARCINOMA CASES

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1 SSK Okmeydani Training Hospital, Department Of Radiation Oncology, Istanbul, Turkey
2 SSK Okmeydani Training Hospital, Department Of Gastroenterology, Istanbul, Turkey

Introduction: We have designed a form to evaluate the characteristics and to observe their prognosis of our hepatocellular carcinoma cases at the end of 2002. This study involved the patients applied between 28.11.2002 – 31.12.2003.

Patients: 49 patients were applied in this period and 41 of them ( 84 % ) have valuable data. Median age was 61 ( 28–77 ), 33 of them ( 80.5 % ) were male. Although 65.9 % of them ( 27 cases ) had history of tobacco usage, just 9.8 % of them ( 4 patients ) were alcohol dependent. Their hepatitis virus infection status were HBV ( 46.3 % ) and HCV ( 12.2 % ). Approximately one fourth of them ( 26.8 % ) were cirrhotic. Mostly they were in late stages of disease ( Stage IVA: 48.8 % ). For of them ( 4.8 % ) had metastasis. According to Pugh-Child's classification; percentage of A, B and C were 1- In the preoperative treatment 5FU 300mg/m2/day was administered in continuous infusion, 5 days a week for 5 weeks; after surgery: 5FU and LV (425/20) in bolus, 5 days a week, every 4 weeks for 4 cycles.

2- In the patients operated on: 5FU and LV (425/20), 5 days a week, for 6 cycles during radiotherapy. 5FU was administered in continuous infusion 225mg/m2/day, during the entire radiotherapy.

Results: Due to detection of disease was so late in most of the patients; majority of cases were received symptomatic treatment. Just 4 of the patients underwent surgical procedures ( 2 complete and 2 partial response ). Chemotherapy were attempted in 10 cases ( 24.4 % ). But stabilization could be managed only in 3 cases. In selected patients, chemoembolization had better results ( we have got stabilization in 4 of 5 cases )

Conclusions: Hepatocellular carcinoma is rather rare but highly progressive tumor. In times of diagnosis, it is detected in late stages and due to patients' age and performance status, it is so difficult to keep it under control by means of radical treatments. As a result; survival data has been so disappointing yet.

World Congress on Gastrointestinal Cancer 16-19 June 2004 Barcelona, Spain
P46  
**A PROSPECTIVE RANDOMIZED TRIAL OF GEMCITABINE ALONE OR GEMCITABINE + CISPLATIN IN THE TREATMENT OF METASTATIC PANCREATIC CANCER**  
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Purpose: To determine the efficacy and toxicity of gemcitabine alone (GEM) versus GEM + cisplatin (G + C) in the treatment of metastatic pancreatic cancer.  
Methods: From Jan-98 to Jun-02, 46 patients with metastatic pancreatic cancer were studied. Twenty-five patients were randomized to receive GEM (1000 mg/m²/week × 3 every 4 weeks), and 21 patients to G + C (GEM 1000 mg/m²/week and cisplatin 25 mg/m²/week × 3 every 4 weeks). The primary endpoint was patients' survival.  
Results: The planned accrual was 24 patients per arm. The reported accrual was 25 patients in GEM group and 21 in G + C group. The median duration of follow-up was 5.3 months. Sex, age, pre-treatment serum biochemistries, tumor size and location, and performance status were similar between both groups. Gemcitabine dose intensity was similar between GEM and G + C (684 ± 32 vs 617 ± 31 mg/m²/wk). Cisplatin dose intensity was 15.1 ± 0.9 mg/m²/wk × 9.9 ± 1.8 weeks. Median survival and median time to progression (TTP) were 4.6 months and 2.8 months for GEM and 5.6 months and 2.8 months for G + C patients (p = 0.75 and p = 0.9). Clinical benefit (including pain control, performance status, and body weight gain) was 36% for GEM and 29 % for G + C (p > 0.05). Quality-adjusted-life-months survival was 5.6 ± 0.3 months for GEM and 3.8 ± 0.2 months for G + C patients (p < 0.01). Response rates were 12% (3 PR) for GEM and 10% (2 PR) for G + C patients (p > 0.05). Grade 3-4 neutropenia (8% vs 19%), anemia (8% vs 10%) or hospitalization days per month of survival (6.8 ± 2.2 vs 6.2 ± 1.6 days) was not significantly different between GEM and G + C patients, but G + C had higher rate of thrombocytopenia than GEM patients (24% vs 4%, p = 0.012). Conclusions: GEM and G + C had comparable and modest response rates for metastatic pancreatic cancer, but GEM produced lesser toxicities than G + C.

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P47  
**RADIOTHERAPY AND GEMCITABINE IN PATIENTS WITH ADENOCARCINOMA OF THE PANCREAS: PHASE I STUDY**  
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Purpose: This open-label, non-comparative, dose-escalation study aimed to determinate maximum tolerated dose and recommended dose of twice-weekly gemcitabine and concomitant external-beam radiotherapy in patients with unresectable adenocarcinoma of the pancreas.  

Material and methods: A total of 12 patients with biopsy-proven adenocarcinomas of the pancreas have been enrolled. Patients were treated with external-beam radiotherapy to a dose of 50.4 Gy in 28 fractions of 1.8 Gy/fraction, 5 days-week, previous simulation with oral contrast agent and CT scan with 5 mm slice. Three or four fields were used with 3D conformational technique, energy 15-MV photon; for each patient dose-volume histogram (DVH) was calculated to verify and optimise the radiation plan. Dose to the critical organs should not exceed for liver 30 Gy to more than 50% of its volume and 20 Gy to the whole kidney, maximum dose to any area of the spinal cord was limited to 45 Gy. Gemcitabine infusion was completed within 30 min before radiotherapy on Monday and Thursday. Gemcitabine was escalated at following dose level: 20 mg/m² (n=3 pts), 40 mg/m² (n=3 pts), 60 mg/m² (n=6 pts).  

<table>
<thead>
<tr>
<th>Gemcitabine (mg/m²)</th>
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<tr>
<td><strong>Toxicity (grade)</strong></td>
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<tr>
<td>Nausea/vomiting</td>
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Two cases of grade 3 toxicity were observed at gemcitabine dose of 60 mg/m² and so three other patients underwent at the dosage of 60 mg/m². None of them showed grade 3 toxicity. One patients had radiographic evidence of response to treatment, 5 had stable disease, 4 progressed and 2 patients were not yet evaluated for response.  
Conclusion: The combination of external-beam radiotherapy and twice-weekly gemcitabine at a dose of 60 mg/m² is well tolerated in our experience.
P48

SALVAGE TREATMENT IN GEMCITABINE RESISTANT PANCREATIC CANCER
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Purpose: this study evaluated the activity and toxicity of an irinotecan (CPT-11) and oxaliplatin (OXA) combination in patients (pts) with advanced pancreatic cancer (APC), progressed despite at least one chemotherapeutic line containing gemcitabine (GEM).

Patients and methods: thirty pts with APC, who progressed while receiving GEM, were enrolled onto this phase II study. Pts received OXA 60 mg/sqm on days 1 and 15, and CPT-11 60 mg/sqm on days 1, 8 and 15, every 4 weeks. Pts were evaluated for objective tumor response, changes in serum tumor marker CA 19-9, clinical benefit response, time-to-treatment progression (TTP), survival (OS) and safety.

Results: three pts (10%) had a CT scan partial response (PR) and 7 (23%) had stable disease (SD). CA 19-9 decreased more than 50% of baseline value in 8 pts (26%). Six pts (20%) had an average clinical benefit response lasting 7,2 months (range 4-15,1). Median TTP was 4,1 months (range 0,7-13,1). Median OS was 5,9 months (range 0,7-46,2+) and the 1-year survival rate was 23,3%. Median survival from diagnosis was 16,1 months with 1-year and 2-year survival rates of 57% and 30% respectively. One patient was downstaged and submitted to radical surgery. Therapy was well tolerated with grade 3-4 hematological toxicity in 3/30 pts (10%), grade 3 diarrhea in 1 (3%), and grade 3 neuropathy in 2 (6%).

Conclusions: the combination of CPT-11 and OXA in pts with advanced pre-treated pancreatic cancer is active and well tolerated. Further studies are awaited.

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INNOVATIVE TREATMENT OF BILIARY TREE CANCER: INTRA-ARTERIAL COMBINED WITH SYSTEMIC CHEMOTHERAPY
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Background: prognosis of advanced biliary tract cancer (ABTC) is very poor. Aim of this study is to evaluate the effectiveness of regional CHT combined with systemic CHT in patients (pts) with ABTC. Methods: from January 2000 to February 2004, we treated 28 pts with the combination of intra-arterial CHT (Epirubicin 50 mg/sqm and Cisplatin 60 mg/sqm, infused bolus by angiographic catheter introduced in proper hepatic artery, on day 1) and e.v. continuous infusion of 5-Fluorouracil 200 mg/sqm/day, from day 1 to day 14. Cycles were repeated every 3 weeks. Fifteen pts were male, 13 female; the median age was 65 years (range 49-75). The performance status was 0-1 in 19 patients, 2 in 9. All had histological confirmed ABTC; 23 pts had cholangiocarcinoma and 5 pts had gallbladder carcinoma, with liver involvement > 50% in 10 and < 50% in 18 pts; three pts had peritoneal involvement, 3 had pleural metastases and 2 had bone involvement.

Results: one hundred twenty eight cycles were administered; no side effects related to angiographic procedure were observed, while 6 cases of deep venous thrombosis related to central venous catheter occurred. Moreover 1 grade 3 leukopenia, 2 grade 3 mucositis and 4 grade 3 alopecia occurred. Two pts are too early for evaluation; the overall response rate, including complete response (CR) partial response (PR) and stable disease (SD) was 21/26 (80%); one patient had CR, evaluated by positron emission tomography (PET), 8 pts had PR, 12 had SD and 5 showed a progression of disease. The CA 19-9 level decreased more than 50% in 11 of 16 evaluable cases (68%). After a median follow-up of 27 months, median survival is 11 months and 1 and 2-years survival is 47% and 12%, respectively. Median time to progression is 7 months (range 1-19). Conclusion: this combined regimen appears feasible and safety and shows an interesting response rate and survival, in pts with ABTC.
A MULTICENTER PHASE II TRIAL OF CAPECITABINE PLUS OXALIPLATIN IN ADVANCED BILIARY SYSTEM ADENOCARCINOMAS

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Objective: To evaluate the feasibility of capecitabine and oxaliplatin combination therapy (CapOx) in unresectable or metastatic adenocarcinomas of the biliary system.

Methods: 56 pts (25M, 31F) were included (median age, 63 yrs). Major eligibility: histologic proven, measurable disease, age ≤ 75 yrs, ECOG PS ≤ 2. A total number of 250 cycles (median: 5; range 1-16) of oxaliplatin (130 mg/m², d1) plus capecitabine (2000 mg/m², d 1-14) were administered 3 weekly for gallbladder carcinoma (GBC) (20 pts), extrahepatic (20 pts), and intrahepatic (16 pts) cholangiocarcinoma (CCC). Pts were assessed for response according to WHO standard criteria. Clinical outcome was determined separately for pts with either GBC/extrahepatic CCC or intrahepatic CCC (mass-forming type), because these two distinct presentations have been supposed to differ substantially from each other according to clinical behaviour.

Results: Grade 4 toxicities (WHO) were diarrhea in 1 pt (1% of cycles), thrombocytopenia in 1 pt (1%), leukopenia in 1 pt (1%), and fever in 2 pts (1%); grade 3 toxicities were: diarrhea in 2 pts (1%), thrombocytopenia in 3 pts (2%), and fever in 1 pt (1%). Grade 3/4 peripheral sensory neuropathy (Lévis scale) was found in 10 pts (15%). Two pts were removed from study due to oxaliplatin-related allergic reactions. One patient with intrahepatic CCC died due to sepsis after the first treatment cycle. The overall disease control rate on 31 evaluable pts with GBC or extrahepatic CCC was 77% (complete response (CR), n=2 (6%); partial response (PR), n=7 (23%); stable disease (NC), n=15 (48%); whereas progressive disease (PD) was found in 7 pts (23%). In 16 evaluable pts with intrahepatic mass-forming CCC, we observed no CR or PR, but 4 pts (25%) had SD, and in 12 pts (75%) PD was encountered.

Conclusions: Our preliminary data suggest the CapOx regimen to be well tolerable and highly active for advanced GBC and extrahepatic CCC (disease-control rate: 77%), whereas outcome might be poorer in intrahepatic mass-forming CCC. Survival data will be presented at the meeting.
CONCURRENT CHEMORADIATION IN UNRESECTABLE PANCREATIC CARCINOMA: IMPACT OF RADIATION DOSE ON CLINICAL OUTCOME

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Purpose. A phase I-II dose escalation study was carried out to evaluate the possible impact of the dose on toxicity, pain relief and outcome in patients with unresectable pancreatic carcinoma.

Methods and Material. 50 patients entered the study. External beam dose was 39.6 Gy in the first 15 patients, 50.4 Gy in the successive 15 patients, and 59.4 Gy in the remaining 20 patients, five 1.8-Gy fractions weekly. During external-beam radiation therapy patients received concurrently continuous infusion of fluorouracil (1,000 mg/m2/days 1-4 and 21-24). Patients were evaluated for toxic reactions, local control of disease, survival and pain relief.

Results. There were no treatment-related deaths due to acute toxicity. Four patients required temporary treatment interruption due to acute hematological (2 pts) or gastrointestinal (2 pts) toxicity, not correlated with the delivered radiotherapy dose. Three patients (6%) developed late toxicity (duodenal ulcer: 2 pts; duodenal stenosis: 1 pt). All patients who developed late toxicity had received a dose of 59.4 Gy. At univariate analysis, only the radiotherapy dose was significantly correlated with the incidence of late toxicity (at 2 years: 39.6-50.4 Gy: 0%; 59.4 Gy: 52.8%; p=0.023). At multivariate analysis also, the radiotherapy dose showed a trend with the incidence of late side-effects (p=0.052). Overall, 6 patients showed partial response (12%) while 44 (88%) were no change. Overall response rate was 8.0% (CI 1.5%-20.5). The rate of response was not different in the three groups. In-field local-regional disease progression was seen in 7 patients (14%). Distant relapse was described in 34 patients (68.0%). None of analyzed variables and in particular the radiotherapy dose delivered, showed a significant correlation with the objective response, local control, incidence of metastasis, disease-free survival, overall incidence of pain symptoms after therapy. The whole group median survival was 9 months. Actuarial survival at 1, 2 and 3 years was 31.3%, 28.8% and 0.0%, respectively. None of analyzed parameters was shown to be significantly correlated with survival at uni- or multivariate analysis.

Conclusion. In a phase I-II study the association of high radiotherapy doses with the incidence of severe toxicity in the treatment of unresectable pancreatic carcinoma, was confirmed. Furthermore, this study of dose escalation did not document a clearcut correlation, in 5-FU based chemoradiation, between radiation dose and clinical outcome.
**P54**
**NEOADJUVANT CHEMORADIATION PLUS IORT IN PANCREATIC CARCINOMA: DEFINITIVE RESULTS**

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3 Surgery Department, Università Cattolica S. Cuore, Roma, Italy

**Purpose:** In recent years preoperative chemoradiation gained a growing interest in the treatment of locally advanced pancreatic cancer. In the attempt to improve resectability and disease control, we used preoperative radiation therapy (RT) and concomitant 5-fluorouracil (5-FU) in a combined modality therapy protocol. Aim of this study was to evaluate definitive results in terms of toxicity, response and clinical outcome.

**Material and Methods:** 28 patients with unresectable (cT4: 19 patients) or resectable (cT3: 9 patients) non-metastatic pancreatic tumors, received RT (39.6 Gy) plus 5-FU (continuous infusion, days 1-4 at 1000 mg/m²/day). After 4 weeks, patients were evaluated for surgical resection. In 9 resected patients, electron-beam Intra-Operative RT (10 Gy) was given before reconstruction. Thereafter, in resected patients, adjuvant chemotherapy (AMF) was prescribed.

**Results:** During chemoradiation, 1 patient (3.6%) developed grade 3 acute gastrointestinal toxicity and 2 patients (7.1%) developed grade 3 hematologic toxicity. Three out of 19 patients with unresectable tumors had tumor downstaging. Two patients (7.1%) showed partial response and 4 patients (14.3%) had minimal tumor response. Four patients (14.3%) showed progression disease after chemoradiation. Four patients (14.3%) showed progression disease after chemoradiation. One postoperative death was recorded. The median survival time was 11.3 months (21.5 and 9.0 months in resected and unresected patients, respectively).

**Conclusion:** Although the response-rate is still low, our preliminary results suggest that preoperative 5-FU chemoradiation is well tolerated and may result in tumor downstaging.

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**P55**
**COMBINED MODALITY TREATMENT IN BILIARY CARCINOMA: FIVE-YEAR RESULTS.**

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**Purpose.** The aim of this study was to evaluate long-term effects of chemoradiation and intraluminal brachytherapy in terms of local control, disease-free survival, overall survival and symptom relief in patients with unresectable or residual extrahepatic biliary carcinoma.

**Methods and Materials.** Twenty-two patients (16 males, 6 females; mean age 60.1±12.0 years; median potential follow-up 108 months, range: 62-142 months) with unresectable (17 patients) or residual (5 patients) nonmetastatic extrahepatic bile tumors (common bile duct: 8; gallbladder: 1; Klatskin's tumor:13) received external beam radiation therapy (39.6-50.4 Gy). In 21 patients, 5-fluorouracil (96h continuous infusion, days 1-4, 1,000 mg/m²/day) was administered. Twelve patients received a boost of intraluminal brachytherapy using 192Ir wires (30-50 Gy) 1 cm from the source axis.

**Results.** During external beam radiotherapy, 10 patients (45.4%) developed grade 1-2 gastrointestinal toxicity. In patients with unresectable tumor who could be evaluated, the clinical response was 28.1 % (4/14). Two patients showed complete response. In all 22 patients, median local control, disease-free survival and overall survival were 44.5 months, 16.3 months and 23.0 months, respectively. Distant metastasis appeared in 12 patients (54.5%). Two patients who received external beam radiation therapy and intraluminal brachytherapy developed late duodenal ulceration. In patients with unresectable tumors, median survival was 13.0 months and 14.5 months in those treated with and without brachytherapy, with 16.7% and 0.0% five-year survival, respectively (p=0.607). Overall five-year survival was 18.0%: 40% and 11.7% in patients treated with partial resection and in those with unresectable tumor, respectively (p=0.135).

**Conclusion.** This study confirmed the role of concurrent chemoradiation in advanced biliary carcinoma, while that of intraluminal brachytherapy boost remains to be further analyzed in larger clinical trials.
P56
OXALIPLATIN FOR PRETREATED PATIENTS WITH ADVANCED OR METASTATIC PANCREATIC CANCER: A MULTICENTER PHASE II STUDY
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Hellenic Oncology Research Group, Heraklion, Greece

Purpose: A phase II study was designed to evaluate the efficacy and safety of oxaliplatin as second-line treatment in patients with locally advanced or metastatic pancreatic cancer. Patients and Methods: Eighteen patients with advanced pancreatic cancer previously treated with gemcitabine-based chemotherapy, received oxaliplatin 130mg/m² i.v. every 21 days. Patients were treated until tumour progression or unacceptable toxicity. Results: No objective response was observed among the 18 treated patients. Three (16.7%) patients had stable disease for more than 2 months. A clinical benefit response was observed in five (27.7%) patients. Toxicity was mild. Conclusions: Oxaliplatin as second-line treatment for patients with unresectable pancreatic cancer is well tolerated and associated with improvement of tumor-related symptoms despite its failure to induce objective responses. LOHP merits further investigation in combination with other drugs as palliative treatment of pre-treated patients with advanced pancreatic cancer.

P57
TREND OF LIVER CANCER AND ITS MANAGEMENT- BANGLADESH PERSPECTIVE
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Introduction:- Liver cancer is a grave disease with high mortality rate and striking geographical variation in the overall incidence. High incidence areas are primarily sub Saharan Africa and far east Asia. The incidence in Bangladesh was found below 5/100,000/year.

Purpose of study:- The aim of this study was to highlights the incidence and management of liver cancer (both primary and secondary) in Bangladesh.

