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AIDS and Cancer

PP 1

CUMULATIVE INCIDENCE (CI) OF NHL IN HIV+ PATIENTS: AN ITALIAN EXPERIENCE.

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Incidence of NHL among HIV+ patients is higher than among the general population. We observed 1819 HIV+ subjects, mainly IVDU (62%) from 1985 to date: 28% developed AIDS and 1.3% had NHL. In 7 patients NHL developed after a mean time of 16 months from diagnosis of AIDS. CI of NHL for HIV+ patients and for the general population were 9.60% and 2.27% respectively. Relative risk for having malignant lymphoproliferative diseases (MLD) in patients who sexually acquired HIV infection was 3.80 (95%CI=1.75 -8.24). A higher incidence of EBV and CMV infection was observed in the group that acquired HIV by sexual intercourse. Conclusion: NHL is more frequent among HIV+ subjects than general population and sexual trasmission seems to be a major risk factor possibly due to higher prevalence of sexually trasmitted lymphotropic viruses. Further investigations are warranted.

OP 3

HIV LOCALIZATION IN HPV-RELATED, HIGH GRADE SIL OF THE CERVIX IN WOMEN WITH HIV INFECTION.

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HIV infection influences the clinical course of HPV- related genital lesions. To evaluate a possible mechanism of HIV and HPV interaction we have identified the cell types in the cervix which harbour HIV with an highly sensitive technique. 39 paraffin embedded, cervical conization specimens with high grade SILs occurring in HIV infected women were studied. From selected intra-epithelial HPV positive (ISH confirmed) not ulcerated specimens we obtained serial , 4-5 μ thick sections that were stained with H&E, anti S100 protein and CD4. The presence of intramucosal Langerhans' or dendritic cells and CD4+ cells was registered. The uncovered slides were examined by an inverted microscope; full thickness specimens of mucosa were microdissected from the underlying myometrium, gently removed and used for PCR analysis (group A). The same, not microdissected, whole sections were used for PCR too (group B) . The quality of DNA was checked by HLA-DQα amplification; then a nested PCR for HIV proviral DNA, giving a product of 114 bp, was performed. 5/39 (12.8%) specimens of the group B were positive whereas HIV was never dectected in microdissected mucosae with or without Langerhans' or CD4 cells. In conclusion our study shows that there is no overlap in the distribution of HPV and HIV; the lack of infected Langerhans'/dendritic cells could indicate a former migration to the proximal lymphnodes of the infected cells; the absence of HIV proviral DNA even in the SILs infiltrated by CD4 cells could be due to a low number of CD4 infected cells in non ulcerated mucous membrane.

PP 2

RISK AND EVOLUTION OF SILs IN HIV-POSITIVE WOMEN: INTERACTION WITH CERVICAL HPV INFECTION.

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From 14 Italian infectious disease and gynaecological Centres, 266 HIV-positive and 193 HIV-negative women with the same risk factors were enrolled and underwent: a) 2 cervical smears, one for Papanicolaou testing and the other for molecular biology testing (HPV-DNA-PCR) and viral typing; b)gynaecological examination; c) colposcopy and directed biopsy/ies if necessary.
Of the 266 HIV+ women, 78 (29%) had cytological smears showing SILs of different degree, while only 20 (10%) of the 193 HIV- women showed SILs of various degree. A koilocyte count was performed on the cervical smears showing HPV-changes using a standard method. The koilocyte count seems to suggest that HIV infection tends to modify the effect of HPV on the cervical cells, increasing the risk of SILs and a widespread koilocytosis.

PP 4

AIDS-RELATED MALIGNANCIES

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Background: An increased risk of malignancies (M) is associated with HIV infection and its cellular immunodeficiency and as a result of this relationship some M were included in the diagnosis of AIDS. As survival of HIV-infected patients (pts) increases it is expected that M become a major problem. Moreover, the management of these pts is difficult and compromised by poor bone marrow reserve, intercurrent opportunistic infections, toxicity to antineoplastic agents and further immunosupression. **Methods:** Retrospective study of the clinical records of 1140 HIV-infected pts observed between 1985-98. Cancer diagnosis was histological and immunocytochemical. Epidemiological, demographic and clinical characteristics were evaluated. Kaposi sarcoma was excluded from this study. **Results:** M were found in 19 pts. Eleven (58%) were male; the median age was 35 years (range: 20-65). Thirteen (68%) M were haematological, three gynaecological, two gastrointestinal and one pulmonary. **Haematologic M.:** Eight (42%) pts had NHL: two primary CNS lymphomas (L), two gastric, two disseminated, one nasopharynx and one Burkitt L. The diagnosis was made at autopsy in four pts. Seven pts were HIV1 infected and one HIV2; four were IDU's, three heterosexuals and one transfused. Cancer was the AIDS-defining illness in six pts. The mean CD4+ T-cell counts was 186±102/cmm. All pts were submitted to chemotherapy (CT). Five (83%) pts died, one to 10 months after the diagnosis. Hodgkin disease (stage IVB) was diagnosed in four (21%) asymptomatic HIV1 pts: two IDU's and two heterosexuals. Their CD4+ T-cell counts were 170±169/cmm. All pts died 8-12 months after the diagnosis. One HIV1 heterosexual male had multiple mieloma; he received CT and radiotherapy (RT) and died after 18 months. **Gynaecologic M.:** Cervical cancer (two *in situ*, one stage IIB) was diagnosed by screening in two heterosexuals and in one IDU. All were HIV1 infected; two were asymptomatic and one had AIDS. Their CD4+ T-cell counts were 988, 90 and 18/cmm. Papilloma and/or Herpes virus cervical infection was seen in all pts. Two were cured by surgery and one, treated with RT, died after two months. **Gastrointestinal M.:** One gastric and one colic adenocarcinomas were found in two HIV2 infected males with 278 and 348 CD4+ T-cell counts. Both died, one and three months after the diagnosis. **Lung M.:** A pulmonary cistadenocarcinoma was diagnosed during surgery in one HIV2 heterosexual male with 983 CD4+ T-cell count. **Conclusions:** We emphasise the predominance of haematologic malignancies, more aggressive course and higher mortality rate. Screening of the cervical cancer in HIV infected women is highly recommended.

Breast Cancer

PP 5

HYALURONAN IN BREAST LESIONS; EXPRESSION AND PROGNOSTIC VALUE

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Background: Hyaluronan (HA) is an extracellular matrix molecule. Its expression is increased when movement of cells is needed e.g. during morphogenesis and in healing wounds. In quantitative analysis the amount of HA has been elevated also in various malignancies. This study examines HA expression in 143 human breast cancer patients.

Method: The paraffin sections of 143 breast carcinoma cases were stained for HA by using the biotinylated hyaluronan-binding region and link protein complex (bHABC) of cartilage proteoglycan as a specific probe.

Results: HA expression was observed in the extracellular matrix around carcinoma cells as well as in carcinoma cells. The intensity of HA staining correlated to axillary lymph node positivity and poor outcome of breast cancer patients.

Conclusion: HA expression is associated with the progression of malignancy.

OP 6

NATURAL HISTORY OF BREAST CANCER: ANNUAL HAZARD OF RECURRENCE AFTER SURGERY.

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Although a percentage of patients (pts) with breast cancer (BC) became long term survival after initial treatment, natural history of BC includes a continuous incidence of recurrence over time. To determine the annual hazard ratio (HR) of recurrence after initial surgery in BC pts and to evaluate the influence of prognostic factors (PF) in the pattern of recurrence, we studied a group of 1724 BC pts treated in a single institution between February 1982 and July 1998. 1474 pts underwent surgery as initial treatment. Median age was 57 years (21-99) and staging included: stage I: 270 (18%); II: 997 (67%); III-A : 83 (6%); III-B: 124 (9%). Involved nodes: 0: 683 (46%), 1-3: 384 (26%), 4-9: 256 (17%), >=10: 151 (11%). Hormonal receptor status: ER +: 918 (63%); ER-: 556 (37%); PGR+: 754 (51%), PGR-: 720 (49%). Tumor size: T1: 424 (29%), T2: 801 (55%), T3: 122 (8%), T4: 127 (8%). Histologic grade: I:139 (9%), II: 328 (22%), III: 118 (8%), unknown: 889 (61%). Conservative surgery was performed in 173 (12%). Adjuvant chemotherapy (CT) was administered in 363 pts and 58 pts were included in high dose CT and PBSC transplantation programs; 605 pts received CT and hormonal therapy (HT); 350 received HT alone, and 156 pts received no adjuvant treatment. With a median follow-up of 5.8 years 490 pts had presented a recurrence of their disease, with an average annual ratio of 5.6 %. The annual HR of recurrence was significantly higher (11% per year) during the second to third year after surgery and then remained stable between the third and eighth year of follow up (5 % per year). After the eighth year the HR progresively decreased but did not reached 0 % at any time. When we analyzed the HR of recurrences according to prognostic factors, pts with poor PF (involved node ≥ 10, hormonal receptor negative, tumor size T3-T4, age ≤ 39) showed a significantly higher recurrence rate, while menopausal status did not have any influence on the recurrence rate. The pattern of recurrences was similar independently of PF. In conclusion, annual HR of recurrence in patients with BC peaks between the second and third years and then remains stable up to the eigth year of follow up. Although the incidence of recurrence is higher for pts with unfavourable PF, the pattern of recurrences is similar in the different prognostic groups. A better understanding of the natural history of BC will allow us to design new strategies to improve long term survival.

OP 7

COMPARATIVE ASSESSMENT BIOPATHOLOGICAL MARKERS IN PRIMARY BREAST CANCER AND LYMPH NODE METASTASES

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During tumour progression and metastasis an accumulation of new genetic alterations is observed. In a series of 22 patients with node-positive breast cancer we analysed with indirect Biotin-StreptAvidin technique the expression of Ki 67 (MIB-1), p53 (DO-1), c-erb B2, HCAM (CD44) (BioGenex Laboratories, San Ramon, CA, kit dilut.) and bcl-2 (124) (DAKO, 1:40 dilut.) in primary tumour and in metastatic lymph node. In 7 cases we performed also a quantitative DNA analysis. Image quantitative analysis of immunohistochemical reaction was used. The proliferative activity in primary IDC (NOS) was between 7,55% for Grade I and 33,57% Grade III, whereas in lymph node metastases the mean Ki 67 values were between 11,29% and 24,625%. Invasive lobular carcinomas had proliferative activity 12,53% and 6,03% in metastasis. In primary tumour we detected p53 positive immunoreactivity in 31,81% of the cases, whereas in metastases the percentage of p53 positivity was 40,91. 22,72% from primary breast cancers were c-erb B2 positive. In lymph node metastases only in 9,1% of cases were positive. Expression of HCAM was detected in 63,64% of all primary tumours, but only 22,72% of metastases were positive. 95,45% of primary tumours were bcl-2 positive. The mean value of bcl-2 positive cells was 78,69%. Bcl-2 positivity was observed in 100% of metastases, but the quantitative bcl-2 expression was 68,73%. The results from this study show that during tumour progression and metastasis neoplastic cells accumulate new genetic alterations, but also lose specific membrane proteins. It can be assumed that tumour cells dedifferentiate during later stages of carcinogenesis and acquire „specific" features determining their aggressive potential.

OP 8

SENTINEL NODE LYMPHADENECTOMY IN PATIENTS WITH EARLY AND ADVANCED BREAST CANCER

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The axillary lymph node status plays a crucial role in the current management of breast cancer patients. As described for melanoma patients the sentinel node (S. N.) concept has been introduced in clinical trials of patients with breast cancer to determine the need for axillary dissection. We evaluated the predictive value of sentinel lymphadenectomy in our breast cancer patients.

From 11/95 to 12/97 114 patients with breast cancer underwent a sentinel node mapping followed by axillary dissection. Sentinel node detection was performed using preoperative lymphscintigraphy with Tc-99m-labelled nanocoll and intraoperative detection with a γ-probe. Tumor size ranged from pT1 (n=57) to pT2 (n=39), pT3 (n=10) and pT4 (n=8). In 89 of the 114 patients (78%) a sentinel node was detectable and subsequently a sentinel lymphadenectomy performed. Postoperative histological findings revealed that 32 of the 89 detected sentinel nodes showed metastasis (36%), 48 were tumorfree (54%) without subsequent tumor detection in the axillary tissue, thus representing the axillary nodal status correctly. In the remaining 9 (10%) patients the S. N. was free of tumor, but metastasis was found in the axillary tissue, giving rise to an overall detection rate of 82% (32/39) and an overall predictive value of 90%. While pT1-tumors (n=57) showed a detection rate of 94% and a predictive value of 98%, both parameters decreased to 80% (8/10) resp. 96% in pT2-tumors (n=39) and to 60% resp. 64% in pT3/T4-tumors (n=18).

We conclude that in patients with T1- and T2-tumors the sentinel lymphadenectomy is an accurate marker for axillary lymph node metastasis and may help to avoid unnecessary axillary dissection. However, for T3- and T4-tumors the concept can not be recommended so far.

PP 9

Molecular forms of prostate-specific antigen in the serum of women with benign and malignant breast diseases

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Using a highly sensitive immunofluorometric procedure, we measured the total prostate-specific antigen (PSA) concentration in 632 sera obtained from female blood donors and women with idiopathic hirsutism, breast cancer or benign breast diseases. A total of 50 sera with total PSA > 15 ng l(-1) were fractionated by high-performance liquid chromatography (HPLC) in order to resolve the two immunoreactive molecular forms, i.e. free PSA (approximately 30 kDa) and PSA bound to alpha1-antichymotrypsin (PSA-ACT, 100 kDa). We found that breast cancer patients have presurgical serum total PSA levels similar to those of blood donors. Total serum PSA concentration decreases with age in women with idiopathic hirsutism, in cancer patients and in patients with benign breast diseases. The major molecular form of PSA in the serum of all normal and hirsute women (n = 15) is PSA bound to the proteinase inhibitor alpha1-antichymotrypsin. The major molecular form in 44% of presurgical cancer patient sera is free PSA. A total of 58% of benign breast disease patients also have in their serum mainly free PSA. We conclude that about half the patients with breast cancer or benign breast diseases have free PSA as the major molecular form in their serum, whereas patients without breast pathologies have PSA bound to alpha1-antichymotrypsin as the major molecular form. The ratio of PSA/PSA-ACT may have value as a simple biochemical test for diagnosis of breast pathologies including breast cancer.

PP 11

ADJUVANT SEQUENTIAL CHEMOTHERAPY IN HIGH RISK PREMENOPAUSAL BREAST CANCER PATIENTS. PRELIMINARY RESULTS.

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Between May 95 and July 97, 48 premenopausal breast cancer patients pT 1-3 with > 3 involved lymph nodes after radical surgery have been treated with sequential adjuvant chemotherapy. Inclusion criteria include ECOG performance status 0-2 and adequate hemotologic and hepatic function. The treatment consisted of 4 cycles of epirubicin 100 mg/m2 iv d 1 and 8) every 28 days. All pts are alive. Metastatic disease has recognised in 8 pts.
Totaly 357 cycles of chemotherapy has been given. 82 cycles (22,9%) has been modyfied (dose reduction or posponed). Leucopenia grade 1 and 2 occured in 26 pts (54,2%). There was no leucopenia > grade 2.
No toxic death has been raported. The mean relative dose intensity was 0,9 for farmorubicin and 0,89 for CMF. In conclusion our preliminary results suggest that early toxicity of sequential epirubicin and CMF is acceptable.

PP 13

"BEING PREJUDICED DOESN'T HELP, PREVENTING DOES". An Health Promotion (HP) intervention.
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In 1994 Calabria deliberated an HP intervention project addressed to the Local Health Companies The ODCS had joined the Project presenting a plan of search-intervention of HP prevention of breast can cer(BC).Aim:reduction of mortality.Motives:inadequate knowledge of the incidence/ mortality by BC, inadequate degree of acquaintance of present therapeutic opportunities;Difficulties of the socio-econo mic conditions in the area and its inhabitans have an widespread fear to wards a special ized check-up. Target:CS and its hinterland(about 250,000 inhabitants)Duration:about 2 yrs whose articulation will be subdivided in 4 phases:a)analysis of starting-point:statistical data;b)planning;c)sensitization; d)eval uation.a)statistic data have been collected and analysed from the information ISTAT and from a direct evaluation of death certifications(1983-1990)and epidemiological-statistic valutations; b+c)After havi ng defined and presented the project we have realized(special specifications of contract)for furniture and service supplyng.Then the operational strategies of the project have been analyzed in the many meetings had with the representatives of the firms which have been adjudged. The following items have been realized:1)a computerized clinical data file prearranged to work in a network for the health centres;2)a logo where the seriousness of the problem as well as its possible solution have been put in the right evidence with a very simple graph representing a sinus inside a concentric target; 3)4,000 lea flets(70x100)four colours process put up in the most important shops, chemist's shops, surgeries banks ,coaches and other places in almost the whole hinterland of the town in different times and periods;4)a depliant,produced in 20,000 copies and distributed during our meetings and during the itinerant-desks(crowded streets,fairs,conferences etc.),characterized the scientific-clinic all aspects and proposed a questionnaire on women who practice prevention or don't practice it;5)Radio and TV campaign realized with an original spot lasting 30'',made together with FONCAM, which has been broad cast during the whole campaign;6)Conferences and meetings(38 in all)with the dual aim of forming a group of educators as well as of directly reaching the female population, have been held and followed by many typical professional exponents(Doctors,Sociologists,Family practioners,Psychologists)and "not typical" exponents(artists,cultured men, politicians and managers)coming from qualified scien tific Institutes known in the whole nation;7)Other particular enterprises have been realized in Mo thers and Woman's Day.d)A primary evaluation of the results has shown an increase in mammograp hic tests made by women in CS public and private structures.Moreover through a first analysis of the questionnaire the 1,608 women interviewed show little know ledge about the operating structures in this sector and very few informations on how joining them.

OP 10

MORPHOPATHOLOGIC ALTERATIONS IN LOCALLY ADVANCED BREAST CANCER TREATED WITH PREOPERATIVE CHEMOTHERAPY.

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We examined the morphopathologic alterations following neoadjuvant chemotherapy in 40 patients with locally advanced breast cancer. All patients underwent large core breast biopsy to obtain histologic and immunophenotypic diagnosis, then received 150 mg/m2 epidoxorubicin every 2 weeks for 3 cycles, followed by modified radical mastectomy. Surgical specimens were compared with core biopsy specimens. The aim of the study was to compare morphopathoical changes seen between core biopsy specimens (pretherapy) and surgical speciment(post neoadjuvant chemotherapy). By core biopsy we obtained biological data (ER; PgR; Ki-67, p53, c-erb-B2) of the lesion. By surgical specimens we obtained the following macroscopic patterns: a) nodule 14 cases, b) dysplasia 18 cases, c) dystrophy 8 cases. No CR were evidenced. Microscopic exam of the surgical specimens demonstrated the following patterns: solid-trabecular or pseudoalveolar structure in nodules, in the other 2 macroscopic patterns (dysplasia and dystrophy) there were small neoplastic cells (isolated, in small groups or diffuse), foci of ductal carcinoma in situ, areas of necrosis, stromal dysplasia, peritumoral lymphocytic elements; large cells with abundant eosinophilic cytoplasm and with vesciculous nuclei and small isolated cells with pycnotic nuclei. Axillary lymph nodes with metastases showed areas of central necrosis and embolic carcinomatosus, lymph nodes without metastases revealed diffuse sinus histocytosis and/or lymphocytic depletion. Comparing macro- and microscopic surgical specimens, we observed 10 NR and 4 PR in the macroscopic pattern nodule, 11 CR and 7 PR in the cases with dysplasia, and 8 CR in the cases with dystrophy. Immunophenotyping of carcinoma after neoadjuvant therapy could provide further insight into the biology of clone resistance to chemotherapy.

OP 12

PREDICTION OF RESPONSE TO PRIMARY CHEMOTHERAPY (PCT) FOR OPERABLE BREAST CANCER.

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Identification of predictors of response to PCT might improve treatment results. We investigated the expression of estrogen and progesterone receptors, Ki-67, bcl-2, c-erbB-2, and p53 in patients with operable breast cancer who subsequently underwent PCT. Treatments: Group A (20 pts): adriamycin 60 mg/m2 and cyclophosphamide 600 mg/m2 day 1; Group B (23 pts): 5-fluororuracil 350 mg/m2 day 1,2,3, folinic acid 100 mg/m2 day 1,2,3 and vinorelbine 20 mg/m2 day 1 and 3; courses were given every 21 days for 3 times. In case of objective partial remission, patients were offered additional 3 courses which, for Group A only was followed by radiotherapy (50 Gy plus 10 gy boost). Surgery was performed in all patients. Pathology material from 43 patients (median age, 50 years; range, 30-67; performance status, 0-1; 37 T_2, 6 T_3) was evaluable. The overall response rate was 58% (95% confidence interval, 42-73%). All 8 patients with p53-positive tumors and only 17 of 35 with p53-negative tumors responded (p=0.01). Thirteen of 18 patients with high Ki-67 (>20%) had a response and 12 of 25 patients in the low Ki-67 group responded (72 % vs. 48%; p=0.04). The Ki-67 expression decreased substantially (≥50%) in 14 patients during treatment. Eleven of 14 patients responded and only 12 of 29 patients with a lower decrease responded (p=0.02). No significant correlation was detected between response and other baseline features. In conclusion, these results indicate that tumors with baseline elevated Ki-67 expression, and positive for p53 had a significantly higher response to primary chemotherapy. Moreover, our data suggest that decrease of Ki-67 during preoperative treatment may predict response. Prospective investigations using these features might be useful for tailoring primary and post-surgical systemic treatments.

PP 14

EXPERIENCE FROM A BREAST DIAGNOSTIC UNIT IN BERGAMO

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Data of the activity of a Breast Diagnostic Unit in the city of Bergamo are reported.
From october 1995 to august 1997 7,895 women were clinically examined, 11,758 mammographies, 3,724 breast ultrasounds and 2,294 fine needle aspirations were performed. Diagnosed carcinomas were 283, of which 160 (56.5%) clinical stage T1, 100 (35.3%) T2, 5 (1.7%) T3 and 18 (6.3%) T4. Ages of the patients ranged between 31 and 80. Our experience shows how a well organized breast unit together with FONCAM (Forza Operativa Nazionale sul Cancro Mammario) diagnostic guidelines application can provide a reliable way of breast cancer early detection.

PP 15

ADJUVANT ANTIESTROGEN THERAPY WITH TAMOXIFEN (NOLVADEX) IN EARLY BREAST CANCER (EBC)

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The aim of the study was to evaluate therapeutic effect and side effects of antiestrogen Tamoxifen (Nolvadex) in women with EBC. 103 patients after radical mastectomy, ER (+) were treated with Nolvadex (20 mg dayly) as a part of adjuvant treatment modality between September 1993 and September 1997. 12% of observed EBC patients had progression of disease. In 6% of all patients treatment was stopped because of "big side effects". Small side effects (in 28%) were more common in premenopausal women.
Our data suggest that, antiestrogen - Nolvadex as a part of adjuvant treatment in EBC has a good therapeutic effect and low level of side effects.

OP 16

NO EVIDENCE OF GERMLINE MUTATIONS FOUND IN THE GENE PTEN/MMAC1 IN FAMILIES WITH HEREDITARY BREAST CANCER.

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Objective: We search for germline mutations of candidate genes in families with hereditary breast carcinoma which show no linkage to the known tumor suppressor genes BRCA1 and BRCA2.
Materials and Methods: During the analysis of MDC families with 2-4 cases of breast cancer by a combination of linkage and mutation screening some families show no linkage to the known breast cancer tumor suppressor genes BRCA1 and BRCA2. By analyzing normal and tumor tissue from 11 of our families we found 27% (3/11) cases of LOH (loss of heterozygosity) in the 10q23 region. We decided to analyze the 10q23 region in more detail, since it contains the tumor suppressor gene PTEN/MMAC1 related to breast cancer in the hereditary Cowden disease. In addition we searched for mutations by direct sequencing of the 9 coding exons of PTEN/MMAC1 in 10 families with hereditary breast cancer (including 5 without linkage to BRCA1 and BRCA2 and the 3 which showed LOH at 10q23).
Results: We found two polymorphisms in intron 1 and intron 8, but no relevant mutations which could suggest a relation to tumorigenesis.
Conclusion: Except in the rare hereditary Cowden disease, PTEN/MMAC1 does not seem to play an important role in the genesis of hereditary breast cancer. Further investigations have to be made to elucidate its role completely.

PP 17

ROLE OF FAC WITH ANTI-ANGIOGENIC AGENTS IN METASTATIC BREAST CANCER INVOLVING LIVER

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Role of chemotherapy in metastatic breast cancer is palliative. We tested addition of anti-angiogenic agents to anthracycline based chemotherapy combination i.e. FAC.
Material and methods: Patients with bi-dimensionally measurable, metastatic breast cancer involving liver (with or without other sites) at first presentation were only included in the study. Other eligibility criteria were as follows: age > 18 and < 80 years, performance status of 0-2, normal serum calcium, absolute neutrophil count >1,5 x 10^9N and platelet count >100 x 10^9N.
All patients were treated with FAC (5-Fluorouracil 500 mg/m^2, Doxorubicin 50mg/m^2) chemotherapy every 3 weeks, alongwith anti-angiogenic agents (Doxycycline 100 mg PO qD and Galoitriol 0.5 mg PO qD) from day 1 and continued till disease progression. FAC was continued till maximum response was achieved.
Results: Total of 17 patients were entered into study. Eleven (64.7%) patients were premenopausal and 6 (35.3%) were post-mehopausal. Twelve patients had bone metastasis, 7 had lung metastasis and 5 had soft tissue metastasis. In 3 (17.6%) liver was the only site of metastasis, whereas 6 (35.3%) had 2 sites and 8 (47.1%) had >2 sites of metastasis. Chemotherapy and anti-angiogenic agents were well tolerated. Only 4 (29.6%) patients developed febrile neutropenia, 3 (17.6%) had grade III GI toxicity, 3 (17.6%) had grade III mucositis. With no complete responders, 10 (59%) patients achieved partial response. Three (17.6%) had stable disease and only 4 (23.5%) patients had progressive disease. Median time to disease progression in all patients was 6,3 months (range 0,20 to 13,7 months) and in responders, it was 8,4 months (range 1,8 to 13,7 months).
Conclusion: FAC chemotherapy with anti-angiogenic agents, is a well tolerated, effective modally in delaying disease progression in patients with metastatic breast cancer involving liver. More studies are needed to confirm these results.

PP 18

THE METALLOTHIONEINS' LEVEL IN THE CELL FRACTIONS OBTAINED FROM THE BREAST CANCER TISSUES

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The metallothioneins' level in the cytosol, mitochondrial and nucleus fractions from the breast cancer tissues and from the non-neoplasmatic breast tissues (masthopathic breast tissues) was indicated in this work.

The samples of the each tissue were watered in the physiological solution and then homogenized in 4-times volume of 10 mM Tris-HCl buffer, pH 7.4 in the glass homogenizer with tephlon pestle. The tissues homogenates were centrifuged for the reason of receive particular fractions. The level of the metallothioneins was determinated by the cadmium-hemoglobin affinity assay (Eaton and Cherian), using the cadmium isotope from Du Pont.

The higher level of the metallothioneins was ascertained in the cytosol and nucleus fractions obtained from the breast cancer tissues.

PP 19

PACLITAXEL PLUS VINORELBINE IN METASTATIC BREAST CANCER PATIENTS WITH CONTRAINDICATIONS TO RECEIVE ANTHRACYCLINES: PRELIMINARY RESULTS OF A PHASE II STUDY.

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Thirty-three metastatic breast cancer patients (pts) with prior chemotherapy (CT) (adjuvant alone 8 pt, CT for metastatic disease alone 14 pt, CT for both 11 both) received paclitaxel 135mg/m2 over 1 hr followed by vinorelbine 30mg/m2 over 10 minutes on day 1 every 3 weeks. The median age of the patients was 51 years (range 27-28). All patients had contraindications to receive anthracycline (ANT) therapy (primary ANT resistance 10 pt, ANT dose reaching the maximum recommended dose and/or myocardiopathy 23 pt). Twenty-eight pt had previously received ANT, while the remaining 5 pt had received prior CMF. The combination of paclitaxel plus vinorelbine was given as first line CT for metastatic disease to 9 pt and for second or third line to the remaining 24 pt. The mean number of metastatic sites was 2 (range 1-5). Twenty-two pt had visceral involvemet.

Overall, 3 complete and 13 partial responses were observed among the 33 pt (objective response rate: 16/33, 48.5%). The response rate for first line CT was 67% (6/9 pt), compared to 42% (10/24 pt) as second or third line CT. Primary ANT resistant pt showed a response rate of 60% (6/10 pt), while the remaining pt had a response rate of 43.5% (10/23 pt).

The main toxicities (CTC clasification) were grade 2 alopecia (92%), grade 3-4 neutropenia (28%), neutropenic fever (16%), grade 1-2 peripheral neuropathy (44%), arthralgias-myalgias (32%), and hypersensitivity reactions (8%). Phlebitis was a significant clinical problem in pt receiving the drugs through a peripheral vein.

One-day paclitaxel plus vinorelbine is safe, easy to administer and active in metastatic breast cancer pt with contraindications to receive ANT. The response rate was not apparently affected by the refractoriness to ANT.

PP 20

PHASE III STUDY: ADJUVANT CHEMOTHERAPY VERSUS ADJUVANT RADIOTHERAPY PLUS CHEMOTHERAPY IN WOMEN WITH NODE-POSITIVE BREAST CANCER. A RETROSPECTIVE ANALYSIS OF 18 YEARS.

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The aim of this study was to compare the results of adjuvant chemotherapy versus adjuvant radiotherapy plus chemotherapy in patients with operable breast cancer with positive axillary nodes. This phase III study was held at Centro Regional de Oncologia de Coimbra between January 1980 and April 1983 and included 112 patients. After modified radical mastectomy 57 patients were randomized to receive Adriamycin 45mg/m^2/i.v. + Cyclophosphamide 600mg/m^2/i.v. day 1 and 28 (6-11 cycles) (arm A) and 55 to radiotherapy (dose between 36 and 45 Gy) plus the same scheme of chemotherapy (arm B). Patients average age, menopausal status and clinical TNM staging presented no statistical differences in both arms. Cardiac toxicity was higher in arm B (23,6%) than in arm A (19,2%) (p> 0,05). Overall survival was similar in both arms (arm A=35,1%; arm B=32,7%). Recurrence rate was 57,9% (33/57) in arm A and 43,6% (24/55) in arm B; recurrence time lapse presented no statistical difference in arm A (38,6 months) when compared with arm B (44,4 months).

PP 21

DOSE INTENSITY OF STANDARD ADJUVANT CMF WITH G-CSF FOR PREMENOPAUSAL NODE-POSITIVE BREAST CANCER PATIENTS.

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As the total dose and dose intensity of chemotherapy is important for treatment outcome, this was studied for standard oral adjuvant CMF (cyclophosphamide, methotrexate, 5-fluorouracil) in premenopausal patients with node-positive breast cancer, using granulocyte-colony stimulating factor (G-CSF).
Treatment consisted of CMF and locoregional radiotherapy on indication. The indication to give G-CSF was insufficient leukocyte count recovery, judged at the start of each cycle.
Fifty-one patients required no G-CSF, 50 patients received G-CSF on indication. Twenty-two patients received no G-CSF support despite insufficient leukocyte recovery ("control"). Following G-CSF, leukocyte recovery was adequate in 83% of the chemotherapy cycles. The percentage of the patients who had a dose intensity $\geq$ 85% was 90% in the group who required no G-CSF, 74% in the group who did receive G-CSF versus 45% in the "control" group ($p<0.05$).
In conclusion an adequate leukocyte recovery after G-CSF was found in 83% of all chemotherapy cycles. The dose intensity of the G-CSF receiving group was higher compared to controls.

