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LOSS OF HETEROZYGOSITY (LOH) AT 18q AND 5q AND SURVIVAL IN DUKES' STAGE B COLORECTAL CANCER.

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We carried out this study to distinguish whether colon tumor progression is linked to the accumulation of mutations and deletions in tumor suppressor genes such as DCC (deleted in colorectal cancer) and APC (adenomatous polyposis coli) whose chromosomal loci are at 18q and 5q respectively. We analyzed 80 sporadic colorectal tumors (B and C stages) for 18q LOH and 5q LOH using the polymorphic DNA markers D18S67 (proximal to DCC gene), D18S58 (distal to DCC gene) and D5S82 (APC gene). DNA from paired tumor and normal tissue at these loci was amplified by PCR. Amplification products were electrophoresed on 6% denaturing polyacrylamide gels. Of a total of 68 (85%) informative cases, 24 (35%) showed allelic losses at either or both of the two 18q chromosomal loci examined. In the locus tested for chromosome 5q, 54 (75%) cases were informative with 22 (41%) showing allelic loss. Median survival time (mst) was 53.5 months in patients with stage B tumors with 18q LOH in comparison with 71 months for those without 18q LOH. Similarly, mst in patients with stage B tumors with 5q LOH was 56 months in contrast to 89 months for those without 5q LOH. No differences in survival were seen for either 18q LOH or 5q LOH in stage C. Our results suggest that LOH at 18q and 5q confer poor survival in stage B colorectal cancer.

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INOPERABLE LIVER METASTASES FROM COLO-RECTAL CANCER TREATED BY SYSTEMIC OR LOCO-REGIONAL CHEMOTHERAPY.

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Eigthy six pts, 46 males, in age from 28 to 75 years, PS = 0-2, with measurable or evaluable unresectable hepatic metastases from colon (53 pts) or rectal (33 pts) carcinoma were assigned to the systemic q 28 Leucovorin (100 mg/m2 i.v.) plus 5-Fluorouracil (375 mg/m2 i.v.) for 5 days, alone (**ARM A;** 27 pts) or in combination with 3×10^6 U ×3 times/week of r-alpha or beta interferon (**ARM B;** 26 pts) or the hepatic arterial bolus of 5-FU (1000 mg/weekly) via Port-A-Cath placed, at exploratory laparatomy, in the gastroduodenal artery with ligation of the rigth gastric artery (**ARM C;** 33 pts). Response was evaluate after 3 cycles of systemic therapy and at 2 months from the beginning the intrahepatic treatment and thereafter quaterly, by means ultrasound and /or CT. **Global response rate** (CR + PR ≥ 50%) was **10.5%** (CR 0%) in the group treated with Leucovorin and 5-FU, **26.0%** (CR 13%) in the group receiving the double modulation of 5-FU with Leucovorin and Interferon and **36.49%** (CR 29.6%) in the regional treated group. The **progression** within three months was 42.8% in ARM A, 26% in B and 13.79% in C. The mean **duration of responses** was 6 (3-14) months in ARM A, 8 (3-20) in ARM B and 10 (3-38) in ARM C. **Overall survival** was 10 (3-14) months, 12.5 (3-36) 13.5 (2-38) in the three arms without statistical diference. NCI g 1-2 **toxicity** was represented by mucositis in the 30% of pts receiving the systemic therapies and flu-like syndrome in the majority of pts submited to Interferon. Grade 1-2 hepatic toxicity (50%), abdominal pain (32%), biliary sclerosis (10%) and catheter displacement (5%) were observed in the intrahepatic treated group. The regional therapy offered higher % in CR and lower in progression within 3 months than the systemic ($p < 0.05$), but doesn't correlate with a significant advantage in survival because of the no systemic effect of hepatic infusion, so that many pts died of extrahepatic metastases. Randomized trials are needed in order to consider the simultaneity or the sequence of the two modalities as a multifactorial approach.

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COLONOSCOPIC CHARACTERISTICS OF SYNCHRONIOUS COLORECTAL CARCINOMAS

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Synchronous colorectal carcinomas (CRC) have incidence from 1.7-12.5% of total CRC cases. The aim of this study was to determine some colonoscopic characteristics of synchronous CRC. In 102 consecutive patients with CRC during colonoscopy, 7 synchronous CRC were diagnosed (6.2%). There were total of 16 CRC, distributed in rectum in 5, sygmoid in 4, descending, transverse and ascending colon in 2, respectively, and in cecum in 1 case. In the same anatomic segment were localised synchronous CRC in 3 (42.8%), but in different segments in 4 (57.2%) of patients. In the adjacent anatomic segments there were synchronous CRC only in 14.2% of patients with synchronous CRC. Barium enema previously performed didn't detect synchronous CRC in 28.5% of patients. Conclusion: Colonoscopy is a method of choice in diagnostics of synchronous CRC.