Methodology:- A total of 118 patients suffering from liver cancer those attended NICRH during the period January to December, 2000 were enrolled in the study. NICRH is the biggest cancer hospital in Bangladesh. Also it is centrally placed and well communicated.

Results:- In the said period total number of liver cancer was found 118, which was 1.75% of total cancer cases. Age distribution of cases varies from 27 to 85 years, majority (33.39%) being in the 55-64 years of age group. Primary Hepatocellular carcinoma (HCC) was noted in 36 cases which is 30.51% of total liver cases and the rest were secondary lesions mostly from gastro intestinal tracts. Majority of cases (85.59) were presented in late or advanced stage (stage 3 & 4) and were treated with cytotoxic chemotherapy and in few cases by radiotherapy. 17 cases (14.41%) cases were presented in early stage ( stage 1&2) and were treated by resection surgery and chemotherapy in few cases. RFA (Radio Frequency Ablation) was consider in limited cases, only in 6 cases in this series. Chemotherapeutic agents used commonly were- 5Fluro-uracil, Leucovorin, Doxorubicin, Mitomycin-C, Cisplatin etc. Less commonly used drugs were- Iphosphamide, Etoposide, Irinotican, capecitabine, Docetaxel etc. Radio therapy dose ranges from 3000 to 4400 cGy in multiple fractionations at megavoltage unit.

Conclusion:- Primary liver cancer is still insignificant in Bangladesh but a large number of secondary cases are there. In the management procedure surgery, chemotherapy and radiotherapy all play the role but chemotherapy is still widely practiced.
P58
ADJUVANT CHEMORADIATION OF PANCREATIC CANCER IN A REALISTIC SETTING: 
RESULTS FROM A COMPREHENSIVE CANCER CENTER IN A POPULATION BASED 
SERIES.

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Background:
Recent report of ESPAC-1 results in the adjuvant setting in pancreatic cancer has questioned the real paper of chemoradiation after complete resection of pancreatic head cancer. We report our results in a single-institution, comprehensive cancer center in a population based series.

Methods:
Between 1996 and 2001, 37 patients with pancreatic head cancer were treated with adjuvant treatment after curative resection. Patients received adjuvance starting before the 8th week post resection. Radiotherapy consisted on 5 weeks of 1.8 Gy daily fractions. Patients with node positive or T4 cancers were treated with 41.4 Gy (26/36 pts-72.3%) and those with positive node status (26/37, 70.3%) or T4 (7/37, 18.9%) received adjuvant chemoradiotherapy. Of those, 33/36 pts (91.7%) finished treatment (3 patients progressed during treatment; 8.3%) with excellent tolerance (toxicity G3-4 in 1 patient -3%-) and without stopping treatment. With a median follow-up (considering those alive) of 3.8 yr, time to recurrence had a median of 11.87 months (10.09-13.64). The 3-years disease free survival was 18.31%. Recurrence was loco regional (8/29), metastasic (10/29) -mainly hepatic-, or both (11/29). Treatment for advanced disease was administered to 10/29 with Gemcitabine. Median survival was 16.43 months (12.35-20.52), One year and three years survival estimates were 72.6% and 29.58% respectively.

Conclusions:
We report the results of chemoradiation in a population based series whose results are similar to those reported in clinical trials. When treated by expert surgeons and dedicated oncologists, adjuvance is feasible and beneficial to selected patients. More effective treatments must be clear and firmly defined, and meanwhile chemoradiation is a good alternative.

P59
FUNCTIONAL IMAGING-GUIDED RADIATION THERAPY (RT) FOR THE PREOPERATIVE 
TREATMENT OF PRIMARY LIVER TUMORS.

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Liver cancer frequently presents as an advanced stage disease. Primary resection is available only for a minority of patients and novel strategies incorporating preoperative cytotoxic treatment for tumor downsizing allowing complete resection and reduced relapse rates are warranted. Imaging-guided preoperative RT for primary liver tumours has been shown to be feasible, leading to significant tumour volume reduction (Robertson et al. J Clin Oncol, 11:1286). Furthermore, 18F-fluoro-deoxy-2-glucose (FDG) - positron emission tomography (PET) has been shown to appropriately define tumor tissue with high sensitivity in a variety of cancer. We have shown that PET/CT-based planning leads to more homogenous target volume definition between oncologists in several cancer entities (Ciernik et al. IJROBP 57:853). However, despite the sensitivity of the PET, the PET signal may cause difficulties in regard of the interpretation of the tumor volume compared to the tumor volume as suggested on the computer-assisted tomography (CT) or magnetic resonance imaging (MRI). We have initiated a phase II trial investigating the possibilities to improve tumor volume assessment using the PET signal from an integrated PET/CT planning system for tailored, PET-based RT for the preoperative treatment of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. The rational, techniques and potential of imaging-guided radiation therapy for liver tumors will be presented.
Results of treatment of advanced BTC patients (pts) are dismal. First-line chemotherapy, including Fluorouracil (FU) and/or Gemcitabine (GEM), shows inconsistent Partial Response (PR) rates according to WHO/RECIST criteria, with occasional Complete Response (CR). Even less frequent are CRs after second-line chemotherapy. Oxaliplatin (OX) aimed interesting results in BTC pts in limited experiences. We recently observed CR in 2 BTC pts (pretreated with FU+GEM) after OX alone or with GEM.

**CASE 1**: E.C., female. On 04.2000 (age 68) diagnosis of advanced unresectable gallbladder carcinoma involving liver hilus (biopsy of gallbladder and lymphnodes = carcinoma; Ca19.9=254 U/ml); treated with GEM + continuous infusion (c.i.) FU with PR at Computed Tomography (CT) evaluation (normal Ca19.9), then undergoing radical surgery (12.2000)(ypT3pN0; no residual disease). After adjuvant GEM alone, biochemical (Ca19.9=80) and imaging (CT=abdominal mass) relapse on 04.2002 treated with GEM+c.i.FU, obtaining normal Ca19.9 and PR at CT not resected due to pt refusal → on 2002-2003 years: twice new (CA19.9 and CT) progression of disease (PD) and twice new PR (with transient Ca19.9 reduction to normal values) after GEM+c.i.FU → massive abdominal PD on 09.2003 (Ca19.9=211, abnormal CT and PET) → 6 courses of GEMOX (GEM 1000 mg/sm d1 + OX 100 mg/sm d2, q 14d) → CR at PET evaluation (Ca19.9=59) → further 4 courses → confirmed CR at PET CT restaging on 03.2004 (Ca19.9=52). **CASE 2**: V.M., male. On 12.2002 (age 51) jaundice and diagnosis of advanced unresectable BTC with hepatic lesions (biopsy = G3 carcinoma), treated with biliary stent and GEM + c.i. FU → PR after 3 courses → after 6th course; on 10.2003, jaundice and CT progression (CEA=1752 ng.ml, Ca19.9=429; ECOG PS=2) → new stent and weekly OX (50 mg/sm/week) → after 2 months (01.2004); CR at restaging CT (no liver lesions)(CEA=28, Ca19.9=37; ECOG PS=0) → further 2 months of weekly OX → liver PD on 03.2004 (CEA=27, Ca19.9=71; PS=0). **CONCLUSIONS**: OX is able to obtain palliative effect on pretreated advanced BTC pts and its evaluation on first-line setting in large multicenter series is warranted.
NO CORRELATION BETWEEN TNM CLASSIFICATION OR PERINEURAL INVASION AND SURVIVAL AFTER CURATIVE RESECTION FOR PANCREATIC CARCINOMA

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Purpose of the Study
The purpose of this study was to evaluate a correlation between pathological TNM classification and survival rates after curative resection for pancreatic cancer. Moreover, biological activity of gemcitabine and FU is schedule-dependent. Phase II studies with gemcitabine-based polichemotherapy in advanced/metastatic pancreatic cancer showed, as compared with single agent gemcitabine, an improved survival and response rate. In these studies varying proportions of patients with locally advanced disease and good performance status were included, while patients with bad prognostic factors, i.e. ascites and migrants thrombosis, were generally not mentioned. In light of these issues, we designed a new schedule to explore a cisplatin, gemcitabine and 5-fluorouracile combination chemotherapy in patients with advanced/metastatic poor prognosis pancreatic cancer. The end-points of the study were survival rates at 6, and 12 months and progression free survival estimate.

Description of the project
Forty consecutive patients, who underwent a Whipple resection for a pancreatic carcinoma, were evaluated retrospectively. Twenty-nine patients were male, 11 were female. The median age was 64.5 years at the time of surgery. An independent pathologist redefined their TNM classification and perineural invasion. Seventeen of 40 patients did not receive any treatment during follow-up time. Twenty-one patients received the following treatment in the course of their diseases: either gemcitabine alone (n=5), gemcitabine + radiation therapy (n=4), gemcitabine + Alimta (n=4), gemcitabine + Tomudex (n=4) or a combination of these therapies (n=6). Their disease free survival and overall survival were compared and correlated with the pathological TNM-classification and presence of perineural invasion.

Results
Twenty-nine patients were staged as T3, 4 were staged as T2, 5 as T1 and 2 as Tx. Seventeen patients were staged as N0 for nodal status, 18 as N1 and 5 as Nx. Median age, T-status and N-status did not differ among the groups. One patient died immediately post-operative. One patient was lost for follow-up. In the group without any treatment after resection (n=17), the mean disease free survival was 19.1 months (95% CI 11.5 - 26.7 months) and the mean overall survival was 21.7 months (95% CI 14.3 - 29.1 months). In the other group the mean disease free survival was 9.7 months (95% CI 5.9 - 13.6 months), and the mean overall survival was 17.8 months (95% CI 13.9 - 21.7 months). Using Mann-Whitney test to compare these data, a significant difference was found in disease free survival (P=0.029), but not in overall survival (P=0.581).

Perineural invasion could be confirmed in 24 of 36 patients, and was absent in 10 of 36 patients. In 4 patients no definite conclusions could be drawn and were excluded for the analysis. In the group with perineural invasion the mean disease free survival was 11.7 months (95% CI 7.9 - 15.9 months) and the mean overall survival was 18.1 months (95% CI 15.7 - 23.3 months). There was no statistical significant difference between disease free survival and overall survival rates according to neither T-status nor N-status.

Conclusions
In this group of patients, there was no significant correlation between TNM classification and disease free survival or overall survival. There was also no significant correlation between perineural invasion and disease free survival or overall survival.

CISPLATIN, GEMCITABINE AND 5-FLUOROURACILE 24H IV CONTINUOUS INFUSION IN ADVANCED PANCREATIC CANCER.

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Preclinical evidences suggest synergistic or greater than additive activity with combination chemotherapy of cisplatin, gemcitabine and 5-fluorouracile (FU). Moreover, biological activity of gemcitabine and FU is schedule-dependent. Phase II studies with gemcitabine-based polichemotherapy in advanced/metastatic pancreatic cancer showed, as compared with single agent gemcitabine, an improved survival and response rate. In these studies varying proportions of patients with locally advanced disease and good performance status were included, while patients with bad prognostic factors, i.e. ascites and migrants thrombosis, were generally not mentioned. In light of these issues, we designed a new schedule to explore a cisplatin, gemcitabine and 5-fluorouracile combination chemotherapy in patients with advanced/metastatic poor prognosis pancreatic cancer. The end-points of the study were survival rates at 6, and 12 months and progression free survival estimate. Tumor responses and toxicity were categorized according to RECIST and NCCI common criteria, respectively. Twenty-three patients with locally advanced (n =3) and metastatic pancreatic cancer (n =20) were enrolled. Ascites and thrombosis were present in 8 patients. All censored patients had >12 months follow-up. Treatment consisted of cisplatin 45 mg/m2 IV followed after a three hour rest by gemcitabine 900 mg/m2 IV and FU 1000 mg/m2 IV 24h continuous infusion on days 1 and 8 of each 21-day cycle. Objective partial responses and stable disease were observed in 7 and 7 patients, respectively. The median PFS estimate (Kaplan-Meier) was 4 months (95% CI 2-6 months) for all patients, and 4 months (95% CI 3-5 months) for metastatic patients. The median OS estimate was 8 months (95% CI 6-10 months), with 69% of patients surviving at 6 months and 30.4% at 12 months; when only metastatic patients were analyzed, the median OS estimate was again 8 months (95% CI 4-12 months). Grade 3-4 haematological and non-haematological toxicity occurred in 56.5% of patients; three patients were hospitalized for treatment-related complications. This chemotherapy combination has significant activity in patients with advanced pancreatic cancer. Toxicity results need further evaluation.
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RADICHEMOTHERAPY FOR PANCREATIC CANCER
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Purpose: The treatment for pancreatic carcinoma is multimodal. Chemoradiation has been constantly used in the last decades, both as an adjuvant or a neoadjuvant approach. The goal of our study is to assess the efficiency and toxicity of CRT in the management of the patients with PC after radical or palliative surgery.

Materials and methods: 30 patients with locally advanced pancreatic cancer and Karmofsky ≥50 were treated in our institute between February 2000-March 2003. 10 patients were completely resected. At the moment of the diagnosis 20 patients presented with locoregional advanced disease with no distant metastasis. Median age was 52 years, gender: 20 male and 10 female. The treatment consisted in concurrent radio- and chemotherapy.

External beam radiotherapy was delivered to a total dose of 50.4Gy. 5 patients received HDR brachytherapy with a dose of 15Gy.

Chemotherapy schedule was: Gemcitabine in weekly administration 1000mg/m2 days 1,8 and 15, repeated at 28 days for 6 cycles.

We evaluated toxicity related to the treatment, rate response, clinical benefit of the response, time to progression and overall survival. Median follow-up was 12 months.

Results: There was no complete response, 13 patients (65%) partial response, stable disease 3 patients (16%) and 4 patients with progressive disease (19%). From the 13 patients with partial response, 2 patients (10%) became resectable. From the patients with radical surgery and adjuvant radiochemotherapy, 8 patients were disease free at 1 year and 2 patients had local relapse.

Time to progression was 10 months.

We measured toxicity on WHO scale. We had: 3-4 grade toxicity neutropenia 16%, thrombocytopenia 11%, diarrhea 27%. Clinical benefit was registered at 26 patients.

Conclusions: concurrent radiochemotherapy in pancreatic cancer was well tolerated, increases the quality of life, leads to a clinical benefit to the patient.

Key words: radiochemotherapy (CRT), gemcitabine, pancreatic cancer (PC)

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CAN 3D-CONFORMAL PLANNING FOR EBRT AND HDR BRACHYTHERAPY WITH CT-MR FUSION AND DVH ANALYSIS PROVIDE TUMORICIDAL DOSE WHILE RESPECTING LIVER TOLERANCE FOR BILIARY CARCINOMA?
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Introduction
Intrahepatic biliary duct carcinoma commonly presents at an advanced and unresectable stage. Tumoricidal treatment with brachytherapy or external beam radiation therapy (EBRT) alone is limited by competing toxicities. This paper reviews the technique of precise clinical target volume characterization and whole organ dose-volume analysis to optimize the balance between tumoricidal dose and normal tissue tolerance.

Method
For a patient presenting with non-metastatic, inoperable intrahepatic biliary duct carcinoma, the decision to administer chemosensitized tumoricidal radiation dose was made. The bile ducts were accessed with percutaneous technique, then underwent angioplasty. A transhepatic sheath was placed within the diseased duct. A brachytherapy catheter with radio-opaque marker was sited. CT and MR imaging were performed and image fusion characterized a clinical target volume based on the gadolinium-enhanced changes of the tumor. Dose volume histograms (DVH) were generated for both modalities. Treatment planning then balanced the optimal combination of EBRT and high dose rate (HDR) fractionated brachytherapy (both administered at 1.8 Gy per day) to give tumoricidal dose whilst respecting accepted whole liver dose constraints (no more than 30 Gy to 30% of the liver). The margins for EBRT were determined by catheter migration at fluoroscopy to be 2.5 cm superiorly and inferiorly and 1.5 cm laterally.

Results

<table>
<thead>
<tr>
<th></th>
<th>Dose (Gy)</th>
<th>BED ((\alpha/\beta =10))</th>
<th>% of total dose to 30% of liver</th>
<th>Dose to 30% of liver (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBRT</td>
<td>25.2</td>
<td>29.7</td>
<td>71</td>
<td>17.9</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>28.8</td>
<td>34.0</td>
<td>40.5</td>
<td>11.7</td>
</tr>
<tr>
<td>Cumulative</td>
<td>54.0</td>
<td>63.7</td>
<td></td>
<td>29.6</td>
</tr>
</tbody>
</table>

The optimal balance of EBRT and brachytherapy was found with the doses tabulated above. The dose received by 30% of the liver was 29.6 Gy.

Conclusion
The use of 3D-Conformal treatment planning with CT-MR fusion and DVH analysis of combined brachytherapy and EBRT allows for a tumoricidal chemosensitized radiation dose to be administered while respecting normal liver tolerance. Isofractionated HDR and EBRT may decrease the risk of complications and allow a higher total dose to be administered. A prospective Phase III study of the optimal balance of modalities is suggested.
Background: Biliary tract cancers are uncommon tumors with a poor prognosis because most patients present an invasive cancer at diagnosis that makes them inoperable. Chemotherapy is a palliative treatment but single drugs or combination schedules have demonstrated a response rate of 14-18% with a duration of response of 8.5 months. We report a single center experience with gemcitabine and/or gemcitabine based chemotherapy in the treatment of patients with advanced biliary tract cancers.

Patients and Methods: Between November 2001 and March 2003 eleven (3M/8F) consecutive patients (pts) with locally unresectable or metastatic biliary tract cancer were enrolled. Median age was 50 years (43-74), Karnofski PS 90% (80-100). Treatment consisted of gemcitabine monotherapy (1000mg/m2 weekly x 3, every 4 weeks) (4 pts) and combination gemcitabine (1000mg/m2, days 1 and 8) with cisplatin (70mg/m2, day 1 every 3 weeks) (7 pts). Seven pts were chemotherapy naive and 2 pts were pretreated with 5–Fluorouracil and platinum based chemotherapy and 2 pts underwent concomitant chemoradiotherapy after cholecystectomy. Median relative dose index of gemcitabine was 0.74 (0.52 - 0.88).

Results: After a median number of courses 3 (2-14) one pts (9%) had a partial response (PR) that last more than 7 months. Additional 3 pts (27%) had stable disease (SD), whereas 7 patients progressed despite therapy. Tumor control rate (OR+SD) was 36% (95%CI 7% -65%). The median survival time was 4,7 months (1 – 10,6+). Four patients are still alive. All pts were evaluated for toxicity (NCI-CTC). Gemcitabine based therapy was well tolerated and showed low toxicity: leukopenia G3/4: 2pts (18%), trombocytopenia G3/4 was observed in 1 pts (9%). Similarly, nonhematological side effects were infrequent and generally mild, with the exception of gastric hemorrhage observed in 1 pts previously irradiated.

Conclusion: Gemcitabine based chemotherapy represent a potentially effective, safe and well-tolerated regimen for the palliative treatment of patients with advanced biliary tract cancer.
EVALUATION OF THE INHIBITORY EFFECT OF ANTISENSE OLIGODEOXYNUCLEOTIDES IN HEPATITIS C-ASSOCIATED HEPATOCELLULAR CARCINOMA
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Abstract: We studied the in vitro effect of antisense oligodeoxynucleotide (AS – ODN) on the rate of growth of the tumor cells grown in fluid culture of HCC associated with hepatitis-C. Core biopsy were taken from 20 patients with HCC associated with hepatitis C, each core biopsy was divided into two parts, group I to which antisense was added, group II no antisense was added and they served as a control group. Colony formation in soft agar was inhibited in group I compared to the control group and the inhibition was statistically highly significant (P < 0.01). The LDH level in culture supernatant reflecting cellular death was higher in group I compared to group II and the difference was statistically highly significant (P< 0.01). The trypan blue exclusion test again reflecting cellular death was higher in group I compared to group II and the difference was statistically highly significant (P < 0.01).MTT assay showed statistically highly significant decrease in cell activation in group I (with AS-ODN) compared to group II (P < 0.01).The percentage of cells in (G0/G1) phase were higher in group I compared to group II and the difference was statistically significant (P = 0.04).There was insignificant difference among both groups in the percentage of cells in S phase (P = 0.378).The inhibitory effect of AS-ODNs on the tumor cells in G2/M phase (Mitosis phase) of the cell cycle was statistically highly significant compared to the control group (P < 0.01).