PP 22

INCORPORATION OF THE AMINO ACIDS INTO PROTEINS IN THE MITOCHONDRIA OBTAINED FROM BREAST CANCER TISSUE

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The mitochondria were prepared from the breast cancer tissues and non-neoplasmatic tissues (masthopathic breast tissues). The pure whole mitochondria were incubated in mixture including radioactive amino acids (glutaminic acid, glycine, asparaginic acid, lysine, isoleucine). The incorporation of amino acids into protein and aminoacylation of tRNA were determined.
Although, the cancerous mitochondria possesed endogenic higher ability of aminoacylation of tRNA but have very lower ability of incorporation of the amino acids into protein in comparison with the control tissue. It was observed that cancerous mitochondria differ from mitochondria of the control tissue.

OP 23

DOSE-INTENSIVE NEOADJUVANT CHEMOTHERAPY WITH GM-CSF IN LOCALLY ADVANCED BREAST CANCER (LABC). A CHEMO-IMMUNOTHERAPEUTIC APPROACH ?.

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Neoadjuvant chemotherapy (NACT) improves survival in LABC patients. Usually 3-4 cycles of conventional-dose NACT are administered prior to local therapy. In an attempt to improve results we increased the dosages and applied GM-CSF, which is also known for its immuno-stimulatory effects, which might enhance the antitumor effect.
Forty-two patients with stage IIIA or IIIB breast cancer were treated with doxorubicin (D)(90 mg/m^2) and cyclophosphamide (C)(1000 mg/m) at 3-weekly intervals. In the second and fourth cycle a 10% dose reduction of both agents was applied. On the second day GM-CSF 250 μg/m^2/day was started and given for 10 days. Initially, some patients were treated with $\leq$ 4 cycles, but as the study progressed and toxicity appeared tolerable, 6 cycles where given whenever possible. After the chemotherapy, patients underwent surgery and radiotherapy.
Response rate for the whole group to DC was 98% (95% CI: 94-100%), with a clinical complete response rate of 50% (95% CI: 35-65%). Six patients had a pathological complete response and in 17 patients only minimal residual disease was present. Median follow-up is 38 months (range 12-86). The disease free survival (DFS) at 3 years is 63% and the overall survival (OS) at 3 years is 76%. Comparison of DFS and OS of patients who received 4 cycles with patients who received 5 or 6 cycles showed a significant trend for improved DFS ($p=0.0000$) and OS ($p=0.0001$) with increasing number of cycles.
Our results with dose-intensive NACT and GM-CSF compares favourably with previous studies. This is most apparent in the group of patients who received 6 cycles of neoadjuvant chemotherapy. We hypothesize that these favorable results rare due to an underlying immuno-stimulatory effect of GM-CSF, and that the extended number of neoadjuvant chemotherapy cycles in the majority of patients have probably contributed to these results.

PP 24

THE EFFECTS OF THE ANTI-CANCER DRUG TAMOXIFEN ON THE CELLULAR REDOX STATUS

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Some recent reports have suggested that the anti-cancer drug Tamoxifen (Tam), widely used in the breast cancer therapy, can be involved in oxidative cellular metabolism with anti-oxidant or pro-oxidant effect. Because both ER-positive as well as ER-negative cells are Tam responsive it is evident that Tam acts not only through a mechanism mediated by ER, but also by an alternative ER-independent mechanism. It is well known that reactive oxygen species (ROS) produced inside the cells during oxidative metabolism are involved in many human diseases, such as cancer. With our research we want to clarify if some undesiderable effects of Tam can be ascribed to oxidative effect produced by this drug. We decided to study the role of Tam in the cellular redox status starting with analysis of oxidative stress enzymes expression in human breast cancer derived cell lines treated with Tam and/or with antioxidant at several concentrations and for different times. We are measuring the activities and the levels of the major enzymes involved in cellular response to oxidative stress by enzymatic assays and western blotting and we are also measuring the intracellular levels of ROS and GSH (reduced glutathione) by flow cytometry.

PP 25

ANTI-HER2/NEU-ANTIBODY BINDING PROFILE IN PATIENTS WITH BREAST-CANCER

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Monoclonal anti-HER-2/neu antibodies have an inhibitory effect on proliferation of HER-2/neu exprerssing cancer cells. There is evidence indicating the presence of auto-anti-HER-2/neu antibodies in patients with tumors overexpressing *Her-2/neu*.
In order to detect these anti-HER-2/neu antibodies an ELISA was developed. The assay relies on the antibody capture technique. A short fragment coresponding to the extracellular domain of HER2/neu gained by peptide synthesis was coupled with activated BSA as a carrier protein and immobilized on a 96-well plate. This peptide was recognized by monoclonal mouse antibodies raised against the extracellular domain of HER2/neu.
In parallel, Western blotting experiments were performed. Membrane fractions from SK-BR3-cells were separated on 6% SDS-PAGE and transferred onto nitrocellulose sheets. Sera were tested for specific anti-HER2/neu IgG. Up to now we screened 20 patients with breast cancer and 20 matched paired healthy controls. We observed a wide range of antibody levels in both groups. Elevated antibody titers of anti-HER2/neu were found in both, patients and control sera. So far there is no clear evidence to discriminate between patients with breast cancer and healthy donors by anti-Her2/neu antibody levels.

OP 26

INHIBITION OF BREAST CANCER TISSUE AROMATASE ACTIVITY AND ESTROGEN CONCENTRATIONS BY THE THIRD GENERATION AROMATASE INHIBITOR VOROZOLE

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Purpose: To study the effects of the third generation nonsteroidal aromatase inhibitor vorozole (Rivizor™) on intratumoural aromatase activity and estrogen concentrations in breast cancer tissue of postmenopausal patients.
Methods: During seven days preceding mastectomy eleven postmenopausal breast cancer patients were treated with vorozole (2.5 mg/d). During surgery tumour tissue samples were obtained, in which aromatase activity and estrogen concentrations were measured and compared to results obtained in nine unpretreated postmenopausal breast cancer patients.
Results: Eight patients were evaluated. In treated patients median tissue aromatase activity was 89% lower than in controls ($p<0.001$). Similarly, median tissue estrone and estradiol concentrations were 64% and 80% lower respectively in treated patients ($p=0.001$ resp. $p<0.05$).
Conclusion: Vorozole is able to significantly lower aromatase activity and estrogen concentrations in breast tumour tissue. Impairing estrogenic stimulation may be an important mechanism in the antitumour activity of aromatase inhibitors, which is further to be tested in clinical investigations.

PP 27

COMPLEX TREATMENT OF ADVANCED BREAST CANCER USING NEOADJUVANT CHEMORADIATION THERAPY

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410 patients with advanced breast cancer (T3-4N2-3M0) were treated with complex and combined chemoradiotherapy. 260 patients (63,4%) had the radiotherapy in dose of 40-42 Gy, 150 (36,6%)- in dose 60 Gy. With radiotherapy the patients were subjected to drug treatment according to various schedules: VAM, CMF, CMFAV, VCAF, FAC. 3 weeks after the completion of curing it was accomplished tire clinic evaluation of efficiency of preoperative measures in accordance with the recommendations of WHO. As an objective curing result it was accounted only the complete and partial tumour regression. In this cases the surgical intervention was carried out. Efficiency of the chemoradiation therapy was observed in 95,1% (390 patients): the complete regression of tumour was in 23,4% (96), partial regression was in 74,4% (305). The stabilization of tumour process was in 2,2% (9). The patients were observed during 102 months. 5 and 7-years survival rates were 75,8% and 69,3%.

PP 28

CARBOXYTERMINAL TELOPEPTIDE OF TYPE I COLLAGEN (ICPT) - A POTENTIAL SERUM MARKER IN DIAGNOSIS OF ADVANCED BREAST CANCER

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We explored where the preoperative serum levels of metabolic fragments of type I collagen (PINP; the aminoterminal propeptide of type I procollagen, PICP; carboxyterminal propeptide of type I procollagen, ICTP; the carboxyterminal telopeptide of type I collagen) correlate with the stage of breast cancer (BC). We also examined the usefulness of PINP, PICP and ICTP in diagnosis of BC.
Methods: The PINP, PICP and ICTP serum concentrations were measured by RIA methods from samples drawn prior to any surgical procedures in 138 BC, 94 BBD patients and 100 healthy controls.
Results: The serum levels of ICTP significantly correlated with increasing stage of BC, especially with stage IV BC ($p<0.001$). The mean value of ICTP was significantly elevated in BC group compared to BBD and controls, but the sensitivity was weak.
Conclusion: Our results demonstrate that ICTP is a potential serum marker in diagnosing of advanced BC. However, none of these markers are useful in diagnosing BC in its early stages.

PP 29

EFFECTIVITY OF BOOST IRRADIATION ON THE LOCAL CONTROL AFTER BREAST CONSERVING SURGERY AND EXTERNAL RADIOTHERAPY

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In our first study (1986-1992) we examined 111 patients after breast conserving surgery: 56 patients received 50 Gy whole breast external irradiation, the local recurrance rate was 10,7%, another 55 patients received 50 Gy whole breast irradiation plus 10-20 Gy interstitial boost radiotherapy, the local reccurance rate 5.4%. The median follow-up were 45.5 and 46.8 months respectively (range 34-89). We identified 6 routinely applicable parameters which were associated with significantly higher local recurrance risk. In our second study started in 1993 every high risk patients had got boost radiation. The median follow-up was 37.2 months (range 19-50 mo.). We treated 44 patients, the reccurance rate was only 2.3% (1/44 pts.). We recommand therefore whole breast irradiation plus boost irradiation in every cases of high risk breast cancer patients. (Significant risk factors were: tumour infiltration close to surgical margin, EIC positivity, high grade histology, endolymphatic spread, invasive lobular cancer, etc.).

PP 30

FREE RADICALS SCAVENGERS AND BREAST CANCER

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Introduction: Early diagnosis in breast cancer is serious clinical problem, so new diagnostic markers are still founding.
The aim of this study was estimate a peroxido-antioxide balance of an organism in a breast cancer.
Patients and methods: We analyzed the two groups pf patients. The first group counted 48 women with breast cancer. They were treated by modified radical mastectomy (removal of only the breast and the axillary lymph nodes). In the second one (the control group) counted 15 women, with diagnosis of benign dysplasia. They were treated by tumorectomy. The patients did not had other complaints. Assay of peroxido-antioxide balance of an organism was performed on the ground of the activity of free radical scavengers, such as superoxide dismutase (SOD) in erythrocytes and glutatione peroxidase (Gpx) in whole blood and lipid peroxidation products in plasma (MDA - malonyl dialdehyde, CD - conjugated dienes, HPETE - lipid hydroperoxide).
The activity of glutatione peroxidase (Gpx) were determined using method of Paglia and Valentine's and the activity of superoxide dismutase were determined using the Kawaguchi's method. Conjugated dienes - CD and lipid hydroperoxide (HPETE) were marked using the method of Buege's and Augusta in Warda's modification. The concentration of malonyl dialdehyde (MDA) were determined using the method of Okava and Yagy. In both groups above-mentioned markers were determined twice times before surgery, ten days after the operation and thirty days after it. The obtain results were statistically analyzed.
Results: The average age of patients was 49 years (rage 33-68 years). In the approximately 65% of patients with the breast cancer the level of lipid peroxidation products was significantly higher before operation than after it. On the contrary the levels of superoxide dismutase (SOD) and glutatione peroxidase (Gpx) in approximately 70% cases were higher before the operation than after the operation, respectively. In patients with diagnosis of benign dysplasia, we have not noticed the considerably changes of the levels of lipid peroxides product and the levels of superoxide dismutase (SOD) and glutatione peroxidase (Gpx) before and after the operation, respectively.
In the group of women with breast cancer were statistically significantly higher levels of lipid perioxides and the levels of superoxide and glutatione peroxidase than in group of women with diagnosis of benign dysplasia.
Conclusion: Our results showed that:

* Breast cancer caused intensity the process of lipid peroxidation in an organism and increased of the activity of free radicals scavengers.
* The determination of levels of lipid peroxidation products and the activity of SOD and Gpx may be of considerable importance in diagnostic of breast cancer.

PP 31

WHICH IS DETERMINED QUALITY OF LIFE (QL) IN BULGARIAN BREAST CANCER PATIENTS (BCP) COMPARATIVE STUDY BETWEEN INDIVIDUAL INTERVIEW (SCIQOL) AND STANDARTISED QUESTIONARIES (EORTC-QOL-30-BR-23)

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The aim of the study was to estimate usefulmes of two different QL instruments in non-metastatic and metastatic BCP in Bulgaria. Since July 1995 we observed 193 BCP - 101 under adjuvant treatment and 92 under palliative treatment; mean age 41,3. BCP were interviewed and asked to complete two QL-instruments at the begining and at the end of the chemiotherapy treatment (adjuvant or paliative).
There is no significant difference in value of "global QL" between two QL-instruments. We found that QL in older BCP (>55 years) depends more on social support (practical help), QL in younger BCP (<55 years) depends mostly on psycho-social support (emotional, friendships).

OP 32

INTRATUMORAL PHARMACOKINETICS OF CYTOTOXIC DRUGS IN CANCER PATIENTS

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The transfer of cytotoxic agents across the tumor endothelium into the interstitial tumor space is considered a critical step in clinical response of solid tumors to antineoplastic chemotherapy. The present study therefore employed an innovative technique, in vivo microdialysis, for measuring interstitial tumor pharmacokinetics and plasma to tumor transfer rates of carboplatin, 5-fluorouracil (5-FU) and methotrexate (MTX) in melanoma- (n=6) and breast cancer- (n=19) patients.

Major pharmacokinetic parameters for the interstitial tumor space were obtained for all compounds. There was a high interindividual variability in transendothelial transfer of all three compounds. Plasma levels were not predicive of corresponding levels in the interstitial tumor space. In contrast to MTX, 5-FU interstitial tumor load was associated with favourable clinical response.

We conclude that assessment of transfer rates into the tumor compartment is feasible by in vivo microdialysis. This information may explain drug resistance in some patients and may help to optimize dosing and administration schedules. In contrast to 5-FU, access of MTX to the interstitial space was not a rate limiting step for clinical response to chemotherapy. In future selection of novel cytotoxic compounds with favorable tumor penetration characteristics may become possible by microdialysis.

OP 33

CONTINUOUS INFUSION OF 5-FLUOROURACIL ($_{d}$FU) GIVEN WITH VINORELBINE (Vi) AND CISPLATIN (P) (ViFUP) IN HEAVLY PRETREATED METASTATIC BREAST CANCER (MBC). F. Nolè, E. Munzone, M.G. Zampino, I. Minchella, M. Colleoni, C. Noberasco, T. De Pas, N. Fazio, F. de Braud, G. Peruzzotti and A. Goldhirsch. Dept. of Medicine and Radiation Oncology, European Institute of Oncology, Milan, Italy.

We investigated the treatment effect of a combination of $_{d}$FU plus V and P (ViFUP) in MBC, assuming that the regimen will be also subjectively very well tolerated. Thirty-one pts, with MBC entered a phase II study; at the time of this preliminary analysis, 26 were evaluable for response (3 too early and 2 because of unmeasurable disease). Pts characteristics: median age 47 yrs (23-64); PS 0-1/2: 22/4; 5 premenopausal, 21 postmenopausal; all pts were pretreated for metastatic disease; 18 pts (58 %) had previous exposure to FU (given as bolus injection): 21 (68%) had previous anthracyclines. The most common site of metastatic disease were soft tissues (58%), liver (52 %), bone (39%) and lung (19 %). Treatment consisted of $_{d}$Fu (200 mg/m^2/d), P (60 mg/m^2 i.v. on day 1) and V, (20 mg/dose, i.v. on day 1 and 3 . Partial responses were observed in 11 of 26 assessable pts (42%; 95% confidence interval, 24 - 60). In addition 9 pts (35%) had stable disease and 6 progressed while on treatment (23%). Analysis of responses according to metastatic sites shows a noteworthy effect on liver metastases (6/11) and on soft tissue diseases (6/11). The median duration of response was 3.8 mos (range 1.5 - 6.1 mos). Ninety-three cycles were administered (range 1-6); grade 3/4 granulocytopenia was observed in 18%/17% of cycles. Grade 3/4 nadirs generally lasted no more than 7 days. Only one episode of neutropenic fever was observed during 1 cycle, requiring hospitalization therapy. The treatment was very well tolerated observing nausea and vomiting in 30% of cycles. Grade 2 alopecia was observed only in 3 pts. Conclusions: we identified a combination chemotherapy with remarkable efficacy in heavily pretreated patients which is also subjectively very well tolerated. The regimen warrants further investigation as first-line and primary chemotherapy.

PP 34

NEOADJVANT CHEMORADIATION THERAPY IN TREATMENT OF ADVANCED BREAST CANCER.

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Combinative neoadjuvant chemoradiation therapy was carried out for 265 patients with advanced breast cancer / T2-4 N1-3 /. For 86 patients radiation was administered in the regime of classic fractioning the dose up to summed nidus dose 40-44 Gy, but for the rest - according to split course up to summed nidus dose 60-70 Gy. Medicinae therapy was carried out according to schemes CMF, CAF, VAM, CMFVP, CMFAV, VCAF. Complete regression of tumour is marked in 21%, the partial regression - in 74,1%. Stabilization of tumour process is observed in 5,9% only. Estimation of curing pathomorphose showed that the complete regression of tumour was observed in 14,4%. Pronounced pathomorphose was found out in 44,5% of observations, but part of weak and moderate pathomorphose was 33,9%. The absence of curing pathomorphose was observed in 7,2%. According to obtaintd data 5- and 10- year total and without relapse survivality for neoadjvant chemoradiation therapy was 69,3%, 56,5% and 57,3% and 42% correspondingly. For combinative chemoradiation therapy the most effective schemes of medicinal curing are CMF and VAM.

Recommendations for carrying out the chemoradiation therapy for any forms and stages of mamma cancer, accompanied by the oedema of skin with the presence of metastases in regional lymphatic nodes as well as node types with multiple metastases in lymphatic nodes.

PP 35

EFFECT OF TAMOXIFEN ON LENS AND VITREOUS BODY IN HUMANS: A SURVEY ON 62 CASES

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Tamoxifen is a non steroidal antiestrogen widely used in the treatment of breast cancer. Previous investigators reported the occurence of retinal toxicity in humans induced by tamoxifen, while *in vitro* studies this compound is responsible for the development of lens opacities. The aim of this study has been to verify the ocular toxicity of tamoxifen on 62 women undergone to hysterectomy and ovariectomy and under therapy from 36 months. A group of 50 age-matched women undergone to hysterectomy and ovariectomy, without tamoxifen therapy, served as control.

After 36 months of therapy, with a cumulative dose of 21.9 g, there were no retinal toxicity. On the contrary, about 50% of women under therapy presented pulverulent opacities situated in the peripheral part of the lens; in the group of women without therapy the prevalence of lens opacities was about 25%. Our findings demonstrate that hysterectomy and/or ovariectomy *status per se* increases the prevalence of lens opacities and that tamoxifen treatment acts with a positive synergism.

PP 36

NEOADJUVANT CHEMOTHERAPY (CT) PRIMARY MEDICATION FOR BREAST CANCER

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Neoadjuvant chemotherapy is a kind of chemotherapy given to regress the primary tumour. Neoadjuvant chemotherapy treatment is given in cases of carcinoma of the breast where the tumours are larger than 3 cm. diameter. Thus, patient would have small surgery or no surgery at all. Besides patients would have good cosmetic results. The regimes used for neoadjuvant CT (NCT) are CMF, MMM, AC and ECF. Details of the regime will be mentioned.

Common Side Effects

General: bone marrow depression, emesis and lethargy.

Specific: with MMM haemolytic uraemic syndrome; with ECF hyperacusis, palmar plantar syndrome, hair loss; with AC hair loss.

Toxicity: Percentage in delay of chemotherapy for neutropenia is more or less the same for all the regimes. Anti-emetics have been given according to the degree of emesis. Among them CMF and MMM have less emesis effects.

Follow-up: Measurements were done with each cycle of treatment. Some patients under ECF were changed to AC regime especially due to central line complications while those under the AC regime need not change treatment. Therefore tunnel line is mandatory for this treatment.

Tunnel line insertion procedure and complications

Response rate: Regarding response rate cases with MMM and CMF were thoroughly reviewed. ECF and AC treatment are still undergoing.

Summary: Neoadjuvant chemotherapy contributes better tumour control, better cosmetic results and better survival.

OP 37

DOSE-FINDING STUDY OF HIGH-DOSE EPIRUBICIN (E) AND DOCETAXEL (D) AS FIRST-LINE CHEMOTHERAPY IN ADVANCED BREAST CANCER (ABC)

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International Breast Cancer Study Group

Aims of the study were to determine the maximum-tolerated dose (MTD) of the combination given every three weeks with and without growth factors (G-CSF) support and to evaluate the toxicity profile and the anti-tumour activity. Twenty-eight patients were entered from July 1996 to July 1997, 75% of whom had visceral disease. E was given as a 15-min infusion followed after 1-hour interval by D given as 1-hour infusion. A three-day steroid medication was administered. A maximum of 4 cycles of ED was given, D alone could then be continued for 4 cycles in responders. Four dose levels were explored: Grade 4 neutropenia was universal ($\geq$ 80% of cycles) at all dose levels and represented the dose-limiting toxicity (DLT). The MTD without G-CSF support was reached at E 90 mg/m^2 and D 75 mg/m^2. G-CSF allowed higher doses to be administered with acceptable toxicity: the MTD with G-CSF was reached at E 120 mg/m^2 and D 85 mg/m^2. Non-haematological toxicity was mild: in particular neither clinical cardiotoxicity (LVEF was monitored every 2 cycles) nor severe mucositis or fluid retention were observed. A significant antitumour activity was observed at all dose levels: a Phase II trial is ongoing at E/D 90/75 mg/m^2.

PP 38

CONSERVATIVE TREATMENT OF EARLY BREAST CANCER USING BRACHYTHERAPY METHODS

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The combined method of conservative surgery was used in our department in 1985-94 (93 women with TI-2, NO, MO stages, with the localisation of the tumour in **the inner, central quadrants**). Conservative managment consisted of quadrantectomy, total axillary dissection plus brachytherapy of the parastemal limphatic collector and iridium implants. There were two groups of patients with these combinations: the patients of the I **group** got radiotherapy on the second day after the operation. We boosted a tumour area by an interstitial implants (15-30 Gy), using a microSelectron - LDR. We performed the catheterisation of the inferior pectoral artery for irradiation of the parasternal lymph node chain, using a microSelectron-HDR (dose of 74 Gy in three fractions). 5 years survival rate 92.3%, 10-year 80.3%. The patients of the II **group** after the conservating surgery got only irradiation of the parasternal lymph node chain, using a microSelectron-HDR in the same doses. The 5th and 10th-year survival rates: 84.6%, 75.5%. The local recurrence rates were in the I group-7.1%, in the II group-11.1%. Patients by themselves evaluated cosmetic results as good in the most of cases.

PP 39

THE ROLE OF TUMOUR MARKERS FOR PATIENTS WITH BREAST DISEASES

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The tumour markers follow-up is especially important for early detection of distant metastases. The authors will present results of study done at the Charles University Faculty Hospital in Pilsen. For the problem of discrimination between benign and malignant breast tumours the data of 230 benign cases and 255 presurgical examinations of breast carcinomas from the Faculty Hospital in Pilsen were used. TK (with sensitivity of 57%), followed by TPS (46%), CA 15-3 (45%) and CEA (28%) show discriminative ability between malignant and benign tumours (for all marker specificity was 90%). The estimation of metastases development was based on tumour markers follow up. After reaching complete remission, the women is followed up in 1 - 3 months intervals in order to detect any metastatic process as soon as possible. Results from Pilsen contain about 1499 serum samples (remission N=1143, progression N=356). TK has proved to be the best tumour marker with sensitivity 88% (specificity 90%) followed by CA 15-3, TPS and CEA. Authors reccomend a combination of CA 15-3 and TK as the best, while TPS (TPA) CA 125, CEA could be added. This work has been supported by IGA MH of the Czech Republic No.3767-3.

PP 40

USE OF TUMOUR MARKERS TO ETIOLOGY DIFFERENTIATION IN PLEURAL EFFUSIONS

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Background: In clinical practice, the differentiation between malignant and benign pleural effusions in patients with breast tumours is of diagnostic importance.
Patients and methods: In 400 patients (185 with breast cancer and 215 with benign diseases associated with pleural effusions), the levels of tumour markers CEA (Pharmacia), CA 125 (CIS), TK (Immunotech) and TPS (BEKI) were followed up in serum and pleural fluid. For all tumour markers the sensitivity has been calculated at a level of 90% specificity. The results of each were correlated with clinical features, an ECG, a chest X-ray and a cytological examination of the pleural fluid.
Results (sensitivity at 90% specificity):

MARKER	PLEURAL FLUID	SERUM
TK	70%	60%
TPS	78%	68%
CEA	63%	42%
CA 125	45%	45%

PP 41

LEUCOCYTE NADIR AS A MARKER FOR CHEMOTHERAPY EFFICACY IN NODE POSITIVE BREAST CANCER TREATED WITH ADJUVANT CMF

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The purpose of the study was to examine the association between experienced leucocyte nadir and prognosis in breast cancer patients receiving adjuvant CMF chemotherapy. 368 patients with node positive breast cancer without distant metastases were treated with 6 cycles of CMF chemotherapy. 60 patients also received tamoxifen. All patients underwent surgery and received local radiotherapy. The impact of hematological toxicity of CMF on DDFS and OS was assessed. A lower leucocyte nadir during the chemotherapy was significantly associated with longer DDFS (p=0.02) in an univariate analysis. The number of metastatic lymph nodes, tumour size, steroid receptor status, surgical procedure, tamoxifen therapy, grade, histological type and age also significantly associated with DDFS in univariate analysis. In multivariate analysis only number of metastatic lymph nodes, tumour size, progesterone receptor status, surgical procedure, age and tamoxifen therapy retained prognostic significance. The leucocyte nadir during the adjuvant CMF chemotherapy might be a biological marker for a chemotherapy efficacy.

OP 42

RESULTS OF RECURRENT BREAST CANCER TREATED BY RADIATION THERAPY (RT) AND HYPERTHERMIA (HT). AN ITALIAN MULTICENTRIC STUDY.

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The incidence of local recurrences of breast cancer is in the range of 10-40%. Using radiotherapy (RT) alone, the rate of local failure is between 40-60%. Current literature data suggest that hyperthermia (HT) combined with RT can increase the local control rates.
From Febrary 1982 to October 1995, 231 recurrent breast cancer were treated with RT and HT. The recurrences were located in the chest wall in 190 cases, within the breast in 19 cases and in the regional lymphnodes in 22 cases. The combined treatment resulted in the total group of treated lesions in 57,5% complete response rate, 36% partial response rate and 3,9% no response. In the remainig 2,6% of lesions, progression was observed. To date, 62 patients are alive without disease, 72 are alive with disease, 72 died for local progression and 25 died for distant metastases with no evidence of local disease. Three, five and seven year actuarial local control are 45, 30 and 25%, respectively. In univariate analysis the dose of RT, the minimum and maximum intratumoral temperature and the size of the lesions resulted statistically significant. In multivariated analysis the variables statistically significant were the dose of RT and the size of lesions. The combined therapy has been well tolerated by the normal tissues with a low rate of major toxicity.

PP 43

DETECTION OF p53 OVEREXPRESSION, p53 ANTIBODIES AND CELL PROLIFERATION FOR AN ADMINISTRATION OF POSTOPERATIVE BREAST CANCER INTENSIFIED ADJUVANT CHEMOTHERAPY

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p53 overexpression is the common genetic abnormality in human carcinomas. We have estimated a high risk of tumor progression using p53 mutation (immunocytichemistry, PAb 1801 - DAKO), p53 Ab (ELISA - Immunotech) in the sera of patients, cell proliferation in tumor (radiochemistry, ^{3}H-timidine-Amersham). Retrospectively 46 breast cancer patients (T_3N_0) after surgical intervention were separated into 2 groups.
I group: 21 patients with p53 positive tumors; the prolif. activity was 23.7 ± 2.1 dep/min/mg DNA; p53 MAb were detected for 16 patients.
II group: 25 patients with p53 negative tumors the prolif. activity was 10.4 ± 2.4 dep/min/mg DNA; p53 MAb were not detected.
p53 overexpression was correlated with ^{3}H-timidine test data and p53 Ab sera levels. All these tests may be used for an administration of postoperative intensive adjuvant chemotherapy in node-negative breast cancer patients.

PP 44

SELECTIVE DECREASE IN SERUM IgG1 - AN INDIRECT, TISSUE NON-SPECIFIC TUMOR MARKER DETECTING CARCINOMAS OF DIFFERENT ORIGINS WITH HIGH SENSITIVITY AND SPECIFICITY

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Malignant diseases of various tissues have previously been found to be associated with a characteristic shift in the serum pattern of IgG subclasses, i.e., a highly significant reduction of the percent of IgG1 and an increase of the percentage of IgG2 relative to the total IgG. Here we summarize the data concerning the diagnostic performance of this tumor marker in a total of 1200 patients with carcinomas of the breast, the female reproductive tract and with colorectal cancer.
Using quantitative affinity chromatography it was found, that (1) mean values for %IgG1 and IgG2 of all cancer patients differed significantly from those of patients with benign disease and healthy controls. This „shift" was found reversible after successful surgical therapy (2). With breast cancer a quantitative dependance on tumor staging was established. A significant shift was found already at early stages (TNM1), allowing to discriminate these tumors from benign lesions with a propability of 63%. The sensitivity increased with stage up to 80 - 90% (3).
With carcinomas of the ovary, corpus or cervix uteri, and with colorectal cancer no quantitative association was found with tumor stages. Based on a calculated cut-off the specificity and sensitivity of %IgG1 to discriminate between controls and cancer patients were found to be 90% and 80% in gynecologic malignant diseases, regardless of localization. With colorectal cancer these values were found to be 88% and 74%, respectively.
In conclusion, the IgG subclass shift is a phenomenon closely related to the growth of malignant tumors, that could be diagnostically used as a screening method to detect early stages, as well as for the postoperative monitoring of malignant diseases.

PP 46

BREAST CANCER GRADING IN CELL SAMPLES

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OBJECTIVE:One of the most important prognostic factors of breast cancer - histological grade of malignancy is obtained by histological investigation of tumor tissue. In patients who receive preoperative chemotherapy this factors cannot be determined. The aim of our study was to evaluate if tumor grade can be assessed from aspiration biopsy samples.
STUDY DESIGN: Aspiration biopsy smears from 85 patients with invasive ductal carcinoma of the breast IDC were analysed. All the smears were stained according to Giemsa method. There were 25 tumor grade I IDC (HG I), 30 grade II IDC (HG II) and 30 grade III IDC (HG III). Size and shape of the nuclei, density, distribution and quality of the chromatin, and number, size and shape of the nucleoli of 200 cells selected independently were evaluated in each cell smear.
RESULTS: The number of nucleoli per cell nucleus and the size of cell nuclei yielded the highest correlation with HG. By combining all the evaluated properties of cell nuclei, the differentiation between HG I and HG III was possible at 80% reliability, whereas the differentiation between HG I and II and between HG II and HG III is considerably less reliable.
CONCLUSION: The reliability of our proposed criteria for the evaluation of tumor grade from cell aspirates should be tested against the survival of patients in a prospective study that would also include the assessment of interobserver and intraobserver reproducibility.