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PROGNOSTIC FACTORS FOR STOMACH AND COLORECTAL CANCER. THE ANALYSIS FROM POPULATION - BASED CANCER REGISTRY

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Survival and prognostic factors of gastric and colorectal cancer were studied using regression models of the proportional hazard type for relative survival rates obtained from population - based Cracow Cancer Registry. The material consisted of 338 stomach cancer diagnosed 1987 - 89 and 1178 cases of colorectal cancer diagnosed 1978 - 89. The following factors for both sites were examined as potencially prognostic : age, sex, subsite, histology, stage, methods, and place of treatment. The 5- year relative survival rate for male stomach cancer patients was 7.3% and for female 15.6% (the "Eurocare" European mean respectively 14.1% and 18.1%). Basing on multivariate analysis, three main factors are worsening prognosis of all stomach cancer patients registered in Cracow : sex- male, unresectability and only systematic treatment. The risk of death among patients with resected stomach cancer /106 /338 e.g. 31.4%/ decreased with decreasing numbers of positive lymph nodes, radicality of resection and treatment at university hospital. The 5 - year relative survival rate for male colon cancer was 18.0% and rectum 11.6 %. The respective percentages for Cracow females were 19.6% and 24.5% (the "Eurocare" European mean respectively 41.1%, 40.4%, 34.4% and 38.1%). The prognostic factors for colon and rectum cancer were almost identical. The risk of death from colorectal cancer shown in multivariate analysis was increased for all registered patients with nodal and distant metastases, no or palliative surgery only and lack of adjuvant chemotherapy. The poor prognostic factors among resected cancer patients (490/1178 e.g. 41.6%) was also the effect of noded and distant metesteses and lack of adjuvant chemotherapy. Moreover for colon cancer patients the prognosis was worsening with unplanned character of surgery and for rectal cancer with non - radical surgery. The adjuvant chemotherapy was found to be important prognostic factors in colorectal cancer.

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FAMILIARITY AND COUNSELLING IN HEREDITARY COLORECTAL CANCER

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The 25% of colorectal cancer (CRC) are correlated with a familiarity. The 5% of familial colorectal cancer are HNPCC and the 1% are FAP.
We present two research projects.
The first one is on a prevalence of colorectal adenomas in subjects with at list two first grade relatives affected by CRC. These subjects aged 55-64 yrs are detected from questionnaires filled up for Trial "once only sigmoidoscopy". A colonscopy will be proposed instead of rectosigmoidoscopy. The data will be correlated with those of a standard CRC risk control group.
The second project is on familiarity and couselling of less than 55 yrs colorectal cancer patients. The aim is to control families with a high risk of hereditary CRC. General Practitioners contact probands and build a nuclear genealogic tree. In case of doubt or clear HNPCC, the genealogic tree will be expanded by specialized group. A personalized programme of sourveillance and follow-up will be provided to the probands and their family.

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EFFECT OF PREOPERATIVE HYPERTHERMIA WITH RADIO-CHEMO-THERAPY ON RESECTABILITY OF LOCALLY ADVANCED RECTAL CANCER. A PHASE II CLINICAL TRIAL.

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In locally advanced rectal cancer pre-operative radio-chemotherapy can increase resectability and may provide local control in unresectable cases, but response rates are still unsatisfactory. In a phase II study we investigated whether regional hyperthermia in combination with preoperative radio-chemo-therapy (HRCT) is feasible and will result in downstaging as well as improve resectability.
18 patients (pts) with primary non resectable rectal cancer entered the trial. Initial tumor stage was assessed by endorectal ultrasound (EU) and computed tomography (CT). Pre-operative treatment consisted of 5-FU (300-500 mg/m^2, dose escalation) and leucovorin (50mg) on days 1-5 and 22-28. Regional hyperthermia (RHT) was carried out using the SIGMA 60 applicator BSD 2000 once a week prior to radiotherapy. Radiotherapy was applied in prone position using a belly board, three-field technique, standard blocks, 5x1,8 Gy up to 45 Gy. Re-staging was carried out using EU and CT. Four weeks after HRCT, surgery was performed.
Treatment-related adverse events were observed in 3 pts with grade III gastrointestinal toxicity requiring a short hospitalisation because of dehydration and /or abdominal discomfort. One patient developed grade IV toxicity with haemorrhagic enterocolitis and treatment was stopped. After treatment 14/18 pts (78%) proved resectable (R0 n=11/R2 n=3; Abdomino-perineal resection n=5 and sphincter saving surgery n=9). Nonresectable disease after explorative laparotomy was found in 4/18 pts. In 5 of 18 pts (27%) postoperative complications were observed with anastomotic leakage (n=2), and perineal abscess (n=3). A complete histological remission (pCR) was confirmed in 2/18 pts (11%). In median follow up of 13 months (range 3-21 months) all but one R0-resected pts (n=11) had no evidence of tumor recurrence. The patients with non-resectable carcinomas (n=4) had a progression free survival with the range of 5-28 months.
Preoperative HRCT is feasible and effective in primary non resectable rectal cancer resulting in a resectability rate of 78% with pCR in 11% of the patients. Treatment related toxicity and postoperative complication-rate are acceptable. Our results suggest that RHT in addition to radio-chemotherapy can improve treatment results in rectal cancer. Therefore a randomized phase III-study has been initiated to validate the effects of HRCT in locally advanced non resectable rectal cancer.