Conclusion: Our in vitro study showed that AS-ODN has a significant inhibitory effect on the growth of hepatitis C-associated HCC cells grown in fluid culture, and would provide a scientific base for the possibility of use of AS-ODN in the treatment of HCC in the future.

Key words: hepatocellular carcinoma, treatment, gene therapy.

COMBINED APPROACH IN TREATING LIVER METASTASES BY RESECTIONALLY-ABLATIONAL METHODS
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Aim: aim of our study was to show experiences in combined approach of the liver resection and treatment of metastatic tumors with radio-frequent thermoablation (RFA) and classic resection (CUSA). Resectionally-ablational method.

Method: In the period of June 2002 till December 2003 49 patients with liver metastatic deposits were operated at our Institute. Complications, changes in biochemical parameters and blood count in the first 7 postoperative days, as well as mortality and recurrence were followed-up and recorded. Resected changes were histopathologically verified and also resection margines in all patients.

Results: From 49 patients, 35 were males and 14 females. Average age of the patients was 52 years; the youngest patient was 31, and the oldest 75. Twenty-six patients had colorectal cancer metastases, 13 pts. had breast cancer, 2 pts. had melanoma metastases, 2 pts. had stomach metastases, 1 pt. had ovarian metastase, 1 pt. was with CaPVU metastases, 1 with kidney tumor metastases, 1 with suprarenal metastases, and 2 pts. had metastases of the tumor of unknown localization. Totally 72 changes in the liver of 0,5-10 cm diameter were treated. Combined resection and RFA was performed in 47 patients, and only RFA was performed in 2 pts. There were no intra and post-operative mortalities. Two patients had febrility rise on the fourth post-operative day. GOT preoperative values were within 13-60U/l, and range of GPT values was 13-50 U/l. On the first post-operative day there was multiple rise of GOT values up to maximum of 1190 U/l, and for GPT also up to maximal values of 2510 U/l. After three days all the values showed decreasing trend, and after seven days, they returned to normal ones. All other followed parameters did not change pre-post operatively. Regarding late complications 2 pts. had febrility in the period of 15-30 days postoperatively and after conservative antibiotic treatment they were discharged.Two patients, out of 49, died in the period of 6-8 months after the operation for onset of the disease which in one patient was extrahepatic and in the other of general type with recurrence in the liver. There were no signs of the disease recurrence in the remaining patients seen in the previous control examinations.

Conclusion: In our study combined approach to liver metastatic tumors by resectionally-ablational (RFA) method showed good therapeutic outcome and may be considered safe surgical procedure with low mortality and complications, and great benefit for patient’s prognosis.

Key words: metastases in the liver, liver resection, radio-frequent ablation.
SURGICAL TREATMENT OF IRRADIATION INJURIES OF THE SMALL INTESTINE AND COLORECTUM THAT OCCUR DUE TO THE RADIOTHERAPY OF MALIGNANCIES IN SMALL PELVIS

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Aim: We have analysed operative results in the five years period in order to evaluate factors that influenced surgical management of consequences in radiotherapeutic injuries of the small intestine and colorectum.

Material and methods: During the period of five years, we have operated 46 patients because of radiotherapeutical injuries of the small intestine and colorectum. Operations due to a relapse or rest tumor are not considered. The following facts have been specially analysed: localisation of the tumor, initial lesion and type and technique of the suture in bypass and resection procedures.

Results: Carcinoma of the cervix and ovarium is the basic cause for radiotherapy treatment. Although the rectum is the most resistant, endocavitary therapy affects smaller areas with high irradiation doses, so the injury of the rectum is in the first place. Endocavitary therapy is closely linked to fistulae and perforations, while a half of patients received only external, percutaneous therapy. Previous operative procedures in the abdomen are significant risk factors for occurrence of postirradiation lesions.

Conclusion: Based on immediate and late operative complications, we can say that the technique is very important for the postoperative course. Suture in one layer individually showed to be better in relation to two layer suture continuous and stapler suture. The direct anastomosis and suture together with protective colostoma, give better results and less complications.

Key word: irradiation injuries, small intestine, radiotherapy, small pelvis

SUBACUTE OCCLUSION WITH COLORECTAL CARCINOMA

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BACKGROUND: The most often complication colorectal carcinoma are subacute malignant colorectal occlusions and they are the most reason for surgical emergency. Diagnosis is state by anamnestic data, physical examinations, laboratory, endoscopie and radiological examinations, pathohistological and by exploratory laparotomy.

METHODS: We have analysed surgical treatment of subcutae malignat colorectal occlusions in period 2001 to 2003. In that period 32 patients with pathohistological diagnosis of colon carcinoma were operated.

RESULTS AND CONCLUSION: The 78.2% have had carcinoma of left colon and male/female score was 65.6%/34.4%. Age distribution is cute colorectal occlusions with carcinoma next were surgical procedures used. Emergent resection of tumor with primary anastomosis/with or without preservative colostoma/ in 15.6%. Emergent resection of tumor with colostoma/Hartman procedure/ in 15.6%. Internal derivation in 18.7% and definitive stomas/ileostoma, cecostoma or bipolar colostoma/ in 53.1%. Postoperative mortality was 15.6%.

Key word: occlusion, colorectal carcinoma
EARLY RESULTS OF LAPAROSCOPIC SURGERY FOR COLORECTAL MALIGNANCIES: AN INDIAN EXPERIENCE INVOLVING 35 PATIENTS
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Aims: The role of laparoscopic surgery in the management of colorectal cancer is controversial. The present study is an attempt to analyze the results of the perioperative course, oncologic quality, and initial follow-up among Indian patients.

Methods: Thirty-five patients underwent laparoscopic resections of their colorectal malignancies at our center, which is a tertiary care referral hospital. Measured intraoperative variables included, operative time, and estimated blood loss. Postoperative parameters consisted of duration of intravenous or epidural narcotic usage, return of bowel function (RBF), length of stay and complications. Surgical, pathologic and follow-up data were recorded in a prospective registry database and analyzed.

Results: A total of 35 patients (males: 24, females: 11) with colorectal malignancies underwent laparoscopic resections. The series included 10 cases of laparoscopic radical right hemicolectomy (RHC), 8 cases of lap radical left hemicolectomy (LHC) and 17 cases of lap abdominoperineal resections (APR). Three patients were lost to follow up. The mean age of the patients was 59 years. None of the procedures was converted to open. Mean operative time was 216 min (150 – 360 min). Mean intra-operative blood loss was 250ml. In lap APR the Foley's catheter was removed on 8th day. Mean postoperative hospital stay was 9 days. The time to RBF after APR was 24 to 36 hrs and these patients were allowed orally at 48 hrs. Intra-operative complications included clipping of ureter in one patient (2.8 %). None of the patients had any vascular accidents or intra-peritoneal dissemination of tumor cells. Post-operative complications included paracolostomy hernia in 1 patient, wound infection in 3 patients, impotence in 2 patients. One patient had positive resection margins. None of the patients had any vascular accidents or intra-peritoneal dissemination of tumor cells. Post-operative complications included paracolostomy hernia in 1 patient, wound infection in 3 patients, impotence in 2 patients. One patient had positive resection margins. None of the patients had port site recurrences after a mean follow-up of 8 months (3-21 months). One patient had minor leak of the anastomosis which was managed conservatively. The mean number of lymph nodes isolated was 15.6.

Conclusions: The present study shows that a laparoscopic approach can in principle meet oncologic requirements of radicality and, with regard to the postoperative course, is associated with considerable benefits to the patient. However studies with larger number of patients and longer follow-up are required before it can be accepted as a standard procedure.

CYTOREDUCTION SURGERY IN TREATMENT OF METASTATIC COLORECTAL CANCER
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Purpose. The treatment strategy of colorectal cancer patients with distant metastases is still controversial. The recent data have shown significant increase of survival after aggressive surgery in combination with chemotherapy in selected group of patients. The study was aimed to establish the role of cytoreduction surgery in patients with distant metastases of colorectal origin.

Patients and methods. From 1985 till 2003 cytoreduction surgery was performed in 81 patients with colorectal cancer metastases. The primary site of the tumor was rectum in 33, sigmoid colon - in 27, other sites of colon - in 21 patients. The most common sites of metastases were lungs in 34, liver – in 23, ovarian – in 13, great omentum – in 8, abdominal wall – in 7 and others – in 4 patients. One organ was affected in 77.5% of patients. Synchronous metastases were revealed in 32, metachronous – in 49 patients. Metastasectomy included 11 non-anatomical liver resections, 9 hemihepatectomies, 1 bisegmentectomy (after liver resection intraarterial port was set up for regional chemotherapy), 13 ovarioectomies with great omentum resection, 7 abdominal wall resections with immediate plastic reconstruction, 18 wedge lung resections, 15 lobectomies and 1 pneumonectomy. Thoracotomy was a standard approach. VATS resections were performed in 3 patients. Results. Postoperative complications were diagnosed in 52.1% after liver resections with mortality rate 8.6%. Morbidity and mortality after pulmonary metastasectomy was 8.8% and 2.9% respectively. One, three and five-year survival after liver resection was 68.8%, 37.5% and 12.5%. Survival after pulmonary resection was about 83.6%, 46.7%, 26.7% at one, three and 5-years. The status of intrathoracic lymph nodes, number of metastases, complete resection, DFI>36 months, prethoracotomy CEA level>5ng/ml were independent prognostic factors.

Conclusion. Aggressive surgical approach in treatment of distant metastases of colorectal cancer is justified. Resection of solitary or multiple liver and lung metastases with adjuvant chemotherapy results in significant increase of survival. En bloc abdominal wall resection with immediate plastic reconstruction should be done in a case of its metastatic lesion.
One of the most usual causes for surgical intervention on the liver are the metastatic tumors.

The purpose of our investigation was to assess the efficacy of surgical treatment of liver metastases. In our department 221 surgical interventions for liver metastases were performed for the period January 1990-December 2002. The patients were 114 males and 107 females ranging in age from 10 to 82 years. In 156 patients the primary tumor was with colorectal localization, in 28 patients—stomach, in 16 patients—pancreas and in 21 patients—with other localizations. Synchronous metastases were found in 122 patients and metachronous—in 99. The metastases size in most of the cases was from 5-15 cm. In 14.02% of the patients the metastases were multiple. Fourteen patients underwent a second resection for local recurrence. The surgical treatment was considered radical when the distance of the resection margins from the tumor was at least 0.5 cm and no lymph node metastases were found. The following surgical procedures were performed: 18 left and 7 right lobectomies, 23 right and 11 left hemihepatectomies, 36 segmentectomies, 48 atypic resections and 76 palliative interventions (including termoaablation) in 36 cases of which a port-jet catheter was placed. Postoperative morbidity and mortality rates were 10.7% and 3.16% respectively.

Our results confirm the efficacy of surgical treatment of liver metastases. Re-resections in patients with local recurrence allow prolonged survival.

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This study includes 66 patients with colorectal cancer subjected to laparoscopic resection including 22 abdomino-perineal resections, 4 Rt. hemicolectomy, 4 transverse colectomy, 12 Lt. hemicolectomy & 24 anterior resections. Male / female ratio is 6/5. Cases are analyzed regarding the operative time, blood loss, perioperative complications, hospital stay, lymph node harvesting & safety margin. Follow up of the series ranges between 6 months - 4 years. The study indicated safety & feasibility of the laparoscopic approach in resection of the different sites of colorectal cancer.
INTRODUCTION: Hepatic resection is presently accepted as the most successful therapy for liver metastases from CRC although in 45-80% of cases the disease will recur. In case of isolated liver recurrence, repeat hepatic resection is recommended because it is potentially curative. Recently, local treatments such as radiofrequency thermal ablation (RFTA) have been proposed for resectable recurrent liver metastases to avoid the risk of repeat surgery. The purpose of this study is assess the risks of repeat resection of recurrent liver metastases from CRC.

METHODS: A retrospective study was performed on 225 patients operated for liver metastases from CRC in our Institution from January 1997 until January 2004. A group of 176 patients underwent a first operation (group FT), while 49 underwent repeat surgery for liver recurrence (22%) (group RT). The male:female ratio was 107:69 and 36:13 in the two groups, respectively (p=0.1). The mean (±SD) age was 61 (±11) (range 25-82) years in FT group and 62 (±11) (range 34-78) years in RT group (p=0.6). In group FT, 50% of patients had single nodules and 50% had multiple nodules, while in group RT 53% had single nodules, and 47% had multiple nodules (p=0.73). Liver metastases were unilobar in 68% of cases and bilobar in 32% in group FT, while in group RT metastases were unilobar in 78% and bilobar in 22% (p=0.27).

RESULTS: In the FT group 156 patients had resectable metastases and 20 (13%) had unresectable disease. In the RT group 38 patients could be resected and 11 (22%) were unresectable (p=0.06). In the FT group, 30% of patients underwent major resections and 70% minor ones; in the RT group, 26% received major resections and 74% minor ones (p=0.7). The mean (±SD) duration of surgery was 4.38 (±1.51) (range: 1.50-9.50) hours in group FT and 4.54 (±1.26) (range: 2.15-8.02) hours in the RT group (p=0.5). Twenty-eight per cent of patients in group FT and 33% in group RT required blood transfusion during surgery (p=0.8). The mean (±SD) amount of blood transfused was 909 (±971) ml in the FT group and 900 (±725) ml in the RT group (p=0.9). In group FT, no patient required re-operation for major complications, while 12 patients developed minor complications treated with percutaneous drainage (7 biliary fistula, 3 subphrenic abscess, 2 pleural effusion). In group RT, no patient required re-operation, while 3 experienced minor complications treated with percutaneous drainage (1 biliary fistula, 2 pleural effusion). No post-operative mortality was observed.

CONCLUSIONS: In our experience, patients with recurrent liver metastases had a lower resectability rate, even though the difference was not quite significant. No difference was observed in terms of duration of surgery, blood transfusions required during surgery, morbidity and mortality rates. On this basis, we believe that repeat hepatectomy in experienced centres should be applied to recurrent metastases whenever curative removal of the tumour is possible. RFTA and other percutaneous therapies should be considered with caution in case of resectable recurrent metastases, until a clear benefit in disease-free and overall survival rates will be available.

World Congress on Gastrointestinal Cancer 16-19 June 2004 Barcelona, Spain
This study was undertaken to review the long-term results of multi-visceral resection of locally advanced colorectal cancer. Between 1983 and 1999, 1509 patients had been curatively operated because of colorectal carcinoma at the Department of Surgery, University Hospital of Ulm, Germany. 125/1509 (8%) patients had locally advanced disease without evident distant or dis-contiguous intra-abdominal metastases. All of them underwent radical en-block resection including primary tumor and the adjacent affected structures. The aim of this study was to evaluate the usefulness of multi-visceral resection in terms of surgical risks and late oncological results.

Results: Clinical symptoms which may indicate an involvement of neighboring structures were found in 8%-17% of the patients. In 33, 37, 23, and 32 patients, a single, two, three or more organs were additionally affected respectively. Resected structures were small intestine, omentum, genitourinary system, spleen and abdominal wall. Tumor infiltration to neighboring structures was confirmed via histological examination in 70% of the cases, while in the remaining patients inflammatory peri-tumor adhesions had mimicked tumor invasion. The post-operative morbidity rate was 18% and the 30-days mortality rate 3%. The 5-years survival rates of all patients, who underwent multi-visceral resections was 60% as equal as to survival rates of colon carcinoma group of patients (n= 790) with conventional non-extended resections (71%). Within this group of 125 patients the survival rate varied according to the TNM tumor classification. The data suggest that the risk of operation and the long-term survival in patients with curative multi-visceral resections of colorectal cancer adherent to neighboring structures is equally as good as those patients with conventional non-extended resections. The oncological result of those patients with involvement of neighboring structures was mainly depending on lymph-nodes involvements rather than on the extent of invasion. These results justify the liberal use of the multi-visceral resections as a treatment of choice in colorectal cancer invading the neighbouring structures.
COLORECTAL CANCER IN ELDERLY PATIENTS: EFFICACY OF THE FOLFOX REGIMEN

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Purpose of the study. Effectiveness of chemotherapy in elderly patients is still a matter of debate, not to mention the concerns about toxicity. We analysed the toxicity and efficacy of a Oxaliplatin/5-Fluorouracil combination (FOLFOX2) in young and elderly patients affected by colorectal cancer (CRC).

Patients and methods. Patients with WHO performance status ≤ 2, metastatic CRC, measurable disease, and adequate renal, hepatic and bone marrow functions and previous adjuvant chemotherapy were eligible. Treatment consisted of: Oxaliplatin 100 mg/m² i.v. over 2 hrs on day 1, folinic acid 500 mg/m² (or equivalent levo-form) i.v. over 2 hrs on days 1 and 2 and 5-Fluorouracil 1.500 mg/m²/22 hrs c.i. on days 1 and 2 of a 2-week cycle. The age cut-off for analysis was arbitrarily set at 65 years.

Results. Sixty-eight were enrolled: median age was: years (range: 38-78); 38 were young (median age: 54; range: 38-64) and 30 were old (median age: 72; range: 65-78).

Toxicities were equivalent in both groups. In fact, only 9 and 8 patients developed grade 3-4 toxicities in the young and elderly population, respectively. Grade 3-4 neuropathy was the only dose-limiting toxicity affecting 2 young and 3 elderly patients, respectively. Overall, 24 of 68 patients (35.2%; 95% c.i.: ± 0.11) obtained an objective response (36% in the young and 33.3% in elderly patients). Among the totally untreated patients, response rate was observed in 4 of 7 and 6 of 9 patients, respectively. Median time to progression was 8.0 and 6.4 months (p=0.56), and the median overall survival was 6.9 and 8.9 months (p=0.94) for young and elderly patients, respectively. However, a similar, statistically significant advantage in median survival (χ² = 4.51, p= 0.03), was observed in responding patients, either young or old, compared with non responding patients.

Conclusions. FOLFOX2 regimen provides equivalent feasibility, efficacy and survival gain in elderly or young patients with metastatic CRC. Our study suggests that the standard treatment for colorectal cancer with the Oxaliplatin/5-Fluorouracil combination is feasible even in elderly population.

GASTRIC SURGICAL ADJUVANT RADIOTHERAPY: A COMPARISON BETWEEN 2-FIELD (AP/PA) AND MULTIPLE-FIELD (MF) TECHNIQUE

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Background

Co-planar anterior-posterior/posterior-anterior (AP/PA) conformal portals are currently recommended in the adjuvant radiotherapy of patients with gastric cancer submitted to radical surgery. However, with this technique a considerable dose to both kidneys may be delivered with an increased risk of late toxicity; in order to spare abdominal organs at risk (OAR), we investigated a multiple-field technique with a 3D dose calculation and compared it with typical AP/PA technique.

Material and Methods

From March 2001 to March 2004 nineteen patients with pathological Stage IB (2 pts), II (3 pts), IIIA (4 pts), IIIB (6 pts), IV (4 pts) gastric cancer were treated in the supine position with 15-MV photons delivered by a linear accelerator. Either a 3-field or 4-field technique was employed to irradiate a target volume including gastric bed, stump and regional node areas. Liver, both kidneys and spine cord were outlined as OARs. Patients received a total dose of 4500 cGy in 25 fractions calculated by comparing, for both kidney and liver, V25, V30 and V40 (i.e. % of volume receiving respectively a dose of 25, 30 and 40 Gy) median values obtained from multiple-field technique or AP/PA field technique arrangement. All patients completed the multiple-field radiotherapy program in association to chemotherapy according to INT 0116 protocol (Mac Donald et al, New Eng J Med 2002) feasibility was good with mild nausea /vomit; so far, at median follow-up of 14 months (range 1-34 months) no patient has presented liver or renal function abnormalities or major abdominal complications.

Results

Rival-treatment-plan analysis carried out by DVH comparison turned out the following results shown in Table below reported.