PP 48

RESULTS OF BREAT CANCER SCREENING PROGRAM

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The aim of this study was to summarise the results of a one year screening program for breast cancer in our department. In Hungary one woman in seven will experience breast cancer at some point in her lifetime. With no primary prevention, early measures remain the main hope of decreasing mortality. We have screened 498 women, mean age 52, using clinical breast examination, mammography or ultrasonography and respective FNAB. We found 205 normal, 167 cases of mastopathy, 75 benign soliter lesions, 30 inflammatory lymph nodes, 5 malignat lesions. In 7 cases we found suspicion of malignancy (positive mammography and sine morbo FNAB diagnoses), in 9 cases conclusive diagnosis was not achieved (these patients are followed up thoroughly). Based on our results we determined the management of different lesions in cases of suspicion of malignancy or uncertain diagnosis, and we discuss the risk factors and social effects.

OP 45

Immunohistochemical Localisation of Gross Cystic Disease Fluid Protein-15, Apolipoprotein-D and Zinc alpha-2 Glycoporotein in Ductal Carcinoma in situ of the Breast.

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Three major proteins present in breast gross cystic disease fluid and expressed by the cyst lining apocrine epithelium are gross cystic disease fluid protein-15 (GCDFP-15), apolipoprotien-D (APO-D; GCDFP-24) and zinc alpha-2 glycoprotein (ZnGP; GCDFP-44). An immunohistochemical study of these proteins was performed in 57 cases of ductal carcinoma in situ (DCIS) of the breast, including 9 cases of morphologically apocrine DCIS. Positivity was seen in 25/57 (43.86%) cases with anti-GCDFP-15, 21/57 (36.84%) cases with anti-APO-D and 23/57 (40.35%) cases with anti-ZnGP. GCDFP-15 positivity was noted in 5/13 (38.46%) of the well differentiated, 11/19 (57.89%) intermediately differentiated and 9/25 (36.00 %) of the poorly differentiated cases (p=0.32). APO-D positivity was seen in 3/13 (23.00%) well differentiated, 9/19 (47.37 %) intermediately differentiated and 9/25 (36.00%) poorly differentiated cases (p=0.37). ZnGP was detected in 5/13 (38.46%) of well differentiated cases, 11/19 (57.89%) intermediately differentiated and 7/25 (28.00%) poorly differentiated cases (p=0.13). In the 9 cases of apocrine DCIS, GCDFP-15 positivity was detected in 7 (7.28%), while 5 (55.56%) and 6 (66.67%) cases were positive for APO-D and ZnGP respectively. The results of this study indicate that there is no significant association between the expression of the studied proteins and the degree of differentiation of DCIS of the breast. Moreover, some morphologically apocrine DCIS cases appear to lose expression of these proteins.

PP 47

WILL DELAYED SURGERY ENABLE TO SPARE LYMPH NODES IN BREAST CONSERVING THERAPY BY CREATING THE POSSIBILITY OF INVESTIGATING PROGNOSTIC FACTORS

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The aim of this study was to establish if delayed mastectomy performed after tumorectomy has any effect on a following period without symptoms. In the years 1985-91 1231 operations for breast cancer were performed. The study included 28 women with I and II degree of clinical advance of the disease, in whom tumorectomy was performed for various reasons and next, after a final diagnosis of cancer (confirmed by histopathological investigations) a modified surgery using Patey's method was performed. On the average radical mastectomy was performed eight days after tumorectomy.
The clinical course of disease in this group was compared with another group where both operations were performed at the same time.
No statistically significant differences were found out. Results suggest that delayed operations have no negative effect on the clinical course and enable, in some particular cases, to define current prognostic factors and possibly spare lymph nodes in breast conserving therapy.

PP 49

COULD CORE BIOPSY BE USEFUL IN ASSESSING AND PLANNING OF NEOADJUVANT TREATMENT OF LOCALLY ADVANCED BREAST CANCER ?

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Percutaneous large needle biopsy (core biopsy) is now commonly used in breast cancer detection. However many works studied only histological findings. Our aim was to correlate histological diagnosis to morphological and immunophenotypical patterns in locally advanced breast cancer. We have correlated these data with clinical response (measured in surgical specimens) to neoadjuvant therapy: Based on our results, we plan to use these findings to individualize the approach to neoadjuvant therapy. We performed core biopsies (16-14 g needle) on 152 women with locally advanced breast cancer, averaging 3 specimens per biopsy. Samples were processed with routine methods, formaline-fixed, paraffine embedded and EE stained; some paraffine sections were processed with immunohistochemical techniques to identify biological data. We studied histological type, hormonal status, grading, Ki-67, c-erb-B2, p-170. 138/152 cases were malignant and in 130/152 we identified the histotype (101 ductal and 29 lobular carcinomas). In 104/138 cases were graded as follows: 2/G1, 74/G2, 28/G3. In 14 cases histological diagnosis was not obtained due to insufficient tissue or scant breast epithelium. In 122/138 cases we had adequate tissue sample for immunohistochemical studies. 60 were ER+ and PgR+, 62 cases were ER- and Pgr-. Over 50% showed high proliferation levels (Ki-67: > 20% positive), and c-ERB-2 and p53 were strongly positive. The 138 women subsequently received neoadjuvant therapy of epidoxorubicin 150 mg/m^2 every 21 days for 3 cycles, followed by radical mastectomy. We then correlated our previous data with the same studies of the surgical specimen. Our subsequent studies will focus on efficacy of using immunohistochemical data in planning neoadjuvant therapy. In particular, we will study histological type, grading, receptor status (ER, PgR), p170 (MDR) c-ERB-2.

OP 50

HISTOLOGIC DETERMINANTS FOR DIFFERENT TYPES OF LOCAL RECURRENCE AFTER CONSERVATIVE SURGERY AND RADIOTHERAPY FOR INVASIVE BREAST CANCER: A MULTICENTRE CASE-CONTROL STUDY IN THE NETHERLANDS

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The purpose of this study was to determine which histologic factors are associated with an increased risk for local recurrence in the breast after breast-conserving therapy for early breast cancer (TNM stage I and II) and whether risk patterns vary according to menopausal status and type of local recurrence.
Through complete follow-up of the patients of eight regional radiation oncology departments, two cancer institutes and one surgical clinic in The Netherlands, 360 patients were identified with local recurrence in the breast after having received breast-conserving therapy (local tumour excision, axillary dissection and irradiation of the breast) during the eighties. For each case two controls with a follow-up of similar duration without local recurrence were randomly selected.
Histologic slides of the primary tumour were reviewed.
Among premenopausal patients the risk of recurrence for those younger than 35 years was significantly higher than that for premenopausal patients of 45 years or older (relative risk: RR, 2.9; 95% confidence interval - 95% CI - 1.3 to 6.6). The risk of recurrence at or near the site of the primary tumour was most significantly increased for patients with high grade extensive intraductal component adjacent to the primary tumour (RR, 4.1; 95% CI, 1.7 to 9.8). Microscopic margin involvement was an important risk indicator for diffuse recurrence and recurrence in the skin of the breast, especially in the presence of vascular invasion (RR, 25; 95% CI, 4.0 to 150). To prevent local recurrence at or near the site of the primary tumour, wide local excision or mastectomy should be considered for patients with high grade extensive intraductal component. Microscopic margin involvement in the presence of vascular invasion significantly increases the risk of diffuse recurrence or recurrence in the skin.

PP 51

CHANGES IN BIOCHEMICAL MARKERS OF BONE TURNOVER IN BREAST CANCER PATIENTS WITH BONE METASTASES

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The understanding and the monitoring of metastatic bone disease remains unsatisfactory. In this study we compared several markers of bone turnover in 25 breast cancer patients with bone metastases, aged 48-70 years. All patients were treated with pamidronate 60 mg i.v. every month in adition to stanadard endocrine or chemotherapy. Blood or urine measurements included total and bone alkaline phosphatase, osteocalcin (BGP),hydroxyproline,pyridinoline(Pyr),deoxypyridinoline(DPyr) and ICTP were performed baseline,1,3 and 6 month after starting therapy. The mean values of alkaline phosphatase, Pyr,DPyr and ICTP were significantly increased in 7/25 (28%),21/25(84%),22/25(88%) and 17/25(68%) patients respectively ($p<0.001$). Therapy significantly reduced Pyr (84.4+/-12.3 vs. 32.5+/-7.6 nmol/mmol creatin) and DPyr (16.7+/-7.1 vs. 9.4+/-3.7 nmol/mmol creatinin). There were no changes in osteocalcin and hydroxyproline levels. These results indicate that sequential measurement of Pyr and DPyr can be used to monitoring the results of therapy of bone metastases.

PP 52

ANALYSIS OF BASIC TUMOR- AND HOST-RELATED FACTORS IS NOT HELPFUL IN THE SELECTION OF BREAST CANCER PATIENTS FOR SERIAL CA 15-3 DETERMINATIONS DURING FOLLOW-UP

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In attempt to identify the subgroup of breast cancer patients which benefits by serial CA 15-3 assays, we evaluated the association between the sensitivity of CA 15-3 test in detecting distatnt metastases and basic tumor- and host-related factors. The retrospective analysis included 103 metastatic patients aged at primary diagnosis 28 to 78 years (median 48), who were followed-up with stanadard procedures and serial CA 15-3 evaluations; totally 731 assays were performed. As a result, we didn't observe any statistically significant relationship between the sensitivity of CA 15-3 test and menopausal status (premenopausal vs. postmenopausal), pretreatment CA 15-3 value (< 30.0 U\ml vs. > 30. 0 U\ml), primary tumor size (T_1+T_2 vs. T_3 + T_4), histological type of the tumor (ductal vs. lobular), axillary lymph nodes status (negative vs. positive), UICC clinical stage of the disease (I + II vs. III + IV) as well as Bloom-Richardson grade (I+II vs. III). Based upon results of the present study, we conclude that assessment of above factors is not helpful in the selection of patients for serial CA 15-3 assays during follow-up.

OP 53

TUMOR-DERIVED TGF-β AND IL-10 CONTRIBUTE TO A TH2 IMMUNE PHENOTYPE IN PANCREATIC CARCINOMA PATIENTS

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Previous studies in experimental animals have demonstrated that the production of immunomodulatory cytokines by tumor cells can down-modulate local or systemic immune responses to tumor cells. In contrast, effects of tumor-derived cytokines on immune parameters in tumor patients are poorly understood. In this study we investigated functional consequences of TGF-β and IL-10 production by human pancreatic carcinomas. We report expression of TGF-β and IL-10 in pancreatic carcinoma tissue associated with significantly elevated levels of both cytokines in the sera of the majority of pancreatic carcinoma patients. Using conditioned media of pancreatic carcinoma cell lines we demonstrate that tumor-derived TGF-β and IL-10 inhibited in an additive fashion both T lymphocyte proliferation and the development of Th1 responses in PBMC preparations of normal donors. The anti-proliferative and Th1-suppressive activities contained in conditioned media of pancreatic carcinoma cells were due primarily to IL-10 and/or TGF-β as shown by the capacity of cytokine-specific neutralizing antibodies to reverse these effects. Finally, enhanced TGF-β and IL-10 serum levels were associated with aberrant Th2 immune responses in PBMC obtained from pancreatic carcinoma patients. These results suggest that tumor-derived TGF-β and IL-10 coordinately regulate systemic immune responses in patients with pancreatic carcinoma.

OP 54

MAP KINASE ACTIVITY IN METASTATIC TUMOUR OF THE LIVER

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Liver metastases are found at 25-55% patients with large bowel cancer. In that case the prognosis is poor and only about 20% cases can be treated by radical surgery. The aim of our study was to evaluation of subunit p42 of MAPK (mitogen activated protein kinase), one of the important factor of proliferation and differentiation, in the metastatic tumours of the liver.
The material consisted of liver biopsies taken from 16 patients during operation for large bowel cancer. The activity of MAPK was evaluated for a central part of tumour, border part (between tumour and macroscopically uninvolved liver) and samples far away for metastases.
We used western-block technique with IgG antibodies against MAPK.
In 13 cases we found increase activity MAPK in the samples taken from liver tumour. In 9 of 13 cases the highest activity of MAP kinase was found in the periphery of tumours.
Our results seem to confirm the role of kinase cascade in the formation and growth of metastatic liver tumours. The high level of MAPK in the periphery of the tumour can explain rapid tumour growth and the high percentage of tumour recurrence after surgery. We suggest that in the case of the liver metastasis the tumour tissue should be resected with wide margin.

PP 55

PSEUDOMYXOMA PERITONEI – Case report and literature review.

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We report a case of pseudomyxoma peritonei (PMP) associated with adenocarcinoma of the appendix and present a review of the literature.

A 75 years old woman, presented with progressive abdominal swelling and with the radiological appearance of a pelvic mass and ascites. The exploratory laparotomy revealed an appendiceal mucocele with PMP, the pathological diagnosis was adenocarcinoma of the appendix. The patient was submitted to cytoreductive surgery followed by systemic chemotherapy with 5-FU and MMC, having completed 7 years of follow up, free of disease.

PMP is a rare and poorly understood entity. Agressive cytoreductive surgery is the main step in the management. The role of chemoterapy is not consensual.

OP 56

HELICOBACTER PYLORI INFECTION IN PATIENTS WITH GASTRIC CANCER IN INDIA: COMPARISON OF YOUNG AND OLD PATIENTS.

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Background/ Aims: Helicobacter pylori infection has been implicated in pathogenesis of gastric cancer. Since there is paucity of reports from developing countries on association of H.pylori with gastric cancer, we performed case control study to find out the relationship between H.pylori and gastric cancer and also compared characteristic of gastric cancer and H.pylori positivity in younger and older patients.
Patients and Methods: Gastrectomy (n=37) or endoscopic biopsy (n=43) samples from area adjoining the cancer were collected from 80 patients of gastric cancer. Tissue specimens were stained with hemotoxylin-eosin and Giemsa stains and histological type of cancer was determined according to Lauren, as intestinal or diffuse type. The presence of H.pylori was assessed by Giemsa staining. Eighty age and sex matched patients with non-ulcer dyspepsia (NUD) served as controls.
Results: Of 80 patients, 48 (60%) had intestinal type, 28 (35%) had diffuse type and 4 (5%) had mixed typed of gastric cancer. Tumour was located in antrum in 37 (46%), in body in 31 (39%), and at other sites in 12 (15%) cases. Intestinal metaplasia was seen in 42 (52%), more commonly in patients with intestinal type than in diffuse type (58% vs 43%, $p< 0.05$) of gastric cancer. H.pylori infection was present in 29 (36%) of patients compared to 36/80 (45%) patients with non-ulcer dyspepsia (p=NS). The positivity of H.pylori was higher in intestinal type than in diffuse type (42% vs 24%, $p< 0.05$) of gastric cancer. H.pylori positivity was similar in patients with growth in antrum and body (40% vs 42%) of stomach. There was no significant difference in tumour type, tumour site, frequency of intestinal metaplasia and H.pylori positivity (39% vs 35%) in younger (≤ 45 yrs) and older (> 45 yrs) patients.
Conclusion: Approximately one-third of patients with gastric cancer show presence of H.pylori infection on histological examination which is similar to H.pylori positivity in patients of non-ulcer dyspepsia. H.pylori infection is more common in intestinal type than in diffuse type of gastric cancer. However, no differences in H.pylori positivity were observed in young and old patients of gastric cancer and patients with cancer at different sites in the stomach.

OP 57

METHOD OF TREATMENT THE IMPOTENCE AFTER COMPLEX THERAPY OF CANCER OF THE AMPULAR PART OF THE RECTUM

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Problem of the impotence therapy in patients received complex treatment on occasion of the rectum cancer including surgical intervention and radial therapy leave to be topical practically to patients of all ages. Radial damage and operational trauma of the prostate is considered to be the main causes of the impotence development. Conventional methods of sexual function renewal are low effective and sometimes contra-indicated to this patients. We have elaborated complex approach for sexual function renewal including as standard methods of stimulation as magnetic-resonance therapy, hyperbaric oxygenation and electrical stimulation of the pastorate. Totally 41 patients with overage 4.5-months duration of postoperative period who received the complex therapy were randomically selected for observation. Surgical operations performed i.e. abdominal-anal and abdominal-above-anal resections, Duamel type operations were sphincter-saving and allow to entrance to the pastorate. Further development of cancer process has not been detected. The course of complex treatment consist of hyperbaric oxygenation (P=1.5 atm, duration= 50—60 min, 10—12 procedures per course), magnetic-resonance therapy (duration= 60—90 min, 10—12 procedures per course), electrical stimulation of the pastorate (rectal electrode, I= 6—20 mA, f= 100 Hz broken and ceaseless regimes, duration= 30—40 min, 10—12 procedures per course). Perfect renewal of sexual function has been detected in 17 patients, partial renewal — in 19 and absence of effect — in 5 patients. We presume that complex approach suggested allow to effectively renew sexual function in patients undergone to sphincter-saving operations.

PP 58

COMBINED TREATMENT IN THE CASES OF COLORECTAL CANCER-preliminary report

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In the years 1992-1995 in our Department the preliminary investigation on the radio-chemoth. in the cases of colorectal cancer was started. To these programm were qualified patients after radical surgery procedure, with Adenocarcinoma Dukes C. There were 28 pts (20 men, 8 women). The median age was 52 years. The RT with ChT were strated simultaneusly 4-8 weeks after operation.The RT was applied in the doses 1,8Gy daily up to 57-70Gy. The ChT 5FU(325mg/m2) + Leucovorin (30mg/m2)during the 5 days was applied at the first and last weeks of RT and at thefourth and nineth weeks after RT. The median survival was 26 months (2-53m). The programm was good tolerated. There were no serious side effects. Our results allows to open the randomized investigation.

PP 59

FAS/APO-1 (CD95) EXPRESSION OF PERIPHERAL T LYMPHOCYTES (Ly) IN COLORECTAL CANCER PATIENTS

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Fas/APO-1 system of T lymphocytes plays important role in immune response - its intense signalizing can act as either an intensifier or a suppressor of the immune reactions via apoptosis. With the aim to characterize the expression of Fas/APO-1 (CD95) system of T Ly in peripheral blood we have examined 32 colorectal cancer patients and 12 patients with benign large bowels diseases. CD95+, CD3+, CD4+, CD8+, CD16+, CD38+ and CD19+ were determined.

Patients with benign large bowels diseases had 23.2% CD95+ cells (424±196 cells/mm^3) but in colorectal cancer patients 29.3% was CD95+ cells (579±203 cells/mm^3) and Fas/APO-1 expression depends from malignant process spread. The elevated number of CD95+ cells in colorectal cancer patients allows us to suggest that T Ly apoptosis is increased and it can contribute tumor escape from immunological control.

PP 60

Comparative analysis of the results of the colorectal cancer surgical treatment

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This presentation is based on the observation of 254 patients of different sex,age and localization of the colorectal cancer,who underwent 268 standard operations and ones with applying of spesial laser equipment. The volure and method of surgical treatment was dependent on the localization of pathology center, accompanying diseases,age of the patients. We performed 63 right and 39 left hemicolectomies,33 Gartman operations,30 Swenson-Hiat-Isakov operations,36 peretoneum-anal resections of rectum with the evagination of sigmoideum,29 exterpations of the rectum,24 restoration of the continuity of the large intestine. Totally 254 patients underwent 268 operations, 138 operations were performed with the applying of laser equipment including laser-mecanical sninching apparatus of our design (license N 1678336 of May 22,1991) with the preliminary aprobation on 98 dogs. Analisis of clinical picture, clinical and biochemical analisis, X-ray,ultrasonic,morphological data prove the advantage of the operations with the laser equipment applying.This report presents) extracts from the histories, dissertations,photos,slides, as well as videofilm with the operation technique.

OP 61

Ki - ras Mutation On Codon No. 12 - Molecular Genetic Marker For Pancreatic Carcinoma.

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Pancreatic carcinoma represents nowadays a difficult medical problem - both for its increasing frequency and for diagnostic and therapeutic problems.
On the field of diagnostic approach, mollecular genetic methods are used more frequently.
The authors describe specific Ki-ras mutation on codone 12 in patients with pancreatic carcinoma, which is being reported in up to 90 per cent of cases.
Detection of this mutation has been performed by polymerase chain reaction method (PCR). Both pancreatic tissue and pancreatic fluid have been obtained during surgery.
Tissue of 5 consecutive pancreatic carcinomas has been analysed - with the mutation beeing found in all five samples.
Pancreatic fluid has been analysed in the same 5 patients - with the mutation beeing found in 4 of 5 samples.
The authors proved the method to be perspective marker for pancreatic carcinoma diagnosis in the settings of clinical practice.

PP 62

IRINOTECAN (CPT-11) IN PRETREATED METASTATIC COLORECTAL CANCER(CRC): A SINGLE INSTITUTION EXPERIENCE.

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From November 96 to May 97, 13 patients (pts) with metastatic colorectal cancer previously treated with 5Fu based chemotherapy (ct) were given 350/m2 of Irinotecan as a 30 minutes IV infusion q3w.
Pts characteristics: Median age: 52 years (40-74), 6 male and 7 female. ECOG: 0-1: 10 pts; 2: 3pts. Primary tumor: colon 10 pts; rectum 3 pts. At diagnosis 10 pts were stage D and in 3 of them the primary tumor was not removed. 12 pts received treatment with 5Fu-based as first line for metastatic CRC. Metastatic sites: multiple: 8 pts; single: 5pts. Liver: 85%. Lymph nodes: 38%; Lung: 15%; Soft tissues: 15%; Peritoneum: 8%.
Number of cycles (cy): 50 median: 3; range 1-8. Inital doses were reduced in 5 pts because of toxicity. Only 8 pts were evaluable for response (2 early deaths and 3 early withdrawal). Data on toxicity are available for 13 pts and 49 cy.
Results: No responses were observed. 4 pts had no changes and 4 progressive disease while therapy. Major toxicities: Grade (gr) 3 / 4 neutropenia: 12 cy (25%) out of which 3 cy (6%) with Gr $\geq$ 2 fever; Gr 2 / 3 diarrhea: 17 cy (34%); Gr 2 / 3 emesis: 19 cy (38%); Gr 3 alopecia: 10 pts (77%). Moderate and intense asthenia was observed in 22 cy (44%). 1 pt died of septic shock after 2 cy. Median survival time: 8 months. 7 pts are dead: 5 from progressive disease, 1 from toxicity and 1 from non related disease.
Conclusion: In our small group of pretreated metastatic CRC patients, CPT-11 showed no activity.

PP 63

SURGICAL TREATMENT OF STOMACH STUMP CANCER

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Till present time the treatment of stomach stump cancer is a complicated problem. For the last 5 years 14 patients have been treated for the above mentioned pathology at the oncologic clinic. 8 patients were males, 6 were females. The patients' age ranged from 46 to 76 years. Before all the patients had been performed surgical intervention in the volume of distal stomach resection. three of them - due to ulcerous disease, eleven of them for malignant tumour. The duration of the period without recurrence was 2,1 years. Stomach stump cancer was developing at average in 26 years after surgical treatment. All the patients have undergone surgical intervention. Stomach stump extirpation has been performed in 5 patients, it has been performed in combination with transverse colon resection and splenectomia in the two patients; the stomach stump resection has been performed in 4 patients. The operation was over with intraoperative revision in 5 patients due to local spreading to tumoral process. During postoperative period 4 patients died and 3 of them after radical operations. The main cause of lethal results was incompetence of esophagointestinal anastomoses. Follow-up results were observed in 5 from 6 patients, undergone a radical operation. After the operation 3 patients died during a year and 1 patient in 5 years. The patient after combined extirpation stomach stump has been living for over a year.

PP 64

THE RESULTS OF EXTENDED RESECTION OF THE RECTUM FOR CANCER

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We analyzed 321 cases of the carcinoma of the rectum. All these patients underwent radical surgery in the Republic Cancer Center. In general, we found that sphincter saving resections were predominating among all surgeries for rectal cancer-169 (52,6%) versus rectal extirpations-135 (42,1%). 64,5% (207 from 321) of all surgeries were extended. We studied indications for extended resections in rectal cancer. In order to make surgery more radical we use extended aortoiliopelvic lymphadenectomy as a part of radical surgery for rectal cancer. Results of surgical treatment were assessed in two groups of patients with rectal cancer.

1. 114 patients underwent classical radical surgery.
2. 207 patients underwent only surgical treatment with extended lymphadenectomy (extended surgery).

The number of complications in both groups wash't significantly different 20,2% versus 23,2% respectively. Mortality was 3,5%. Remote results showed that 5-year survival in patients from the first group with regional metastases was 9.1%. It was significantly lower than in patients without metastases (39,5%). in the second group 5-year survival was 26,3% in patients with regional metastases and 42,9% without.

PP 65

The experience of using of Roncoleikin(Interleikin-2) for the patients with colorectal cancer.

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Under our observation there were 22 patients with the colon cancer of different localization,who extept usual coservative therapy and surgical standard treatment,had paranterally Roncoleikin (IL-2). The given drug preparation was administered after operations intravenously,intraversically(into urinary bladder) and intrarectally. The goal of using of this drug is the stimulation of the adaptive antitumor therapy for the better overcoming of the surgical treatment, metastasis prevention, cancer regression. To estimate the patients condition the method of SAPS was used,including clinical and laboratory work, X-ray,ultrasonic diagnosis and computer tomography. All the patients were under observation (the maximum observation period is a year and a half). there were no negative results. All the patients with IL-2 overcame the operation clinically more easy. We didnot reveal any metastasis after operation. One patient with the rectum cancer underwent the sphincterosaving operation. One patient had the regression of inoperative turnour of urinary bladder mouthes, germinating from the rectum cancer. No mortal cases were reported. Extracts from the histories, clinical, biochemical and morphological data, photos,slides, pharmacological instructions are presented.

PP 66

Some facts about hepatocellular carcinoma (HCC) in south of Iran

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Prevalence and rate of hepatic tumors varies according to geographic areas, genetics and other factors in different parts of the world. HCC has been reported more in whites over the age of 40, but below this age in Africa and Indonesia.

The records of 228 patients, admitted with diagnosis of hepatic tumor in our hospitals in past 15 years were reviewed. Out of these, 133 had metastatic and 91 primary hepatic tumors including 73 (85%) patients with HCC. Hbs Ag was positive in 44% of HCC patients, and 11% of them had liver cirrhosis. 61% of HCC patients were in 5th and 6th decades of life, and only 16% were below 40 years of age. Out of these, 75% had laparotomy, and 9% of them were treated with liver resection.

Conclusion:

1. ***The etiology of HCC is seemed to be hepatitis B in our area***
2. ***A low percentage of patients are cirrhotic***
3. ***Most of the patients are above 40 years and non resectable at the time of diagnosis.***

PP 67

FAS/APO-1 (CD95) EXPRESSION IN PERIPHERAL BLOOD OF GASTRIC CANCER PATIENTS

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The stimulation of the immune system can give both an intensification and the contrary - the suppression of the immune reaction via apoptosis. The central role in this process is played by Fas/APO-1 system of the T lymphocytes. By that reason we analysed Fas/APO-1 (CD95) expression in peripheral blood of 23 gastric cancer patients and 12 patients with gastric benign diseases. CD95+ expression and CD3+, CD4+, CD8+, CD38+, CD16+, CD19+ in patients peripheral blood was determined by laser flow cytofluorimeter Ortho Spectrum III. Patients with gastric benign diseases had 424 (230-620 cells/mm^3) CD95+ cells but in comparison gastric cancer patients had elevated CD95+ cell level 609 (265-1336 cells/mm^3). We suggest that in that way gastric tumor escapes from immunological control. The CD95+ cell level will be analysed in connection with vastness of the malignant process.

OP 68

TOTAL MESORECTAL EXCISION (TME) WITH OR WITHOUT PREOPERATIVE RADIOTHERAPY IN THE TREATMENT OF PRIMARY RECTAL CANCER

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One of the major problems in the treatment of rectal cancer is the appearance of local recurrences. Two important factors that have been reported to reduce local recurrence rate are Total Mesorectal Excision (TME) surgery and preoperative radiotherapy. However, no study has evaluated the effect of preoperative radiotherapy in combination with standardized TME surgery.

These considerations led us to set up a trial in which TME surgery is standardized, in which randomization takes place for preoperative radiotherapy, and in which strict quality control is being performed for the surgical, radiotherapeutical, and pathological disciplines. We evaluated the first 500 patients with respect to their baseline characteristics and short-term morbidity in order to judge the feasibility of the trial.

Since the start of the trial in january 1996, over 700 patients have been randomized from 78 Dutch hospitals. Complications during operation were reported in 20% of the cases. Postoperative complications were divided in general, infectious, and surgical complications. These percentages were respectively 17%, 31%, and 30%. Leakage was reported in 15% of the cases. The number of readmission, reintervention, and hospital death were respectively 6%, 18%, and 3%. Acute toxicity due to radiotherapy was reported in 28% of the irradiated patients in various degrees. We found significant differences between the randomization groups with respect to blood loss during operation (larger in the RT-group) and examined lymph nodes (less in the RT-group).

The TME trial is the first in the world in which the effect of preoperative radiotherapy in combination with TME surgery is evaluated. Standardization of surgery, radiotherapy, and pathology has been achieved. The feasibility of the trial has been shown good which can be concluded from the large number of randomized patients and participating hospitals, and the number of surgical and radiotherapeutical complications.

OP 69

NATURAL HISTORY OF LATE RADIATION PROCTOSIGMOIDITIS TREATED WITH TOPICAL SUCRALFATE SUSPENSION

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Introduction: Rectal bleeding due to late radiation proctosigmoiditis is often difficult to manage. We had earlier reported the efficacy of topical sucralfate enemas in controlling rectal bleeding (Dig Dis Sci 1991; 36:103). We now present the longterm results of rectally administered sucralfate in hemorrhagic proctosigmoiditis.

Methods: 26 women (mean age 52 + 10.7 years) with rectal bleeding due to radiation proctosigmoiditis following radiotherapy for genital malignancy were included. Clinical severity of bleeding was graded as Severe (> 15 episodes/week); Moderate (8-14 episodes/week); Mild (2-7 episodes/week); Negligible (< 1 episode/week) and nil (no bleeding). 10 patients had moderate and sixteen patients had severe bleeding. Sigmoidoscopy revealed severe changes in 9 (34.6%) moderate in 15 (57.69%) and mild in 2 (7.69%) patients. All patients were treated with 20ml of 10% rectal sucralfate suspension enema twice daily till rectal bleeding ceased or failure of therapy was acknowledged. Clinical follow up was done 4 weekly till 16 weeks and every 2-3 months thereafter. Response was considered good whenever clinical severity of bleeding showed improvement by a change of two grades.

Results: Median radiation dose received was 80G (range 45-95G). Median time interval between radiation and onset of rectal symptoms was 11 months (range 3-39 m). 20 patients (76.9%) achieved good response at 4 weeks, which increased progressively to 84.6% and 92.3% at 8 and 16 weeks respectively. The reduction of bleeding with treatment in general and the change in the status of rectal bleeding at 4 weeks intervals was significant by Wilcoxom matched pairs signed ranks test. Two patients did not respond requiring diversion colostomy. All the patients were followed over a median duration of 45.5 months (range 5-73 m). 17 (70.8%) patients remained free of bleeding while seven (22.2%) had recurrence. All recurrences responded to a short term reinstitution of therapy and remained free of bleeding over a median duration of 35 months (range 9-56 m). There were not treatment related complications. Ten (38.5%) patients had other associated late toxicity due to pelvic irradiation in the form of asymptomatic rectal stricture (n=3), rectovaginal fistula (n=1), intestinal stricture (n=1), vaginal stenosis (n=1) and hematuria (n=6). 3 patients had progression of the primary disease in the form of pelvic recurrence (n=2) and hepatic metastasis (n=1).

Conclusions: Sucrulfate enemas induce a lasting remission in a majority of patients with moderate to severe hemorrhagic late radiation proctosigmoiditis.

PP 70

EFFECT OF THE MULTIPLE MODULATION 5-FU IN ADVANCED GASTRIC CANCER.

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FA+Mtx+I are well known as modulators of 5-FU. We used this effect in following regimen of chemoterapy for treatment patients with metastatic gastric cancer: Intron A-3 Mil IU/m2 s/c daily, 1-10 ds ,+Mtx 20 mg/m2 i.v. bolus ds 2 and 9 ds ,+FU 300 mg/m2 (in 1 hour after Mtx) i.v. infusion ds 2 and 9 ds, +FU 300 mg/m2 i.v. bolus with FA 20 mg/m2 i.v. ds 4 and 6 ds, + DDP 40 mg/m2 i.v. ds 1 and 8. 36 untreated patients with metastatic gastric cancer (mean age 47) recived 106 courses of following regimen .19 pts (27 courses) revealed disease PR.17 pts received 79 courses (mean 4,8). 3/17 (17,6 %) pts had complete response (confirmed by histology), from 6 to11 mths (mean 8,5). 5/17(29,4%) pts -PR , from 4 to 9 mths (mean 6,5) 9/17 (52,8 %) pts - STAB,from 3 to 8 mths (mean 5,5). One pt follow up without treatment (after 6 courses) more than 11months , CR was proved by UST, CT. Overall response - 17/36 (47,2 %) .During this treatment we admeated such side effects: fever (38)-15 pts (41,6 %) , higher than 38 -3 pts (7,9 %) , nausea 11/36 (30,5 %),vomiting (I-II gr) - 10/36 (27,7 %) , neutropenia (I-II gr) - 6 /36 (16,6%) . Those side effects are not sever and don't deteriorate quality of life.These results suggest that this regimen can be active in advanced gastric cancer with an accepteble toxity.

PP 71

A PHASE I DOSE ESCALATION OF HYDROXYUREA (HU) IN ADDITION TO CONTINUOUS INFUSION 5-FLUOROURACIL (5FU) IN PATIENTS WITH ADVANCED COLORECTAL CANCER

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Introduction: 5FU is the most effective chemotherapy agent with activity against colorectal cancer. Continuous infusion 5FU has equal efficacy to bolus 5FU but with less toxicity. Hydroxyurea can potentiate the inhibition of thymidylate synthetase induced by 5FU, by reducing the production of dUMP. The clinical significance of such a potentiation is not known. We set out to determine the maximum tolerated dose (MTD) of HU administered orally in combination with protracted infusion 5FU (300mg/m^2/day) in patients with advanced colorectal cancer.

Patients and methods: Consenting patients with histologically confirmed inoperable or metastatic colorectal cancer were commenced on palliative continuous infusional 5FU. All patients were fit to receive chemotherapy (PS<2, adequate haematological, renal and hepatic function) with no uncontrolled intercurrent illness. Oral HU (800mg/m^2/day) was administered from day 3 of the infusion. Cohorts of 3 patients received HU at escalating dose levels. Level I was one day HU per week and each subsequent level added HU for one extra successive day. Full blood count and all toxicity were monitored weekly.

Results: Entry to level 5 has been completed, with 20 patients entered (11 M, 9 F; age 51-85 years; 85% metastatic). Two patients had previous adjuvant 5FU/Levamisole, and 2 pelvic radiotherapy to recurrent tumour. 61% of patients completed a full 24 weeks of treatment, 39% stopping between 13 and 20 weeks with progressive disease. There have been 4 episodes of grade 3 palmar plantar syndrome (level 3 and 5) and stomatitis (level 4 and 5). All resolved after a 25% dose reduction in 5FU. There has been no grade 3 or 4 haematological toxicity. The overall response rate is 29%.

Conclusion: A combination of continuous infusion 5FU with oral HU is well tolerated and recruitment continues to define the MTD. Early response data are in line with that expected for continuous infusion 5FU.

OP 72

AUTO-ANTIBODIES AGAINST PEPTIDE EPITOPES OF GA733 TUMOR-ASSOCIATED ANTIGEN IN COLORECTAL CANCER

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In more than 90% of colorectal cancer the GA733 tumor-associated antigen is overexpressed. Autoreactiv humoral and cellular responses were shown to target the antigen. In this study B cell epitopes were mapped against the antigen. Sera from 136 patients reacting against the antigen and 30 healthy blood donors were tested in ELISA for naturally occuring IgG antibodies against 23 peptides synthesized from the entire aminoacid sequence of the external domain of GA733 antigen. 13% and 3% of healthy blood donors had autoantibodies against peptide 2 and peptide 8, respectively. No autoantibodies were detected in the control group against the other peptides. Antibodies were found in cancer patients mostly against peptide 2 (50%) and to a lesser extent (8-9%) against peptides 1, 4, 7, 8 and 20, respectively. Inhibition ELISA using mAb17-1A and mAbC215 indicated that the serum antibodies were specific for the antigen and peptide 2. More patients in advanced stage had antibodies against peptide 2. No correlation was found between reactivity to peptides and overall survival. 64% of the patients with colorectal carcinoma who had IgG antibodies against the GA733 antigen had peptide - particularly peptide 2 - specific autoreactiv B cells and followingly probably also specific T cells. Thus the GA733 antigen maybe a good target for immunotherapy.

PP 73

SYNCHRONOUS BENIGN AND MALIGNANT COLORECTAL TUMORS. COLONOSCOPIC FINDINGS

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Benign and malignant colorectal tumors are associated in 12-87% patients in dependence of number of colorectal carcinomas: 12-62% in patients with solitary carcinoma and 57-86% in patients with synchronous carcinomas. We analysed colonoscopic findings in 40 patients with synchronous benign and malignant tumors. Multiple colorectal carcinomas we found in 7 (17.5%), solitary carcinoma and solitary adenoma in 18 (45%), solitary carcinoma and multiple adenomas in 12 (30%) multiple carcinomas and solitary adenoma in 1 (2.5%) and multiple carcinomas and multiple adenomas in 2 (5%) patients. Synchronous benign and malignant tumors were localised in the same (25%) and in the different (75%) colorectal segments.
Conclusion: Total colonoscopy in patients with colorectal tumors (benign or malignant) detect synchronous colorectal tumors in huge number of patients. Detection of synchronous tumors may prevent development of metachronous colorectal carcinomas.

PP 74

RADIO-CHEMOTHERAPY IN THE TREATMENT OF GASTRIC CANCER WITH THE RISK FACTORS-preliminary

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In the 1993 the preliminary investigation on programm for the gastric cancer with the risk factors was started. For these programm were qualified patients who were undergone radical surgery procedure, the morphology of tumor was Adenocarcinoma, with microscopic risk factors. Since August 1993 to Marz 1995 for these programm were qualified 7 pts (5 men, 2 women) with the median age 51,8 years.Four - six weeks after operation the programmRT + ChT was started.There was: RT - 1,6Gy daily, 5 days a week up to 56Gy.ChT - 5 FU (325mg/m2) + Leucovo rin (30mg/m2) aws applied at the first and last weeks of RT.Three weeks after RT the second ChT was started.There was: 5FU (600mg/m2) + Adriamy cine (30mg/m2) + Mitomycine C (10mg/m2).These ChT was repeated 4 times every 3 weeks. The tolerance of whole programm was good. There were no serious side effects. During RT there was leucopenie only in one patient. The patients 10, 11, 25, 26, 35, 52 months (3 pts died).

OP 75

ANGIOGENESIS IN ASTLER-COLLER B2 COLON CANCER

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The growth and maintenance of solid tumors depends on a process called angiogenesis whereby the ingrowth of new vessels provides nutrients and a means of eliminating waste products by a process other than simple diffusion. Recent works in breast cancer, NSCL cancer and others, has demonstrated that tumor with low angiogenesis activity have reduced risk of recurrence and metastasis. We studied 99 patients with Astler-Coller B2 colon cancer resected between 1972 and 1990. Immunohistochemical studies were performed on formalin-fixed and paraffin-embedded tissue using the monoclonal QB-END 10 for CD34 endothelial antigen and a policlonal F-III antibody. Our hypothesis was that quantitative assessment of angiogenesis might identify a subset of node-negative colon cancer patients at high risk for recurrence or death.

OP 76

JUVENILE POLYPOSIS IN INDIAN CHILDREN

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Introduction: Polyps occur in as many as 1% of children and 90% of them are juvenile polyp. They are solitary and hamartomatous in nature whereas juvenile polyposis (≥ 5 juvenile polyps) is a rare condition with a neoplastic potential. This is first time we are reporting a series from India.
Objective: To study the clinical profile, malignant potential and management of juvenile polyposis in children (≤ 12 years).
Methods: 17 children with juvenile polyposis were evaluated clinically and endoscopically from March 1991 to October 1996. Colonoscopy and polypectomy were done 3 weekly until colonic clearance was achieved and thereafter 2 yearly. All polyps were subjected to histological examination.
Results: Mean age was 7.7 years, with a male preponderance (3:1). Presentation was with rectal bleeding (94%), pallor (65%), stunted growth (53%) and edema (47%) and the mean (SD) duration of symptoms was 33 (27) months. None had positive family history or any congenital anomaly. Two children had six polyps upto the transverse colon; the rest had numerous polyps all over the colon. All children had juvenile polyps on histology and 10 (59%) had **adenomatous changes (low grade dysplasia).** None had high grade dysplasia, adenoma or adenocarcinoma. Total colectomy was done in 6 for intractable symptoms. Colon clearance was achieved in 8 after an average 3.4 polypectomy sessions, and 3 were still on polypectomy programme.
Conclusions: Juvenile polyposis is commonly associated with low grade dysplasia, serial colonoscopic polypectomy is effective but colectomy is required for intractable symptoms and when clearance of the colon is not possible.

PP 77

LUNG RESISTANCE PROTEIN (LRP) IN COLORECTAL CARCINOMAS

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To determine the clinical role of the lung resistance protein (LRP) in patients with colorectal carcinomas, we immunohistochemically assessed the expression of this protein in primary colorectal carcinoma specimens (n=68). Immunostaining was performed on frozen sections by means of the monoclonal antibody LRP-56. Binding of the primary antibody was detected with the avidin-biotin-peroxidase method. SW1573 and SW1573/2R120 cells were used as negative and positive controls, respectively. LRP staining was detected as characteristic granular cytoplasmatic staining. LRP was negative in 7 (10%), low in 18 (26%), intermediate in 18 (26%) and high in 25 (38%) carcinomas. As in normal tissues of the digestive tract, the apical side of the mucosa showed strong and diffuse staining. Positive LRP expression was independent of size and localization of the primary tumour, histologic grade, regional lymph node involvement, distant metastasis and tumour stage. In addition, overall survival of the LRP- positive patients was similar to LRP- negative patients.

OP 78

INHIBITION OF TUMOUR TAKE BY SPILLING BLOOD IN THE PERITONEAL CAVITY: AN *IN VIVO* AND *IN VITRO* STUDY

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Previous experimental studies proved that red blood cells (RBC) in the abdominal cavity inhibit local tumour take. We investigated by what mechanism this effect comes about. *In vivo study*: 1.0×10^6 CC531 coloncarcinoma cells were injected ip in rats. In addition, in exp I 1.5ml RBC were injected, in exp II 1.5ml RBC were injected after CC531 cells had adhered. Control groups received 1.5ml PBS. In exp III group 1 received 1.5ml RBC and group 2 the contents of 1.5ml lysated RBC. After 21 days abdominal tumour take was scored. *In vitro study*: RBC in increasing amounts were added to CC531 cells (group 1+3) or a cultured monolayer mesothelium plus CC531 cells (group 2+4). In groups (1) and (2) RBC and tumour cells were added simultaneously. In groups (3) and (4) RBC were added after CC531 cells had adhered. After 48 hrs tumour take was measured by DNA assay after washing away unbound cells. Results: In the *in vivo* exp the mean score with regard to tumour take was significantly less in exp I as compared to the control group ($p<0.005$). In exp II there was no effect of the added RBC. There was no significant difference in tumour take between groups in exp III. In the *in vitro* exp there was a significant inhibition of tumour take in groups 1 and 2 in a dose dependent manner ($p<0.01$). This effect was not seen in group 3 and 4. Conclusion: Intra red blood cell substances prevent tumour cell adhesion to the peritoneum and consequently tumour recurrence. Most likely free radical scavengers are responsible for this phenomenon.

OP 79

TUMOUR CELL ADHESION TO SURGICALLY TRAUMATIZED PERITONEUM INVOLVES INTERLEUKIN-1β (IL-1β) AND COLLAGEN

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Surgical trauma of the peritoneum leads to cytokine production and denuding of underlying extracellular matrix components. In oncologic surgery, both facors may influence adhesion of peroperatively spilled tumour cells, and consequently tumour recurrence. We investigated *in vitro* tumour cell adhesion to the peritoneum and underlying extracellular matrix (ECM) components.

Materials and methods: Cytokines produced after abdominal trauma were obtained by rubbing both uterus horns of a rat and lavaging the abdomen after 5 hours. Tumour cell adhesion was quantified in a reproducible assay employing CC531 colon carcinoma cells. CC531 cells were left to adhere to a cultured monolayer of mesothelial cells after pre-incubation with the collected lavage fluid, IL-1β, IL-6 or TNF-α. Also, adhesion to collagen, the largest ECM component, was assessed.

Results: Tumour cell adhesion began within 5 minutes and peaked at 60 minutes, with a significant increase between 5, 30 and 60 minutes ($p<0.005$). Adhesion to collagen and a mesothelial monolayer preincubated with the lavage fluid and IL-1β showed statistically significant more tumour cell adhesion ($p<0.01$). TNF-α and IL-6 pre-incubation had no effect.

Conclusion: The results of this *in vitro* study indicate that tumour cell adhesion is markedly enhanced by cytokines produced due to surgical trauma. Taken together with the excellent adhesion to collagen, these factors may account for the habitual tumour recurrence at the site of inflicted surgical trauma.

OP 80

FOLLOW-UP OF COLORECTAL CANCER

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Intensive follow-up of patients who have been operated on for colorectal carcinoma is advocated by many authors, since it lead to early detection and possible resection of recurrence. It is however controversial whether such aggressive and expensive diagnostic methods could be as effective in increasing survival rate as cheaper protocols.

From 1976 to 1997 287 patients who have been curatively treated for colorectal carcinoma were enrolled in the follow-up program of the Oncologic Day Hospital.

The follow-up schedule included phisical examination, tumor markers and laboratory tests every three months for the first two years and then every six months for the next three years; US and chest x-ray every six months for the first two years and then every year for the next three years; colonoscopy and CT scan annually. All these diagnostic procedury have been performend every year after the fifth follow-up year.

In 125/287 (43,5%) patients polyps, distant metastases, locoregional recurrences, metachronous cancers or second malignancies were detected.

In 25% of patients with stage I, II and III desease a recurrence was detected, polyps were detected in 11% of the same patient group, in 2,2% methacronous cancer and in 3,5% second malignancies were also detected. 61% of lesions were detected within the first 2 years and 95% within the first 5 years of follow-up. No statistical difference in median survival was found between symptomatic and asymptomatic patients who enrolled in follow-up program.

35% of patients with stage I, II and III desease who had a recurrence were treated by curative surgery. 60% of this patient group was considered desease free at the end of this study.

The average cost of the follow-up program per each of the 125 patients who weren't found desease free has been 10181291 italian liras (5940 US dollars).

The results of the present study could be compared to the results of similar studies reported in literature. A prospective randomized trial about the effectiveness of expensive versus cheap follow-up programs is however needed.

OP 81

FINAL RESULTS OF A PHASE II MULTICENTRIC TRIAL WITH 5-FU (F), LEUCOVORIN (LV), ETOPOSIDE (E) AND ALFAINTERFERON (I) (ELFI REGIMEN) IN THE TREATMENT OF ADVANCED GASTRIC CANCER

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Leucovorin (LV) enhances the activity of 5-FU (F). We performed a phase II trial of (F) AlfaInterferon (I) and (LV) double modulation. The purpose of our study was to investigate activity, toxicity and management of modified ELF (ELFI) in advanced gastric cancer (AGC). From August 1994 to May 1997, we enrolled 28 patients, (19 males and 9 females, with an average age of 63.5). Treatment schedule was: (E) 80 mg/m^2 i.v. days 1,2,3 - (LV) 100 mg/m^2 days 1,2,3 - (F) 500 mg/m^2 days 1,2,3 - (I) 3.000.000 UI s.c. three times a week during the interval between courses (1-28). We evaluated 27 patients for toxicity and 24 patients for response (at least three courses done). We had 4 patients not evaluable: one for therapy's refusal before starting the treatment, one for address changing, one for suspected AMI after one course, one for therapy's refusal not toxicity-correlated after two courses. We administered 107 courses of chemotherapy (average 4 courses/patients, range 1-6). We achieved 3/24 CR (12.5%), 4/24 PR (16.6%), with an overall response rate of 29%; moreover we obtained 6/24 SD (25%). Time to progression for the CR, PR and SD was 10.8 months. Responders' (CR + PR) median survival was 12.3 months (range 3 - 15). All patients' (CR + PR + SD + P) median survival was 8.1 months. About grade 3 hematological toxicity, we observed transitory neutropenia in 5/27 patients, leucopenia in 3/27 patients, thrombocytopenia in 3/27 patients and anemia in 2/27 patients. We registered grade 3 mucositis/sthomatitis in 2/27 patients, grade 3 vomiting in 2/27 patients, grade 3 diarrhoea in only one patient. The (I)-correlated fever was frequent but always moderate and transitory. In two cases occurred the flu-like syndrome. We observed a moderate asthenia in 21/27 patients. We did not observe any grade 4 toxicity. The ELFI regimen seems to be easy to manage on Day-Hospital base, with a fairly good activity in AGC and an accetable toxicity. With the aim to increase the ELFI's activity, we are now trying a new schedule (ELFI-E) containing Epirubicin (60 mg/m^2 on day 4). This phase II multicentric trial started in September 1997.

OP 82

FREQUENT MAGE GENE AND PROTEIN EXPRESSION IN ESOPHAGEAL SQUAMOUS CELL CARCINOMAS IN CONTRAST TO ADENOCARCINOMAS AND ITS IMPLICATION FOR ADJUVANT TUMOUR THERAPY

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The genes MAGE-1 and MAGE-3 code for tumour-associated antigens (TAAs) which are recognized by cytotoxic T lymphocytes (CTLs). Both might serve for tumour vaccination strategies, since they are not expressed in normal tissues expect testes. We analyzed 55 shock frozen tumour tissue samples of carcinomas of the esophagus and esophagocardial junction for the expression of MAGE-1 and -3 using RT-PCR as well as monoclonal antibodies (mAbs) directed against the MAGE-1 (mAb 77B) and MAGE-3 (mAb 57B) proteins which were applied on formalin-fixed paraffin sections employing the catalyzed signal amplification (CSA) system. No MAGE gene expression was seen in any of the 55 normal tissue specimens. In squamous cell cancers, 10 of 23 (43%) primary carcinomas and 3 of 5 (60%) metastases yielded a MAGE-1 or -3 mRNA-positive result. By immunohistochemistry 2 additional cases were positive for MAGE-1 and -3. However, adenocarcinomas expressed MAGE-1 or -3 mRNA in only 3 of 21 (14%) primary tumours. The MAGE-1 or -3 protein detection rate was 4 of 21. Tumour tissue with different histology (e.g. undifferentiated carcinomas) revealed MAGE-1 or -3 mRNA in 1 of 6 and MAGE-1 and -3 protein in 3 of 6 cases, respectively. Because the gene products of MAGE-1 and -3 are presented to CTL by MHC-class I molecules, the proportion of patients who could be treated by MAGE vaccination would be at best 21% (MAGE-3 presentation by HLA-A2). Interestingly, the mAb 77B directed against MAGE-1 stained purely cytoplasmic whereas the mAb 57B directed against MAGE-3 revealed a more membranous staining indicating another advantage of the latter for vaccination strategies. Our data indicate further differences in tumour biology between esophageal squamous cell and adenocarcinomas.

PP 83

ANTICOLOSTOMA - PREVENTION AND REMOVAL OF THE PERMANENT COLOSTOMA

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Modern state of medical requires the application of the most recent achievements in science and technology in diagnostics and treatment. More 500 colorectal cancer patients were subjected by use to Fiber Optics diagnostics and thus were fully prepared for surgical intervention, performed in much earlier terms.

For treatment of patients with colorectal cancer, prevention and removal of permanent colostoma the application photophrin injection and He-Ne laser for photodynamic therapy in complex of the new method surgical operation ("insuture of anal anastomosis")

The application of the photodynamic therapy for treatment of colorectal cancer in complex of the new method surgical operation, prevention and removal of permanent colostoma giving of positive result - not formed of permanent colostoma and liquidate of timely colostoma.

I reccomend of the treatment methods phototherapy, new surgical intervention for prevention and removal of permanent and timely colostoma as new direction in oncoproctology - Anticolostoma.

PP 84

COLONOSCOPIC SURVEILLANCE FOR SYNCHRONOUS LESIONS IN COLORECTAL CARCINOMA IN NORTH INDIA

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Background: Synchronous polyps in colorectal carcinomas are seen in upto 30% and an additional malignant lesion elsewhere in the colon in 2-6% of the patients.

Aim: To study the prevalence of synchronous lesions in colorectal malignancy in North Indian patients.

Methods: 147 consecutive colonoscopies carried out for colorectal malignancy were reviewed retrospectively and presence of additional lesions elsewhere in the colon was noted.

Results: In a total of 147 patients (M:F = 3:1; mean age 46.19 years), 117 pre-operative and 30 post-operative colonoscopies were done to look for additional lesions. Primary carcinomas were found on the left side of the colon in 60.53% and on the right side in the rest. In 90 patients colon could be screened upto the hepatic flexure or cecum while in 57 patients full lenght could not be screened due to non-negotiable growth. In all, 22 patients (14.96%) had an additional lesion other than the primary growth, of which 13 were adenomatous polyps (8.84%) and 9 were carcinomas (6.13%).

Conclusions: Synchronous polyps in North Indian patients with colorectal carcinoma are less frequent as compared to West though, synchronous malignancy is as common.

PP 85

SURGICAL TREATMENT OF MALIGNANT OBSTRUCTION OF COLON

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Choice of surgical options in the treatment of colonic obstruction is still controversial. In the period 1992-1996 at the Surgical Clinic in Nis 270 patients were surgically treated because of the colon cancer (rectum excluded). In 81 patients (30%) the disease manifested as an acute obstruction. The cause of cancerous disease on the right was 29.6% (24 patients) while on the left colon was 70.4% (57 patients). In surgical treatment we used: decomprensive colostomy in 23% (19 patients), one stage resection in 62% (50 patients), in 12% (10 patients) two stage resections and ileotransversoanastomosis in 3% (2 patients). Postoperative mortality in the group of treated with decompresive colostomy was 42% (8 patients), in the group of treated with two stage resections was 30% (3 patients), in the group with ileotransversoanastomosis 50% (1 patient) and in the group with one stage resection was 12% (6 patients). Our opinion is that the least postoperative mortality in group of treated with one stage resection justify application emergency resection as the safe method in the treatment of many obstructive cancers of colon when performed by experienced surgeons in colorectal surgery.

PP 86

GEOCHEMICAL ECOLOGY OF STOMACH CANCER ON THE TERRITORY OF CHUVASHIA

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Stomach cancer takes the first place in morbidity and mortality among the inhabitans of Chuvashia. The aim of the present work is to study the peculiarities of prevalence of disease in different ecological and biogeochemical provinces of the republic. The findings of the investigation allow us to work out a technology for managing the oncological service taking into account the biogeochemical zoning of the disease.
Modern, complex, methodical approaches used in this study enable to make the following conclusions:
1) the spreading of stomach cancer in Chuvashia is irregular. Very high mortality indices two times as large as the average republican are constantly registered in the South-West part and very low ones two times as little as the average republican are registered in the east part;
2) material of the ecological and biogeochemical zoning of the Chuvash territory show the essential difference in the content and ratios in the provinces with contrasting levels in mortality on stomach cancer;
3) clinical, biochemical, hormonal, immune and microbiological characteristics of reactions of pratically healthy people give us the possibility to draw up the hypothetical diagram of cause - and - effect relations of stomach cancer with the environment.

PP 87

PRIMARY TUMOURS OF THE SMALL INTESTINE

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The diagnosis and treatment of primary tumours of the small intestine challenge the surgeon because are relatively rare, comparing with the other gastrointestinal malignancies.
A retrospective study from 1986 to 1997 identified only twelve patients with primary neoplasms of the small intestine. During that eleven years period, from the hospital records, 12.184 patients were admitted in the surgical department and 7.778 patients underwent general surgical procedures.
The natural history, diagnostic procedures and overall survival after surgical treatment were reviewed. The preoperative diagnosis rarely was made (only in 2 patients) because symptoms were vague and nonspecific. The optimal treatment is surgical resection in adenocarcinomas and sarcomas, beside in lymphomas adjuvant chemotherapy or iradiation therapy or both for patients with positive nodes or margins in recomended.

PP 88

ACCELERATED MODIFIED FAMTX-REGIMEN IN ADVANCED GASTRIC CANCER BY OPTIMAL USE OF G-CSF

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For advanced irresectible gastric cancer, sequential high-dose methotrexate and 5-fluorouracil combined with adriamycin on day 15 (FAMTX-regimen), cycled every 28 days, is effective but toxic, with a high incidence of neutropenic fever and toxic deaths. In order to shorten chemotherapy duration and diminish side-effects, we treated 7 consecutive advanced gastric cancer patients with all three FAMTX drugs on day 1 followed by G-CSF for 10 days, in 21-day cycles (FUMA-regimen). Major side effects consisting of mucositis and fatigue occurred, and forced 4 of 7 patients to stop treatment. The next 7 patients were treated with the same drugs in the same doses, but with adriamycin one day prior to MTX/5FU (AFUM-regimen). AFUM toxicity was unexpectedly mild and dose reductions were not necessary, suggesting that FUMA toxicity was the result of the sequencing of cytostatic drugs. There were no toxic deaths and no dose delays. We conclude that the accelerated AFUM schedule with G-CSF is feasible and safe in advanced gastric cancer, with the unanticipated observation of sequence-dependent adriamycin toxicity.

OP 89

PORT-SITE METASTASES:
IS AEROSOLISATION A PIVOTAL FACTOR ?

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Port-site metastases are possibly caused by floating viable tumor cells in the pneumoperitoneum. In order to determine the importance of this mechanism in the pathogenesis of port-site metastases, we performed the following experiments.
Methods: The peritoneal cavities of two WAG rats were connected with a plastic tube (length 2,5 cm, lumen 7mm). One trocar (5mm) was introduced in each rat and a pneumoperitoneum (6 mm Hg) was established. $2x10^6$ CC-531 tumour cells were injected intraperitoneally in rat 1 and a gasflow from rat 1("donor") to rat 2 ("recipient") was induced. After leakage of 10 l. of CO_2 in 12-15 minutes, the pneumoperitoneum was relieved and the rats were closed. The experiment was repeated with injection of $16x10^6$ instead of $2x10^6$ CC 531 cells in the donor.
Results: *experiment 1:* At inspection of the 10 recipients 6 weeks postoperatively, no tumour growth was found. *experiment 2:* After 4 weeks there was a small solitary tumour (2-3mm) in 3 of 5 recipients.
Conclusion: Aerosolisation of tumour cells is possible, but taking into account the extreme circumstances which are needed, this mechanism is not likely to play a major role in the pathogenesis of port-site metastases.

Genito-urinary Tumours and Gynaecological Cancer

Genito-urinary Tumours

OP 90

THORACIC METASTASECTOMY FOR GERM CELL TUMOURS: LONG TERM SURVIVAL AND PROGNOSTIC FACTOR

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This study evaluated the results of thoracic metastasectomy for germ cell tumours to assess long term survival and identify prognostic factors. A series of 144 patient who underwent resection of thoracic metastases at Royal Brompton Hospital were retrospectively reviewed. The disease involved the lung in 73 cases, mediastinum in 34 and both sites in 37. Median follow-up time of surviving patients was 56 months. Kaplan-Meier estimates of survival were calculated for clinical variables related to primary tumour and thoracic metastases, using the Cox model for multivariate analysis.
Complete resection was achieved in 125 cases (87%); pathology showed viable malignant elements in 44 (31%), necrosis or fibrosis in 31, differentiated teratoma in 61 and teratoma not otherwise specified in 8. The overall survival was 77% at five years and 65% at 15 years, being significantly shorter in patients with malignant teratomatous elements (51% at 5 years, P=0.0001) or incomplete resection (52% at 5 years, P=0.018). At multivariate analysis these factors retained their prognostic value, with a relative risk of death of 5.7 for malignant teratomatous elements and 2.8 for incomplete resection. In addition, the Cox model revealed a 3 times higher risk of relapse in patients with retroperitoneal disease at the time of thoracic metastasectomy.
These data confirm the value of thoracic metastasectomy as a staging procedure after chemotherapy and a potentially curative treatment for chemoresistant disease. Malignant pathology, incomplete resection and concurrent retroperitoneal disease were independent prognostic factors.

PP 91

COMPARATIVE STUDY BETWEEN TWO REGIMES OF RECOMBINATED α-INTERFERON-2β (INTRON A) FOR ADVANCED RENAL CANCER (ARC)

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We estimated the role of rec. α-INF-2β (Intron A) in treatment of ARC in two regimes. For 27 patients with prooved metastases (Pul, Hep, Ple) and lacking preliminary radio-, chemio- and chormonotherapy a treatment with Intron A s.c. for a period of 6 weeks was held in the two following regimes: 3 x 3 mln IU weekly and 3 x 9 mln IU weekly.
The aim of the study taking into consideration the therapeutic effect, immediate and late side effects, as well as the continuity of the remission and quality of life (EORTC-QOL-30).
Our initial results suggest, that ARC-patients with higher doses regime have slight better response rate than others, without significant difference in the side effects. In both groups QL was improved - physicial functioning (p=0.0001) and disease-symptom relief (p=0.003).

PP 92

A non-randomised trial comparing 6-field *vs* 3-field technique of *3D*-conformal radiation therapy (*3D*-CRT) in 40 prostate cancer patients. Technique and preliminary results.