<table>
<thead>
<tr>
<th>OAR / technique</th>
<th>V25</th>
<th>V30</th>
<th>V40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right kidney (AP/PA)</td>
<td>1.50 %</td>
<td>0 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Right kidney (MF)</td>
<td>0 %</td>
<td>0 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Left kidney (AP/PA)</td>
<td>33.20 %</td>
<td>30.20 %</td>
<td>8.90 %</td>
</tr>
<tr>
<td>Left kidney (MF)</td>
<td>15.00 %</td>
<td>9.80 %</td>
<td>4.35 %</td>
</tr>
<tr>
<td>Liver (AP/PA)</td>
<td>13.30 %</td>
<td>11.60 %</td>
<td>8.10 %</td>
</tr>
<tr>
<td>Liver (MF)</td>
<td>51.30 %</td>
<td>22.30 %</td>
<td>8.90 %</td>
</tr>
</tbody>
</table>

Conclusions

By using 3-field or 4-field 3D technique, the right kidney may be completely spared; a significant reduced radiation dose (p<0.05) may be similarly delivered to the left kidney respect to AP/PA technique; on the other side, by multiple field technique, a significant higher percentage of liver volume receives an increased radiation dose (p< 0.05 for V25 and V30) that implies a careful long-term monitoring of hepatic function.
HEPATIC ARTERIAL INFUSION (HAI) OF OXALIPLATIN (OXA), LEUCOVORIN (LV) AND 5-FLUOROURACIL (5FU) IN LIVER METASTASES FROM COLORECTAL CANCER (CRC).

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Oncological Department, Carrara, Italy

INTRODUCTION: HAI is an effective treatment of unresectable liver metastases from CRC. Fase I and II studies have already showed the feasibility and efficacy of HAI with OXA. We clinically examined 30 patients (pts) with liver metastases who received HAI with OXA/LV/5FU at our Division between March 2000 and November 2003.

METHODS and PATIENTS: 30 pts: M/F=18/12; mean age: 64 years (41-78); primary cancers: colon/rectum=21/9; sincrone/metacrone metastasis: 13/17; liver replacement: <25% (4 pts), <50% (18 pts), >50% (8 pts); untreated/pretreated pts: 7/23 pts. All pts received a percutaneously implanted catheter into the hepatic arterial through a femorally or transaxillary access. Treatment: OXA 100 mg/m2 12-hours infusion day 1+LV 100 mg/m2 infusion day 1,2+FU 2600 mg/m2 continuous infusion day 2,3 every 14 days.

RESULTS: 186 cycles have been administered with a mean of 6 cycles for pts (1-12). Grade 3-4° toxicity: nausea and vomiting (1/30), neutropenia (1/30), thrombocytopenia (1/30), asthenia (3/30), neuropathy (1/30), transaminase elevation (2/30), pain (4/30). Main dose limiting toxicity was right upper quadrant pain. Response: 3,3% CR, 30% PR, 30% SD and 36,6% PD. 5 pts became operable and 4 pts underwent complete resection of their metastasis (1 pt refused surgery). The median OS from the start of HAI was 13,2 months. The median TTP was 8,6 months. The median OS from liver metastasis diagnosis was 21 months. One-year and 2-year survival rates were 80% and 35%, respectively.

CONCLUSION: this regimen is feasible with a low toxicity. Overall tumor growth control (63,3 %) and median OS (21 months) are interesting in this group of heavy pretreated pts. Intra-arterial OXA/LV/5FU combined with systemic chemotherapy might be considered for an integrated strategy in the treatment of liver metastases of CRC.

A LOW TOXIC OXALIPLATIN-CONTAINING REGIMEN AS FIRST LINE CHEMOTHERAPY IN PATIENTS WITH ADVANCED COLORECTAL CANCER

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European Institute Of Oncology, Milan, Italy

Purpose: To assess the efficacy and toxicity of fluorouracil (FU), leucovorin (L), methotrexate (M), and oxaliplatin (OX) (FULMOX) in patients with advanced colorectal carcinoma (ACC). To evaluate the correlation of serum vascular endothelial growth factor (VEGF) and clinical response. Patients and methods: main inclusion criteria were untreated histologically confirmed ACC, age <75 yrs, ECOG-PS<2, measurable disease, life expectancy >3 mos, written informed consent. The regimen included: M 200 mg/m2 i.v. days 1,15; FU 600 mg/m2 i.v. bolus days 2,16; L rescue 15 mg p.o. q6hours for 6 times starting just after FU bolus; FU 200 mg/m2 i.v. continuous infusion days 29-56; OX 130 mg/m2 i.v. over 2 hours days 29,50. The treatment was repeated every 10 wks after 2 wks rest period in responsive patients. Peripheral blood samples for serum VEGF were collected at baseline and before every cycle. Results: the main characteristics of 59 enrolled pts are: M/F 35/23, median age 60 yrs (range 28-75), PS 0/1/2 35/20/3, colon/rectum 49/12, adjuvant chemotherapy 9, advanced disease at diagnoses 46, disease sites: liver alone 31, liver and other 23. Three CR, 23 PR (OR: 45.6%; 95% CI, 34.3%-57.3%) and 14 SD were seen among 57 evaluable pts (1 pt out-trial for G2 renal toxicity after 1st dose of M and 1pt never started). Eight patients underwent surgery after a median time of 6.5 months since the beginning of chemotherapy. After a median follow-up of 14.3 mos, median TTP was 7.8 mos (95% CI, 6.4-10.1), median OS was 19.4 mos (95% CI, 15.3-24.2), and 2-year survival rate was 31.4 % (95% CI, 18.9-52.3). Among 114 administered courses the main toxicity was: NCI-CTC Grade (G) 3/4 diarrhea 7%, G3 nausea/vomiting 10%, G2 peripheral neuropathy 14%. In 23 evaluable pts serum VEGF showed a reduction regardless clinical response. Conclusion: the activity and very low toxicity of our regimen is interesting in pts with inoperable ACC. Serum VEGF did not correlate with clinical efficacy.
ANALYSIS OF 305 PATIENTS WITH ADVANCED COLORECTAL CANCER TREATED WITH ONE OR MORE LINES OF PALLIATIVE CHEMOTHERAPY

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PURPOSE: Chemotherapy (CT) in advanced colon cancer improves quality of life and survival, and increases the resectability of local disease. Immediate CT has better results than delayed treatment. There are different active schemes for metastatic colon cancer; though the optimal duration is still uncertain. The tendency is to continue administration of CT until progression. The aim of the study is to identify which advanced colorectal patients could benefit from an intermittent treatment without detriment in terms of survival.

PATIENTS AND METHODS: This is a study based in cases of a database from a single institution. We recorded prospectively all patients with colorectal carcinoma visited in our centre. All pts were included in the same assistance protocol. The population of the study were pts with advanced unresectable colorectal carcinoma. Descriptive analysis was performed. Kaplan-Meier survival curves were compared with log rank test. We used χ² tests to determine the association between the continuous or intermittent CT with certain prognostic variables.

RESULTS: From 01/96 to 12/01 305 pts (187 M/118 F) with advanced colorectal cancer were treated with CT. Median age was 61 years (23-83). 188 had distant metastases, 43 loco regional, and 74 loco regional and distant. The most frequent localization of metastases was liver (39.3%), peritoneum (11.1%), and lungs (8.8%). The presentation was synchronous in 67% and metachronic in 33%. All pts were treated with CT: 145 (47.5%) with one line of 5-FU(LV) (group 1), 49 (16.1%) one line of either CPT11 or Oxaliplatin (group 2), and 111 (36.4%) with 2 or more lines (group 3). In 65 pts we stopped CT between lines ≥ 3m (55 with 2 lines, 10 one line). The median time of the interval was 10m (3-69m). In 50/65 pts we stopped CT due to maintained response. Partial response was achieved in two patients. We used X² tests to determine the relationship between the continuous or intermittent CT with certain prognostic variables.

Conclusions: The combination of chronomodulated 5-FU/LV + L-OHP is a regimen that merits further investigation as salvage treatment in heavily pretreated patients with MCC.

<table>
<thead>
<tr>
<th></th>
<th>Median survival (m)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent CT</td>
<td>47.3</td>
<td></td>
</tr>
<tr>
<td>Continuous CT</td>
<td>15.83</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Group 1</td>
<td>12.43</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>15.53</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>26.63</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CONCLUSIONS: Our data suggest that there is a group of pts that could benefit from interrupting the treatment and restart CT when they progress. However, we need randomized trials to establish the optimal duration of treatment.
PHASE I STUDY OF BIWEEKLY OXALIPLATIN (LOHP) WITH CAPECITABINE (XELODA) IN COMBINATION WITH ZD1839 (IRESSA) IN PATIENTS WITH PRETREATED ADVANCED COLORECTAL CANCER

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Purpose: Data from in vitro studies demonstrate a strong synergistic interaction between ZD1839 and 5'-DFUR when ZD1839 is applied before or concurrently with 5'-DFUR. A phase I study was designed in order to determine the dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of LOHP with Xeloda plus the administration of Iressa in patients with pretreated advanced colorectal cancer.

Methods: Patients received standard dose of LOHP (85 mg/m²) as 120 minutes iv infusion on day 1, followed by escalated doses of Xeloda (starting dose 1000 mg/m²) po in two divided doses starting on day 1 until day 7 followed from one week rest and Iressa 250mg daily starting 2 days before the administration of first cycle. The cycle was administered every two weeks. At least 3 patients were treated on the same dose-level. Dose-limiting toxicities were evaluated in the first cycle and were defined as: WHO G4 or febrile neutropenia, G4 thrombocytopenia, any ≥ grade 3 non-hematologic toxicity and any treatment delay due to toxicity. The MTD level was defined at the first cycle as the dose-level immediately below that at which DLT was observed in at least 50% of the treated patients.

Results: Twelve patients (male/female 9/3; PS (WHO) 0-1 in 100%) with advanced colon, were treated on 3 dose-levels. Eight (89%) patients had received two prior chemotherapy regimens, 1 (11%) one. Dose-escalation and DLTs are listed in the table. A total of 48 treatment cycles have been administered (median 3 cycles/patient). Overall, toxicity was generally mild; no G3-4 hematologic toxicity was observed; G3/4 diarrhea was reported in 1 (9%) patients and G3 vomiting in 1 (9%), and grade II "hand and foot syndrome" in one patients (9%). The DLT level has not yet been reached and the accrual of the study is continued.

<table>
<thead>
<tr>
<th>Dose level</th>
<th>IRESSA mg/m²</th>
<th>LOHP mg/m²</th>
<th>5FU mg/m²</th>
<th>No of patients</th>
<th>DLT (No of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150</td>
<td>85</td>
<td>1000</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>85</td>
<td>1150</td>
<td>6</td>
<td>1 patient grade 3 diarrhea</td>
</tr>
<tr>
<td>3</td>
<td>150</td>
<td>85</td>
<td>1300</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

COMBINATION OF IRINOTECAN (CPT-11) AND GEFINITIB (ZD1839) FOR PATIENTS WITH METASTATIC COLORECTAL CANCER (MCC) REFRACTORY TO IRINOTECAN-BASED 1ST LINE CHEMOTHERAPY: A PILOT PHASE II STUDY


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Purpose: Predclinical studies suggest that the inhibition of tyrosine kinase of EGFR by very low concentrations of ZD1839 is able to reverse the resistance in SN-38 in two different colon cancer cell lines (Brown at al ASCO2002). In addition it is well known that C-225 is able to reverse the resistance to CPT-11 in patients with MCC (Bond trial).

Patients and Methods: Nineteen patients with MCC, (immunohistochemistry evidence of EGFR expression measured in a single laboratory was required), who had progressed during or with 3 months after the discontinuation of irinotecan-based first line chemotherapy, were enrolled. Their median age was 68 years; performance status (WHO) was 0 in 2 (10.5%) 1 in 14 (73.7%) and 2 in 7 patients (15.8%); the median number of target lesions was 2. CPT-11 was administered at the same dose and schedule as in first line treatment. Gefinitib was administered at the dose of 250mg po daily. Analysis of the expression of key enzymes implicated in the EGFR pathway was planned using RT-PCR. Results: All patients were evaluable for toxicity and response to treatment. No complete or partial response was recorded. Two patients (10.5%) had stable disease, and 17 (89.5%) disease progressions. The median time to disease progression was 3 months and the median survival 4 months. Neutropenia grade 3-4 occurred in 2 (10.5%) patients, while none of the patient presented febrile neutropenia. Anemia and thrombocytopenia didn't exceed grade 2. Diarrhea grade 3-4 was observed in 5 (26.3%) patients; skin reactions grade 2 in 6 (33%) patients and mucositis grade 2 in 2 (10.5%). Conclusions: The combination of chronomodulated CPT-11 plus gefinitib in patients with MCC refractory to CPT-11 based first line chemotherapy could not be considered as an active regimen and in the present study the results of the in vitro studies couldn't be confirmed.
SURVIVAL IMPACT OF A MULTIDISCIPLINARY APPROACH OF COLORECTAL CANCER IN A SINGLE INSTITUTION COMPREHENSIVE CANCER CENTER.
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2 Cancer Epidemiology and Cancer Prevention and Control departments, Institut Català d’Oncologia, Barcelona, Spain
3 Department of Surgery, Ciutat Sanitaria i Universitaria de Bellvitge, Barcelona, Spain

Background
Colorectal cancer is the third most important neoplasm in our population. A strict analysis of the impact of actual oncologic management in its outcomes is mandatory in order to evaluate results from future therapeutics.

Objectives
To determine the relative survival due to colorectal cancer (CRC) in a single institution, comprehensive cancer centre (HUB-ICO), depending on sex and tumoral stage. To compare these data with those from European and American registries. Only patients completely diagnosed and treated in our institution were analyzed.

Methods
A database was created in 1995 to collect prospectively patients refered to our institution. Data from 868 pts were obtained from whom we analyze 591 treated in our institution (HUB-ICO) between 1/96 and 12/1998. To obtain the vital status and mortality causes data were crossed with the Catalan mortality register until 12/2001. Observed survival and disease free survival was calculated through the Kaplan-Meier procedure. Cox model with Catalan mortality tables was used to get the estimated survival. Relative survival was then calculated dividing observed/estimated survivals. Our results are compared with those published in the American Surveillance and End Results Registry (SEER 1975-2000) and European EUROCARE (1990-1994).

Results
Median age of 591 pts (245 W, 345 M) was 68.25 yr and the median follow-up of this series was 3.33 (0.08-5.92) yr. Tumour localisation was C 398 and R 193. Stages (S): SI 17.6%, SII 26.2%, SIII 28.9%, SIV 26.1% Unknown S 1.2%. Relative survival at 5 years for colon cancer was 58.3 (52.7-64.5) and rectal cancer 59.3 (50.9-69.2).
Relative survival at 5 years with CRC was 59.3 (52.6-66.9) and in M 58.0 (51.5-65.3). In Europe was 50.5 (49.7-51.3) for women and 47.6 (46.7-48.4) for men.
When comparing our institution results by stage (relative survival/disease free survival) and those in SEER, HUB-ICO: SI 89.5 (77.3-100)/93.4; SII 77.1 (68.5-86.8)/75.95; SIII 68.3 (60.0-77.7)/64.11; SIV 12.92 (6.19-18.2). SEER: Localized 90.1; Regional 65.5; Metastatic 9.2 Unknown 35.5

Conclusions
We conclude that a multidisciplinary approach could increase survival in patients with CRC and that our data will be useful to compare with results from other institutions and to evaluate the impact in survival that future therapeutics could produce.
Background. Elderly patients completely resected for node positive colon cancer stage III are often in good performance status and may thus be candidates for adjuvant chemotherapy. However, it is not clear if the results from the original randomized trials on adjuvant 5FU therapy in younger patients, usually age ≤70 years, can be extrapolated and applied on an elderly population. The concern is that a gain in survival may be offset by marked toxicity to the chemotherapy.

Aim. The primary objective was to compare the survival and toxicity to adjuvant chemotherapy following complete resection for colon cancer stage III (Dukes C) for patients aged ≥75 years and their younger counterparts.

Method. In a retrospective study among consecutive patients completely resected for colon cancer stage III from 1996-2003 we compared recurrence free and overall survival, toxicity and dose intensity of adjuvant bolus 5-FU according to the Mayo-regimen chemotherapy in patients aged 19-74 and ≥75 years. The Kaplan-Meier survival estimates were analyzed by Log-Rank-test. Frequency data were analyzed by Mann-Whitney and Chi²-test.

Results. A total of 207 patients aged 19-74 year and 24 patients aged 75-85 years were treated. Four patients died during chemotherapy, and 71 patients died during follow up mostly from recurrence of disease. The estimated 3- and 5-year proportional survival rates were 0.76 and 0.65 for patients age less than 75 years compared to 0.75 and 0.65 (P=0.96) for their elderly counterparts, respectively. The frequencies of CTC grade 3 or 4 toxicity in elderly patients were: Leucopenia 4%, infection 8%, bleeding 0%, emesis 0%, mucositis 17%, diarrhoea 13%, cutaneous 0%, myocardia ischaemia 0%, fatigue 0%, alopecia 4%, performance status 8%, which were not significantly different from younger patients (P=0.05). 5-FU dose reduction was necessary for significantly more elderly patients (51%) as compared to younger patients (28%) (P=0.001). Significantly fewer elderly patients (54%) completed the scheduled 6 treatment courses as compared to younger patients (82 %) (P=0.001).

Conclusions. Elderly patients age ≥75 years completely resected for stage III colon cancer and receiving adjuvant chemotherapy seem to have a prognosis similar to younger patients. This benefit is not offset by marked chemotherapy induced toxicity, though dose reduction and reduced treatment duration were more frequent. Adjuvant 5-FU chemotherapy should be considered to elderly patients in good performance at high risk of recurrence of resected colon carcinoma.

Background: Colorectal cancer has a maximum incidence into the seventh decade of life; there is also a high incidence of this cancer over 70 years. These patients have other comorbidities and usually they not receive chemotherapy. Treatment of 5 FU with leucovorin is considered adjuvant standard therapy for stage III colon cancer patients. In this study, we assessed toxicity, compliance to treatment and time to progression in stage III colon cancer in patients aged over 70 years.

Material and methods: From October 1998 to December 2000, 84 patients with stage III colon cancer have been enrolled in this study. Patients characteristics: there were 45 male and 39 female, median age 76 years (range 70 – 83), performance status ECOG 0-1. All patients received curative surgery. Beginning 6 –8 weeks after surgery, they received six courses chemotherapy. The regimen consists of Leucovorine 20 mg/m²/day iv bolus followed by 5 fluorouracil 375 mg/m²/day iv bolus daily for 5 days repeated every 4 weeks. Patients were evaluated every two weeks during the treatment (for toxicity and compliance) and every three-month after that. Comorbidities were evaluated with cumulative illness scale prior to the treatment and every six weeks during the treatment and every three-month after that.

Results: 79 patients received all six chemotherapy cycles; 3 patients received four cycles and 2 patients received 3 cycles. This 5 patients refused further chemotherapy because of toxic events (diarrhea, stomatitis, coronary spasm). The main toxicities were mild to moderate: gastrointestinal (grade 1-2 vomiting 9 patients, grade 1-2 diarrhea 13 patients, grade 1-2 stomatitis 5 patients), hematological (grade 1-2 neutropenia 11 patients, grade 1 trombocitopenia 4 patients, grade 1-2 anemia 3 patients), coronary spasm (3 patients). 7 patients have grade 3 toxicities (3 neutropenia, 1 anemia, 3 diarrhea). No grade 4 toxicity or toxic death occurred. 37 patients developed metastatic disease: 19 hepatic metastasis, 17 lung metastasis, 11 peritoneal metastasis, 7 pleural metastasis, 2 bone metastasis. 37 patients died, 25 because of cancer and 12 because of other conditions.