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Facing a steep increase in our recruitment of prostate cancer patients, a new 3-field technique was developed in an attempt to reduce the daily treatment delivery time. Between July 1997 and August 1997, 20 consecutive patients with clinically localised adenocarcinoma of the prostate were treated with a 3-field conformal external beam irradiation using three-dimensional treatment planning. Patients were simulated with rectum and bladder empty in a supine position, the films corresponding to the beam portals being obtained for 0°, 110° and 250°. To ensure reproducible positioning, custom-made polyurethane foam or thermoplastic casts were produced for each patient. Based on serial CT scan slices with 0,5 cm thickness, the target and critical organs (rectum and bladder) were identified on each slice and afterwards, reconstructed in *3D*. A beam's eye view (BEV) technique was used to display these structures spatially on digitally reconstructed radiographs (DRR), on which, the treatment portals were subsequently designed, applying non-uniform margins around the outline of the target volume, that is, 1 cm towards the rectal wall and 1.5 cm towards the bladder anteriorly and also for the upper and lower portal margins around the target. Next, the treatment portals were transfered from DRRs onto simulator films. The shaping of the beam apertures was realized by conventional cerrobend blocks. The total target dose was prescribed at the ICRU point and was 76 Gy for the prostate delivered by a 15 MV linear accelerator in 38 fractions and 56 days (mean). The seminal vesicles were excuded at 70 Gy. The 6-field technique was different only in positioning of the patient (prone) and arrangement of portals (45°, 90°, 135°, 225°, 270°, 315°). For the purpose of this study the records of 20 consecutive patients treated with 6 fields 3D-CRT between June and July 1997 were analysed and served as basis for comparison.

Technical details and data regarding cumulative dose-volume histograms analyses, acute toxicity and early PSA profile will be discussed.

OP 93

BLADDER SPARING BY CHEMOTHERAPY AND RADIATION IN PATIENTS WITH INVASIVE BLADDER CANCER. A FIVE-YEAR FOLLOW-UP

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48 consecutive patients with muscle-invasive bladder cancer were treated between November 1988 and May 1993. All patients had pure transitional carcinoma, absence of diffuse Tis, and clinic NoMO stage. 39 patients had T2-3, stages and 9 had T_3-4. The treatment consisted of RTU, neoadjuvant chemotherapy (CT) M-VAC (2-4 cycles), and radiotherapy (RT) (44 Gy). RT was continued to 64 Gy in patients with biopsyproven absence of invasive cancer (CR). Cystectomy was performed in patients with residual invasive tumour. 9 patients did not receive RT: 6 with failure to CT underwent immediate cystectomy, and 3 with CR received only CT.
The CR rate to neoadjuvant treatment was 75%. After a mean follow-up of 61 months (51-86), the actuarial survival and disease free survival at 5 years were respectively 47% and 45%. The 5 years overall survival rate with an intact functioning bladder is 36.5%. Of the 21 currently surviving patients 81% have their bladder preserved. 8 patients required salvage cystectomy for recurrent invasive cancer (5) or diffuse Tis (3). 12 patients had recurrent superficial bladder tumours, and 5 of them preserved their bladder after further RTU and BCG.
The response to CT had prognostic value for survival (p<0.01). Severe complications were: 1 death for fulminant hepatitits after CT, 1 late radiation cystitis that required cystectomy and death in postoperatory, and colovesical fistula that needed rectosygmoidectomy.
The long-term bladder preservation is feasible in a selected group of patients by multimodality treatment. The survival is similar to cystectomy-based studies.

PP 94

THE USEFULNESS OF PSA, PAP TUMOR MARKERS SERUM LEVELS IN THE DIAGNOSIS OF BENIGN AND MALIGNAND PROSTATE DISEASES. CORRELATION WITH BONE SCINTIGRAPHY.

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In this study we evalutate the PSA, PAP levels in the diagnosis and monitoring of patients with prostate gland diseases.
We studied 50 normal persons (blood-donors) to estimate the cut-off values, 39 patients with benign deseases (hypertrophy of the prostate) and 85 with Ca of the prostate in several stages (48 with no metastases and 37 with metastases). We used the immunoradiossay Method (IRMA) with kits for PSA and PAP. Bone Scans with Tc-99m M.D.P. were performed in all the patients with Ca of the prostate. The cut-off value for PSA was 10 ng/ml and PAP was 2,3 ng/ml.

	PSA serum levels > 10 ng/ml		PAP serum levels > 2,3 ng/ml	
Benign diseases				
hypertrophy	5/39	19%	4/39	16%
Ca Prostate M°	26/48	54%	40/48	42%
Ca Prostate M'	33/37	89%	27/37	74%

The 96% of the patients with positive bone scans for metastases had elevated PSA serum levels. In the follow up of the patients with Ca with no metastases after therapy, 19/26 and 20/26 had PSA, PAP serum levels back in normal values.

The PSA is a usefull marker in the diagnosis and the follow up patients with Ca of the prostate. Is more sensitive than PAP, but in combination increases the sensitivity of the diagnosis. Elevated PSA serum levels had patients with multiply bone metastases.

OP 95

RUPTURE OF A RENAL ANGIOMYOLIPOMA.
AN UNUSUAL CAUSE OF MASSIVE RETROPERITONEAL BLEEDING

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Renal angiomyolipomas are benign neoplasms and occasionally related with tuberous sclerosis. However when the presenting symptom retroperitoneal bleeding were not associated with tuberous sclerosis and this type of tumour is unilateral and solitary. The made of presentation may be variable and only 4,5% of the patients have rupture and retroperitoneal hemorrage. Herein we report an additional case of a small size (1cm x 1.3 cm) renal angiomyolipoma with spontaneous massive retroperitoneal and intraperitoneal bleeding requiring emergency laparotomy.

OP 96

ABNORMAL EXPRESSION OF THE E-CADHERIN-CATENIN COMPLEX CORRELATES WITH POOR PROGNOSIS IN BLADDER CANCER PATIENTS.

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We used an avidin-biotin immunoperoxidase technique to investigate the immunoreactivity and cellular localisation of a-, b-, g- catenin, and E-cadherin, which are the prime mediators of cell-cell adhesion. We examined 68 transitional cell carcinomas (TCC) and 14 normal bladder biopsies and correlated these results with pathological and clinical parameters. The E-cadherin-catenins complex was expressed in a normal membranous pattern in all normal bladder epithelium specimens. Loss of normal surface E-cadherin, a-catenin, b-catenin and g-catenin expression was found in 52/68 (76.4%), 57/68 (83.8%), 54/68 (79.4%) and 54/68 (79.4%) of tumours ($p<0.001$). There was a significant correlation between the loss of normal membranous expression of catenins and E-cadherin and increased grade ($p<0.001$) and T stage ($p<0.001$). The abnormal expression of g- catenin as well as E-cadherin was correlated with poor survival ($p<0.05$). Our data indicate that the E-cadherin-g-catenin complex may be a useful prognostic marker in bladder cancer.

PP 97

OUTCOMES OF RADICAL TELERADIOTHERAPY IN THE PATIENTS WITH INVASIVE BLADDER CANCER

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From 1984 till 1994 47 patients with invasive bladder cancer were given radical irradiation in our department. Average age of patients was 60.7 years. There were 45 males and 2 females. Pretreatment staging was as follows: 29 patients-T2, 18 patients-T3. Fitness on Karnofskysscale was 70 or more. There were no distance metastases, no urinary stasis with proper kidneys function. Bladder capacity was at least 100 ml. Irradiation was performed with the cobalt unit or X9 MeV linear accelerator. Bladder and region of minor pelvis was irradiated with the radical intent by multifield technic methods to the total dose 60-66Gy. All of patients completed the therapy. Overall actuarial 5-years survival and true 4-years survival were analysed. Overall actuarial 5-years survival rate was 39%: 44% in T2 group and 34% in T3 group. True 3-years survival rate was 40% in the whole group. Irradiation was well tolerated. Results of treatment are comparable with the results described in the literature.

OP 98

PROGNOSTIC FACTORS FOR SURVIVAL IN ADVANCED AND METASTATIC UROTHELIAL CELL CARCINOMA (UCC) TREATED WITH CHEMOTHERAPY

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Only a few studies have been reported on prognostic factors in advanced or metastatic UCC. Studies in unselected patients are especially limited.
Seventy nine patients treated with chemotherapy for locally advanced (T4 tumor, regional lymph node metastases, or locoregional recurrence) or metastatic UCC were retrospectively studied to determine prognostic factors for survival. Univariate and multivariate analyses were performed on baseline patient variables, tumor characteristics and chemotherapy regimens.
Univariate analyses showed a significantly better survival for locally advanced than for metastatic UCC, and for treatment with MVAC vs other chemotherapy regimens. Metastases to lymph nodes, lung and bone did not influence survival, but metastases to liver, skin and other organs were found to be poor prognosticators. Using multivariate analyses 3 prognostic groups could be distinguished: I. locally advanced disease or MVAC-treated metastatic UCC without liver or skin metastases, median survival (MS) 15.9 mnths; II. non-MVAC-treated metastatic UCC without liver or skin metastases, MS 8.9 mnths; III. liver or skin metastases, MS 6.0 mnths.
A simple prognostic index for UCC may be used for stratification in randomized trials and may help in the clinical decision making proces whether to treat a patient with chemotherapy.

OP 99

BLADDER PRESERVATION BY BRACHYTHERAPY IN A SELECTED GROUP OF PATIENTS WITH TCC ≥ T1G3 BLADDER CANCER

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Introduction: Interstitial irradiation using Iridium-192 is a bladder sparing therapy for patients suffering from solitary bladder cancer ≥ T1G3.
Methods: In the period from 1985 to 1997 115 patients with solitary bladder carcinoma (14 patients T1G3, 100 patients ≥ T2, 1 patient T1G3N1) were treated with external radiation and implantation of Iridium 192. Depending on tumour size, stage and grade, two different irradiation schemes were applied, either external beam irradiation of 40 Gy, followed by 30 Gy interstitially or 10.5 Gy externally followed by 60 Gy interstitially. Histologically all patients, except 6 with adenocarcinoma, had transitional cell carcinoma. Mean size of the tumours was 2.5 cm. Partial cystectomy was performed in 24 patients. The mean follow-up was 48 months (ranging 1-144 months). Quality of life domaines (EORTC-QOL-C30, IPSS, sexual activity questionaire) were measured. In addition micturition was recorded in a volume/frequency diary.
Results: Local failure was observed in 15 patients (13%), and distant metastasis without bladder relapse in 13 patients. Globally the 5-years survival (according to the Kaplan-Meier method) was 65%. Almost all patients complained of transient urgency and bladder spasms. If the implantation was combined with PLND prolonged lymphleakage (3) and ileus (4) were seen. A late complication was small bladder capacity (≤ 100 cc) in 2 patients. Radiation cystitis with repeated gross haematuria was seen in 4 patients and successfully treated in the hyperbaric oxygen chamber. Self-assessment of QOL (ongoing) globally delivered a score of 60 - 100% (where 100% is the best achievable score).
Conclusion: For a highly selected group of patients with solitary bladder carcinoma ≥ T1G3 brachytherapy with Iridium 192 is a well tolerated bladder sparing treatment with a high percentage of local control and survival rates comparable to radical cystectomy.

OP 100

DETECTION OF (MICRO-) METASTASES OF HUMAN CANCER CELLS IN THE NUDE MOUSE MODEL: A GENERALLY APPLICABLE METHOD.

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The study of the metastatic process depends inevitably on an *in vivo* model system, including a reliable, preferably quantitative method to detect (micro-)metastatic foci. Micometastases are generally detected microscopically, which strongly depends on spatial distribution of the metastatic foci in the organ and number of examined sections. The present study describes a new, polymerase chain reaction (PCR)-based method to detect the presence and increase of human cells in nude mouse organs.

Human prostate cancer cell lines, LNCaP, DU145, PC-3 and PC-3N, and the mouse bladder cancer cell line MB-49 were grown under standard conditions. Metastatic spread towards local lymph nodes and lungs was obtained by orthotopic injection with 10^6 PC-3N cells. After 48 days, lungs were either microscopically evaluated (10 sections/lung) or analyzed by RT-PCR.

Specifically designed primers generated the (expected) 496-bp and 256-bp fragments of human β-actin mRNA (from prostate cancer cell lines) and mouse β-actin mRNA (from mouse MB-49 cell line), respectively. No human β-actin mRNA RT-PCR fragments were detectable in MB-49 cells, confirming the specificity of the human β-actin mRNA RT-PCR. Addition, at serial dilutions, of LNCaP, DU145, PC-3 and PC-3N cells to mouse lung tissue indicated a sensitivity of 100-150 cells per lung. Applying this method after orthotopic injection of PC-3N cells showed human β-actin mRNA (or human cells) in 6/7 lungs. In contrast, microscopic examination revealed only 2/7 lungs containing metastases.

In conclusion, a generally applicable, rapid, relative easy to perform, sensitive and microscopic examination-independent method was developed to detect human micrometastases in organs of the nude mice.

Gynaecological Cancer

PP 101

GESTATIONAL CHORIOCARCINOMA – Report of four cases and literature review.

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Gestational Choriocarcinoma (G.C) is the most malignant entity in the spectrum of Gestational Trophoblastic Diseases, with a high metastasizing potential.

It is very important to recognize this disease, because of its life-threatening potential and high curability.

Four cases of G.C. are presented. Clinical appearance, diagnosis, risk score (WHO), therapy and outcome are discussed. All patients were treated with chemotherapy, are alive and in complete remission at a median follow-up of 22 months (2-42).

G.C., is a very chemosensitive tumor, and must be treated with curative intent.

OP 102

ORAL ETOPOSIDE AND CONTINUOUS 5-FU INFUSION IN RECURRENT EPITHELIAL OVARAIN CANCER

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Therapeutic options in recurrent ovarian cancer (EOC) are relatively limited. We present the preliminary results of a pilot study using the combination of oral etoposide and continuous 5-FU infusion in patients with recurrent EOC.

Aim: To assess the efficacy and tolerability of oral etoposide 50mg bid for 7 days, 3weekly and continuous 5-FU infusion 200mg/m2/day via CADD pump in patients with recurrent EOC.

Methodology: N=10, WHO PS=<2. All had evaluable disease and/or raised CA125 with adequate haematologic hepatic and renal functions. Age range 50-68 yrs, Mean=56.2 yrs. A subclavian line was inserted for the infusion and 5-FU was given via the CADD pump. All patients completed a minimum of 6weeks of 5FU infusion and 2cycles of oral etoposide. Adverse events were recorded as per the common toxicity criteria. Imaging and CA125 were assessed at 8 weeks.

Results: All the 10 patients were evaluable for response and toxicity. There were 2 patients with radiological partial response and >50% in CA125 levels. Time to progression in these two patients was 10 and 34 weeks respectively. 4 patients had stable disease with two exhibiting >50% marker response. 4 patients needed dose reduction of 5FU by 25% because of >grade 2 haemtologic/oral toxicity. There were no treatment related deaths.

Conclusions: The combination of oral Etoposide and continuous 5-FU seems to have activity in recurrent EOC. However, the effect of addition of 5-FU to etoposide may be only subadditive. Interestingly, even in patients who achieved a minor response or stable disease, there was a clinical benefit response in the form of diminished requirements for paracentesis, improved bowel function, and better pain control.

OP 103

FAVORABLE OUTCOME OF OVARIAN GERM CELL MALIGNANCIES TREATED WITH CISPLATIN OR CARBOPLATIN -BASED CHEMOTHERAPY: A HELLENIC COOPERATIVE ONCOLOGY GROUP STUDY.

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Purpose: To evaluate the outcome and the prognosis of patients with ovarian germ cell malignancies who were treated with platinum-based chemotherapy immediately after initial surgery. **Methods:** We conducted a retrospective review of patients with ovarian germ cell tumors who were referred for consideration of treatment to the Departments of Medical Oncology participating in the Hellenic Cooperative Oncology Group. **Results:** Over a 14-year period 53 patients were included in our study. There were 13 patients with dysgerminoma, and 40 patients with nondysgerminomatous tumors. Forty percent of patients underwent complete resection of their tumors. Platinum -based chemotherapy consisted primarily of cisplatin, vinblastine and bleomycin (PVB) in 9 patients, bleomycin, etoposide and cisplatin (BEP) in 15 patients and bleomycin, etoposide and carboplatin (BEC) in 25 patients. With a median follow-up of 39 months, 5 patients developed progressive disease and died of their tumor and one patient died of bleomycin-induced lung toxicity with no evidence of active tumor. The 5-year overall survival was 100% for patients with dysgerminoma and 85% for patients with nondysgerminomatous tumors. Eighty-percent of patients with advanced nondysgerminomatous tumors and residual disease after surgery, remain disease-free.

Conclusion: With this study we confirm that patients with ovarian germ cell malignancies have a favorable outcome when treated with platinum-based chemotherapy. Substitution of carboplatin for cisplatin did not have an apparent negative effect on patient outcome.

PP 104

OVARIAN CANCER. INFLUENCE OF SURGERY AND ADJUVANT TREATMENT IN SURVIVAL. RETROSPECTIVE STUDY 1986-1996 IN OUR SERVICE.

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Ovarian cancer is the fourth most common cause of cancer death in women and the leading cause of gynecologic cancer death. Most of series revised have arround 40% of global survival. This survival rates can be modifided by the different prognostic factors (associated to the tumour or to the patient).

Our revision has been about our own experience between 1986-1996, with a total of 66 patients, the medium age was 55 years (29-81), the most histologic subtype the endometrioid (47%), and the histologic grade I (30%) was the most frequent. The distribution by FIGO stage: I 29%, II 26%, III 32%, IV 13%. The surgical treatment, and consequently the postsurgical stage: without residual disease 58%, with residual disease 42% (suboptimal disease 35%, and only biopsy 7%). The complementary treatment was indicated in 88%: QT 47%, RT 9%, QT + RT 32%. After an average following of 46 m. the most relevants results are: the 5-years global survival were 33%, in those patients with complete surgery 48% vs 13% in suboptimal surgery and biopsy, ($p<0.001$). In those patients with clinical complete response were 34% vs 0% if no response ($p<0.001$).

We can conclude that an optimal surgery in the ovarian cancer is the main aim; and eventhough it is clear that with residual disease we must used aggresive treatments (included surgical rescue), and so it is necessary to define those patients with radical surgery who will benefict from an adjuvant treatment and the best of those strategies.

OP 105

IMMUNOSCINTIGRAPHY BEFORE SECOND LOOK: AN ALTERNATIVE TO SURGERY IN OVARIAN CANCER PATIENTS ?

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The main non-invasive diagnostic tests available to detect the presence of recurrent ovarian carcinoma, including ultrasonography (US) and magnetic resonance (MR), have a low accuracy. The diagnosis of recurrent disease is often determined at surgical re-exploration (second look); however about 50% of patients undergoing this intervention are disease free, and 60% of patients with a negative second-look will relapse. Thus, it would be desiderable to have a non-invasive diagnostic procedure with a high accurancy. Immunoscintigraphy (ISG) with monoclonal antibodies against ovarian cancer has the potential to be a method to diagnose minimal residual disease. A high negative predictive value of ISG could result in avoiding unecessary surgery. To verify the reliability of this hypothesis we have evaluated with 3-step-ISG 31 patients affected by ovarian cancer scheduled for surgical intervention of second-look. At time of ISG, 29 patients had negative CT scans as well as tumor marker (CA 125); 2 patients had a doubtful CT scan and increased tumor markers. Of these 31 patients, 5 were negative (true negative) and 26 positive for the presence of disease at ISG. In 21/26 ISG was istologically confirmed. The diagnostic accurancy, the positive and the negative predictive value were 84%, 81% and 100%, respectively. These results show that 3-step-ISG can detect minimal residual disease, and above all in detecting peritoneal carcinosis, where CT scan is often inconclusive. If these data will be confirmed in a larger number of cases, the introduction of ISG in the follow up of patients with ovarian cancer could result in a different clinical management, where only patients with positive ISG will be scheduled for second look surgery.

OP 106

p53 AND WAF1 EXPRESSION IN EPITHELIAL OVARIAN CANCER: PROGNOSTIC AND PREDICTIVE IMPLICATIONS

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WAF1 is an inhibitor of cell cycle progression and of DNA replication whose expression is regulated by the p53 tumor suppressor gene. Tumor tissues from 148 consecutive patients with primary epithelial ovarian carcinoma were assayed both for WAF1 protein using colorimetric immunoassay and for p53 protein using an immunofluorimetric assay developed by the authors. Detailed clinicopathologic information, as well as patient response to treatment, were collected and related to p53 and WAF1 concentrations in the tumor extracts. Elevated p53 concentrations were associated with advanced stage ($p=0.002$) and high grade disease ($p=0.05$), the presence of residual tumor ($p=0.005$) in suboptimally debulked patients ($p=0.008$), and elevated post-operative CA-125 values ($p=0.004$). p53-positivity was also more common in patients who did not respond completely to chemotherapy ($p=0.05$) and whose tumors had lower WAF1 levels ($p=0.06$). Trends suggested that WAF1 positivity was associated with endometrioid histotype, optimal debulking surgery, small residual tumor and high CA-125 pre-operative values. While p53 positivity was a significant indicator of increased risk for patient death ($p<0.001$), WAF1 positivity indicated a trend for decreased risk for relapse. p53-positivity indicated poorer prognosis in patients given chemotherapy ($p=0.01$) and was suggestive of increased risk of treatment failure ($p=0.01$) while WAF1 expression was not associated with treatment outcome. These results strongly suggest the prognostic and predictive value of p53 protein accumulation in ovarian cancer while the functional status of the WAF1 protein accumulation needs further investigation.

PP 107

CERVIX CARCINOMA, TREATMENT AND RESULTS

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For intracavitary brachytherapy of cervical cancer the Agat-B HDR (with a ^{60}Co), Selectron-LDR/MDR (with a ^{137}Cs source) were used. This study was performed in 304 patients with stage I, II, III cervical cancer, treated with a combination external beam radiotherapy and brachytherapy during 1982-1996. The regime prescribed to point A was as follows: brachytherapy with HDR of 20-30 Gy/h was given as 10 Gy per frasction, once a week, total dose (TD) 40 Gy; with LDR/MDR of 2.0-2.5 Gy/h was given as 10-12 Gy, once a week, TD 40-50 Gy. The external gamma-therapy or photon therapy (15 MeV) to the whole pelvis was identical in the two groups, TD 20-30 Gy. The external gamma-therapy parametral cellular tissue and pelvic lymph nodes was performed on days free from intracavitary radiotherapy, upto a point B TD 26-30 Gy. The 5- and 10-year survival results are the following: HDR - stage 1: 85.1% and 56.9% and 85,7% and 85,4% in group LDR/MDR ($p>0.05$). Evaluation of follow-up results in stage II patients discovered somewhat better 5- and 10-year survival rates in group HDR (67.5% and 65%) as compared to group LDR/MDR (61% and 46.5%) ($p<0.05$). Among stage III patients the best results were achieved in group LDR/MDR: 57.7% survived 5 years and 51.3% survived 10 years free from disease: against 42.6% and 42%, respectively, ($p<0.05$) in group HDR.

OP 108

PILOT STUDY OF OVARIAN CANCER SYSTEMIC CHEMOTHERAPY WITH CYCLOPHOSPHAMIDE, EPIRUBICIN, CARBOPLATIN WITH CONCOMITANT INTRAPERITONEAL CARBOPLATIN

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For thirty years now the epidemiologists have been observing permanent increase of morbidity and mortality due to ovarian cancer in women of the Polish society. Ovarian cancer is treated with debulking surgery followed by chemotherapy. Among all used protocols against ovarian cancer the best results have been observed with regiment: cyclophosphamide (CTX), epirubicin (FRBC), carboplatin (CBDCA). Therefore, we enrolled 17 women (aged 42-77) with ovarian cancer (range of FIGO staging I-IV), clinical status of 70-90% Karnofsky's score. All patients were investigated between February 1995 and January 1997. They received a modified regiment consisting of: CTX-600 mg/m^2 i.v., FRBC-50 mg/m^2 i.v., CBDCA (Carboplatin-Ebewe) - 400 mg/m^2 i.v. plus intraperitoneal CBDCA (Carboplatin-Ebewe) - 200 mg. All patients were operated because of ovarian tumours and the operation was menat to reach the surgical cytoreductive effect or complete resection (10 and 7 respectively). After the surgery all patients received 152 cycles of chemotheraphy according to the above mentioned regimen. Prior to admission to Gynecology Unit all investigated women have been assessed with imaging techniques such as: (sonography, abdominal & pelvical axial CT, chest X-ray), hematological & biochemical parameters and levels of serum marker-Ca-125. Toxicity was assessed using the WHO score schedule. Moreover, laparoscopic assessment of peritoneal cavity was done when 3 and 6 chemotherapy cycles were completed. In the group of 17 patients we observed: 59% (10) CR including 47% (8) histopathological responses, 29% (5) PR and 12% (2) PD. Overall response rate of 88% (15 females) was observed in seven patients with dimension of residual disease < 2 cm (seven CR) and eight with dimension of residual disease larger than 2 cm (three CR and five PR). Progressive disease was noticed in 2 women after debulking surgery without optimal cytoreduction with residual tumour size larger than 2 cm. We collected all data after completion of six and eight cycles of adjuvant systemic and intraperitoneal chth in 71% (12) and 29% (5) patients, respectively. Among the total number of 152 chemoterapeutic cycles in 8 cases the time intervals between cycles have been prolonged due to myelosuppression. Ten cycles have required giving GM-CSF or G-CSF. Hepatotoxicity (3rd WHO degree) was observed in one patient. Two patients had to stop chemotherapy because severe toxicitics. Early results indicate an important role of systemic and intraperitoneal chemotherapy in patients with ovarian cancer after debulking surgery.

Key words: Ovarian cancer, chemotherapy with concomitant intraperitoneal carboplatin, results, toxicity.

OP 109

COMPLICATIONS AFTER CONCOMITANT RADIOTHERAPY FOR FEMALE GENITAL CANCER

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Severe damages of adjacent organs and tissue occur in some cases following concomitant radiotherapy for female genital cancers. The patients with late postradiation complications, including rectovaginal fistulas - 24 cases, vesicovaginal fistulas - 14 cases, mucometra - 25 cases, have been treated at the Donetsk Regional Centre for Cancer. Treatment options are related to early detection of complications. However, cure and improved survival result only from surgery in patients with late destructive complications.

PP 110

CASE REPORT: INTRAPERICARDIAL PACLITAXEL INSTILLATION IN METASTATIC PERICARDIAL EFFUSION BY OVARIAN CARCINOMA

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Paclitaxel (P) is widely used for ovarian carcinoma treatment. Pharmacodynamic characteristics make P suitable for intracavitary use: in the serosal cavities it has a high serosal fluid / plasma concentration ratio and a long half-life. It does not act as a sclerosing agent. P is used by the intraperitoneal route. We used it by intrapericardial instillation to treat a pericardial effusion due to metastatic ovarian cancer.
CASE REPORT. O.L. (66 years old). 1994 october: diagnosis of ovarian carcinoma stage IIIc; surgical treatment and adjuvant chemotherapy with Cisplatin iv. 1997 june: diagnosis of cardiac tamponade. A 750 ml pericardiocentesis of bloody effusion was performed. Cytology was positive for CA125+ neoplastic cells. After 5 days of continuous drainage (daily amounts of fluid between 100 and 250 ml), 30 mg of P were instilled and the catheter was removed. An echocardiogram was performed daily for two weeks and then monthly. Performance status improved from ECOG 4 to 1. After one month from P instillation systemic therapy with P and Cyclophosphamide was begun. To date (27/11/1997) no relapse was seen.
Previous studies demonstrated that direct cytotoxic effect plays a minimal role in the activity of drugs used for serosal treatment of neoplastic effusions. Their sclerosing action inhibits effusion recurrences. The need of a strict and longlasting contact between the two serosal surfaces makes the treatment of loculated and quickly forming effusions difficult. Our report suggests that drugs with very high intracavitary concentration may have a direct cytotoxic activity and may be useful in such cases, even if they do not act as sclerosing agents.

OP 111

GUIDLINE FOR TREATMENT OF ADVANCED OVARIAN CANCER

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The patients with ovarian cancer confined to the pelvis - stage I - have a good chance for surgical cure of their disease. But the majority of patients have advanced disease at initial diagnosis. These patients start their treatment with cytoreductive surgery followed by systemic cytotoxic therapy. The prognosis of these patients remains poor, since disease will recure in the majority of these cases.
The most significant prognostic factor for patients is the duration of response to initial therapy. Patients, who relapsed within 6 months after initial chemotherapy have in majority of cases chemotherapy resistant tumor.

Many chemotherapeutic agents have demonstrated activity in the treatment of ovarial cancer. Secondary cytoreductive surgery may be indicated in pacients with focal recurrence after long term disease free survival. The best response rate have alkylating agents combined with platinium . Such combinations produced complete responce rates of 30% to 40%, overal response 60% to 70%, median progression free survivel duration from 13 to 15 months and 10 years disease free survival rates of 10% to 15%. Taxol in combination with platinium based drugs is currently considered standard initial treatment following cytoreductive surgery for patients with stage III and IV ovarial cancer.
Carboplatin had in combination with Taxol shown equivalent efficacy with a lower incidence and severity of nonhematologic toxicities / neurotoxicity, renal function, ototoxicity and emetogenicity / compared with cisplatin. The combination taxol /carboplatin is being evaluated in randomized trials that are currently in progress compering carboplatin / Taxol and cisplatin/ Taxol in previously untreated advanced ovarian cancer.

PP 112

CAN FLUDARABINE ERADICATE MALIGNANT CLONE IN LLC ? A CASE REPORT

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Introduction: The CLL standard therapy gives a complete remission (RC) in low rate percentage. The new therapy with the purine antimetabolite cytarabine (Fludarabine) leads overall (complete plus partial) response rates of 40 to 80%. However the criteria for complete response are largely clinical rather than biological: peripheral lymphocytes count < 4000/mmc, bone marrow relative lymphocytes count < 30%, impalpable liver and spleen, no pathologic nodes, normalisation of cytopenias.

We report here a case of a CLL characterised by the desappearance of a monoclonal B-cell population after fludarabine treatment.

Case report: S.A., a 70 yrs old female, affected (1988) by CLL, RAI stage 1, was treated with Chlorambucil 0.5 mg/Kg in bolus every 15 days, for a total of 37 courses. In September 1995 our patient had a relapse characterised by the increase of nodes, liver and spleen, the expansion of clonal CLL-B lymphocytes (WBC = 13.730, L = 70%; CD5 = 27%; HLA-DR = 84%; CD20 = 73%; SmIg-k = 66%) and the appearance of sieric paraprotein IgM-k (1643 mg/dl). A Fludarabine treatment (30 mg/mq/day for 5 days each month, for a total of 5 cycles) was started. At the end of the therapy, a complete response was achieved with the disappearance of paraprotein (IgM = 297 mg/dl) and LLC clones (CD5 = 64%, HLA-DR = 54%, CD20 = 2, SmIgk = 11%)

Conclusion: Current criteria of CR linphoproliferative disorders evaluation referring to clinical parameter don't seem to be very reliable: the certainty of the cure is given out by the documented disappearence of the marker's monoclonality and, if possible, of the structural genic abnormalities (oncogenes).

In our patient the disappearence of both the limphoid surface SmIg-k restriction and of the sieric IgM-k paraprotein suggests complete eradication of malignant clones after Fludarabine treatment.

PP 113

TREATMENT OF AGGRESSIVE NHL IN ELDERLY

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We investigated the course of patients (pts) older than 60 with aggressive NHL unable to tolerate conventional aggressive anthracycline based chemotherapy. We identified 12 pts with centrocytic/centroblastic (CC/CB),centroblastic (CB),and peripheral T (T) NHL,and 3 with large cell lymphoma (LCL); and compared them to 25 pts with CC/CB,CB, and T NHL, and 24 with LCL from the same age group who received anthracycline based chemotherapy.There were not enough pts with LCL to enable intergroup comparisons but LCL pts fared worse than non-LCL.In the non-LCL group there were more CRs with more intensive treatment (16/25,vs.4/12),but survival was similar (median 30 mo,vs.27 mo).We conclude that less intensive chemotherapy, like COP, is a feasible option in pts. with intermediate grade NHL.

OP 114

PATIENT-SPECIFIC MOLECULAR ANALYSIS IN EXTRANODAL MARGINAL ZONE LYMPHOMA (MZL)

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Regression of low-grade gastric MZL (MALT lymphoma) has been demonstrated after *H. pylori* eradication in a large proportion of cases. PCR monoclonality in gastric biopsies has been proposed as a procedure in the evaluation of response after antibiotic treatment. However, the common presence of a poly- or oligoclonal background usually limits the sensitivity of this PCR assay, in addition, false-negative and false-positive results can affect the analysis. To overcome these problems, we implemented a more sensitive and more specific PCR approach using allele-specific-oligonucleotides (ASO) designed from the CDR3 sequence of the individual MZL immunoglobulin heavy chain (Ig) genes, to allow patient-specific monitoring. The CDR3s were amplified using semi-nested PCR with consensus primers from DNA extracted from paraffin-embedded sections. Eighteen gastric low- and 5 high-grade MZL clones have been already sequenced. Ten low-grade (56%; 95%CI:31-78%) clones showed a D-D recombination pattern suggesting that MZL has undergone antigen selection. Twelve CDR3 sequences matched previously reported Ig sequences, including several autoantibodies. In 4 (33%, 95%CI:10-65%) of these, autoantibodies were the closest matches. CDR3 sequences were used to design ASOs, which specifically amplified only the clone from the corresponding MZL sample. ASO-PCR analysis of post-treatment biopsies allowed molecular monitoring of antibiotic-treated patients showing that the lymphoma clone can persist for several months after histologic regression. In fact, the MZL clone was often detected in histologically normal samples, sometimes showing no monoclonal band with consensus primers PCR. Moreover, ASO-PCR allowed detection of the lymphoma clone in gastric biopsies performed several years prior to the MZL diagnosis and histologically compatible with chronic gastritis, thus confirming that the gastric MZLs originate from this chronic inflammation background.

PP 115

TREATMENT OF HISTOLOGICALLY AGGRESSIVE NON-HODGKIN'S LIMPHOMA: PILOT STUDY.

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Background: The treatment of histologically aggressive non-Hodgkin's lymphoma (NHL) is still a great challenge for oncologists. We are conducted a pilot study to evaluate the treatment outcome when increasing the dose intensity of the standart dose CHOP by shortening the interval between each treatment cycle to 2 weeks.

Patient and methods: Nineteen cases of biopsy proven histologically aggressive NHL were selected to enter the study. All of them received 4 cycles of CHOP every two weeks with granulocyte colony-stimulating factor support (G-CSF). Another 4 cycles of the standart CHOP were administrated thereafter.

Results: All patients were assessable for response. There was a 73,7% complete response (CR); a 21% partial response (PR) and only one case of failed therapy(FT). The main cause of toxicity was haematologial. No treatment-related deaths were observed.

Conclusion: Increasing the dose intensity of the standart CHOP in the treatment of histologically aggressive NHL might be more efficient than the standart CHOP therapy. The G-CSF support allows acceptable haematological toxicity levels during the treatment.

PP 116

PRIMARY EXTRANODAL NON HODGKIN'S LYMPHOMA OF THE HEAD AND NECK IN ADULTS:A CLINICOPATHOLOGICAL COMPARISON BETWEEN TONSILAR AND NON TONSILLAR LYMPHOMAS

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Primary extranodal NHL of the head and neck (HN-NHL) accounts for 10-20% of all cases of NHL. Despite their frequency, natural history and biological behavior of these lymphomas are poorly understood. In this study we analysed the data of 118 cases of HN-NHL. There was 65 males and 51 females with a median age of 58 years. The distribution among different anatomical sites was: tonsils 58 cases (48.3%), nasopharynx 15 (12.9%), mandible/gingiva 9 (7.8%), hard palate 7 (6%), parotis 6 (5.2%), nasal cavity 6 (5.2 %), hypopharynx/larynx 6 (5.2%), thyroid 5 (4.3%0, ocular adnexa 4 (3.5%), paranasal sinuses 2 (1.7 %). The patients were treated with radiotherapy alone (14 cases), combined chemotherapy (52 cases) and combined modality (50 cases). According to the WF histological classification 73 cases (62.9%) had intermediate, 32 (27.6%) high and 11 (90.5%) low grade.

Patients were separated in two groups: Tonsillar NHL (58 cases) and NHL of all other sites (non-tonsillar group - 60 cases).

A comparison between the two groups showed that there was no statistically significant difference with respect to age, sex, and histological subtypes. Also treatment response was similar (82.1% for the tonsillar vs 83.3% for the non-tonsillar).

The two groups differed in stage distribution, survival and pattern of relapse. Stage I was more frequent in the non-tonsillar NHL (60%) in contrast to tonsillar where stage II was more prominent (51.8%). Median survival was 88 months for the tonsillar while it has not been reached yet for the non-tonsillar. Patients in stage I and II of the non-tonsillar group had better survival compared to stages I and II of the tonsillar patients. Finally, GI tract was a common site of relapse were observed in the non-tonsillar group while a considerable number in CNS relapses were observed in the non-tonsillar group.

We concluded that HN-NHL constitute a heterogeneous group of patients. Tonsillar lymphomas represent a distinct group with some special clinicopathological findings.

PP 118

FULMINANT CARDIAC TAMPONADE IN CHRONIC LYMPHOCYTIC LEUKAEMIA: AN UNUSUAL COMPLICATION

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We report of a patient with chronic lymphocytic leukaemia (CLL), stage Rai 0 at the initial diagnosis, who died unexpectedly of acute cardiac failure. He had undergone oral anticoagulation because of venous thrombosis. At autopsy, cardiac tamponade due to massive leukaemic infiltrates in the epi- and pericardium were found.
This rare outcome of CLL is discussed regarding a literature review.

PP 120

EARLY ASSESSMENT OF RESPONSE TO CHEMOTHERAPY BY FDG-PET IS HIGHLY PREDICTIVE OF OUTCOME IN PATIENTS WITH HIGH-GRADE NON-HODGKIN'S LYMPHOMA (NHL)

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High-grade NHL are curable by intensive chemotherapy, but many patients either fail to enter complete remission (CR) or relapse after CR. Early assessment of therapeutic efficacy may be important to identify poor responders and offer them other potentially effective treatment modalities and may have prognostic value for patients eventually entering CR. Tumor volume reduction based on radiological criteria is only a late sign of effective therapy. On the other hand, positron emission tomography using ^{18}FDG fluorodeoxyglucose (FDG-PET) can provide information about metabolic changes within days after the start of chemotherapy. Therefore, we evaluated response by FDG-Pet after 2-3 cycles of polychemotherapy in 20 patients with NHL. The absence or presence of abnormal FDG uptake was correlated to clinical outcome. Seven of the 20 patients still presented increased FDG uptake in one or more sites previously shown to be involved by lymphoma at diagnosis. Four of them did not enter CR after completion of chemotherapy and re-progressed 4, 4, 5 and 15 months after diagnosis, respectively. Two CR patients relapsed at 12 and 20 months after diagnosis and only 1/7 remains in CR at 30 months. FDG-PET was negative in 13 patients and all of them achieved CR. Eleven remain in CR after intervals ranging from 8 to 36 months from diagnosis. Two relapsed at 6 and 14 months and died of lymphoma. The probability of achieving CR (33% vs 100%, p=0.0009) was significantly lower in patients with positive FDG-PET. Overall survival (29 ± 17% vs 75 ± 15% at 3 yrs, p=0,0086) and progression-free survival (14% ± 13% vs 82 ± 12% at 3 yrs, p=0.0039) were also different between the two groups of patients. We conclude that FDG-PET after 2-3 cycles of polychemotherapy for high-grade NHL is highly predictive of outcome, including the probability of achieving CR, progression-free survival and overall survival.

OP 117

IN-FIELD RELAPSE IN MANTLE IRRADIATED PATIENTS WITH HODGKIN'S DISEASE

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Introduction: The purpose of this retrospective analysis was to find out the supradiaphragmatic nodal sites with the most frequent occurence of relapses of the Hodgkin's disease after mantle field irradiation.

Patients & methods: From 1975 to 1992 170 patients with Hodgkin's disease were irradiated using mantle technique with or without irradiation of the infradiaphragmatic nodal sites with or without prior chemotherapy. Patients who had relapsed were divided into three groups dependent on the site of relapse (in-field, off-field, both). Analysis of failures was performed to identify the most frequent sites of relapse above the diaphragm.

Results: Of 170 patients 44 (25,8%) have relapsed. There were 18 (10,5%) in-field relapses, 17 (10%) off-field and 9 (5,25%) both sites relapses. The median time to relapse was 23 months. Of the supradiaphragmatic nodal sites the most frequent site of relapse was the left hilar region followed by right axilla and right hilus.

Conclusion: In accordance with previous studies in our study as the critical site of relapse was identified the lower mediastinum, especially the left hilus, where a significant share of tumors may be shaded by lung blocks in effort to spare as much lung and heart tissue as possible.

PP 119

TOXICITY OF HIGH-DOSE METHOTREXATE (HD-MTX) ADMINISTRED WITHOUT DETERMINATION OF SERUM LEVEL IN CHILDREN WITH ALL AND NHL

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Since introducing HD-MTX the determination of serum levels of the drug in regular intervals has been the pre-requisite for calculating adequate timing and dosage of folinic acid (FA) rescue. Being unable to assess MTX serum level routinely we have undertaken special precautions to diminish potential toxic effects. The major therapeutic strategy was longer duration of forced alcaline diuresis and not increasing FA. The study included 5 children treated for ALL relapse (23 doses of MTX 1g/m2) and 7 children treated for B NHL (23 doses of MTX 1-2g/m2) according to BFM protocols. MTX toxicities were accessed using WHO criteria. We observed mucosal toxicity grade 3-4 in 1 episode in ALL children and 45% episodes in children with NHL. Gastrointestinal toxicity grade 3-4 was observed only in 4 episodes in children with NHL. Transiently elevated transaminases grade 3-4 were seen in 4 episodes in children with ALL, who were all HbS positive and 5 episodes in children with NHL. One child with NHL died 10 days after HD-MTX administration on CNS bleeding. Observed toxicities are in agreement with studies of HD-MTX side effects. We conclude that MTX up to 2g/m2 can be used in children without determination of serum level, if otherwise impossible, providing that renal function is carefully monitored.

OP 121

WHOLE-BODY FDG-PET FOR POST TREATMENT EVALUATION IN HODGKIN'S DISEASE (HD) AND NON-HODGKIN'S LYMPHOMA (NHL) HAS HIGHER DIAGNOSTIC AND PROGNOSTIC VALUE THAN CLASSICAL CT SCAN IMAGING

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Differentiation of tumor from fibrosis within residual radiographic masses represents a problem when assessing response to chemotherapy after treatment of HD and NHL. Metabolic imaging with PET using ^{18}fluorodeoxyglucose (FDG-PET) offers the advantage of functional tissue characterization that is largely independent of morphologic criteria and specifically depicts foci of increased glucose metabolism. Twenty-seven patients (11 HD, 16 NHL) underwent CT scan imaging and whole-body FDG-PET at the end of their chemotherapy program to assess response and identify possible residual disease. Residual masses were found in 13 patients with routine methods (8/11 HD vs 5/16 NHL, p=0.0341) and FDG-PET was positive in 6 patients (2/11 HD vs 4/16 NHL, NS). All 6 patients with positive FDG-PET vs 7/21 with negative FDG-PET had residual masses by classical imaging (p=0.0039). Among those with residual masses, FDG-PET was positive in 2/8 HD vs 4/5 NHL patients (p=0.0530). While only 1/7 patients with residual masses but negative FDG-PET relapsed, all patients with FDG uptake in residual masses progressed (p=0.0020): the persistance of tumor was demonstrated by biopsy in 1 case of HD and the other patients relapsed after1, 1, 1, 2 and 2 months. Progression-free survival (PFS) was thus significantly different among the 2 groups (p=0.0004). Among the 6 patients with HD and residual masses but negative FDG-PET, 5 remain in clinical CR (median follow up: 7 months) and 1 relapsed 8 months later. The patients with NHL and residual masses but negative FDG-PET is still in CR after 25 months. Among the 14 patients with no residual masses and negative FDG-PET, 3 patients with NHL relapsed at 7, 8 and 13 months, respectively. Overall, positivity of FDG-PET was associated with poorer PFS (6/6 relapses) compared with negative FDG-PET (4/21 relapses) (p<0.0001). On the other hand, the presence of residual masses was less consistantly associated with lower PFS (6/13 relapses) compared with no residual mass (3/14 relapses) (p=0.0203). In conclusion, the detection of vital tumor by FDG-PET after the end of treatment for HD or NHL has a higher predictive value for outcome than classical CT scan imaging. FDG-PET was mainly useful for the evaluation of residual masses, whereas there was no case of positive FDG-PET with no residual masses. However, a negative FDG-PET cannot exclude the presence of minimal residual disease possibly leading to a later relapse.

OP 122

SEPTIC INFECTION DELAYS STEM CELL MOBILIZATION IN PATIENTS WITH LYMPHOMA

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Autologous blood cell transplantation (ABCT) is commonly used treatment modality in lymphomas. ABCT and high-dose therapy improves survival in relapsed non-Hodgkin lymphomas. Successful CD34+ cell mobilization is a prerequisite to ABCT. The aim of this study was to see, if septic infection influences stem cell mobilization. Thirty-three lymphoma patients underwent successful peripheral blood stem cell (PBSC) collection following mobilization with chemotherapy (cyclophosphamide 4g/m^2) and granulocyte colony-stimulating factor. Sixteen patients caught neutropenic septic infection. The target of collecting CD34+ cells > 4,0 x 10^6/kg was achieved in 23 pts, whereas 4 pts had poor harvests < 2,0 x 10^6/kg. Onset of leukapheresis was determined by blood CD34+ cell count. In the septic and non-septic patients, medians for the maximum blood CD34+ counts (10^6/l) were 61,7 (quartiles 25 to 176) and 182 (57 to 219), the day of onset of leukapheresis 12 (quartiles 11 to 14) and 10 (quartiles 10 to 11), the yield of CD34+ cells in harvests (10^6/kg) 5,85 (2,3 to 10,65) and 8,1 (3,8 to 15,5), respectively. Sepsis delayed the start of leukapheresis by two days (p=0,004); however, sepsis did not seem to prevent stem cell mobilization (p=0,4). There was a subgroup of patients with septic infection, in whome leukapheresis was significantly delayed.

OP 123

LOCOREGIONAL TREATMENT OF HUMAN LOW-MALIGNAT B-CELL NON-HODGKIN'S LYMPHOMA WITH CD3xCD19 BISPECIFIC ANTIBODIES AND CD28 MONOSPECIFIC ANTIBODIES

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Bispecific antibodies are considered to be of clinical value in the immunotherapy of malignant diseases and are currently being tested in clinical studies. In this study, ten patients with end-stage low-malignant Non-Hodgkin's lymphoma (B-cell type, CD19-positive) were treated locoregionally with CD3xCD19 bispecific antibodies and CD28 monospecific antibodies for the activation of T cells at the tumour site. Costimulation via the CD28/B7-pathway by CD28-antibodies was included into the treatment schedule to generate prolonged T cell activation for the induction of anti-tumoral immunity.

Peripheral lymphomas were either injected with therapeutic antibodies directly, or treated by intralymphatic injection into an afferent lymph vessel at different dose levels (30µg to 1600µg each antibody). Patients were monitored for toxic effects, clinical and immunologic parameters. On day five a treated and a contralateral lymphnode were excised for comparative studies.

Two out of ten patients (dose level 810µg) developed therapy-related WHO-toxicities (I°/II°). Three patients showed minor clinical responses although no remission of the disease could be induced. In peripheral blood and antibody treated lymphnodes increases of T-lumphocyte activation markers could be demonstrated. Cytotoxicity assays revealed enhanced NK-cell activity.

These preliminary clinical findings suggest a potential role of CD3xCD19 bispecific antibodies and CD28 costimulation as a treatment modality for low-grade B-cell Non-Hodgkin's lymphoma.

PP 124

THERAPEUTIC CHALLENGE OF MANTLE CELL LYMPHOMA

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The REAL classification clearly outlined and defined "Mantle Cell" Non-Hodgkin's Lymphoma (MCL) as an independent and clinically important unit. The disease represents some 4-9% of all non-Hodgkin's lymphomas. It predominantly affects males and its incidence rises with age. "Mantle cell" morphology is variable, but its phenotype is characteristic, i.e. cells express sIgM, CD 19, CD 20, CD 79a, CD 5, but do not express CD 23 antigen. The typical cytogenetic abnormality is t(11;14)(q13;q32) involving bcl-1 locus on the long arm of chromosome 11.

We describe a group of 23 patients (11 females, 12 males) with the median age of 63 years (39 - 87 years). Bone marrow involvement was documented in 91% of patients, one third of them had the blastic variant of the disease. The elevation of serum LDH, ß$_2$mikroglobulin or thymidinkinase levels was found in 83%, 78% or 78% of cases respectively. Most patient were classified as high-intermediate- or high-risk according to the International Prognostic Index (IPI) value, median being 4 (1-5) points. Twelve patients had IPI value higher or to equal 4 points.

Twenty-two patients were treated with combined chemotherapy, i.e. COP (4 patients), CHOP (11 patients) or ProMACE-CytaBOM (7 patients). 1 CR and 7 PR's were achieved. No response to COP was observed. Two PR's were achieved by CHOP. The effect of ProMACE-CytaBOM was PR in 5 patients and CR in 1 patient. Median survival from diagnosis of 13 still living patients is 12 months (2-31), median survival of 10 deceased patients was 15 months. High dose chemotherapy (BEAM) followed by autologous peripheral blood stem cells (PBSC) support was given to 2 female patients (age 43 years, one in CR and the other in very good PR). Both of them achieved sustained CR (duration d.+150. or +250.).

Our experience document the extremely unfavorable prognosis of MCL and the need for aggressive first-line treatment with a perspective of high dose chemotherapy with PBSC support in younger patients.

OP 125

IL-6 IN NON-HODGKIN'S LYMPHOMA (NHL) PATIENTS

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51 NHL patients were observed, IL-6 was revealed in 24 patients' blood sera. IL-6 was revealed more often in patients with NHL of high grade malignancy ($p < 0.05$), then in patients with low grade malignancy. The most numerous group of IL-6 positive patients included NHL patients with lymphomas from lymph node germinal centers (65%, vs. 35%). The IL-6 serum level was significantly lower in untreated patients with II and III stages of disease, than in patients with IV stage of NHL. IL-6 significantly decreased in remission as compared with its level before the beginning of treatment. Analyzing the dependence of prognosis of disease upon the IL-6 serum level it was shown, that in group of patients with good (index SNLG < 2) and intermediate (index SNLG > 2 – < by 2,6) prognosis the concentration of this cytokine was significantly lower, than in patients with the poor prognosis (index SNLG > 2,6). Hence, IL-6 is a good prognostic marker in NHL and is relates with the activity of malignant process. Additionally it was revealed, that the increased IL-6 serum level positively correlated with NK-activity and LPS-stimulated production of TNF by mononuclear of peripheral blood (MPB) and negatively correlated with the number of activated lymphocytes (CD25+, CD71+) and LPS-stimulated production of IL-1 by MPB.

PP 126

RESULTS OF THE TREATMENT IN ELDERLY HODGKIN'S DISEASE (HD) PATIENTS - SINGLE INSTITUTE EXPERIENCE

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Since 1980 to 1993 70 HD patients older than 60 years (group 1) and 130 patients 40-59 years (group 2) received various treatment programs. Unfavourable prognostic factors were similar in both groups. Local stages HD (26 patients in group 1 and 62 patients in group 2) were treated with combined modality therapy: 3CVPP + IF in dose 40 Gy + 3CVPP. In advanced stages (52 patients in group 1 and 41 patients in group 2) used only chemotherapy - 8 CVPP.

Results:	group 1	group 2
CR	72%	77%
RFS	38%	53%
OS	64%	96%

Thirty one (44%) of elderly patients had concurrent pathology. Myelotoxic complications were in 40% patients (group 1) and 21% patients (group 2). High number concurrent diseases and seriouse complications may explained the unfavourable long-term prognosis HD in the elderly.

PP 127

AML IN ELDERLY PATIENTS - A RETROSPECTIVE ANALYSIS

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We report the results of a retrospective 3 years analysis regarding the hematological profile, the response to treatment and survival in an over 60 years aged group (n=61) diagnosed with AML. The sex ratio was 1.25 and the mean age 72.2 years. Five patients were aged over 80. According to the FAB classification, we found 10 LAM0, 9 LAM1, 12 LAM2, 0 LAM3, 11 LAM4, 7 LAM5, 2 LAM6, 1 LAM7. Five cases were unclassificable on morphologic criteria and 4 cases had a "mixed lineage" acute leukemia. Patients presented features mainly related to pancytopenia, but there were, also cardiovascular problems (n=27), hepatosplenomegaly (n=20), adenopathies (n=5), skin lesions (n=5). Peripheral blood studies showed anemia (n=39), trombocytopenia (n=30), pancytopenia (n=31). Among the treatment strategies, we used Ara-C +/– an antracycline in standard doses, Ara-C in medium dose, (up 500 mg) or low dose Ara-C 10 mg/m^2/day. No treatment proved to be superior. The mortality rate during the first 8 weeks of treatment was 47.54%, with a 6 months survival of only 40.98%. The high mortality rate was mainly due to resistant relapsed leukemia, infection, and cardiovascular events age-dependent. We actually concluded that in our group of aged patients, the AML had a bad prognosis, according to the biological profile, the poor response to chemotherapy and the aged-related mortality.

PP 128

RANDOMIZED, OPEN LABEL, MULTICENTRE TRIAL ON THE LOCAL TOLERABILITY OF A READY-TO-USE FORMULATION OF IDARUBICIN FOR I.V. INJECTION.

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INTRODUCTION : Idarubicin hydrochloride (Ida) for injection (Zavedos®, Idamycin®) is approved in many countries for the first-line treatment of acute myeloid leukaemia (AML) and as a second-line treatment in adult and pediatric patients with acute lymphocytic leukaemia (ALL). This Phase I trial was conducted in Italy with the primary objective to compare the tolerability at the injection site of a new ready-to-use (RTU) formulation with that of the marketed freeze-dried formulation. Given the presence of glycerol in the RTU formulation serum osmolality was monitored for changes occurring after administration of the assigned Ida formulation.

METHODS : A total of 94 patients requiring Ida-based chemotherapy (ALL, AML, APL, Lymphomas or Myeloma) were randomized to receive either Ida RTU (49) or freeze-dried (45) formulation. The assigned Ida formulation was administered during one treatment course according to the clinical plan of the patient. Both Ida formulations had to be injected in a peripheral vein over a period of 15 minutes.

RESULTS : At comparable dose and duration of infusion, no local toxicity was observed in the 93 evaluable patients. The upper limit of 95% confidence interval of the proportion of patients with local events in the two treatment arms was found to be equal to 5.8% and 6.4% in the Ida RTU and freeze-dried arm, respectively. Therefore, we can assume with a confidence level of 95% that local reactions are expected at most in 6% of patients treated with either of the two formulations. As regards serum osmolality, this resulted comparable in both study arms and not significantly affected by treatment. Thus the presence of glycerol in the RTU formulation does not appear to exert any effect on this parameter.

CONCLUSIONS : In this patients population, the administration of Ida RTU formulation appears to have good local tolerability with no additional effects on serum parameters, such as osmolality, when compared to the marketed freeze-dried formulation.

Lung (NSCLC, SCLC) and Head and Neck Cancer

Lung Cancer

OP 129

PLASMA TGF-β IN STAGE III NSCLC PATIENTS PRIOR TO AND DURING RADIOTHERAPY WITH OR WITHOUT CARBOPLATIN.

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Transforming growth factor-β (TGF-β) has been indicated as a predictor for the risk of radiation-induced pneumonitis. We measured plasma TGF-β levels weekly in 48 patients (pts) with stage IIIa/b non-small cell lung cancer (NSCLC) prior to and during radiotherapy (60 Gy, 2Gy/day) with or without concurrent carboplatin (20 mg/m²/day) as radiosentisizer. A bioassay using mink lung epithelial cells transfected with a plasminogen activator inhibitor-1 promoter-luciferase construct was used for TGF-β measurement. Normal (SD) TGF-β levels are 9.0 (1.9) ng/ml. Three pts had normal baseline TGF-β levels. Mean (SD) baseline TGF-β was 48.2 (25.7) ng/ml. Baseline levels were not related to ECOG PS, age, sex, disease stage, treatment, response or pneumonitis. During treatment TGF-β levels decreased significantly in 13 pts and persisted at high levels in 25 pts. Nonresponding pts had significantly higher TGF-β levels during treatment than responding pts. Nine pts developed pneumonitis. We found no correlation between TGF-β and the occurrence of pneumonitis. Treatment with carboplatin had no influence on TGF-β levels. Conclusion: Non-responding pts had higher TGF-β levels during radiotherapy than responding pts. No relation of TGF-β-levels with pneumonitis was found.

OP 130

Does chemotherapy affects Disease Related Symptoms (DRS) and Quality of Life (QoL) in advanced NSCLC ? A review of 70 phase 2-3 published studies since 1990.

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Lung cancer is among the most commonly occurring malignancies in the world and is one of the few that continues to show an increasing incidence. There are almost a million deaths a year and over 1.3 million cases worldwide. Only 7-12% of patients are alive 5 years after diagnosis. NSCLC accounts for about 85% of all cases of lung cancer. At the time of diagnosis about 80% of patients present with metastatic or unresectable locally advanced disease. Nearly all patients with advanced NSCLC present symptoms related to their initial disease. For example pain, dyspnea and cough are present in about 50%, anorexia in 30%, weakness in about 55%. Starting chemotherapy in advanced NSCLC is often a difficult clinical decision and there is a huge need of quantitative data to support it. For these reasons we reviewed the published literature (1990-1997) concerning phase 2-3 trials, covered in the Medline Database. Seven major papers were analyzed, for a total of 70 studies, involving 6347 patients. Of these studies 20 (29%) were randomized and 62 (89%) were phase 2 trials. Only 16 studies (23% - 1351 pts) included a QoL and/or a DRS evaluation. Two articles presented a QoL evaluation based on validated scales (2.9%), while the rest used non validated instruments, eventually combined with QoL validated tools. Performance Status evaluation at entry, during therapy and at outcome, was reported in only 4 studies (6%). These data do not completely support the view, expressed by different authors, that chemotherapy positively affects QoL and DRS in advanced NSCLC. A wider use of validated QoL and of DRS instruments is essential.

OP 131

PALLIATION IN LOCALLY ADVANCED LUNG CANCER: A PROSPECTIVE RANDOMIZED COMPARISON BETWEEN EXTERNAL RADIOTHERAPY (XRT) ALONE AND IN COMBINATION WITH HIGH DOSE RATE (HDR) INTRALUMINAL BRACHY THERAPY (ILBT)

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Introduction: Ideal palliation for locally advanced lung cancer has remained elusive over the years. Effectiveness of ILBT combined with XRT was compared with XRT alone in a randomized prospective study in patients with non resectable carcinoma of lung.
Setting: A tertiary level institute in northern India.
Study period: October 1995 to October 1997.
Patients and methods: 60 patients (<59 males, 1 female) were randomized into two groups. Group I (n=30) received XRT (30Gy/10#/2 weeks) and simultaneous two sessions of ILBT (8 Gy at 1 cm). Group II (n=30) received only XRT in the same dose. Responses were recorded both objectively and subjectively at the end of the treatment and subsequently monthly for minimum six months.
Results: The mean age was 54.8 and 58.7 in the two groups respectively. The distribution of clinical stage, histology, symptom profile and the site of obstruction was similar in two groups. Patients receiving ILBT when compared to group II had higher subjective response rates for haemoptysis (100% vs 81%), cough (65% vs 50%), pneumonia (60% vs 50%) and dyspnoea (66% vs 60%); but these differences were not significant statistically ($p>0.05$). Objectively (on bronchoscopy and radiology) the relief of obstruction was better in group I (89% vs 50%, $p<0.05$), acute complications of ILBT included mild increase in haemoptysis (6 patients), increase in cough (2 patients) and mild esophagitis (2 patients).
Conclusion: Intraluminal brachytherapy provides effective relief of obstruction in palliative treatment of non-resectable lung cancer.

OP 132

RISING INCIDENCE AND DECREASING SURVIVAL OF PULMONARY ADENOCARCINOMA: CHANGES IN DIAGNOSIS OR AGGRESSIVENESS?

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We studied the changes in incidence and survival rates for pulmonary adenocarcinoma, using data of the Eindhoven Cancer Registry (1975-1994), that serves an area of 1 million inhabitants. There was a good access to specialised care.
The age-standardized incidence rate (WSR) of non-small cell lung cancer for males increased from 59 per 100,000 person-years in 1975 to 67 in 1983 and then decreased to 52 in 1995. The peak incidence rate for squamous cell carcinoma was reached in 1978, while for adenocarcinoma it was 1985. The incidence rate for females increased from 3 per 100,000 in 1975 to 9 in 1995, increasing for every histological type. Among males the proportion with adenocarcinoma increased from 10% in 1975-79 to 18% in 1990-94. Among females, this proportion had decreased from 43% to 39%.
There was a trend toward a more advanced stage among adenocarcinoma patients and the relative 1-year survival has decreased from 59 to 45%; this decline was greatest for patients younger than 70 years of age and for men. However, survival according to stage has remained unchanged.
Most of the increase in incidence appeared to be real, probably related to changes in exposure to smoking-related risk factors. Despite improved diagnosis, the proportion with early stage disease and the prognosis have decreased. The biological behaviour of adenocarcinoma may thus have shifted toward a more rapidly metastasizing tumour.
Conclusion: in areas with increasing incidence pulmonary adenocarcinoma may have become a more aggressive tumour, especially for males, which might be due to a shift in (probably smoking-related) risk factors.