Conclusions: These results prove that the combination of leucovorin and 5 Fluorouracil is a feasible treatment for colon cancer, with a good toxicity profile, even in ancient patients.
Background: Since mid-2002 in British Columbia (BC) the BC Cancer Agency Provincial Gastrointestinal Tumour Group has recommended FOLFIRI or FOLFOX combination chemotherapy [bolus plus infusional 5-FU with irinotecan (IRI) or oxaliplatin, respectively] as standard first line treatment options for good performance status patients with MCRC. However, many smaller cancer centres have limited resources and facilities for the provision and management of central venous catheters and ambulatory infusion pumps. Furthermore, medical and ancillary staff may be unfamiliar with infusional chemotherapy. A CAPIRI regimen of oral capecitabine (CAP) and intravenous IRI (modelled after Kerr et al, Proc ASCO 2002, abstract 643) was developed to permit administration of aggressive chemotherapy in smaller cancer centres and communities. Aims: To evaluate the feasibility, safety, and cost of CAPIRI chemotherapy delivered in large catchment areas with significant rural or remote populations (BC Interior and Vancouver Island). Patients and Methods: Since July 2003, 20 patients (15 male, 5 female) with MCRC have begun CAPIRI chemotherapy. CAPIRI consists of CAP 1000 mg/m2 po bid for 14 days with IRI 250 mg/m2 IV day 1 infused over 90 minutes; cycle length is 3 weeks. Indications for CAPIRI chemotherapy were reviewed through the CAIS (Cancer Agency Information System) electronic chart, clinic charts, and the regional Meditech information system. Chemotherapy doses were extracted by chart review. Drug and delivery cost analysis for FOLFIRI and CAPIRI was performed using a Canadian health care costing model. Results: Eighteen of 20 patients approved for CAPIRI chemotherapy have received 1-8 cycles of CAPIRI; 16 are evaluable for response. Median age was 66 years (range 43-76). A total of 51 cycles of chemotherapy have been delivered. Five partial responses were observed for an objective response rate of 31%. Toxicities were as anticipated, with grade 3/4 toxicity observed for nausea, emesis, anorexia, diarrhea, hand-foot syndrome, and myelosuppression. Five patients were hospitalized during the course of their chemotherapy. There were no treatment-related deaths. Comparative drug costs of FOLFIRI and CAPIRI for a 6-month course of treatment are $15,960 and $18,890 ($9,975 and €11,810) respectively. Drug plus delivery costs for FOLFIRI and CAPIRI for a similar 6-month course are $23,590 and $20,340 ($14,740 and €12,710) respectively. Conclusion: CAPIRI can be administered safely in smaller cancer centres and communities. A multidisciplinary cancer care team knowledgeable in managing treatment-related complications is needed as chemotherapy-related complications are at least similar to other combination MCRC regimens. The response rate for CAPIRI is comparable to that reported by other groups.

Aims: To demonstrate the feasibility, tolerability and efficacy of preoperative chemoradiotherapy (CT-RT) in locally advanced (PAC) in elderly patients (pts).

Methods: 32 pts with age ≥ 65 years with clinical T3 and T4 PAC were treated with CT-RT. Pretreatment evaluation included endorectal ultrasound and pelvis TC scan. Pts who had lesions extending through the bowel wall were considered eligible. CT-RT consisted of pelvic hyperfractionated RT (1.25 Gy twice a day with 6 hours interval between fraction) concomitant to continuous infusion of 5-Fluorouracil at a dose of 250 mg/m2/day. A total dose of 45 Gy over three weeks was delivered. Time interval between neoadjuvant treatment and surgery was 6-8 weeks. Techniques of surgery were standardized and included total mesorectal excision (TME). Characteristics: Median age 72 (range 65-81). Median distance from the anal verge was 5 cm. T3/T4 stage: 26/6. 19/32 pts had invasive tumor involving the distant half of the rectum and clinically required an abdomino-perineal resection.

Results. 26 pts underwent surgery (1 refused). 4 pts completed the RT-CT program, 1 pt is still on treatment. The operative procedures were as follows: low anterior resection in 21 pts with 10 coloanal anastomosis (reconstruction by colonic J-pouch in 6 and coloplasty in 4 pts). Abdomino-perineal resection was performed in 5 pts. All pts was radically resected. The pathologic TNM stage were as follows: pathologic complete remissions: 5, T1N0: 2, T2N0: 5, T3N0: 9, T3N1: 4, T4N1: 1. Dowstaging was observed in 19/26 pts (73%) and all pts with clinical T4 became resectable with clear margins. Moreover 11/19 (58%) pts with lesions allocated in lower rectum were able to undergo a sphincter preservation. Toxicity: acute toxicity (RTOG) of CT-RT was moderate: diarrhea and proctitis G3 with significant skin reaction was recorded in 13% and 10% of pts respectively but a therapeutic split of RT was not necessary. Although one post-operative death was recorded, overall surgical morbidity was acceptable with no anastomotic leaks. 19 pts were evaluable postoperatively by anorectal-manometry assessment: 13/19 (68%) showed a well functioning sphincter. Adjuvant chemotherapy was performed in 10/25 pts with De Gramont schedule for 4 months. Among the 25 evaluable pts after two years of follow-up, 4 local recurrence occurred with an overall control rate of 84%; 3 pts had visceral failures (2 liver, 1 peritoneum) and 5 cancer-related deaths were observed.

Conclusion: Our study, although limited in number, demonstrated that concomitant CT-RT is feasible even in elderly pts and is associated with significant downstaging and sphincter-saving surgery.
CHRONOMODULATED DELIVERY SCHEDULE OF OXALIPLATIN (OHP), 5FLUOROURACIL AND FOLINIC ACID (FFL4/10) ALLOWS TO INCREASE SIGNIFICANTLY DOSE INTENSITY RATE OF OHP BASED SCHEDULE: 2 YEARS EXPERIENCE IN GASTROINTESTINAL CANCERS
Marco Pirovano, Riccardo Valsecchi, Alessandro Quintè, Maurizio Meregalli, Giancarlo Martignoni, Donata Tabiadon
San Carlo B.Hospital Oncology Dept., Milan, Italy

Oxaliplatin (OHP), 5Fluorouracil (5FU) and Folinic acid (LFA) combination conventional schedule (FOLFOX4) has a scheduled dose intensity of 42.5 mg/sqm/w for OHP and 1 gr/sqm/w for 5FU; observed dose intensity in MOSAIC trial was 34.2 mg/sqm/w for OHP and 844 mg/sqm/w for 5FU with 41.1% of gr.3 neutropenia (12.2% gr4), 10.8% of gr.3 diarrhoea and 12.4% of sensitive peripheral neuropathy.

From January 2002 to December 2003 41 untreated colorectal and gastric cancer patients were treated with FFL4/10 chronomodulated delivery schedule: OHP 25 mg/m²/d1-4,q14 (sinusoidal 12 hour infusion with flow rate peak at 4:00pm); 5FU 900 mg/m² and L-Folinic Acid (LFA) 150 mg/m² d1-4,q14 (sinusoidal 12 hour infusion with flow rate peak at 4:00am). 247 cycles (6.02 average per pt.) were performed: average dose intensity was 49.34 mg/sqm/w, 243.2 mg/sqm/w 1750.35 mg/sqm/w for OHP, LFA and 5FU respectively. All cycles have been delivered using Mélodie® infusion system in outpatient regimen. No cycle was delayed due to toxicity. Haematological and hepatic toxicity weren’t observed, neither was any gr. 4(WHO) toxicity. Radiological Objective Response evaluation has been performed in 36 pt (Tab.1). ORR(CR+PR) was 62%. Median survival reached 12.63 months but only 35.71% of pt. died with median follow up of 13.91 months. Our experience confirms that FFL4/10 chronomodulated schedule allows to reach significantly higher dose intensity rate than conventional flat schedule FOLFOX4 without any toxicity improvement although in metastatic set patients.

<table>
<thead>
<tr>
<th>Tab1</th>
<th>OHP (mg/sqm/w)</th>
<th>L-AF (mg/sqm/w)</th>
<th>5FU (mg/sqm/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tot</td>
<td>49.34</td>
<td>312.21</td>
<td>1.705.22</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surv (median)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tox</td>
<td>Gr.4</td>
<td>Gr.3</td>
<td>Haemat</td>
</tr>
<tr>
<td>one</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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NEOADJUVANT CHRONOCHEMOTHERAPY FOR RESECTION OF UNRESECTABLE METASTASES FROM COLORECTAL CANCER: 2 YEARS EXPERIENCE OF AN INNOVATIVE MULTIDISCIPLINARY MODEL APPROACH
Marco Pirovano, Angelo Ferrandi, Alessandro Quintè, Maurizio Meregalli, Giancarlo Martignoni, Riccardo Valsecchi, Donata Tabiadon
San Carlo B.Hospital Oncology Dept., Milan, Italy

About 80-90% of patients with colorectal cancer liver metastases are not resectable at diagnosis and their chance of being alive at 5 years, even with gold standard chemotherapy, is no more than 2%. In this context that chemotherapy can have a critical role in transforming at least a proportion of unresectable patients into patients in whom surgery is possible. With this goal in 2001 has been created a multidisciplinary team for the approach of this patients: the “Nucleo Operativo di Cronochemioterapia e Terapie Integrate Locoregionali (N.O.C.TI.Lo)”. From January 2002 to December 2003 28 unresectable metastatic colorectal cancer patients (pt) have been evaluated from N.O.C.TI.Lo (Tab.2) as not suitable for surgical approach. All patients have been treated with FFL4/10 chronomodulated delivery schedule with OHP 25 mg/m²/d1-4.q14 (sinusoidal 12 hour infusion with flow rate peak at 4:00pm); 5FU 900 mg/m² and L-Folinic Acid (LFA) 150 mg/m² d1-4.q14 (sinusoidal 12 hour infusion with flow rate peak at 4:00am). 164 cycles (5.86 average per pt.); average dose intensity(Tab.2) was 49.34 mg/sqm/w, 243.2 mg/sqm/w 1750.35 mg/sqm/w for OHP, LFA and 5FU respectively. No cycle was delayed due to toxicity. Haematological and hepatic toxicity weren’t observed, neither was any grade 4(WHO) toxicity. Radiological, surgical and clinical Objective Response evaluation has been performed in 24 pt (Tab.1) after 4-6 cycles. ORR was 66.67% and 7 became suitable for surgical resection of residual disease with radical intention. Median survival reached 14.37 months. Our experience confirms that FFL4/10 schedule has very interesting activity as neoadjuvant treatment of unresectable metastatic colorectal patients and this approach allows to offer to our patients a new important cure chance.

<table>
<thead>
<tr>
<th>Tab.1</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Resected</th>
</tr>
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<tbody>
<tr>
<td>OHP (mg/sqm/w)</td>
<td>16.67</td>
<td>50%</td>
<td>12.5%</td>
<td>20.83%</td>
<td>29.17%</td>
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<tr>
<td>L-AF (mg/sqm/w)</td>
<td>243.2</td>
<td>1750.35</td>
<td>15</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>5FU (mg/sqm/w)</td>
<td></td>
<td></td>
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</table>
INTERACTION BETWEEN ZD-1839 (IRESSA) AND OXALIPLATIN IN HUMAN COLORECTAL CANCER CELL LINES.

Sandra Van Scheybroeck1, Leona Galligan1, Daniel B. Longley1, William N. Scott1, Donal Kelly1, Eric Van Cutsem1, Patrick G. Johnston2

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2 Department of Digestive Oncology, KUL, Louvain, Belgium

Introduction: The epidermal growth factor receptor (EGFR/HER1/erbB1), member of the Human Epidermal Growth Factor Receptor (HER) sub-family, is overexpressed in a wide range of solid tumours including colorectal cancer. Upon binding of its cognate ligand, receptor dimerization and tyrosine kinase activation occurs, ultimately leading to mitogenic intracellular signalling and promotion of cell growth/survival. Targeting of this receptor has become an important therapeutic strategy in recent years.

Aims: To examine the cytotoxic effect of the selective EGFR-TKI, ZD-1839, in combination with the platinum compound Oxaliplatin, assess possible sequence-dependent effect of either drug and to elucidate the biochemical mechanism of interaction in human colorectal cell lines.

Methodology: Cell viability was assessed using MTT and clonogenic survival assays and analysed by ANOVA. Apoptosis was measured by flow cytometry and PARP activation. EGFR protein expression and activation were detected by Western Blotting and flow cytometry.

Results: Significant antagonism was observed between ZD-1839 and Oxaliplatin-induced cell death in the HCT 116 p53 wild type, HCT 116 p53 null and RKO cell lines, exhibiting low basal EGFR activation. This effect was most prominent following concomitant treatment and pre-treatment with ZD-1839. ZD-1839 treatment resulted further in a marked decrease in Oxaliplatin-induced cell death in those cell lines. The combination of Oxaliplatin and ZD-1839 induced additive inhibitory effects in H630 and LOVO cells, exhibiting high basal EGFR activation. To elucidate the mechanisms behind these interactions, EGFR phosphorylation was determined following Oxaliplatin treatment. In the HCT 116 p53 wild type, HCT116 p53 null and RKO cell lines, a dose-dependent decrease in EGFR phosphorylation was observed. In contrast, in the LOVO and H630 colorectal cell lines, Oxaliplatin exposure resulted in increased EGFR phosphorylation. It is possible that the decrease in EGFR activation observed in HCT 116p53 wild type, HCT116 p53 null and RKO cell lines in response to Oxaliplatin, decreased sensitivity to ZD-1839, whereas the increased EGFR activation in Oxaliplatin-treated LOVO and H630 lines sensitised these cells to ZD-1839 induced growth inhibition.

Conclusions: In cell lines with low EGFR activation, co-administration of ZD-1839 with Oxaliplatin results in significant antagonism, whereas in the cells exhibiting high EGFR activation, the combination of both drugs results in an additive effect. These novel findings support the value of detecting EGFR activation levels prior to the introduction of new therapeutic regimens involving ZD-1839 in colorectal cancer.
A PHASE II STUDY OF 5-DAY ORAL TOPOTECAN (5-OT) VS 21-DAY OT (21-OT) VS CPT-11 (IRINOTECAN) FOR SECOND-LINE THERAPY IN PATIENTS (PTS) WITH COLORECTAL CARCINOMA

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3 Ochsner Cancer Institute, New Orleans, United States
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5 GSK Pharma, Philadelphia, United States
6 GSK Pharma, Collegeville, United States
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Topotecan and CPT-11 (irinotecan) are both specific inhibitors of topoisomerase-I. The latter is approved for the treatment of advanced colorectal cancer. Some phase II studies with intravenous topotecan have shown evidence of activity in first-line colorectal cancer pts. As the oral formulation could provide a convenient treatment option, this study was undertaken to evaluate the activity of OT using two different dosing schedules; 5 and 21 days. The primary objective was to compare survival in the 3 treatment arms; secondary objectives included toxicity and response. The study employed a 2:2:1 randomization scheme and targeted a sample size of 125 patients, based on accrual feasibility. Pts were stratified by gender and ECOG performance status (PS 0-1 versus 2) and randomized to oral topotecan 2.3 mg/m2 daily x 5 q 21 d (50 pts), oral topotecan 0.5 mg/m2 bid x 21 d (49 pts) or CPT-11 350 mg/m2 (300 mg/m2 for pts >70 years or with PS of 2) on d 1 q 21 d (26 pts). Eligibility included: advanced colorectal cancer (previously treated with 5-FU); measurable or evaluable disease; adequate marrow, renal and hepatic function (serum transaminases and alkaline phosphatase <5 upper limit of normal permitted if liver metastases); PS ≤ 2, and life expectancy ≥ 3 months. Age, gender and PS were balanced across treatment arms.

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>5-OT (N = 49)</th>
<th>21-OT (N = 26)</th>
<th>CPT-11 (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior XRT/Surgery</td>
<td>8 (16.0%)</td>
<td>9 (18.4%)</td>
<td>6 (23.1%)</td>
</tr>
<tr>
<td>Radiation Therapy</td>
<td>49 (98.0%)</td>
<td>49 (100.0%)</td>
<td>25 (96.2%)</td>
</tr>
<tr>
<td>Prior Surgery</td>
<td>34 (68.0%)</td>
<td>36 (73.5%)</td>
<td>20 (76.9%)</td>
</tr>
<tr>
<td>Absent</td>
<td>6 (12.0%)</td>
<td>8 (16.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Present</td>
<td>18 (36.0%)</td>
<td>13 (26.5%)</td>
<td>9 (34.6%)</td>
</tr>
<tr>
<td>Liver Metastasis</td>
<td>32 (64.0%)</td>
<td>36 (73.5%)</td>
<td>17 (65.4%)</td>
</tr>
</tbody>
</table>

*some not reported

Results: Dose-limiting (grade 3) diarrhea on the 21-OT arm resulted in a reduced dose to 0.4 mg/m2 bid after the first 17 pts. Median number of courses (n): 5-OT (2), 21-OT (2), CPT-11 (4). Median survival times (weeks): 5-OT (35.7), 21-OT (35.0) and CPT-11 (43.6); a statistical difference favoring CPT-11 in overall survival for CPT-11 vs 5-OT (Log-Rank p=0.03); and a trend favoring CPT-11 as compared to 21-OT (Log-rank p=0.54). Responses were seen in the 21-OT and CPT-11 arms. Grade 3/4 neutropenia was reported in 5-OT (64.0%), 21-OT (14.3%) and CPT-11 (33.3%). Grade 3/4 thrombocytopenia (5% pts) 5-OT (26.0%), 21-OT (10.2%) and CPT-11 (8.0%). The most common nonhematologic adverse events were nausea and diarrhea: 5-OT (25% and 29%), 21-OT (0% and 12%) and CPT-11 (15% and 9%). Conclusion: 5-OT and 21-OT (at the 0.4mg/m2 bid dose) were well tolerated. The CPT-11 arm produced the longest survival time. Factors that might account for the differences in treatment regimens will be evaluated.

SURVIVAL DIFFERENCES OBSERVED BETWEEN BOLUS VERSUS INFUSIONAL IRINOTECAN CONTAINING COMBINATION CHEMOTHERAPY USED IN THE TREATMENT OF METASTATIC COLORECTAL CANCER – A RETROSPECTIVE CHART REVIEW

Anil Abraham Joy 1, Heather-Jane Au 2, Anthony LA. Fields 3, John Hanson 4, Sheryl Koski 5, Karen Mulder 1, Michael B. Sawyer 1, Andrew G. Scarfe 1, Patricia Tang 2, Charles A. Butts 1
1 Cross Cancer Institute, Edmonton, Alberta, Canada
2 Tom Baker Cancer Institute, Calgary, Alberta, Canada
3 GSK Pharma, Philadelphia, United States
4 GSK Pharma, Collegeville, United States
5 GSK, Harlow, United Kingdom

BACKGROUND:
The treatment of metastatic CRC has evolved to the point whereby the use of combination chemotherapy with irinotecan or oxaliplatin/5FU/leucovorin is standard first line therapy. In North America, irinotecan and bolus 5FU regimens (IFL) were favored while in Europe, irinotecan and infusional 5FU (Douillard or FOLFIRI) have become standard. There have been no randomized trials directly comparing IFL to infusional irinotecan containing regimens.

PURPOSE:
To examine whether survival differences exist between metastatic colorectal cancer patients treated with either bolus or infusional irinotecan/5FU/leucovorin combination chemotherapy at the Cross Cancer Institute, Edmonton, Alberta, Canada. Charts on 166 patients receiving first-line irinotecan combination chemotherapy from January 2000 to July 2003 were reviewed as there has been a change in institutional guidelines from bolus to infusional irinotecan combination therapy during this period. Patients treated in the “bolus” group received standard Saltz regimen whereas patients in the “infusional” group received either Douillard or FOLFIRI regimens.

RESULTS:
One hundred sixty-six patients were reviewed (96 male, 70 female) with a median age of 59.5 (range = 29 - 82). Bolus IFL chemotherapy was administered to 89 patients while infusional chemotherapy was administered to 77 patients. Kaplan-Meier survivals were calculated for all individuals from the date at which first chemotherapy was administered to the date of death or last follow-up. Survival data for all patients was updated as of March 31, 2004. A statistically significant difference in survival was noted between those treated with bolus IFL chemotherapy versus infusional (median = 13 versus 19 months respectively, logrank p=0.037). No difference in survival was seen between females treated with either bolus (n=35) or Infusional (n=35) chemotherapy (median survival = 20 months, logrank p=0.786). Males treated with infusional chemotherapy (n=42) appeared to live longer than those treated with bolus IFL (n=42) (16 versus 11 months median survival respectively, logrank p=0.017). Increased rates of hospitalization were seen in the bolus IFL group compared to the infusional group (65% vs 37% respectively, p=0.01) with gastrointestinal toxicity being the most common reason for admission.

CONCLUSIONS:
Superior survival and improved toxicity profile was observed in patients treated with infusional versus bolus irinotecan/5FU/leucovorin chemotherapy. In terms of survival, women tended to have better outcomes compared to men irrespective of treatment used, and men treated with bolus chemotherapy tended to do poorly. Our institutional experience supports using first-line infusional irinotecan/5FU/leucovorin rather than bolus IFL chemotherapy in the treatment of metastatic colorectal carcinoma.
INCIDENCE, SEVERITY AND TREATMENT OF ANEMIA IN PATIENTS WITH METASTATIC COLORECTAL CANCER RECEIVING IRINOTECAN CONTAINING COMBINATION CHEMOTHERAPY - A RETROSPECTIVE CHART REVIEW.