OP 133

HUMAN AP ENDONOUCLEASE 1 (HAP1) NUCLEAR EXPRESSION CORRELATES WITH SURVIVAL IN OPERABLE NON-SMALL CELL LUNG CANCER

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Human AP endonuclease (HAP1) plays a major role in the repair of apurinic/apyrimidicin (AP) sites in cellular DNA, either arising spontaneously or through the action of various DNA damaging agents. A second role of this bifunctional protein, in reactivation of oxidised transcription factors, has been established. We used immunohistochemistry to examine the expression of HAP1 in normal lung and in 103 primary non-small-cell-lung carcinomas (NSCLC). In normal lung the staining for HAP1 was found to be both nuclear and cytoplasmic in the pneumocytes of the alveoli. Superficial ciliated cells of the bronchial epithelium presented cytoplasmic staining while the staining for the basal cells was mostly nuclear. Bronchial glandular cells demonstrated a mixed nuclear and cytoplasmic staining. Lung carcinomas showed all patterns of expression for HAP1. Stromal fibroblasts in both normal lung and NSCLC had nuclear staining whilst the staining for macrophages and giant cells was both nuclear and cytoplasmic. A strong relationship was found between cytoplasmic localization of HAP1 and bcl-2 negative expression (p=0.001). Loss of HAP1 expression was found to associate with bcl-2 positivity (p=0.02), with low proliferation index (p=0.001), and with squamous histology (p=0.04). A survival benefit was been for patients presenting nuclear HAP1 expression (p=0.01). This finding may indicate the nuclear HAP1 localization may be relevant to its role as an activator of wild type p53. Cytoplasmic expression may be related to differences in relative oxygen tensions in lung cancer and disruption of the normal pattern of development in bronchial mucosa.

PP 134

ALPHA 1-ADRENERGIC RECEPTORS IN HUMAN LUNG CANCER AND THEIR ROLE IN PREVENTION OF SECOND PRIMARY GROWTH.

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The adrenergic part of the autonomic nervous system is not investigated in the pathogenesis of lung cancer. In this study alpha 1-adrenergic receptors have been investigated in human lung parenchyma obtained at the resection of adenocarcinoma patients. The number of the receptors sites markedly increased in the cancer lung-membrane preparation, including bronchioli, alveoli and blood vessels. The latter are known to contain postsynaptic alpha 1-adrenoceptor activity mediating contractile responses of the vascular smooth muscle. The increase of alpha 1-adrenoceptor activity might be caused by an enhancement of vascular proliferation. The above processes may lead to a strong vascular smooth muscle contraction in lung cancer parenchyma and result in the prevention of second primary growth. The above findings suggest cancer-induced enhancement in alpha 1-adrenergic activity which may be involved in the prevention of second primary lung malignant growth. The results obtained may be of obvious prognostic value in diagnisis of lung cancer.

OP 135

CONCURRENT WEEKLY DOCETAXEL AND RADIOTHERAPY FOR NON-SMALL CELL LUNG CANCER. A PHASE I AND II TRIAL WITH IMMUNOLOGICAL TOXICITY EVALUATION.

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Docetaxel, a novel semisynthetic taxoid, induces cell arrest in G2/M radiosensitive cell cycle phase and is also involved in bcl-2 anti-apoptotic protein phosphorylation. 30 patients with stage IIIb/IV non-small cell lung cancer (NSCLC) were treated with 64Gy of accelerated chest radiotherapy (in 5 weeks using concomitant boost technique) and Taxotere administration on a weekly base. The dose of Taxotere was escalated starting from 20mg/m2/week and increasing by 10mg/m2/week every 10 patients. Complete response of the primary tumour, assessed 2 months after treatment, was obtained in 8/30 (27%) of patients (4 of them with known resistance to Taxotere). PR+CR rate was 77% (23/30) and only one patient progressed during radio-chemotherapy. Weekly Taxotere dose of 20 and 30mg/m2 was very well tolerated with granulocytopenia grade III observed in only 2 patients. Marked asthenia was observed in the 40mg/m2 dose level and 4/10 patients had a 50% dose reduction after the first 2-3 weeks. Severe grade III neutropenia was observed in 3/10 patients Severe monocytopenia and lymphocytopenia was observed during the 4th week of treatment, especially in patients treated for pelvic cancer. IgG and IgA immunoglobulins were also reduced. This coincided with the onset of asthenia and severe mucosal toxicity. Preliminry results from a subsequent phase II study in 25 stage IIIb pts treated in the 30mg/m2 dose level show a 40% complete response rate. The high response rate observed encourages further investigation. Immunological support with GM-CSF and immunoglobulin administration may be important in the efficacy and tolerance of taxane based radiochemotherapy.

PP 136

HIGH DOSE FARMORUBICIN VERSUS FARMORUBICIN PLUS CARBOPLATIN IN ADVANCED NON-SMALL CELL LUNG CARCINOMA: PRELIMINARY REPORT

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25 patients with NSCLC (IIIb-IV) previously untreated were randomised into two groups: group A (14 patients) received Farmorubicin 130mg/m^2 given in i.v. bolus and group B (11 patients) Farmorubicin 120mg/m^2 plus Cisplatin 60mg/m^2 given in the first day of treatment. Both regimens of treatment were repeated every 21 days up to the max. dose 840mg/m^2 of Farmorubicin. Patients with liver metastases were excluded. Mean age of both groups were 64 (42-69), the patients were males, histological types were: adenocarcinoma 5 patients (20%), planopitheliale 20 patients (80%). There were 14 patients in the group A and 11 patients in the group B. Grade III-IV toxicity achieved in the group A and B, as follows: leukopenia 14.3% and 9.1% of patients, trombocytopenia 28.6% and 9.1% of patients, anemia 7.1% of patients in the group A, local reaction 9.1%, neurotoxicity 9.1% of patients in the group B. Cardiac complications confirmed by UCG and ECG were observed in one patient. Following response rates were observed in the groups retrospectively: PR + S (Partial Remission + Stabilisation): 7.1% and 36.4% of patients. Eight patients (57.1%) from group A and four patients (36.4%) from group B were died within the time of observation. The median survival was 9 months (range 1-20) in both groups.

PP 137

INDUCTION OF CELL DEATH BY CISPLATIN AND VINORELBINE IN THE LUNG ADENOCARCINOMA CELL LINE A549.

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In non-small cell lung cancer, the combination of cisplatin and vinorelbine results in response rates of about 30%. Our aim was to determine whether there is an association between inhibition of cell proliferation and increase of cell death by cisplatin in combination with vinorelbine. We also wanted to characterize the kind of cell death. A549 cells were treated with different concentrations of either cisplatin, vinorelbine or both drugs and the nuclear changes were studied by using flourescent (Hoechst-33258 staining) and electron microscopy. At 5µg/ml cisplatin, nuclear condensation/fragmentation typical of apoptosis was seen in 12% of the cells after 24h with further progression of cell destruction after 48h. At 100 ng/ml vinorelbine, mitosis was seen in 38% of the cells after 24h, but in none after 48h. Rather, most of the cells had detached from the substrate. The remaining cells exhibited extensive nuclear fragmentations. We did not observe mitotic nuclei in cells treated with the combination of both drugs, which could be explained by the fact that the cell damage due to cisplatin induced nuclear changes were present in as many as 57% of the cells treated with 100ng/ml vinorelbine/5 µg/ml cisplatin. There was a time- and dose dependent increase in histological signs of cell death. These changes could be observed by both fluorescent microscopy and electron microscopy.

OP 138

PREOPERATIVE CHEMOTHERAPY WITH CISPLATIN, 100 MG/M2 VERSUS 50 MG/M2 IN STAGE IIIA (N2) NON-SMALL CELL LUNG CANCER (NSCLC): A RANDOMIZED STUDY BY THE SPANISH LUNG CANCER GROUP.

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Although cisplatin is one of the most active drugs in the treatment of NSCLC, the optime dose of cisplatin in combination is still unclear. The aim of our trial was to determine whether higher cisplatin dose (100 mg/m^2 versus 50 mg/m^2) results in improved survival and increase in downstaging in patients with stage IIIA (N2 proven by mediastinoscopy). From March 1993 to February 1997, 83 patients were randomized to receive either cisplatin 100 mg/m^2 or 50 mg/m^2, on day 1, in combination with ifosfamide 3 g/m^2 on day 1 and mitomycin 6 mg/m^2 on day 1. Chemotherapy was administred every 21 days for 3 cycles, surgery was performed on day 63, and postoperative radiotherapy was scheduled. 46 patients received higher cisplatin dose (group A), 37 received lower dose (group B), both groups were well balanced for clinical characteristics. Grade 3-4 anemia was significantly more common in group A (p=0.01). Radiologic response rate was 59% for group A and 30% for group B (p=0.01). Thoracotomy was performed in 71% (86%), 58 of whom had resectable disease. Complete resection rate was 61% for group A and 51% for group B (p=0.5). Postoperative mortality was 11%. 17 patients were downstaged, 24% in the 100mg/m^2 group and 16% in the 50 mg/m^2 group. Complete pathologic remission was objectived in one patient who received 50 mg/m^2. Overall median survival was 13 months. Median survival for completely resected patients was 17 months, and 10 months for patients with incomplete resection or unresectable disease (p=0.04). Median survival in group A was 13 months and 11 months in group B (p=0.3). We conclude that preoperative treatment with cisplatin, mitomycin and ifosfamide achieves a moderate response rate and an acceptable resecability. In patients treated with cisplatin 100 mg/m^2, anemia is significantly higher and there are no differences in pathologic complete remission nor overall survival.

PP 139

P53 MUTATIONS IN NON-SMALL CELL LUNG CANCER IN POLAND

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The study was initiated (a) to determine the frequency, location and nature of p53 mutations in NSCLC in Poland and (b) to compare p53 status with clinical data. We examined 214 NSCLC samples using PCR-SSCP and DNA sequencing. P53 mutations were found in 89 of 214 tumors (42%), while G:C to T:A transversions were the most frequently observed mutations. We note that no p53 mutations at codon 273 which is a known hot spot in American patients have been found in Poland.
No relationship was demonstrated between p53 status and clinicopathological data. In multivariate analysis (logistic regression model) however, the presence of p53 mutations is closely associated with lifetime cigarette consumption. According to Cox's regression model, p53 mutations were found to be independent prognostic factor.

PP 140

THE PROGNOSTIC SIGNIFICANCE OF TTF-1 EXPRESSION IN NON SMALL CELL LUNG CARCINOMA

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This study investigated the frequency and prognostic significance of immunohistochemical expression for TTF-1 in a consecutive series of 96 surgically resected nonsmall cell lung carcinomas (NSCLC). Tumour immunoreactivity for TTF-1 was categorized as follows: TTF-1 (++): ≥50% TTF-1 positive neoplastic cells; TTF-1 (+): 1-49% positive cells; TTF-1 (-): <1% positive cells. TTF-1 stain was always limited to nuclei. Of the 96 specimens of NSCLC, 59 (61%) were TTF-1 (-), 20 (21%) were TTF-1 (+) and 17 (18%) were TTF-1 (++). TTF-1 expression was significantly higher in adenocarcinomas (AC) than in squamous cell carcinomas (SCC) ($p<0.0001$). The Kaplan-Meier method was used to estimate survival and Cox regression model was performed for multivariate analysis. The relationship between TTF-1 expression and postsurgical survival was analysed for 88 patients (60 SCC and 28 AC). Survival curves among the TTF-1 (-), TTF-1 (+) and TTF-1 (++) groups resulted significantly different (logrank test, $p=0.04$). Multivariate analysis showed that TTF-1 (++) NSCLC were associated with a bad prognosis ($p=0.009$) independently from pN status ($p=0.01$) or pStage ($p=0.0006$). We also separately analysed subsets of patients with SCC and with AC and found that TTF-1 may be a useful prognostic factor only in SCC patients ($p=0.04$).
In conclusion, our study showed that immunohistochemical detection of TTF-1 protein is a promising indicator to predict clinical outcome of primary, resected NSCLC patients, especially in those with squamous cell type.

OP 141

LUNG CANCER AND PULMONARY TUBERCULOSIS
- COEXISTENCE OR COINCIDENCE -

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Authors analysed 13.526 patients suffering from lung cancer (LC), threated in Institute for Lung Disease and Tuberculosis in Belgrade in a period 1985-1996 years. We're found 599 cases (4,43%) LC associated with pulmonary tuberculosis (PT), divided in two groups: A-92 patients with LC and active PT, and B-507 patients with LC and PT. In A groupe the most frequently pathohistological type LC was squamous cell carcinoma (72 cases, 78,3%, $p<0,0001$), and microcellular carcinoma and adenocarcinoma was in 9 cases (9,8%). Both squamouscell type LC and active PT we're found in 45 patients ($p<0,0001$) in same side. In B group the most frequently pathohistological type was too squamous Lcn (357 cases - 70,4%, $p<0,0001$), than microcellular was 72 cases (14,2%) and adenocarcinoma 54 (10,6%).Both squamous cell LC and old PT we're found in 136 patients (38%) in same side, and in 152 patients (42,6% $p<0,001$) old TB was billateral, and LC in one side. Also, we're found 24 patients (44,4%, $p<0,005$) with adenocarcinoma and old PT situated in same side.
We're concluded:
1.Squamous cell carcinoma was the most frequently pathohistological type in our patients with LC and PT;
2. May be strong connection between LC and PT.

OP 142

SIGNIFICANCE AND CLINICAL IMPLICATIONS OF THE PRESENCE OF ANTI p53 ANTIBODIES IN THE SERA OF PATIENTS WITH VARIOUS TYPES OF CANCER

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Abnormal accumulation and structural alteration of p53 in tumours, together with subsequent release of p53 protein from transformed cells, may initiate immune response with generation of circulating autoantibodies to p53 protein (p53-Abs).
The aim of our studies was: (a) to determine the prevalence of p53- Abs in patients with various type of cancer, (b) to study the origin of this immune response that is only found in cancer patients, (c) to correlate the presence of p53-Abs with various clinical parameters, (d) to study the variation of p53-Abs during the treatment of patients.
We have found that the presence of p53-Abs is strictly correlated with the accumulation of p53 protein in tumour cells. Analysis of this immune response clearly showed that p53-Abs recognize immunodominant epitopes localized in the amino- and carboxy- terminus of p53. Such immune response is similar to that of animals hyperimmunized with human p53 suggesting that the accumulation of p53 is strongly involved in this humoral response.
In breast cancer, the prevalence of p53-Abs is about 15% as tested by ELISA, immunoprecipitation or immunoblotting. We found a close correlation between the presence of such antibodies and poor prognosis parameters such as high histological grade and the absence of hormone receptors. Furthermore, we showed that patients with p53-Abs had a shorter survival time compared to patients without p53-Abs.
Analysis of the sera from patients with high risk lung cancer showed that p53-Abs can be detected several months before the clinical diagnosis of pulmonary cancer. In a recent work we performed a prospective analysis of patients with lung cancer. The follow up of 25 patients over a period of 30 months showed a good correlation between the evolution of the p53 antibodies titer and response to therapy. Rapid and specific decrease of these antibodies during the therapy suggests that a constant presence of p53 is necessary to maintain this immune response.
We conclude that screening for serum p53-Abs may facilitate the early diagnosis and may be a useful technique for assessing alterations in p53 and monitoring the response to therapy in patients with lung cancer.

OP 143

A PHASE I STUDY OF ACCELERATED HIGH DOSE EPIRUBICIN (HDE) AND CISPLATIN WITH G-CSF SUPPORT IN PATIENTS WITH ADVANCED NON SMALL CELL LUNG CANCER (NSCLC)

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HDE and P chemotherapy (Cx) is active in NSCLC (Martoni et al. Ann. Oncol. 1992; 3:864). In this phase I study we investigated whether dose intensity of this regimen could be increased with G-CSF support. Eligibility criteria: age 18-75 years, pathological proof of NSCLC, stage IIIA-IV, last cytotoxic treatment > 4 weeks, ECOG PS $\leq$ 3, WBC > 3.0 x 10^9/L, platelets > 100 x 10^9/L, bilirubin < 25 umol/L, creatinine clearance > 60ml/min. Toxicity (WHO criteria) was monitored day 10, 14 and 21: physical examination, CBC/differential, alkaline phosphatase, LDH, ALAT, ASAT, bilirubin, creatinine. Response (WHO criteria) was determined after each course. At each dose level at least 6 patients were entered. Dose limiting toxicity (DLT) was defined as hematological toxicity grade IV lasting > 4 days, neutropenic fever, any other toxicity exceeding WHO grade III in $\geq$ 2 patients at one dose level. The dose of P (60 mg/m^2) was constant, HDE was escalated from 120mg/m^2 (level I) to 135mg/m^2 (level II), subsequently G-CSF 5 ug/kg/day, days 3-12 was added (level III) and the interval between courses decreased from 3 to 2 weeks (level IV). From March 1997 to September 1997 26 patients: 4 female, 22 male, median (range) age 58 years (38-72), were included; 2 st IIIA, 10 st IIIB, 14 st IV, median ECOG PS 1 (0-2), 11 pretreated with Cx, 1 Cx and radiotherapy (RT), 3 RT, 11 no pretreatment. At the first three dose levels 2 patients encountered DLT (renal failure (dose level I) and neutropenic fever (dose level II)); at level IV (6 patients, 10 courses) no DLT was encountered; WHO grade III/IV (no courses) leucocytopenia 3, trombocytopenia 0, hemoglobin 0. All patients were fully recovered at scheduled retreatment day 14. Nausea and vomiting was the predominant non-hematological toxicity, 1 patient died in renal failure presumably due to P. Responses (all dose levels, 22 patients evaluable) Nine PR, 2 MR, 2 SD, 7 PD, 1 TD, 1 TE. Eleven patients are on treatment, five refused further treatment, seven patients went off study due to PD, 3 due to renal toxicity.

Conclusion: HDE 135mg/m^2 and P 60mg/m^2 with G-CSF 5 ug/kg/day, days 3-12 q 2 weeks is feasible, this study continues as a phase II study in pretreated NSCLC patients.

PP 144

SMALL BOWEL METASTASES IN NON-SMALL CELL LUNG CANCER (NSCLC). A CASE REPORT AND A CLINICAL AUTOPSY SERIES INCLUDING 218 AUTOPSIES TOGETHER WITH A LITERATURE REVIEW AND DIFFERENTIAL DIAGNOSTIC CONSIDERATIONS.

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Case report: Fourtythree-year old female with complete left side pneumonectomy november 1996 for stage I (pT2N0M0) NSCLC. Histology was poorly differentiated adenocarcinoma mixed with foci of large cell carcinoma. No postoperative adjuvant treatment was administered. Extrathoracic recurrence occured october 1997 (11 months disease free survival) as acute explorative laparotomy was performed due to diffuse purulent peritonitis caused by perforation of a jejunal tumor measuring 6 x 6 cm. Resection of intestine with the tumor and liver biopsy was done. Histology was large cell carcinoma, identical with the previously resected lung tumor as reviewed by an external pathologist. Performance status was to poor to allow platin-based cytotoxic treatment. **Autopsy series:** Ten patients with small intestine involvement at autopsy (1.4%) were found in three clinical defined autopsy series published by the authors above, including 733 NSCLC patients with 218 autopsies (4.6%). **Literature review:** Most frequent primary tumor with metastatic spread to the small intestine was malignant melanoma (60% of cases), though similar cases have been reported also in several other common cancers such as: breast, cervix, kidney, and lung. In a selected autopsy series of 431 autopsies in 1650 patients 11% of the patients had spread to small intestine from NSCLC, with large cell carcinoma as the most frequent major histologic type. **Differential diagnostic considerations:** Primary carcinomas of the small intestine are rare. Especially in cases which are not carcinoid tumors, the possibility of metastatic spread from one of the common primary cancers cited above, should be kept in mind, as treatment options and prognosis may be very different from that of a primary small bowel carcinoma.

PP 145

MULTIMODALITY THERAPY FOR STAGE III A (N2) NON-SMALL-CELL CARCINOMA OF THE LUNG: IMMUNOLOGICAL STATUS OF THE PATIENT DURING AND AFTER INDUCTION CHEMOTHERAPY AND ITS CORRECTION.

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We reviewed the records immunological status and methods of its correction of 18 patients who underwent resection for locally advanced NSCLC after two cycles of induction (neoadjuvant) chemotherapy - VP=P: platinol 75 mg/m2 (day 1), vepesid 120 mg/m2 (days 1 through 3) (BMS): every 3 weeks. Preoperative immunocorrection neutralizes immunosuppresive effect of tumor growth and induction chemotherapy. Preoperative therapy with α-2b interferon-laferon and some vegetable adaptogenes (rhodiola rosea, eleutherococcus) as immunomodulators promotes recovery of humoral and cellular immunity to basal level on day 10-14 following surgery.Therapy with α-2b interferon-laferon in combination with other adaptogens brought to decrease common toxity chemotherapy and imprure adaptation possibility of patients.

OP 146

THE EFFECT OF MICROVESSEL DENSITY ON PROGNOSIS IN HEAD AND NECK CANCERS

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To determine how microvessel density coraletes with prognosis in head and neek cancers, we counted microvessels within the epidermoid carcinomas of 81 patients who were treated with external radiotherapy, in Cukurova University Faculty of Medicine Radiation Oncology Department, between the years of 1990 and 1996. Microvessels were highlighted by factor VIII related antigen. Microvessels were counted in a X400 field in the most active areas of neovascularization. The mean microvessel count in all tumours 25.27 (median 26). The counts within carcinomas from patients without lymphatic metastasis (27). Multivariate analysis showed the stage of discase is significant and independent predictors of prognosis butonly microvessel density is not independent predictors of prognosis. Median 70Gy (60-76Gy) dose was given to primary tumour and lymphatic metastases with Co60 and Linear Accelerator. The overall radioresponse ratio was 66.6%, response qualities were 49.4% CR, 17.2% PR, 20,9% S, 12,3% P. The patients who were given radiotherapy above 70Gy, showed significantly higher survival.

OP 147

CONCOMITANT RADIOTHERAPHY AND DAILY LOW-DOSE CARBOPLATIN IN LOCALLY ADVANCED, UNRESECTABLE HEAD AND NECK CANCER. DEFINITIVE RESULTS OF A PHASE III STUDY.

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Radiathion therapy (RT) alone is currently considered as the standard treatment for patients with locally advanced uresectable squamous cell carcinoma (SCC) of the head and neck (H & N). However, response rates are limited and survival rates low with the majority of patients dying of locoregional recurrence. In attemps to improve the results, between November 1992 and January 1996, 164 consecutive patients with Stage III-IV inoperable squamous cell carcinoma of the head and neck were randomized to receive standard fraction RT (70 Gy/7w) versus RT plus CBDCA (45 mg/m2 on days 1-5 of the 1-3-5-7w). Thus, 145 were evaluable for response and toxicity. 129 (89%) patients were male and 16 (11%) were female. The median age was 60 years (range 39-75). The majority (52%) had a performance status of 1 (range 1-3) and histology grade II (59%) .Treated subsites included : oral cavity (n°=28 ; 19%), oropharynx (n°=81 ; 56%), hypopharynx (n°=15 ; 10%) and larynx (n°=21 ; 15%). Using AJC criteria, the tumor was Stage III in 33 (23%) cases and Stage IV in 112 (77%). Of note, 58.6% of patients had T4 primary tumor and 50% had N2-N3 disease. The two groups (72 pts arm RT and 73 pts arm RT+CBDCA) were equally balanced according to site, stage and N status. With a median follow up of 16 months (range 6-51) the results are :

	CR	LRC% (48m)	DFS% (48m)	OS% (48m)
RT	22 (15%)	10%	6%	18%
		p<0.05	p<0.05	p<0.01
RT+CBDCA	39 (26.8%)	28%	19%	22%

Leukopenia was the most common drug-related side effect in radiochemotherapy arm. The incidence of mucositis was not different between the two treatment groups.

OP 148

p53, BCL-2 AND RESPONSE OF LOCALLY ADVANCED SQUAMOUS CELL HEAD AND NECK CANCER TO PLATINUM BASED CHEMOTHERAPY AND CHEMO-RADIOTHERAPY.

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The role of apoptosis regulating oncoproteins in defining response to cytotoxic therapy remains poorly understood. Loss of wild type p53 function and bcl-2 protein overexpression are well known to inhibit the apoptotic pathway in in vitro studies.We immunohistochemically examined the nuclear accumulation of mutant p53 and the cytoplasmic overexpression of bcl-2 proteins in 76 patients with locally advanced inoperable squamous cell cancer of the head and neck area. Patients were treated with platinum based chemotherapy and radiotherapy (37 with induction and 39 with concurrent chemotherapy). The median follow up period was 72 months. Thirty five (46%) cases were positive for p53 and 41 (54%) negative, whilst 19 (25%) and 57 (75%) cases were positive and negative for bcl-2 respectively. High percentage of bcl-2 positive cells associated with low incidence of nodal involvement. A statistically significant higher percentage of p53 positive cells was observed in the group of patients with complete disappearance of the disease as compared to the group with residual disease after treatment (p=0.01). High percentage of p53 positive cells and concurrent chemoradiotherapy associated with better local progression free survival (p=0.05 and 0.02). In multivariate analysis, the type of chemotherapy (concurrent vs induction) was the only significant prognostic variable for local relapse (p=0.02) and overall survival (p=0.03). The present study provides evidence that p53 nuclear accumulation may associate with better response to DNA damaging cytotoxic agents. Association of wild type p53 loss with decreased DNA repair enzyme activity is a possible explanation. Induction platinum based chemotherapy may contribute to the selection of clonogenic cells with radioresistant phenotype.

PP 149

The results of combinated therapy - surgery, radiotherapy and/or chemotherapy - in advanced carcinoma of the oral cavity and oropharynx

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Abstract: The authors present the results of a combined therapy surgery, radiotherapy and/or chemotherapy in 39 patients with oral cavity and oropharynx advanced carcinomas, treated in the department of Head and Neck Surgery of the Oncological Institute "Prof.Dr.I.Chiricuţă" Cluj-Napoca.

A descriptive and univariated study as a function of the tumour growth, lymph node, hystological type and grading, localisation and treatment sequence was made.

The results were estimated from local control and survival rate at 3 years. The best results were obtained in the sequence: surgery-radiotherapy. Worse results were in the sequence: radiotherapy-salvage surgery.

OP 150

PHASE II PILOT STUDY OF CAELYX (DOXORUBICIN HCl, PEGYLATED LIPOSOMAL) IN PATIENTS WITH INOPERABLE SQUAMOUS CELL CANCER OF THE HEAD AND NECK

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Squamous cell cancer of the head and neck (SCCHN) account for approximately 5% of all neoplasma in Europe and the Usa. Patients presenting with inoperable SCCHN are frequently treated with neoadjuvant chemotherapy (usually cisplatin and 5-FU) followed by radical radiotherapy. Biodistribution studies using ^{111}In-DTPA-labelled Stealth liposomes (IDLSL) have demostrated positive uptake in 7/7 patients with advanced SCCHN. In two patients who received 0.7 mCi IDLSL before radical surgery, tumour uptake was 8.8 and 15.0% of the injected dose per kg.Tumour uptake exceeded that in adjacent normal mucosa by a mean ratio of 2.4:1. Following these studies we have commenced a Phase II pilot study of Caelyx in patients with inoperable SCCHN. The objectives of this study are: (1) to assess the response of SCCHN to two cycles of Caelyx 40 mg/m^2 every three weeks followed by a standard radiotherapy regimen and (2) to evaluate the tolerability and efficacy of a synchronous third cycle of Caelyx at escalating doses between 10 and 25 mg/m^2 delivered at the start of radiotherapy. After the first 8 assessable patients, the response rate to the initial 2 cycles of Caelyx was 62,5% (5 PR, 3 SD). In 5 assesable patients who have completed radical radiotherapy there have been 4 complete responses and one patient with a residual neck node. Two patients have undergone neck dissection after completion of radiotherapy - one pathological CR and one single involved node. Caelyx has been very well tolerated; nausea and vomiting 0/8, alopecia 0/8, oral raucositis 3/8 (median Grade 1), hand-foot syndrome 3/8 (median Grade 2). There were no treatment delays during radiotherapy and no increase in the incidence or severity of acute radiation reactions.

PP 152

EXPRESSION OF PROLIFERATIVE ANTIGENS (PCNA AND Ki-67), c-erbB-2, p53 AND bcl-2 IN ENCAPSULATED FOLLICULAR THYROID TUMORS.

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The aim of this study was to analyze the expression of proliferative antigens (PCNA and Ki-67), c-erbB-2 oncoprotein, p53 oncoprotein and bcl-2 tumor suppressor protein in follicular adenomas and encapsulated follicular carcinomas of the thyroid gland. The study was carried out by immunohistochemistry on paraffin embedded archival material using primary antibodies purchased from DAKO. Tissue sections of 10 follicular adenomas and 10 encapsulated follicular carcinomas were analyzed. The alkaline phosphatase and horse-radish peroxidase methods were used. The majority of adenomas showed slight to moderate positivity for PCNA, Ki-67, bcl-2, and c-erbB-2 and negative staining for p53. The majority of encapsulated follicular carcinomas showed moderate positivity for PCNA, Ki-67 and bcl-2 and slight positivity for c-erbB-2. However, strong positive immunostaining for p53 was observed in three cases of encapsulated follicular carcinomas. Data from the literature suggest that the expression of PCNA, Ki-67, c-erbB-2, p53 and bcl-2 is related to the degree of differentiation of thyroid tumors. We observed positive immunostaining for p53 in 30% of cases of encapsulated follicular carcinomas but negative reaction in adenomas. Furthermore, it seems that at present the distinction between follicular adenomas and encapsulated follicular carcinomas should be based on histological analysis. However, it is very difficult to predict behavior of encapsulated thyroid carcinomas on the basis tumor morphology only. Therefore, future studies on the expression of these and additional markers should be performed. Further investigation of a larger series of patients with a long-term follow-up is obviously needed.

PP 154

ANALYSIS OF FACTORS INFLUENCING PROGNOSIS IN LARYNGEAL CANCER

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In order to estimate the factors that influence the recurrence rate of laryngeal cancer, we retrospectively studied 514 cases which were treated at our department during the period 1992-1996. TNM staging was as follows: T1a 126 patients, T1b 21, T2 101, T3 156, T4 110, N0 447, N1 33, N2a 10, N2b 4, N2c 8, N3 12. Endolaryngeal resection 23 pts, cordectomy 67, vertical laryngectomy 33, supraglottic laryngectomy 21, total laryngectomy 255 (205 as primary treatment and 50 due to recurrence). One hundred sixteen pts were treated primarily with radiotherapy only and 43 with a combination of radiotherapy and chemotherapy.
Results: Among the 479 patients who were followed up closely for a median time of 3 (1-5)years, 158 (33%) presented progressive or recurrent disease and 108 (22.5%) were deceased. Analysis of the parameters having to do with the site of the tumour and the histology revealed that the recurrence rate was significantly higher when the tumour was subglottic (80% recurrence rate), when differentiation was poor (G3) 65,7%, when primary site was T4 46,4%, when there were positive lymph nodes 47.7%, when there was extension of the tumour to the arycepiglottic fold 42.6%, to the subglottic region 53% and finally to the base of tongue 77,7%. The percentage of recurrences according to the treatment modality used were as follows: Endolaryngeal resection 13%, cordectomy 11,9%, vertical lar. 27,2%, supraglottic lar. 19%, total lar 24,3%, radiotherapy 41%, radiotherapy plus chemotherapy 58%.