Charles A. Butts, Heather-Jane Au, Anthony LA. Fields, John Hanson, Sheryl Koski, Karen Mulder, Michael B. Sawyer, Andrew G. Scarfe, Patricia Tang, Anil Abraham Joy

Cross Cancer Institute, Edmonton, Alberta, Canada

BACKGROUND:

Previous reviews exploring the incidence of anemia in cancer patients report base line rates of anemia from 17– 37% and anemia developing on treatment in 35 – 50% of individuals. The incidence of anemia varies with the cancer type and chemotherapy regimen used. However, few of these studies included colorectal cancer patients. Those that did included primarily 5FU based monotherapy in the combined adjuvant and metastatic treatment settings. Patients with colorectal cancer have multiple risk factors for anemia including acute and chronic blood loss, nutritional deficiencies, and anemia of chronic disease. In addition, there has been a change in the patterns of treatment for metastatic colorectal cancer with more aggressive combination chemotherapies being used and the treatment duration extending for longer periods of time.

PURPOSE:

To explore the incidence and severity of anemia in patients with metastatic colorectal cancer receiving combination irinotecan/5FU/leucovorin chemotherapy at the Cross Cancer Institute and to determine how these patients were managed. Charts for 166 patients receiving irinotecan containing combination chemotherapy between January 2000 and July 2003 were reviewed. Data for hemoglobin is currently available on 123 patients.

RESULTS:

Seventy patients were male and 53 were female. Median age was 63 years (32 – 82 years). (Neo) adjuvant chemotherapy was delivered in 24 patients (19.5%). Sixty-eight patients (55%) received IFL (Saltz), 32 Douillard, and 35 FOLFIRI. Only 4 patients (3%) had a baseline hemoglobin less than 100 g/L and no patient had a base line hemoglobin less than 80 g/L. During treatment, 43 patients (34%) developed a hemoglobin less than 100 g/L and 5 (4%) developed hemoglobin less than 80 g/L. Twenty-three patients (18.5%) received red blood cell transfusions for a total of 77 units. Twelve patients (9.7%) received iron supplementation and 5 patients (4%) received subcutaneous injections of erythropoetin.

CONCLUSIONS:

The incidence of significant anemia in patients with metastatic colorectal carcinoma is low at the initiation of chemotherapy. Approximately one third (34%) of patients develop anemia with a hemoglobin less than 100 g/L while receiving irinotecan-based combination chemotherapy. However, even on treatment, the hemoglobin rarely dropped below 80 g/L implying that treatment is initiated earlier. Primary management for these patients was red blood cell transfusion.

CONCLUSION:

Our experience is still limited and preliminary but we have not noted yet grade 3 neurotoxicity even among those patients treated with the highest doses of oxaliplatin (expected neurotoxicity incidence 50%) it was never necessary to stop chemotherapy because of neurotoxicity. As far as we have experienced GSH seem to be able to prevent oxaliplatin cumulative neutrotoxicity incidence, but further randomized and controlled studies are necessary.
BACKGROUND: After reducing doses of CPT-11 from 125 to 100 (doses in mg/m²) and 5FU from 500 to 400 (LV unchanged, 20) due to increased toxicity & early mortality (Rothenberg, JCO 2001), Intergroup N9741 concurrently randomized 355 of a planned 600 patients (pts) with CRC to FOLFOX-4 or R-IFL. Randomization was terminated early due to superior results on FOLFOX.

METHODS: The regimens were: FOLFOX 4 (Oxaliplatin 85 d 1 + LV 200/5-FU 400 bolus + 800 as a 22 hour infusion d 1,2 q 2 week); R-IFL (CPT-11 100 + LV 20/5FU bolus 400 weekly x 4, q 6 week).

RESULTS: Pts/arm were: FOLFOX-154, R-IFL-151. 60 day all-cause mortality was FOLFOX 2.0%, R-IFL 2.7%. Common grade >3 toxicities are below.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>FOLFOX (%)</th>
<th>R-IFL (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>16%</td>
<td>20%</td>
<td>0.21</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8%</td>
<td>6%</td>
<td>0.49</td>
</tr>
<tr>
<td>Dehydration</td>
<td>6%</td>
<td>4%</td>
<td>0.60</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17%</td>
<td>11%</td>
<td>0.12</td>
</tr>
</tbody>
</table>

With median follow-up of 18.0 months, median time to progression (TPP) (primary endpoint) for FOLFOX is significantly better than for R-IFL: 10.1 vs 6.5 months (mo) respectively (Logrank p<0.0001). The median survival (OS) is significantly greater for FOLFOX than for R-IFL: 20.5 vs 16.3 mo (p = 0.026). Confirmed response rates (RR) were improved for FOLFOX vs. R-IFL (47% vs 32%, p=0.007). Sixty-five percent of pts received second line Rx. In each arm 75% of pts who received 2nd line treatment received the agent not used first line (in contrast to earlier study phases when access to Oxaliplatin was limited).

With median follow-up of 18.0 months, median time to progression (TPP) (primary endpoint) for FOLFOX is significantly better than for R-IFL: 10.1 vs 6.5 months (mo) respectively (Logrank p<0.0001). The median survival (OS) is significantly greater for FOLFOX than for R-IFL: 20.5 vs 16.3 mo (p = 0.026). Confirmed response rates (RR) were improved for FOLFOX vs. R-IFL (47% vs 32%, p=0.007). Sixty-five percent of pts received second line Rx. In each arm 75% of pts who received 2nd line treatment received the agent not used first line (in contrast to earlier study phases when access to Oxaliplatin was limited).

CONCLUSIONS: R-IFL lessens the toxicity burden of IFL, and results in efficacy similar to full dose IFL (median TTP 6.9 mo, RR 32%, median OS 15 months (Goldberg, JCO 2004). FOLFOX improves RR, TTP, and OS compared to R-IFL and to full-dose IFL. The significant survival benefit related to FOLFOX over R-IFL was maintained in the presence of common usage of 2nd line oxaliplatin after IFL. Supported by NIH Grant CA25224, Pharmacia and Sanofi-Synthelabo.
MVA-FCU1: A HIGHLY POTENT GENE-BASED CHEMOTHERAPY PROVIDING 5-FU LOCAL DELIVERY

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Transgène SA, Strasbourg, France

Background: Direct transfer of pro-drug activation systems into tumours was demonstrated to be an attractive method for the selective in vivo elimination of tumour cells. Besides its local cytotoxic impact, this strategy was further demonstrated to enhance the host anti-tumour immune response through the local release of cellular debris that can be presented by the antigen presenting cells.

Material and methods: We describe a novel and highly potent suicide gene derived from the Saccharomyces cerevisiae cytosine deaminase (FCY1) and uracil phosphoribosyltransferase genes (FUR1). This suicide gene, designated FCU1, encodes a bifunctional chimeric protein that combines the enzymatic activities of FCY1 and FUR1 and efficiently catalyses the direct conversion of 5-fluorocytosine (5-FC), a non-toxic pro-drug, into the cytotoxic metabolites 5-fluorouracil (5-FU) and 5-fluorouridine-5-monophosphate (5-FUMP). Interestingly, the cytosine deaminase activity is 10-fold higher in the chimeric protein compared to the natural protein.

Results: In this study we demonstrate that a MVA (Modified Vaccinia Virus of Ankara) engineered to express the FCU1 gene significantly enhances the sensitivity of numerous human tumour cells to 5-FC (LD50 5-FC = 1µM in the FCU1 treated cells compared to LD50 5-FC = 10µM in the CDase treated cells; p<0.01). Moreover, passive diffusion of the 5-FU ensures an impressive bystander effect with the ability to kill 100% of a in vitro tumour cell population with only 1% FCU1-transduced cells.

Intratumoral injections of MVA-FCU1 into human tumour-bearing mice, with concomitant systemic administration of 5-FC, led to a sustained control of tumour growth. The FCU1-induced tumour growth suppression was observed in different human colorectal tumour models whereas 5-FU administered IP at the maximum tolerated dose did not show any anti-tumour effect in the same models.

Finally, a 10-fold higher concentration of 5-FU is detected inside the tumour compared to a systemic administration of 5-FU while no detectable 5-FU is found in the circulation, ensuring a higher safety profile with no systemic toxicity.

Conclusions: The FCU1 suicide gene is a unique combination of an innovative approach and a validate and secure chemotherapy that makes it a novel and powerful candidate for treating all 5-FU sensitive tumours. A Phase I clinical trial is scheduled early 2005 in metastatic colorectal cancer patients.

OXA is a third-generation platinum complex with a different spectrum of activity as compared with cisplatin and carboplatin. Clinical data have shown that OXA is active in the treatment of ACRC patients (pts), both as single agent and as combination therapy. The dose-limiting toxicity of OXA is a peripheral sensory neuropathy. Between October 1997 and March 2004, 185 ACRC pts were enrolled in three consecutive studies and treated with different OXA chemotherapy regimens: 1) phase I-II (63 pts) OXA 100-130 mg/m2 d1 + 5FU 200-250 mg/m2 d1-21 every 21d; 2) phase II (59 pts) OXA 100-130 mg/m2 d1 + raltitrexed 2-3 mg/m2 d1 every 21d; 3) phase III (ongoing) (63 pts) OXA 130 mg/m2 d1 + 5FU 250 mg/m2 d1-21 every 21d vs OXA 130 mg/m2 d1 + capecitabine 2000 mg/m2 d1-14 every 21d. The pt characteristics were: men 114 (61.6%), women 71 (38.4%); median age 65 years (33-79); median Karnofsky PS 90 (60-100); treated 80 (43.3%), untreated 105 (56.8%). Lévi grade (G) 1-3 neurotoxicity was observed in 136 pts (73.5%): 44.8% G1, 22.2% G2, 6.5% G3. Neurotoxicity was related with OXA cumulative dose: ≤260 mg/m2 (32 pts) 40% G1-2; OXA 261-520 mg/m2 (50 pts) 66% G1-2; OXA 521-780 mg/m2 (49 pts) 75.5% G1-2, 6.1% G3; OXA 781-910 mg/m2 (15 pts) 66.7% G1-2, 20% G3; OXA >910 mg/m2 (21 pts) 74.9% G1-2, 21.1% G3. G2-3 neurotoxicity was present in 34/141 pts (24.2%) of age <70 years and in 19/44 pts (43.1%) of age >70 years (p=0.0146). The severity of neurotoxicity with the Kruskal-Wallis test appeared to be significantly related to the increase in the OXA cumulative dose (=0.000) and patient age (=0.017). Neurological toxicity was completely reversible in 90% of pts within 6 months from the end of treatment. Due to neurotoxicity, the OXA dose was reduced by <25% in 3 pts (1.6%) and by 25-50% in 2 pts (1.1%). These neurotoxicity data show that: 1) OXA regimens are well-tolerated; 2) pts with age >70 years developed higher neurotoxicity; 3) no dose reduction was required in pts before a total cumulative dose of 521 mg/m2; 3) no dose reduction was well-tolerated in 97.3% of pts.

P108 EVALUATION OF OXALIPLATIN (OXA) NEUROTOXICITY IN THREE ADVANCED COLORECTAL CANCER (ACRC) CONSECUTIVE STUDIES

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Neurotoxicity was related with OXA cumulative dose: ≤260 mg/m2 (32 pts) 40% G1-2; OXA 261-520 mg/m2 (50 pts) 66% G1-2; OXA 521-780 mg/m2 (49 pts) 75.5% G1-2, 6.1% G3; OXA 781-910 mg/m2 (15 pts) 66.7% G1-2, 20% G3; OXA >910 mg/m2 (21 pts) 74.9% G1-2, 21.1% G3. G2-3 neurotoxicity was present in 34/141 pts (24.2%) of age ≤70 years and in 19/44 pts (43.1%) of age >70 years (p=0.0146). The severity of neurotoxicity with the Kruskal-Wallis test appeared to be significantly related to the increase in the OXA cumulative dose (=0.000) and patient age (=0.017). Neurological toxicity was completely reversible in 90% of pts within 6 months from the end of treatment. Due to neurotoxicity, the OXA dose was reduced by <25% in 3 pts (1.6%) and by 25-50% in 2 pts (1.1%). These neurotoxicity data show that: 1) OXA regimens are well-tolerated; 2) pts with age >70 years developed higher neurotoxicity; 3) no dose reduction was required in pts before a total cumulative dose of 521 mg/m2; 3) no dose reduction was well-tolerated in 97.3% of pts.
P109  
SAFETY AND COMFORT DURING COLONOSCOPY - A COMPARISON OF THREE METHODS OF ANAESTHESIA  
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Background & goal: colonoscopy is rarely performed under anaesthesia for fear of complications and prolonged stay. Indications for anaesthesia incl. pain, fear and specific wishes of the patient. We compare three methods of anaesthesia for colonoscopy assessing their efficacy in outpatient conditions.

Material & Method: 207 ASA I-II pts undergoing outpatient colonoscopy randomised into 3 groups statistically comparable as to mean age and body weight. Standard monitoring incl. constant ECG and SaO2, BP every 3 min. In all groups i.v. premedication consisted of fentanyl 0,0015 mg/kg, midazolam 0,015mg/kg, atropine 0,01mg/kg. Anaesthesia: Group I: (GI) bolus of propofol 0,5 mg/kg (DIPRIVAN, AstraZeneca), then titrated in 10-20 mg doses, Group II: (GII): 2 mg/kg propofol infusion after an 0,5 mg/kg initial dose; Group III: (GIII) bolus of etomidate 0,02mg/kg (ETOMIDATE LIPURO, Braun), then titrated in 2-4mg doses.

Results: we analysed changes in the initial BP, HR and SaO2 exceeding 10% of initial values, time to awakening, orientation, discharge criteria after 60 min, evaluation by the colonoscopist and by the patient, and all observed complications. Hemodynamic instability GI and GII - 20.3% of pts; GIII - 10.1% of pts (NS). All other analysed parameters failed to reach statistical significance. 3 pts from GII (4.3%) had myoclonias, 1 pt (1.4%) nausea. The frequency of other complaints (pain on injection, lightheadedness, dry mouth) was similar in all groups (NS). Mean duration of procedure 30.4 min., SD ± 16.1. All patients fulfilled discharge criteria after 60 min.

Conclusions: outpatient colonoscopy under anaesthesia is a safe and comfortable procedure (both for the pt and the physician). The methods are comparable therefore the choice of anaesthetic depends on the anaesthesiologist. Although the observed differences failed to reach statistical significance yet pts ASA III and over may benefit from etomidate sedation.

P110  
SENTINEL LYMPH NODE TECHNIQUE IN COLORECTAL CANCER  
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Background. Sentinel lymph node (SLN) biopsy is currently used and investigated for melanoma and breast cancer staging. Its utility in gastrointestinal malignancies is still under debate. Prognosis of colorectal cancer patients is strongly related to the lymphatic involvement of the disease. Aim. The aim of this study is to evaluate the feasibility of SLN mapping technique in colorectal cancer and to assess its impact on pathological staging and treatment. Methods. We injected blue dye in 50 patients affected from colorectal cancer during surgery. After resection of the tumor the specimen was examined to identify blue-stained lymph nodes and these lymph nodes were sent separately to the pathologist. Routine haematoxylin-eosin examination was performed on all nodes (included blue ones). No other techniques (like immunohistochemistry or PCR) were performed. Results. Sentinel lymph nodes were successfully identified in 45 patients of 50. We observed only 5 false negative (10%) and concordance between SLNs and other lymph node status was 80% (40/50). One patient was upstaged: SLN was positive for metastases and other lymph nodes were negative. Conclusions. Lymphatic mapping using patent blue dye is feasible in colorectal cancer. The identification of lymph nodal metastases by this technique may have upstaged one patient who may benefit from adjuvant therapy. Initial results suggest further investigation of this procedure as an accurate staging and a minimally invasive approach to early colorectal cancer. Our study is ongoing in order to evaluate the role of SLN mapping in the colorectal cancer management.
Negative correlation between calcium intake and the incidence of colorectal cancer has been reported in epidemiological studies. The ability of calcium to complex bile acids and free fatty acids into insoluble salts might be responsible for this protective effect. However, different forms of calcium have been used in experimental carcinogenesis and controversial results have been observed.

**Purpose of the study:** The purpose of this experiment was to determine whether calcium forms (carbonate, lactate and gluconate) affect the colon carcinogenesis in Wistar rats fed a high fat diet. This was evaluated through fecal pH measurement and histological examination.

**Summarized description of the project:** Wistar rats fed high fat diet (24%) were supplemented with different chemical forms of dietary calcium and intra-rectally instilled with N-methyl-N-nitrosoareua. Supplemental calcium was administered at 1.5% Ca++ (w/w of total diet) complexed with either carbonate, gluconate or lactate in three groups 1, 2, and 3 respectively (n = 30 per group). The tumor incidence of colon cancer was compared to a control group 4 (n = 29), fed the same diet without supplemental calcium. Feces and urines were collected to determine fecal pH. After 34 weeks experiments, rats were killed and lesions were examined histologically.

**Results and conclusions:** Colon carcinoma incidence was 24%, 10%, 7%, and 25%, in groups 1, 2, 3, and 4 respectively. The calcium supplementation exhibits a protective effect depending on the chemical form used. Calcium lactate and gluconate provide better protection than carbonate form. The poor effect of calcium carbonate may be linked to fecal pH increase. Indeed, fecal pH, measured in rats fed calcium lactate or gluconate is lower than in rats fed calcium carbonate supplement (p < 0.001). The ability of calcium to form soaps with colonic free fatty acids and bile acids contributes to an alkalinisation of colonic pH. For instance, long-term adaptation of the colon to calcium carbonate induces a basic fecal pH whereas calcium salts with metabolizable or fermentable components such as calcium lactate or gluconate maintains an acidic colonic pH, probably through bacterial degradation, and thus prevents the mutagenic effect on the intestinal mucosa by some end products. The lowering of colonic pH by organic calcium forms may inhibit the 7α-dehydroxylase which catalyzes the formation of cytotoxic secondary bile acids, deoxycholic and lithocholic acids, from primary bile acids, cholic and Chenodeoxycholic acids respectively. Hence, the different calcium forms have various effects on fecal pH, and consequently on colon carcinogenesis. Fecal pH may explain the controversial effects of different chemical forms of calcium observed in experimental studies.

**Conclusions:** These results suggest that p53-independent mechanisms of Fas/CD95 induction may be drug-specific and that anti-Fas therapies may still have a role to play in the p53 null setting. Importantly, synergy between rTRAIL and each of the cytotoxic drugs did not appear to be p53-dependent following MTT analysis. These results characterise the role of p53 in regulating death receptor-mediated apoptosis in colon cancer cells following treatment with chemotherapy.
MEAT, COOKING METHODS AND RISK OF COLORECTAL CANCER: A CASE-CONTROL STUDY IN ARMENIA

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Objectives: The study aimed to explore an association between meat consumption, its cooking methods and risk of colorectal cancer in Armenia. Colorectal cancer is the third most common cause of death among patients with neoplastic diseases and the sixth cause of death in Armenia.

Study Methods and Design: The study utilized a case-control design. Seventy-seven patients diagnosed with colorectal cancer during the study period from August 17, 2002 to August 20, 2003 were included in the study as cases. The control group was selected from healthy hospital visitors, who were free of the disease, and were not related to the patient. The controls were matched with the cases by age and gender. Information was collected using telephone or face-to-face interviews by means of interviewer-administered questionnaires.

Results: The analysis showed that the risk of having colorectal cancer increased with everyday meat use compared with not-daily meat use (adjusted for frequency of fried and boiled sausage use and preference of fried meat surface: OR=3.2; 95% CI 1.0-18.5; p-value 0.044), with preference of heavily browned surface of fried meat compared with lightly browned (adjusted for daily meat use and frequency of fried and boiled sausage use: OR=15.4; 95% CI 2.8-85.8; p-value 0.002). There was no statistically significant risk of having colorectal cancer across different types of meat as well as across preferred cooking methods for different meat types. The results of the study have also shown a protective effect of frequent use (more than once/week) of boiled and fried sausage use on risk of colorectal cancer (adjusted for daily meat use and preference of fried meat surface: OR=0.03; 95% CI 0.004-0.3; p-value 0.002, and OR=0.1; 95% CI 0.008-0.5; p-value 0.008, respectively).

Conclusions: The study has demonstrated evidence that there is a need for a nutrition educational program to make the information available for the public. Based on the results of the study, it is recommended to avoid use of heavily browned surface meat and shift from daily to more rare meat use. However, more research is needed to obtain data that might serve for decision-making regarding nation-wide preventive programs. Further, protective effect of frequent use of boiled and fried sausages need to be proved by additional research, as the results are controversial compared with previous studies.
Aim: The interplay between immune cells and death receptors in apoptosis confers the ability of the tumour to evade the immune system. In addition, antiapoptotic molecules are also fundamental in immune evasion. The objective of this study was to determine the phenotype of immune cell infiltrates in colorectal cancer specimens in Malaysian patients.

Methods: Fifty-three archived colorectal cancer specimens managed in Hospital Kuala Lumpur over a 1 year period in 2000 were randomly selected for immunohistochemistry analysis. Death receptor Fas and Fas ligand were enumerated to determine its apoptotic significance for tumour escape. Expression of antiapoptotic molecules, FLIP and Bcl-2 were determined to identify their implications in immune evasion. In addition, the phenotypes of immunocytes and expression of Fas, FasL, FLIP and Bcl-2 were compared with clinicopathological data (age, sex, race, pathologic stage, histologic grade of the carcinoma and tumour site) to determine their relationship. Seven further colorectal cancer specimens from patients operated in Hospital Kuala Lumpur from April 2002 to August 2002 were included in this study using universal sampling. Flow cytometry was performed on the surgical samples. Antibodies used were anti-HLA-DR, anti-CD3, anti-CD19 (B cell marker), anti-CD56 (natural killer cell marker), anti-EP4 (epithelial marker), anti-FLIP and anti-Bcl-2. Data from flow cytometry were expressed as the percentage of positive immunoreactive cells from the gated cells.

Results: The percentage of activated T-cells in tumour tissue were found to be significantly and positively correlated to the percentage of tumour cells expressing Fas ligand and Bcl-2 (p<0.05, independent t-test). Younger patients had significantly higher percentage of B-cells co-expressing Fas (p<0.05, independent t-test). The left colon were found to have a significantly higher percentage of T-cells co-expressing Fas, but lower natural killer cells co-expressing Fas (p<0.05, One-way ANOVA, Bonferroni post hoc correction).

Conclusions: These findings further confirm the role of the immune system in responding to tumour cells in an attempt of suppressing invasion. Protective antiapoptotic mechanisms devised by the tumour however exist to escape and counterattack the immune system.
Inactivating germline mutations in the tumour suppressor E-cadherin (CDH1) cause predisposition to diffuse gastric cancer (DGC). Essentially all E-cadherin mutation carriers present with multiple gastric intramucosal foci (multifocal lesions, MFLs) containing signet ring cells. These lesions are pathologically defined as stage 1a DGC. We have investigated the genetic and biological properties of MFLs and compared them to advanced (≥T2) hereditary DGC and normal mucosa. MFLs are negative for E-cadherin expression (Chun et al. 2001). This is frequently due to CDH1 promoter hypermethylation, which was detected in lesions at a similar rate as has been reported previously for advanced hereditary DGC (Grady et al. 2000). Based on a microarray screen for differentially expressed genes in advanced DGC, MFLs were examined by immunohistochemistry for the expression of specific proteins. As an example, the oncprotein src was strongly expressed in all examined advanced DGCs. In contrast, signet ring cells contained in the MFLs never expressed src protein. However, src expression could be detected in the larger lesions that show signs of stromal reaction in their deeper part. Src expressing cells were confined to these regions and appear to have undergone a phenotypic change. Furthermore, data on the proliferative and apoptotic index as assessed by Ki67 staining and Tunel-assay will be presented.

Together our results indicate that signet ring cell MFLs differ from advanced DGC in important aspects. They are slow growing and appear to be the precursors of advanced DGC. These findings have implications for the clinical management of hereditary DGC. Furthermore, we propose a multi-step process for the development and progression of DGC, which could help to clarify the difficult classification of its early stages.
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GERMLINE MUTATIONS OF HMLH2 AND HMLH1 GENES IN SARDINIAN PATIENTS WITH COLORECTAL CANCER.
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Background: Colorectal carcinoma (CRC) represents one of the main causes of morbidity and neoplastic mortality in all the western Countries. Sardinian patients seem to be instrumental to better understand the genetic counterpart of a complex disease like cancer. In fact, Sardinian population is homogenous from the genetic and cultural point of view, and also from the environmental viewpoint.

Patients and Methods: Patients (N=362) with histologically-proven diagnosis of CRC were included in our study. Among them, 55 patients presented a low familial recurrence cases (only 2 family members affected by CRC), 48 cases were classified as familial probands (at least 3 CRC cases in family: distinguished in CRC family (24) and colorectal and endometrial cancer family (24); finally, 259 patients were classified as unselected. In all subjects, genomics DNA was amplified by PCR for all hMLH1/hMSH2 exons and screened using DHPLC. All PCR products with abnormal DHPLC profiles were sequenced on the ABI3100 Automated Sequencer.

Results: We identified a total of 22 germline mutations in 21 patients [21/362, 6%]: 2 in hMLH1 and 20 in hMSH2 (two of them in the same family probands). Among 17 patients younger than 40 years at the time of diagnosis, 5 cases (29%) were hMLH1/hMSH2 mutation carriers: no association between presence of mutation and localization of the primary CRC was observed. Familial cases presented a higher mutation frequency [14/48, 29%] in comparison to cases with low familial recurrence [2/55, 6%] or without familial recurrence [5/259, 2%]. A majority (10/14) of the mutations was found among probands with CRC familiar history, and presence of at least four affected family members greatly increased the frequency of hMLH1/hMSH2 mutations (6/8, 75%). In contrast to previous report, the families that showed an association between colorectal and endometrial cancer had a lower mutation frequency [4/24, 17%] in comparison to cases with only CRC familiar recurrence [10/24, 42%]. Finally, two hMSH2 mutations (Gly322Asp and Ser38Ile) were found at the highest level into the entire collection of 362 patients (1.7% and 1.4%, respectively), strongly indicating that they may represent founder mutations into our population.

Conclusion: In contrast to previous report from the other populations, hMSH2 gene seem to have a larger impact in Sardinian CRC patients. Our results may pave the way for genetic counseling and mutational analysis in mutation positive families and should stimulate further molecular studies in hMLH1/hMSH2 mutation negative CRC families. Work was funded by Regione Autonoma Sardegna and Fondazione Banco di Sardegna.

P120
HISTOPATOLOGIC CRITERIA AND THEIR IMPORTANCE IN SURVIVAL PATIENTS WITH COLORECTAL CANCER: MULTIVARIATE ANALYSIS
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Background: Risk factors predicting the presence of lymph node metastasis have been fully investigated. To determine the criteria for local excision of colorectal cancer, histopathologic factors independently predicting the lymph node metastasis were investigated.

Methods: We performed a retrospective histological study on 144 patients who underwent resection of colorectal cancer and dissection of regional lymph nodes between 1986 and 2003. Patients who have been less than 3 node metastases (n=79) were compared with those who have been 4 and more than node metastases(n=65).

Results: In multivariate analysis when we compared patients who have been less than 3 node metastases (n=79) with patients who have been 4 and more than node metastases(n=65) were characterised by tumor larger than 60 mm (28% vs. 0%), serosal invasion (46% vs. 19%), venous invasion (33% vs. 21%), histologic grade II - III (62% vs.28%). Multivariate analysis showed that factors independently associated with lymph node metastasis were serosal invasion, venous invasion and histologic grade. When these three risk factors were negative, lymph node metastasis was rare (5%). When one, two or three factors were negative, lymph node metastasis was 38%, 66% i 85% respectively.

Conclusions: Factors independently associated with lymph node metastasis are serosal invasion, venous invasion and histologic grade. When these three factors are favorable, local tretmen of colorectal cancer does not require additional lymph node dissection.
P121

MUTATIONAL ANALYSIS OF APC GENES IN MUTATION CLUSTER REGION IN COLONIC CARCINOMA

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Introduction: The age-standardized incidence rate for colorectal cancer (CRC) in Malaysia is 25.6 and 17.9 per 100,000 men and women respectively (National Cancer Registry, 2002). The adenomatous polyposis coli (APC) gene is the main tumor suppressor gene implicated in the development of CRC. Previous published data have shown that mutations of APC occurred in 80% of all CRCs. The vast majority of these mutations are insertions, deletions, and nonsense mutations that lead to frame shifts and/or premature stop codons in the resulting transcript. This results in a stable truncated APC protein without the carboxyl-terminus. A mutation cluster region exists within the 5' end of exon 15, between nucleotides 3000 and 4800 and represents approximately 60% of reported somatic mutations.

Methods: As the incidence rate of APC mutations in CRC's in Malaysia have yet to be determined, we examined 11 pairs of CRC tissues with apparently normal adjacent tissues for APC mutations in its mutation cluster region (MCR) from nt 3801 to nt 4576 [geneBank™ accession number: NM_000038]). Genomic DNA was isolated from CRC tissues, PCR performed followed by direct sequencing of PCR products.

Results: APC mutations were found in 4 out of 11 CRC tissues examined. 4 out of 5 mutations were point mutation at nt 3999 (4 cases), 4043 (4 cases), 4069 (4 cases), 4047 (3 cases), 4065 (3 cases), and 4074 (3 cases). The point mutation that occurred at 4096 in the other 4 samples generated a stop codon UGA. No APC gene mutations were observed in the remaining 6 CRC tissues. The results from APC gene analysis at the mutation cluster region were in accordance with immunohistochemical staining which showed that truncated APC was present in 23 /47 (49.9%) of CRC tissues.

Conclusion: Inactivating mutations of APC may play a causative role in colorectal carcinogenesis in Malaysia and further analysis with larger sample size will be required to support this finding.

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THE PARADOX OF ELEVATED SOLUBLE TNF RECEPTORS IN COLORECTAL CANCER: THE P55 TNF RECEPTOR IS A MARKER OF DISEASE AGGRESSIVENESS, IMPENDING RELAPSE AND SHORTENED SURVIVAL, WHILE LONE ELEVATION OF THE P75 TNF RECEPTOR IS A MARKER FOR CURE.

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Rationale: In-vitro studies suggest that TNF and its soluble p55 receptor (p55sTNF-R) are released by tumor cells. On the other hand, the p75sTNF-R is shed by activated T-cells on whose membrane this receptor predominates. We aimed to study the possible correlation between the serum sTNF-Rs and the prognosis of colon cancer patients.

Patients and Methods: The sTNF-Rs (p55sTNF-R, p75sTNF-R) were examined in the sera of 120 consecutive colorectal cancer patients. In 87 patients the examination was conducted after completion of the adjuvant treatment, following a curative operation. In 16 patients the receptors were examined soon after relapse and in 17 patients at diagnosis of metastatic disease. The serum concentration of the sTNF-Rs was determined by ELISA (Bender MedSystems, Biosource International Inc, Camarillo, Ca). Sera of 116 healthy individuals served for determination of the normal serum levels of the sTNF-Rs.

Results: 87 patients were followed up after adjuvant therapy. All 5 patients with elevated p75sTNF-R only survived 5 years compared to 90% of patients with both sTNF-Rs normal and to only 60% of those with both receptors elevated (p<0.02).

Relapse: In 16 patients the patients were examined 6 months before relapse and in 16 shortly after. 19 of these patients had both STNF-Rs within the normal range while 13 had elevation of both receptors. The survival from the actual date of clinical relapse was 32 and 12 months respectively for these two groups (p<0.0008). None of the patients with elevated sTNF-Rs survived 3 years while 25% of the patients with normal sTNF-Rs were alive at 5 years. In metastatic patients, the higher were the p55sTNF-R or the p75sTNF-R, the shorter was their survival (p<0.001).

Conclusions:
1. Elevation of both sTNF-Rs in a patient after adjuvant therapy is a marker of impending relapse despite normal CEA levels.
2. In metastatic colorectal cancer patients, elevated sTNF-Rs are a marker for a shorter survival.
3. The higher the increase in the receptor levels, the shorter is the survival.
4. Paradoxically, after adjuvant treatment, while elevation of p55sTNF-R (released by tumor cells) or concomitant elevation of both sTNF-Rs heralds relapse, lone elevation of the p75sTNF-R, released by T-cells, is a marker of cure (similar to what was observed in ovarian cancer patients).
5. These observations suggest the existence of two biologic types of colon cancer: one that may be TNF-growth accelerated while the other TNF-independent. Alternatively, high TNF producers due to a genetic polymorphism in the TNF promoter region, may have an adverse outcome due to excess TNF-growth promoted colon cancer. Our observations may have significant clinical implications.
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Background and objective:
Colorectal Adenocarcinoma is the major risk factor of mortality in cancerous patient, In spite of lower prevalence of this disease in Asia (including Iran), empirical experiments showed these patients diagnosed in high stages. The objective of this research is comparing the DUCK grading of Colorectal Adenocarcinoma in developed countries and Mashhad University hospitals’ patients between “1991-1999”.

Materials and Methods:
In this research according to 300 files of Colorectal Adenocarcinoma patients’ data which includes surgical reports & post-operative histological reports, & radiological findings, duck grading determined. Then, the results compared with the results of developed countries, Data analyzed with SPSS software.

Most of patients were male (58.7%) & age peak is 7th decade (26.7%), & 40.3% of patients were below 50 years old. The most common part of affection were rectum (25.4%) and sigmoid (24.4%), And the most common part for metastasis were liver and peritonea (48.51%).

The results of DUCK grading were includes:
A = 0%  B1 = 4.6%  B2 = 28%  C = 33.7%  D = 33.7%

Comparing the results of DUCK grading in our research with documental statistic data. In developed countries, which is in reference books such as Gastroenterology of Yamada and other researches, indicates that onset of Colorectal Adenocarcinoma in this research in compare of developed countries begins in lower age (P<0.0001) and there is more prevalence of high grade (C, D) at the time of diagnosis.

Conclusion:
Colorectal Adenocarcinoma in our research in compare of developed countries, begins in lower age and diagnosed in higher grades, Perhaps it could say the cultural and social features that limits expressing complain and no urgent referring to special centers in our country leads to higher grade of disease at the time of diagnosis, We suggest screening of high-risk population and more research in cause of late diagnosis and lower age onset.

THE IMPORTANCE OF NF1 GENE ALTERNATIVE SPlicing IN COLON CANCER
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Tumorigenesis of colon cancer is a multistep process of mutation accumulation in a number of oncogenes and tumor suppressor genes. NF1 protein product, neurofibromin, acts as a tumor suppressor by turning the active form of Ras into an inactive one. This molecular switch has an important role in the control of cell cycle and differentiation and the changes in the Ras activity are involved in number cancers. Several different isoforms are formed by alternative splicing of NF1 mRNA. Isoform type I was the first isolated isoform that lacks any insertions. Isoform type II contains an additional 63 bp insertion (exon 23a). These two isoforms are expressed at varying ratios in different cell types Several studies have shown that alterations in the type I vs. type II mRNA ratio can be associated with the development of certain malignancies.

In this study we investigated the loss of heterozygosity (LOH) of the NF1 gene in 100 sporadic colon cancers. Quantitative RT-PCR was used to determine the NF1 mRNA expression in tumor and corresponding normal mucous tissue. Relative ratio of NF1 types I and II expression was examined as well. The results were correlated with the patients’ clinicopathological features. LOH was observed in 20.7 % of informative samples. Expression of NF1 mRNA was higher in well differentiated tumors and tumors classified as Dukes’s A. NF1 isoform type II was dominantly expressed in normal mucous tissue, while the isoform type I was dominantly expressed in tumor tissue.
P125
EFFICACY OF AN IMMUNE FECAL OCCULT-BLOOD TEST FOR THE SCREENING OF COLORECTAL CANCER
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Objective: To assess the efficacy of an immune fecal occult-blood test (FOBT) for the screening of colorectal cancer in an asymptomatic moderate-risk population

Material & Methods: A total of 1,414 asymptomatic individuals (age range, 50 to 75 years) were enrolled in the screening. Patients were previously assigned to three different general practitioners, two of them in an urban setting while the third one in a rural area. Recruitment was performed by mailing, open conference for candidates and telephone call to those who initially refused to participate as well. Subjects were excluded if prior disease of the colon (colitis, polyps, cancer), examination of the colon within the previous 5 years (including sigmoidoscopy and colonoscopy), terminal condition, psychiatric severe disease or anticoagulation. Results were sent by mail to all participants and those individuals who had a positive FOBT were offered colonoscopy. Sigmoidoscopy was performed to subjects who initially rejected colonoscopy. If polyps or cancer was observed a complete colonoscopy was carried out. If the sigmoidoscopy was negative, a barium enema was performed and, in case of pathological findings in proximal colon, a complete colonoscopy was addressed.

Results: A total of 1,414 people were enrolled and 967 (68.4%) participated in the screening. The number of excluded subjects was 111 and 437 (31.6%) refused to participate. Out of the 856 individuals who participated, 836 handed over the FOBT and 36 (4.3%) had a positive result. As many as 32 of them underwent endoscopy while 4 people refused to it. Three tumors (Dukes A) were diagnosed and 4 patients had high-grade dysplasia.

Conclusions:
- A high participation (68.4%) was achieved in the screening.
- The prevalence of positive FOBT was 4.3%.
- Colorectal cancer or high-grade dysplasia was observed in 19.4% of individuals with a positive FOBT.
- Immune FOBT is an effective method for the screening of colorectal cancer or adenomatous polyps, allowing an early diagnosis of the disease.

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ANALYSIS OF THE PATIENT’S REASONS FOR PARTICIPATING IN A COLORECTAL CANCER SCREENING
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Objective: To find out the opinions and attitudes towards a colorectal cancer screening of both participating and non-participating subjects.

Material & Methods: Between January and May 2002, a colorectal cancer screening was performed on 1,414 individuals in Navarra, Spain. Three different groups for discussion were established:
- Group 1. Individuals who never attended for the initial consultation in spite of receiving an invitation letter and a strengthening phone call in case they did not respond to the letter.
- Group 2. Individuals who attended for the initial consultation.
- Group 3. Individuals who did not attend for the initial consultation but acceded to join the screening after a strengthening phone call.

All groups were constituted by men and women in similar proportion (aged 50-70 years), keeping the same number of individuals for each decade. They presented an average medium social, economical and educational status. The place where groups’ meetings were held had no connection with the National Health System. All meetings were recorded and literally transcribed. The results are based on the analysis of these texts.

Results:
- People mostly supported the implementation of cancer screenings.
- Initial participation in the screening was 54.8% but it rose up to 68.4% after making a strengthening phone call to subjects who didn’t initially respond.
- The quality of information about the screening and the confidence on the health-system professionals were the main reasons for participation.
- Fear of both cancer and medical tests were the main reasons for refusing to participate in the screening.
EARLY DETECTION OF COLORECTAL CARCINOMA USING STOOL-BASED DNA MARKERS

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Colorectal cancer (CRC) is one of the main causes of mortality in the world. In Egypt, CRC ranks as the seventh type of cancer. Screening for CRC has been a major goal of many research studies. The rationale for colorectal cancer screening lies within the observation that early cancer detection offers the best chance for cancer prevention and treatment. Three common screening tests for CRC have been used, FOBT, Endoscopy and barium enema. The goal of this study is to devise a simple non invasive screening test for colorectal cancer. The stool based DNA test has been used for this purpose. Three common screening tests for CRC have been used, FOBT, Endoscopy, and barium enema. The goal of this study is to devise a simple non invasive screening test for colorectal cancer. The stool based DNA test has been used for this purpose. Three

Microsatellite instability (MSI) is a consequence of defects in the mismatch repair pathway system that may lead to the accumulation of mutations in the genome. There is general agreement about the occurrence of three populations according to the degree of instability: stable (MSI-L), low-grade of instability (MSI-L) and high-grade of instability (MSI-H) patients, that seem to share the same mutational processes. The analysis of molecular, clinical, and pathological factors, that may predict clinical outcome, can be of main importance in the management of colorectal cancer.

MSI status, losses at 4p15.1 and other pathological characteristics were also evaluated as potential predictors of outcome. Patients & Methods: We have classified 120 colorectal cancer patients into three groups according to their MSI status: MSS, MSI-L and MSI-H. The occurrence of k-ras mutations and losses of heterozygosity (LOH) at marker D4S391 that maps to 4p15.1 region were also evaluated using PCR and fluorescent hybridization. Results: MSI-H patients had a significant higher percentage of k-ras mutations than MSS patients (P=0.03). In our population, LOH at D4S391 was a significant bad prognosis factor for survival time (P=0.025). Conclusion: MSS and MSI-L tumors seem to show different molecular background and different clinicopathological characteristics than MSI-H tumors.
THE ROLE OF ULTRASOUND AND COMPUTER TOMOGRAPHY AT THE DIAGNOSIS FOR PRIMARY RETROPERITONEAL TUMORS

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Materials: For the period 1995-2002 years stationary treatment concerning was spent at 205 patients with primary retroperitoneal tumors (PRT). At receipt in clinic for finding - out of character of tumor used method of ultrasonography (US) and computer tomography (CT).

Taking into account the used methods of all patients have divided into 2 groups. Thus I-group have made 93 (45.3 %) patient, with which was carried out a combination of X-ray and US methods without CT. In II - group at 112 (54.7 %) patients were applied combination of US and CT.

The results, received during research, in both groups was estimated in comparative aspect with an estimation of sensitivity and accuracy of each method for definition of diagnostic efficiency.

Results: The analysis of results has shown, that in I-group the sensitivity of US was made 83,4 %, accuracy - 77,9 %. After 62 (68,8 %) patients from I-group subjected to surgical treatment. By comparison of results of researches to the data of operational finds diagnostic informative of US estimation of prevalence of a tumor on the next anatomic structures has made - 80,6 %. At 31 (50,0 %) patients are executed radical operations, from them in 12 (19,3 %) cases the operation carried the combined character (resectability - 50,0%), palliative surgery - at 12 (19,3%), and in 19 (30,7%) cases operation was finished by diagnostic laparotomy (DL). In II-group the sensitivity of US has made 81,3 %, accuracy - 82,5%. At realization CT at 44 patients the sensitivity has made 92,8 %, accuracy - 85,2%. By comparison results is established, that the data of US have appeared authentic at 65 patients from 78 operated (informative - 83,3 %). As against it the results of CT have proved to be true at 41 patients from 44 (informative - 93,2 %). Being based on the received data from 107 patients of II-group at 78 (74,2 %) are executed of surgical intervention. The radical operations are made at 52 patients (resectability - 66,6 %), from them in 24 (30,7 %) cases are executed the combined operations. Palliative surgery are executed at 17 (21,8 %) patients. The frequency DL with biopsy has made in 11,5 % (9 patients).

Thus, wide use noninvasive methods of research at PRT allows to improve results of surgical treatment, to what the increase parameters of resectability at the patients II - group testifies.

Conclusions:
1. At application of US its accuracy was increased from 77,9 % in I-group up to 82,5 % in II – group and informative makes 83,3 %.
2. At application CT in the diagnostic for PRT sensitivity makes - 92,8 %, accuracy - 85,2 %, informative - 93,2 %.
3. The realization of complex diagnostics at PRT promotes increase of frequency operability from 68,8 % up to 74,2%. Besides the increase of cases resectability from 50 % up to 66,6% is marked.
THE APOPTOTIC EFFECT OF HUMAN RECOMBINANT S100A8/A9 ON COLON CANCER CELL LINE

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Introduction: Colorectal carcinogenesis is a multistep process concerning mutation of tumor suppressor genes, activation of protooncogenes, which may lead to uncontrolled mucosa, and finished by the invasive carcinoma development.

Purpose of the study: S100A8/A9 increases in feces in colorectal cancer. Previous research showed that human S100A8/A9 had apoptotic effect on some cell line. Therefore this study was designed to investigate the apoptotic effect of recombinant S100A8/A9 on colon cancer cell line (HT29/219 and SW742 cell line) benefit from its therapeutic effect in the management of colon cancer. Summarized description of the project:

Materials-Methods:
HT29/219 and SW742 cell lines were treated with different concentrations of recombinant S100A8/A9 (50-500 µg/ml) in different times (12-72 hrs). The cytotoxic effect of recombinant S100A8/A9 on treated cells. Caspase-3, -8, and -9 activities were determined in treated cells. The effect of divalent metal ions (calcium, magnesium, copper, zinc), and reactive oxygen species (ROS) were investigated on recombinant S100A8/A9 treated cells. The intracellular concentrations of zinc ion were determined by Zinquin in recombinant S100A8/A9 treated cells. The possible recombinant S100A8/A9 specific binding sites on these cell lines were investigated by flowcytometry method.

Results and conclusions:
Treatment of both colon carcinoma (HT29/219) and adenocarcinoma (SW742) cell lines with recombinant S100A8/A9 resulted in significant cell death. The recombinant S100A8/A9 caused typical apoptotic changes in the nuclear morphology in Hoechst 33258 and Annexin V/PI staining. The results demonstrated that the activity of caspase-3 and -9 were significantly (p<0.05) increased in both cell lines treated with recombinant S100A8/A9. There was no significant increase in caspase-8 activity in recombinant S100A8/A9 treated cells. A significant reduced apoptotic effect of recombinant S100A8/A9 was observed after the addition of zinc and copper, whereas calcium and magnesium had no modulatory activity. N-Acetyl-L-cysteine (NAC) (ROS scavenger) potently and in dose-dependent manner protects from recombinant S100A8/A9 cytotoxic/apoptotic effect. The intracellular zinc ion decreased significantly (p<0.05) in recombinant S100A8/A9 treated cells. Both cell lines showed recombinant S100A8/A9 binding sites by flowcytometry method.

The recombinant S100A8/A9-induced apoptotic activity was induced through the classical mitochondrial, cytochrome-c-dependent pathway as verified by the caspase-9 and caspase-3 but not by activation of caspase-8. In our study, we were able to show that pre-treatment of the cells with th antioxidant NAC, prevented apoptosis induced by recombinant S100A8/A9. As zinc and copper did not fully reverse the apoptotic effect of recombinant S100A8/A9, and there are recombinant S100A8/A9 binding sites on the cell surface of HT29/219 and SW742 cell lines, we conclude that recombinant S100A8/A9 induces apoptosis through a dual mechanism, one might zinc exclusion from the target cells and the other might be through binding to the cell surface of the target cells.

RELATIONSHIP BETWEEN CELL PROLIFERATION PATTERN AND THE ADENOMA-CARCINOMA PROGRESSION SEQUENCE OF HUMAN COLON AND RECTUM

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Introduction: Colorectal carcinogenesis is a multistep process concerning mutation of tumor suppressor genes, activation of protooncogenes, which may lead to uncontrolled proliferation of intestinal epithelial cells. This progression starts with the emergence of mucosa, and finished by the invasive carcinoma development.

Materials-Methods: 178 patients with colorectal polyph-adenoma and/or colorectal carcinoma underwent endoscopic polypectomy or surgical resection. The PCNA expression was examined in 28 non-neoplastic epithelial polyps, 82 neoplastic adenomatous polyps showing different degrees of dysplasia, 12 in situ carcinomas, 6 malignant polyps, 66 colorectal adenocarcinomas and their adjacent mucosa specimens. The PCNA protein levels were determined by immunoblot analysis quantified by densitometry. Logistic regression was used to examine the predictive role of PCNA on adenoma-carcinoma sequence.

Results: The PCNA expression was detectable in the visibly normal mucosa of 69% of patients with polyps. This alone is a proliferative zone, but does not mean bad prognosis. Moving further in the adenoma-carcinoma sequence, different in the expression difference between normal and altered tissue was more frequent. This kind of difference was never found hyperplastic and hamartomatous polyps or inflammatory pseudopolyps. Low difference was found in 2% of tubular and in 6% of tubulo-villous adenomas, and further 6% of the latter had high difference. In case of villous adenomas the degree of dysplasia well correlated with the frequency of difference. In mild dysplasia the expression difference was found in 3% of the cases, in moderate it was in 21% and in severe dysplasia the difference was found in 55% of the cases. The expression difference has been found in 57% of in situ carcinomas grown on base of a polyp, and in 65% of the malignant polyps. In adenocarcinomas, the Dukes classification paralleled well with PCNA expression difference between tumor – peritumoral mucosa, in contrast with the only in tumor measured PCNA expression.

Conclusion: These results indicate that PCNA expression difference between normal and altered tissue progressively increased along the sequence from normal mucosa via low grade, middle grade, and high grade dysplasia, adenoma to advanced cancer. The PCNA expression difference is one parameter that contributes to the definition of the degenerative risk and allows selection of patients with high expression difference for constant monitoring.
TUMOUR DNA CONTENT AND TREATMENT RESPONSE IN COLORECTAL CARCINOMA.

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Background: The aim of this study was to identify markers that might predict response to chemotherapy. Postoperative chemotherapy improves the outcome in stage III colon cancer and is widely accepted as a standard therapy, but there are currently no reliable predictors to identify and select patients that will benefit. Patients and methods: Using DNA image cytometry the DNA content was determined from the isolated nuclei of 56 primary colorectal carcinomas of patients who received chemotherapy (either irinotecan/irinotecan plus 5-fluorouracil and folinic acid) for advanced disease. Response to chemotherapy could be reliably evaluated in 53 patients. Results: The modal DNA content (ploidy status) of the tumour correlated with the observed response to chemotherapy (p=0.01). An objective response was observed in 56% of patients whose tumour histograms displayed tetraploid, peri-tetraploid or multiploid pattern of peaks, compared with 19% in patients with diploid, peri-diploid or aneuploid peaks. Notably, 86% (6/7) of patients whose tumour displayed a multiploid peak pattern showed an objective response and one patient had stable disease. Conclusion: This study suggests that modal DNA content can be used to predict a patient’s response to chemotherapy in advanced colorectal carcinoma. This may help in identifying patients who will benefit most from therapy for advanced colorectal cancer.

Key words: 5-FU, colorectal carcinoma, image DNA cytometry, irinotecan, ploidy, response.

COLORECTAL CARCINOMA IN SOUTHERN CROATIA (PERIOD 2001-2003).

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Abstract: Cancers of the colon and rectum are a major cause of illness and death in patients living in the United States and Western Europe. Because these cancers arise over a long period of time as the result of interactions between genetic predisposition and environmental influences, it is possible to identify preneoplastic and early neoplastic lesions and improve survival rates. The incidence begins to rise at age 40 and reaches a peak from 60 to 75 yr. Adenocarcinomas represent the vast majority of colorectal cancers (98%). In the proximal colon they tend to grow as polypoid masses whereas in the distal colon they grow as encircling lesions. The microscopic characteristics are independent of localisation, and tumor may range from well to poorly differentiated. The widely used staging system as the single most important prognostic indicator based on the extent of the tumor at the time of diagnosis is proposed by Dukes (Dukes A- tumor confined to the mucosa, submucosa and muscularis propria, Dukes B- like A with extending into pericolonic fat and serosa without involving lymph nodes, Dukes C- involved lymph nodes, Dukes D- distant metastases or tumor is present on resection margins of specimen).

Results: Six hundred seventy three (673) cases of histologically proven adenocarcinoma of the large bowel were seen in the Clinical Hospital Split in the three years period (2001-2003). The age, sex, distribution of the lesion in the colon and rectum were analyzed in all the cases. The mean age of the patients included in this study was 62 years and male:female ratio was 3:2. Location: Most of the colonic tumors were located in the sigmoid colon (25%) and rectum (25%), followed by ascending/cecum colon (25%), transverse colon (15%) and descending colon (10%). Dukes classification: According Dukes classification on our biopsy material we have Dukes A in 15%, Dukes B 38%, Dukes C 37% and Dukes D 10% of the cases.

Conclusion: Rectosigmoid carcinomas (50%)
Dukes A+B (53%)
Dukes C+D (47%)
The Bowel Cancer Awareness Project (BCAP) is a partnership between Forth Valley and Lanarkshire NHS Boards (Scotland, United Kingdom), funded by the New Opportunities Fund (NOF) for a period of three years (June 2002 – June 2005), to raise awareness about Bowel Cancer. The Project targets 36 local communities in both Health Board Areas, with particular attention paid to addressing health inequalities via the prioritisation of work in designated Social Inclusion Partnership and rural areas.

In Scotland Bowel Cancer is the second most common cancer in males and third most common in females, and lies second to lung cancer as a cause of death in both men and women. Evidence from a number of sources indicates that around 2/3 of cases diagnosed can be accounted for solely by the environment, primarily dietary, smoking and lack of physical activity. Scottish diet is still high in animal fat and red meat and low in green vegetables, fruit and fibre. There is strong association between smoking and bowel cancer, and there is also evidence to show that people who are physically active have a reduced risk of developing bowel cancer. Research carried out by the Scottish Needs Assessment Programme (SNAP), however, indicated that the public knowledge and understanding of bowel cancer is poor.

There is significant evidence, on the other hand, to say that by raising awareness of signs and symptoms, and by addressing healthy lifestyle messages, we can reduce both the incidences and the mortality of bowel cancer in the population, as well as improve the quality of life of patients suffering from this condition. The Bowel Cancer Awareness Project (BCAP) is taking this message forward to encourage earlier diagnosis in those “at risk” within the general population, and in “high risk” groups.

With a consistent public campaign, along with a well accepted tagline, “KNOW THE SIGNS, REDUCE THE RISK”, endorsed by BCAP partners, the Project aims to raise awareness of bowel cancer in a responsible manner, thereby reducing a possible influx of the worried well to Primary Care Services. BCAP understands that only a well co-ordinated primary and secondary prevention programme will help to cut death rates in Scotland and to improve the quality of life of patients. BCAP proposes that this rationale should be shared and its implementation actively promoted by all of the key partners involved in the project. The Project relies heavily on its collaboration wherever possible with Primary and Secondary Care staff, including pharmacists across each Health Board. Based on the identified needs, BCAP offers a flexible and accessible training programme on bowel cancer to the general population and to health professionals. This training aims to improve the patient journey through increasing staff knowledge and confidence, as well as supporting and facilitating, where feasible, colorectal service re-design within the life-span of the project.

Results: A total of 354 referrals were made. 127 referrals failed to adhere to the guidelines and 300 were incomplete. The occurrence of incomplete referrals was higher amongst the noncompliant referrals (n=118; 92.9% of 127), than compliant referrals (n=182; 80.2% of 227) [p=0.001]. A total of 77 GPs were responsible for making all the noncompliant referrals. Further analysis showed that a total of 50, 12, 9, 4 and 2 GPs made 1, 2, 3, 4 and 5 such noncompliant referrals each respectively (mean 1.649 ±1SD 1.048). The high SD suggested a skewed distribution of such referrals. We explored the groups of GPs who made i) 3 or more and ii) 2 or less such referrals (based on reference range of 0.601- 2.697). The subgroup of GPs who made ≥3 noncompliant referrals (n=15, 19.5% of 77) was responsible for making a significantly higher proportion (n=63; 49.6% of 127) of noncompliant referrals, compared to the group which made ≤2 referrals (p<0.00000001).

Conclusions:

Majority of noncompliant referrals are made by a small group of GPs. Our model, based on the standard distribution of data, can be helpful in identifying this group of GPs. Once identified, a selective approach in educating this targeted group of GPs will then be possible.

Reference:
IDENTIFICATION OF A PREDICTIVE LIVER METASTATIC GENE EXPRESSION SIGNATURE IN COLORECTAL CANCER

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Aims / Introduction:
The development of liver metastases is the principal cause of distant treatment failure in colorectal cancer patients. It is difficult to identify accurately patients who will progress to such systemic disease. Metastasis is a step-wise process modulated by numerous genetic and epigenetic changes. DNA microarrays now allow global tumour gene expression profiling in a single experiment. We aimed to identify a characteristic expression signature in primary colorectal cancer that contributes to the development of successful liver metastases. Furthermore, we assessed the predictive value of this metastatic signature on an independent set of primary colorectal cancers.

Methods:
Tumour samples from 3 distinct groups were snap frozen at operation: 28 “non-metastatic” colorectal primary tumours (patients with disease-free survival > 3years), 17 “metastatic” colorectal primary tumours (patients who developed liver metastases) and 31 unrelated colorectal liver metastases. Total RNA was extracted, quantified and quality assessed. Microarray experiments were performed using the Affymetrix HG-U133A GeneChip. Data analyses were performed using GeneSpring 6.0 (Silicon Genetics). The primary tumours were randomly allocated to form a training set (36 samples) and test set (9 samples). Genes common to a three-way comparison of the expression profiles of “non-metastatic” primaries, “metastatic” primaries and colorectal liver metastases constituted a liver metastatic signature. This liver metastatic signature was utilised in an algorithm to predict the development of liver metastases in an independent test set of 9 primary tumours with known clinical outcome.

Results:
102 genes constituting the liver metastatic signature were identified by a three-way comparison of the expression profiles of “non-metastatic” primaries, “metastatic” primaries and colorectal liver metastases. The genes identified are involved in biological processes pivotal to metastasis. Based on this liver metastatic signature, prediction of clinical outcome in an independent test set of 9 primary tumours was correct in 7 cases (78%). Of the remaining 2 cases, the algorithm was unable to make a prediction in one case and the other was incorrectly predicted.

Conclusions:
We have identified a distinct metastatic signature in colorectal cancer that is able to correctly predict the development of liver metastases correctly in over 75% of patients in an independent test set. This signature will form the basis of a predictive neural network algorithm that may improve prognostic stratification of patients for targeted treatment and follow-up.
A tandem repeat polymorphism has been identified in TSER, which contains either double (2R) or triple (3R) repeats of a 28-bp sequence, and is demonstrated to correlate with TS cellular levels so affecting DNA repair activity of normal cells. TSER polymorphism distribution presents a large difference on a racial/ethnic basis and, together with environmental factors and nutritional habits could influence colorectal cancer risk. In this study we examined the effect of TSER polymorphism on the risk of CC in an Italian district. We also investigated whether this polymorphism correlated with age, site of onset and diagnosis stage.

Materials and methods
85 consecutive patients, living in Polesine district and treated for Dukes’ stage B and C primary CC in the local general hospital, were enrolled; blood samples from 290 healthy individuals of the same population origin were also obtained. Genomic DNA was extracted, TSER was amplified by PCR and the polymorphism was revealed by 5% agarose electrophoresis.

Results
Genetic profiles in patients and healthy people were distributed as in the following table:

<table>
<thead>
<tr>
<th></th>
<th>n 2R</th>
<th>2R %</th>
<th>3R 2R</th>
<th>3R %</th>
<th>3R 3R</th>
<th>3R %</th>
<th>2R Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy people</td>
<td>290</td>
<td>21</td>
<td>43</td>
<td>34</td>
<td>34</td>
<td>34</td>
<td></td>
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<tr>
<td>Colon cancer patients</td>
<td>85</td>
<td>21</td>
<td>47</td>
<td>31</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right colon cancer</td>
<td>33</td>
<td>27</td>
<td>30</td>
<td>43</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left colon cancer</td>
<td>52</td>
<td>17</td>
<td>56</td>
<td>25</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 years old</td>
<td>39</td>
<td>15</td>
<td>51</td>
<td>33</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 65 years old</td>
<td>46</td>
<td>26</td>
<td>43</td>
<td>30</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dukes’ stage b</td>
<td>28</td>
<td>11</td>
<td>57</td>
<td>32</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dukes’ stage c</td>
<td>57</td>
<td>21</td>
<td>47</td>
<td>32</td>
<td>47</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistical analysis revealed no significant difference in TSER polymorphism distribution between CC patients and healthy people. No difference appeared between patients grouped in relation to age and stage. On the contrary a significant low heterozygote level was demonstrated in right colon cancer patients in relation to the left (chi square <0.05).

Conclusions
TSER polymorphism distribution in a healthy people sample of a northeastern Italian district was similar to the reported ones in other Caucasian populations (1) and to the colon cancer patients of the same origin. No relation was demonstrated between thymidylate synthase genetic profile and age or stage at the diagnosis. Recently one study in the Hungarian population observed that 2R3R heterozygotes were less susceptible for CRC (2); and another study suggested that 2R2R homozygotes had a reduced risk of CRC in a caucasian-american population (3); in our study no TSER profile seemed to influence colon cancer risk in an Italian population, but primary onset site seemed to be related to different genotypes: the data may support the hypothesis that TS may play a role in colon carcinogenesis, probably modulated by other genetic and environmental factors.

3) Chen Jia et al. Cancer Epidemiology, Biomarkers and Prevention 2003; 12:958