OP 151

BIFRACTIONATED RADIOTHERAPY WITH OT WITHOUT CHEMOTHERAPY IN LOCALLY ADVANCED, INOPERABLE HEAD AND NECK CANCER

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Recently much attention has been paid to the combination of radio- (RT) and chemotherapy (CT) and to new fractionation RT schemes in head and neck cancer (HNC) resulting in improved local control and/or survival. We report preliminary results of bifractionated RT alone or combined with CT in locally advanced HNC. Out of 28 patients (pts), 8 were treated with RT alone, 2 with concomitant RT+CT, 6 with induction CT followed by concomitant RT+CT and 12 with induction CT followed by RT alone. RT was performed with shrinking field technique up to 74.4 Gy given with 1.2 Gy/twice a day for 5 days a week. Induction CT included cisplatin (CDDP) and fluorouracil (FU) (11p pts) or CDDP, FU and navelbine (VNL) (6 pts) up to a median of 4 cycles. Concomitant CT included weekly CDDP. A supportive care protocol, including administration of pilocarpin, fluconazol etc, was employed. All pts completed therapy; the mean RT time was 48 days, mean follow-up - 12 months. Acute toxicity was considerable. The most common side effect was mucositis (28 pts), followed by hemotological toxicity (26 pts), weight loss (25 pts), skin toxicity (25 pts), nausea, vomiting (9 pts) and others. In 19 pts (68%) G3 or G4 mucositis and in 6 pts (21%) G3 leukopenia were observed. The most severe and early toxicity was seen in pts treated with induction CT followed by RT+CT; in 4 of them opioids were introduced, 3 were hospitalised and treated with parenteral nutrition, in 2 RT was temporarily interrupted, one therapy-related death was seen. Thus, this treatment option has been stopped. Response has been achieved in 23 pts (82%); 16 CR and 7 PR. Except for xerostomy, no other late effect has been observed. In conclusion, combination of CT and bifractionated RT seems promising, however, high acute toxicity calls for research of optimal supportive therapies and less toxic treatment schemes.

PP 153

10-YEAR OUTCOME OF TREATMENT OF MALIGNANT TUMORS OF THE NASAL CAVITY AND PARANASAL SINUSES

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We evaluated the incidence, treatment modality, and survival in a group of 53 patients (35 M, 18 F) with malignant tumors of the nasal cavity and paranasal sinuses hospitalized at the ENT Clinic in 1988-1997. The mean age of patients was 60 years (range, 18-85 years). Carcinoma was found in 33 patients (39%). Moreover, malignant melanoma was found in 9 patients. Chondrosarcoma was demonstrated in 3 patients while aesthesioblastoma in 4 and malignant lymphoma in 3 patients, and Grawitz' tumor metastasis (in the maxillary sinus) and malignant myeloma (Kahler's disease) were detected in one patient each. Involvement of individual sinuses was as follows: nasal cavity in 20 cases, maxillary sinus 19, ethymoid sinuses 13, frontal sinus in one case. TN classification in maxillary sinus carcinoma: T4 in 8 cases, T3 in three, T2 in two. Involvement of regional cervical nodes, N2 in two cases. The most frequent therapeutic option was surgery (47 patients, 88%) with postoperative radiotherapy. Radiotherapy was combined with chemotherapy in 3 patients with malignant lymphoma and carcinoma. Chemotherapy was also indicated in 3 patients. The five-year survival rate was evaluated in 25 patients treated over the 1988-92 period, with 10 patients surviving (40%). Of the total of 53 patients on 1-9 year follow-up, 31 patients have survived to date (58%). The patients show common symptomatology, the most frequent condition was unilateral occlusion of the nose; the final diagnosis was established late; local propagation into surrounding structures; unsatisfactory results on long-term survival.

OP 155

HIGH DOSE EPIRUBICIN (EPI) AND CISPLATINUM (C) IN LOCALLY ADVANCED UNDIFFERENTIATED NASOPHARYGENAL CARCINOMA (UNPC)

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Aim: The chemosensitivity of UNPC is well recognized and a recent randomized study evaluating neoadjuvant chemotherapy with cisplatin/epirubicin/bloomicin has resulted in better disease free survival and a trend for better overall survival in the chemotherapy aim. It requires hospitalization because of bleomycin infusion and this combination has resulted in serious pulmonary toxicity. This study is to evaluate the efficacy and toxicity of P with increased dose of EPI given on the same day in patients with locally advanced UNPC.
Methods: Fourty-six patients with locally advanced nonmetastatic UNPC were treated with P mg/m^2 and EPI mg/m^2 IV given on day 1 every 21 days for 3 cycles before definitive radiation therapy with 70 Gy for 7 week. There are 20 female and 26 male patients with median age 44 (range 17-67). 17 (%37) patients had T primer tumours and 32 (%72) patients had N_{2c} or N_3 nodal involvment according to TNM (UICC/AIC 1986).
Results: 43 patients (%93) achieved a major objective response after chemotherapy. There was 13 (%28) complete response after 3 cycles of chemotherapy. Three planned cycles of chemotherapy were given with more than one week delay only in 7 patients. There was no dose reduction for toxicity. The regiment has been well tolerated. Grade 3 leucopenia occured in %22 of the total cycles. There was onlyone cycle with grade 4 leucopenia, grade 3 emesis was seen in %20 of the patients, 42 patients achieved radiotherapy, 16 patients who don't achieve CR after chemotherapy, became CR after radiotherapy. We achieved 29/46 (%63) CR after chemo- and radiotherapy. Median follow-up time is 17 months (range 4±52 months), 2 years PFS is %67.

OP 156

SENTINEL NODE LOCALISATION IN CUTANEOUS MELANOMA: LYMPHOSCINTIGRAPHY WITH COLLOIDS AND ANTIBODY FRAGMENTS VERSUS BLUE DYE MAPPING.

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In stage I cutaneous melanoma, biopsy of the first tumour-draining lymph node (sentinel node, SN) may replace routine elective lymph node dissection (BLND). We investigated the value of three methods to locate the SN: intraoperative patent blue dye (PBD) mapping, lymphoscintigraphy (LS) with non specific tracer (HSA), LS with specific tracer (MoAb).

50 patients with diagnosed melanoma were studied. In 25 of 50 pts a LS was performed the day before surgery with 55 MBq of Tc-99m HSA particles (Albures) injected intradermally surrounding the primary melanoma. In the others 25 pts, 185 MBq of Tc-99m-(Fab')2 MoAbs225 28S fragments (TECNEMAB-K-1), binding a melanoma-associated antigen, were injected intradermally both around the site of primary lesion and in the controlateral sitc. All pts had in addition blue dye injected intradermally at the same site of radiotracer prior to the surgical procedure. Early and delayed images were acquired with gamma camera. In all pts except one, injected with MoAbs, the SN(s) was visualized and marked on the skin. When a blue node was identified intraoperatively, its radioactivity level was measured with a gamma detector probe (GPD). In the absence of blue coloration, the probe was used to detect the SN. LS visualized 70 of 73 excised SN(s) (38/39 with colloids; 32/34 with MoAbs) in 55 basins (96%). With GDP 71 SN(s) were detected (97%). Instead 59 were found using only PBD (81%). A tumour positive SN was found in 13 pts (26%). This study demostrates that LS combined with GPD is a safe and more effective method of detecting SN than PBD technique. LS with MoAbs confirmed the results of LS with colloids in SN detection. There were no evidence of increased uptake of MoAbs in the involved SN compared to controlateral non involved nodes.

OP 158

DIFFERENTIAL EXPRESSION OF TRANSCRIPTS IN A MODEL OF MELANOMA PROGRESSION.

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To identify genes differentially expressed during the progression of human cutaneous melanoma, we took advantage of an experimental model of tumor progression previously developed. WM35 cells isolated from an early stage RGP human melanoma lesion were mutagenized by insertional mutagenesis and aggressive variants, expressing several biological features associated with clinically advance stage melanoma, were established.

To discover genes which were differentially expressed in the cell populations, messanger RNA was isolated from the parental WM35 and the aggressive variant T35-31 cells and compared by suppression subtractive hybridization to generate subtracted libraries. Screening, by Northern blot analysis, of 90 cloned subtracted cDNAs confirmed that about 35% are candidate cDNAs differentially expressed. Specifically, 20% corresponded to transcripts only expressed by the aggressive variants, 6% showed increased expression in the agressive variants compared to the parental cells, 9% showed differences in trancript size. Further work is underway to identify the nature of the transcripts and to determine their involvement during melanoma progression.

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PP 157

INTRA-OPERATIONAL IRRADIATION OF THE BONE REPLANTS AT SAVING OPERATIONS OF THE BONE SARCOMA PATIENTS

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Treatment of the support and motion apparatus malignant tumour patients envisages the complex use of ray- and chemotherapy and surgery. An adequate radical operation remains the main and leading part in this complex.

Tha complicated bone and plastic operations that are impossible without transplantation are spread during the recent years. Allo- and autoplastics, endoprothesis making are traditionally used to replace the bone defects. Along with the advantages, these methods have their own drawbacks. Massive allografts may be broken, resolved of fragmented with time. Endoprothesis may cause the reaction of the surronding tissues in the form of metalosis or late supporations. Therefore, the search for a new plastic material is justified and actual.

Recently, experimental works on the use of irradiated bone grafts to replace the bone defects under oncology operations (V. Mitin, et al., 1997) were published. As autografts with the joint grounds, they have a number of advantages over the allografts, especially for children and teenagers, for whom it is difficult to find a congruent joint end.

In the radiological department of the Medical Radiological Research Center of the Russian Academy of Medical Sciences transplantation of the grafts of the irradiated resected bone, effected by tumour, was done on 10 osteogenous sarcoma patients since 1994. All patients were done distant gamma therapy between one and six months before the operation in the Accumulated Focal Dose 36 Gray along with the chemotherapy courses.

Intra-operational irradiation of the resected bone was done extra-corporal, under sterile conditions by the electric beam on the medical accelerator Microtron-M. Electron energy was 12-18 MeV, the bones were irradiated by two opposite fields, Distance-Source-Surface was 100 cm, focal seat dose was 60 Gray, at 80% isodose. The bone after irradiation was replanted and fixed by commonly used methods.

Control for the reconstruction of the transplanted bone was done by X-ray-grams when gypsum bandages were changed. The preliminary analysis showed that the reconstruction processes in the replants began already a month after the operation and were denoted in the formation of the delicate periostal corn between the fragments of the mother bone and replant. The maximum peak of the recontruction in the replants was in the 6th - 7th months after the operation. The corn between the fragments at these time periods looked like dense coupling shadow. The cortical layer of the mother fragment was imperceptibly changing into the cortical one of the replant. In the period between 18 and 30 months the essential changes in the replants structure did not occur. The functional character osteoporosis due to the long immobilization of the mother bone and replant was registered.

Thus, the preliminary data let us consider that the irradiated replants of tumour bone fragments may under definite conditions be used to replace big defects of the bones upon the removal of the tumour. Single irradiation by the big single dose had no negative influence upon the consolidation of the bone fragments. The search of the optimal irradiation parameters of the replant is continued with the experimental dosimetry research.

OP 159

SENTINEL NODE MAPPING IN CLINICAL STAGE I MELANOMA PATIENTS.

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Management of clinically negative lymph nodes in clinical stage I melanoma patients is still a major controversy. Sentinel node (SN) biopsy can be used to select patients with primary melanoma for therapeutic lymphadenectomy. The aim of the study was to assess the efficacy of two methods to locate the SN: patent blue dye (PBD) and gamma detecting probe (GDP) using ^{99m}Tc labelled colloid particles of human serum albumin. We studied 66 patients (M:F, 36:30; mean age±SEM, 51±1.8; range 18-80 yrs) with cutaneous melanoma and clinically negative lymph nodes. Within 24 hours prior to surgery, 7 Mbq of ^{99m}Tc labelled colloid was injected intradermally around the site of the primary melanoma. The patients were studied using dynamic lymphoscintigraphy, visualising a total of 88 SN in 70 lymph node basins. All the patients had in addition blue dye injected at the same site immediately prior to the surgical procedure. When the blue stained node was identified intraoperatively, its radioactivity level was measured with the GDP. In the absence of blue coloration, the GDP was used to trace the SN. Sentinel nodes were identified in the regional draining basin during intraoperative lymphatic mapping using PBD in 73/88 (82.9%) patients and by GDP in 85/89 (95.5%) patients. Combining the two methods SN were detected in 88/89 (98.9%) patients. Sixteen out of 66 (24%) patients had pathological positive SN, and were subsequently subjected to regional lymphadenectomy. In 14 out of 16 patients (87.5%) the SN was the only node with metastasis. No major complications were encountered. Two cases of recurrence (12.5%) in patients with microscopic SN metastasis and two (4%) in a patient without SN micrometastasis were found during a median follow-up of 371 days. Preoperative dynamic lymphoscintigraphy, intraoperative mapping with PBD and GDP seems to offer a simple and reliable method of staging regional lymph nodes without subjecting to a regional lymphadenectomy all the patients.

OP 160

A STUDY ON S-PHASE FRACTION AND MIB-1 IN SOFT TISSUE SARCOMA PATIENTS WITH RESPECT TO PROGNOSIS

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Proliferation rate was measured by Mib-1 staining and S-phase fraction (SPF) from primary tumors and the results were correlated to soft tissue sarcoma (STS) patients' prognosis.
155 STS patients' primary tumors SPF were measured in the context of our previous work. (Huuhtanen-96). These patients had either extremity or superficial trunk STS treated in our clinic. We found that SPF had prognostic value only in diploid tumor group but not in the whole material. Low SPF predicted longer survival. 123 Mib-1 stainings were done to the same study population. Median Mib-1 was 18 (range 1-55). The median Mib-1 was 11 (range 1-48) in diploid tumors. The median Mib-1 was 24.5 (range 3,5-55) in non-diploid tumors. The correlation with Mib-1 and grade, ploidy and SPF were strong. Correlation with Mib-1 and size were not seen. Low Mib-1 predicted longer metastasis free survival (MFS) (p=0.008). Low Mib-1 predicted also longer overall survival (OS) (p=0.020). The results were not significant when analyzed separately in different ploidy groups. When we used the cut point value of 10% represented by Choong in 1994, the prognostic significance of Mib-1 was strong in whole material, OS analysis p=0.0058 and MFS analysis p=0.017.
Conclusion: Ki-67 (Mib-1) can be used to evaluate the prognosis of STS patient. Based to our result Ki-67 is better prognostic factor than SPF in STS. The cut point 10% value suggested by Choong-94 worked well also in our material.

OP 161

ROLE OF LOCAL RADIATION IN THE NEOADJUVANT PROTOCOL IN OSTEOSARCOMA.

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Radiation therapy for local control of non-metastatic high-grade osteosarcoma of the extremities is a still a controversial issue. The net worth of XRT as a part of neoadjuvant combined modality treatment was investigated in 27 patients treated in our institution between 1991 and 1995. The treatment protocol incorporated two cycles of cisplatinum and epirubicin: radiation at the dose of 35Gy over 10 days being given in between cycles. Local wide excision of the tumour was performed at the 5th week from the start of treatment followed by four additional cycles of chemotherapy. Mean patients age was 18,9 (11-38). Tumour localization included 12 femur, 7 tibia, 1 femur and tibia, 3 humerus and 4 fibula. 26 patients underwent limb-sparing surgery, one patient had an above the knee amputation for progressive disease. After the primary treatment, 90% or more necrosis was observed in 18 patients, 15 of them irradiated. Necrosis rate varied between 60-90% in 6 patients, 4 of them irradiated. The remaining 3 patients had necrosis rate less than 60%, none of them irradiated. Chi-square test showed a significant correlation between radiation therapy and necrosis rate. None of the irradiated patients progressed prior to surgery. Mean overall survival was 50 months (37-63, 95% CI) no significant difference was observed between irradiated and non-irradiated groups. Mean disease-free survival for the irradiated and non-irradiated group of patients was 22 months and 17 months, respectively. This difference however, was not found to be significant it can be explained in terms of patients heterogeneity and an imbalance of patients within two groups. We conclude that radiation treatment improves the necrosis rate with better local control but with no significant impact on disease-free and overall survival.

OP 162

COMBINED HYPERTHERMIA AND RADIATION THERAPY IN THE TREATMENT OF RECURRENT MALIGNANT MELANOMA.

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Malignant melanoma is considered to be one of the most radioresistant tumors. In the past decade various strategies are employed in the attemp to evoke better local tumor control then that achieved with radiation (RT) alone.
From September 1983 to July 1994 48 patients affected with recurrent primary or metastatic malignant melanoma, were treated with a combination of RT and hyperthermia (HT). The number of lesion submitted to the combined therapy was 86. The lesion were located in head and neck area, chest wall, upper and lower extremities. Overall response rate was 72%, with 36% of completed response rate ; local tumor control was 24% at 60 months. The detailed analysis of the treatment result shows that the tumor control rate is dependent on the dose per fraction, the number of heating session, the core temperature and the size of the lesions.
In general, no enhanced skin and subcutaneous reaction developed after combined treatment relative to those obtained after radiation alone.
I n conclusion, the association of RT and HT can be effective when large dose per fraction (400-800-cGy) of RT and adequate thermal dose can be delivered in a tumor of less then 3 centimeters.

OP 163

UVEAL MELANOMA: POSSIBLE MICROSATELITE INSTABILITY

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Microsatelite instability (MSI) evaluation results in uveal melanoma (UM) patients are presented.
Two groups were tested - choroidal melanoma (CM) - 16 patients and iris&ciliary body melanoma (ICM) - 4 patients. The analysis was performed on 8 MSI primers of non tumour (ocular tissue, blood, mouth washout cells) and parafin embedded tumour DNA, extracted from each patient - 80 samples total, reproducing polyacrylamide gel interpretation.
Although determination of MSI status in UM patients can be usefull for screening and possible prognosis, defining exact criteria appeared still debateble, concerning specificity of this type of melanoma.

PP 164

TOXICITY PROFILE OF HIGH DOSE METHOTREXATE (HD-MTX) IN OSTEOSARCOMA (OS) PATIENTS

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Though its well known activity in the treatment of osteosarcoma, use of HD-MTX may have some limitations due to possible toxicity. We evaluated the toxicity profile of HD-MTX (12 g/m^2-max:20 g) used for OS patients together with cisplatin, adriamycin and ifosfamide in our conditions. Between august 1995-october 1997, 20 patients were administered 194 cycles of HD-MTX in either neoadjuvant or adjuvant setting. With hydration and alkaline therapy urinary volume kept more than 1800 cc/m^2/day and pH>7 just before and for at least five days after HD-MTX administration. Serum MTX levels were measured beginning at 24th hour to adjust dose of leucovorine. In 181 cycles (93.2%) the elimination of MTX were normal. Early MTX elimination were delayed in 3 (1.5%) and late MTX elimination were delayed in 10 (5.1%) cycles. Reversible acute non-oliguric renal failure were observed in 2 patiens with delayed early elimination. Two of those patients with delayed early MTX elimination had successful rechallange without significant nefrotoxicity and with normal elimination in other cycles. One out of three refused rechallange and further therapy. Leucovorine 15 mg/q6h for 10 doses were enough for patients with normal MTX elimination but 40970 mg/15 days, 17700 mg/10 days and 6500 mg/8 days were needed to manage those with delayed early elimination. Liver enzymes stayed normal in 13 cycle (6.7%), increased 2 to 15 times of normal in 166 (85.5%), and more than 15 times normal in 15 (7.7%) cycle. No persistant liver disfunction was observed. Hematological toxicity were limited to 21 cycles, 17 (8.7%) grade 3, and only 4 (2%) were grade 4, 2 (1%) with febrile neutropenia. Gastrointestinal toxicity observed as grade 1-2 emesis in 25 (12.8%), grade 1-3 mucositis in 11 (5.6%), and grade 4 mucositis in 1 cycle. In 2 cycles (1%) exfoliative dermatitis, 2 (1%) fever and 2 (1%) conjuktivitis were observed. In one cycle although MTX elimination was normal, encephalopathy was observed on the 4th day of administration and improved without neurological deficit with supportive care. There was no fatal side effect due to the HD-MTX. The high cost of HD-MTX treatment is comparable with any intensive chemotherapy regimen. With known effectiveness and lack of late toxic effects, its manageable acute toxicity must not cause abstain from its use in young patients with curable malignant disease.

OP 165

PREREQUISITES FOR EFFECTIVE ISOLATED LIMB PERFUSION USING TUMOR NECROSIS FACTOR α AND MELPHALAN IN RATS.

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Isolated limb perfusion (ILP) with TNFα in combination with Melphalan has been reported to yield high reponse rates in patients with advanced soft tissue sarcoma and 'in transit' metastasized melanoma. Similar response rates and histopathological characteristics are obtained by TNFα and Melphalan in rat osteo- and soft tissue sarcoma models. These models provide us with a pre-clinical model to determine prerequisites for an optimal perfusion.
The present study is to determine the minimally required TNFα concentration in combination with Melphalan and optimal perfusion time in ILP in rats. Furthermore, the influence of hyperthermia and hypoxia were studied for their potential to enhance anti-tumor effects.
Various TNFα concentrations (10, 20, 50 and 100 μg) in combination with 40 μg Melphalan were added to the perfusate. Perfusion times of 10, 20, 30 and 60 minutes were used. ILP was performed at room temperature (24-26°C), with 'mild' hyperthermia (38-39°C) and with 'true' hyperthermia (42-43°C).
This study demonstrates that 50 μg TNFα is the minimally required concentration in combination with 40 μg Melphalan in our rat model. Optimal perfusion time is preferably 30 minutes. Hypoxic ILP has no benificial effects over oxygenated perfusions. Addition of hyperthermia is mandatory to induce anti-tumor effects of TNFα and Melphalan in ILP.

Novel Therapeutics and Pharmacology

OP 166

SUCCESSFUL TREATMENT OF LIVER METASTASES BY SELECTIVE RADIOTHERAPY WITH IN^{111}-OCTREOTIDE.

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Somatostatin receptor (SSR) positive tumours can be visualised by Octreoscan which uses low dose radioactive ^{111}Indium coupled to Octreotide (^{111}In-Oct). ^{111}In-Oct is selectively bound to the SSR. We wanted to investigate whether it was possible to perform selective SSR-targeted radiotherapy with a high dose of ^{111}In-Oct.

Methods: SSR positive and negative tumour cells were injected into the portal vein on day 0. ^{111}In-Oct therapy (370MBq, 0.05mg) was given iv on day 1 and 8. Control rats received 0.05 mg"cold" octreotide without ^{111}In. Tumour colonies in the livers were counted on day 21.

Results: Tumour colonies of SSR-positive pancreas tumour cells (CA20948) were significantly reduced (0,0,0,0,3,15) vs. (3,20,38,60,>100,>100) in the control group ($p<0.01$). This result suggests a strong effect of targeted radiotherapy. We repeated the experiment and blocked the SSR with a saturating dose of 1 mg "cold" octreotide. The effect of ^{111}In-Oct therapy was annihilated. The presence of the specific SSR seemed to be necessary for therapy. When SSR-negative colon adenocarcinoma cells (CC531) were used the number of tumour colonies for this SSR-negative tumour was not reduced by ^{111}In-Oct. Also in this experiment the receptor dependency is demonstrated.

These experiments show the SSR-mediated effect of selective radiotherapy with ^{111}In-Oct as "harpoon". These promising results could be a basis for clinical application because a wide range of tumours do express SSR.

PP 167

THE RISK OF RADIATION CARCINOGENESIS AFTER TREATMENT OF AGE-RELATED MACULAR DEGENERATION

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In order to assess the risk of radiation carcinogenesis after treatment of age related macular degeneration (ARMD=subfoveal choroidal neovascular membrane=CNVM), we made some dosimetric calculations with thermoluminescent dosimetric (TLD) chips on a male randophantoma using our treatment technique.We use 6 MV X-ray for the treatment of ARMD and our total dose is 1200 cGy. Our dose per fraction is 200 cGy. All dosimetric calculations were made 3 times.We found that the dose the lens received was 217 mGy per fraction.To calculate the risk of radiation carcinogenesis after this treatment, we measured doses received by red bone marrow, thyroid, oesophagus, lung, bone surface, skin and brain by TLD.Average doses received consecutively were: 42, 52, 43, 16, 11, 76 and 211 mGy. Then, using the tissue weighting factors (which have been defined previously by the International Commission of Radiation Protection - ICRP), we estimated total effective dose. The total effective dose for our dosimetric calculation with TLD is 17.86 mGy. The risk factor for fatal cancer development in human epidemiological data is presently assumed to be 10% per Gy. Consequently, for fatal radiogenic cancer development,a risk of 0.0018 (or 2 per 1000 persons or 0.2%) exists in patients treated for macular degeneration.

OP 168

RIBOZYME-MEDIATED INHIBITION OF HPV-16 E6/E7 IMMORTALIZATION OF HUMAN KERATINOCYTES.

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HPV-16 E6 and E7 genes are required to efficiently immortalize a broad spectrum of cell types including cervical keratinocytes. Therefore, the E6/E7 gene can be considered relevant targets for anti-cancer therapy. We produced several engineered hairpin (HP) ribozymes with the purpose of specifically disrupting HPV-16 E6/E7 mRNA, HP ribozymes are catalytic RNA molecules able to hybridize and cut RNA targets provided they contain the GUC sequence. After extensive *in vitro* characterization, one anti-E6 HP ribozyme (R434) was selected for *in vivo* testing because of its superior catalytic capabilities. An inactive version of R434 (R434i) able to hybridize but unable to cut was used as control. *Cis*-expression of R434 or R434i with HPV-16 E6/E7 genes in normal human keratinocytes reduced cell survival after eight weeks of continuous growing. R434 was more effective with less than 15% overall survival compared to HPV-16 E6/E7 transfected cells while R434i had a survival mark close to 40%. RNA analysis by RT-PCR showed that full-lenght E6/E7 transcripts were virtually absent in both cases. However, R434 showed multiple bands suggesting processing. Trans-expression was done by cloning R434 downstream of human $tRNA^{Val}$ subsequently transfecting of previously immortalized HPV-16 E6/E7 keratinocytes and Caski cells. After selection of transfected cells, both R434 and R434i significantly inhibited cell growth compared to the vector tranfected cells; however no significant differences were noticed between R434 and R434i transfected cells. Therefore, although R434 has a low level of effectiveness the present results are encouraging because they prove that R434 is able to hybridize and process its target in the cellular environment.

OP 169

TGFβ AND TNFα MODULATION BY TOREMIFENE IN FIBROMA AND DESMOID TUMORS

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In vitro studies on cultured desmoid cells have demonstrated that proliferation and collagen synthesis are stimulated by 17β-estradiol, while Tamoxifene inhibits this effect. Toremifene (T) is a triphenylethylene derivative related both chemically and pharmacologically to Tamoxifene. At high doses, T appears to exert a cytolitic effect independent of its anti-oestrogenic action as evidenced by its antitumor effect in mice with estrogen receptor negative uterine carcinoma and in patients with desmoid tumours. Other authors have demonstrated the regulation of TGFβ in humans in vivo in response to anti-oestrogens. This drug may alter the balance of growth factors with regression of the tumour. In the present study we evaluated the effects of T on cell growth and TGFβ and TNFα activity. We utilized three cell lines: healthy fibroblasts (HF), fibroblasts from fibroma (FF) and desmoid (DF). Our results show that T 0.5 and 1 μM induced a slight reduction of cell viability dosed using the colorimetric method. Moreover, T decreased TGFβ activity revealed through biological assay on MV1Lu cell line more markedly in HF and FF than in DF. The cellular lines utilised are unable to produce TNFα both in the presence and absence of T. We are evaluating TNFα production by macrophages in the presence of T. Since TGFβ induces an increase of extracellular matrix, TGFβ reduction following T administration may explain the regression of fibroma and desmoid tumours in which extracellular matrix is particularly abundant.

PP 170

BIOLOCATION DIAGNOSIS - A KIND OF PROPHECY

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1.Method is preventiv,because make diagnosis of change in the organs in early phase of development of oncology illness.
2.Method determine rational cure in concrete phase of illness-surgical,chemical therapy,radiation or another therapy.
3.Method help test and determine effective medicine for concrete patient.
4.Method is enable prognosticate during of illness for concrete patient.
This method I have using in my doctor`s practice about 15 years.When I make diagnosis,I have on my hand antenna,and the time,which I need is about 20 minutes.
I am able make diagnosis also from photo.
I have a lot of patients from all Europe.
I have excellent results of cure.

PP 171

A RADIOBIOLOGICAL COMPARISON OF PHOTON AND NEUTRON BEAM IRRADIATION IN CELL CULTURES IN VITRO

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Boron neutron capture therapy (BNCT) offers a new method of targeted cancer treatment.
The aim of the study is to compare the radiobiological effects (photon, neutron, beam) in cell lines (glioblastoma, head and neck, HeLa, melanoma). Different boroncarrier mediums, are tested. The location of the cell destruction is estimated. The cytotoxicity of 4 chemotherapy agents (paclitaxel, carpoplatin, mitomycin etc.) are tested.
The cell curvival curves and dose-response curves will be presented. The characteristics (RBE) of the Fir1 neutron beam is presented.

BNCT offers a new method of targeted cancer treatment. The main interest is in the treatment of glioma-patients and promising results with melanoma.lung cancer treatments presented.

PP 172

ANTICANCER EFFECT OF ULTRA LOW DOSE OF METHYLNITROSOUREA (MNU).

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Experimental *in vivo* study of tumor cell proliferative reaction on ultra low dose of MNU (0,2 ml of 10^{-10}M MNU water solution x 1, i.p.) was carried out. Proliferative activity was estimated by measuring of the intensity of tritiated thymidine incorporation in tumor cells. It was found that on the 1st day MNU caused considerable increase of radioactivity per minute per 10^6 tumor cells (67,5±4,4 - control; 144,7±23,4- treatment). After that took place stable decrease of this index. Besides that MNU administration led to the significant increase of average life duration of tumor-bearers (38,3±4,5 days - control; 58,6±8,9 days - treatment). Received results shown that ultra low dose of MNU has an anticancer activity which is based on the inhibition of tumor cell proliferation.

OP 173

MANIFESTATION OF ACUTE CARDIOTOXICITY IN PATIENTS WITH MALIGNANT DISEASES DURING ANTHRACYCLINE ADMINISTRATION

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Anthracyclines are one of the largest groups of cytotoxic agents with probably the most expressed cardiotoxicity. Cumulative doses and late toxicity are well investigated. Manifestation of acute cardiotoxicity seems to be less important although some cases of sudden deaths during anthracycline administration were described (Wortman et al. Cancer 44;1979 and Ragab et al Cancer 57; 1986). A total number of 99 patients, 36 with soft tissue sarcomas, 28 with non-Hodgkin lymphoma, 23 with nasopharyngeal carcinoma, 7 with breast cancer and 5 with lung cancer (75 male and 24 female, age 16 - 76 years, median 51) were treated with different anthracyclines. Zorubicin, Doxorubicin, Epidoxorubicin and Mitoxantron were applied in 40, 21, 20 and 18 patients respectively. Standard 12-lead and continuous electrocardiograms were recorded in all patients by "holter"-EKG monitoring, before, during and after anthracycline administration. Each patient was a control for him self, in a second control group were patients anthracycline naive during first application of drug and in the third control group were 29 patients without malignant disease on intravenous symptomatic therapy. Analysis of 238 "holter" EKG records in comparison with control demonstrated significant QT shortens, increase of sinus tachycardia, a number of atrial ectopic beats (AEBs) and ventricular ectopic beats (VEBs) during anthracyclines application. In sporadic cases VEBs were multifocal (Lown III grade). The number of AEBs remained or even increased a certain time after drug administration. All these electrocardiographic changes were most expressed during the first anthracyclines application. All of them were transient, so they didn't request interruption of anthracycline used or additional therapy. But some cases with multifocal VEBs point to a possibility of serious arrhythmias.

OP 174

MEASUREMENT FO THE IDIOTYPIC NETWORK RESPONSE TO MONOCLONAL ANTIBODY THERAPY FOR OVARIAN CANCER

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Overall survival from ovarian carcinoma is in the region of only 30%. Complete remissions (CR) are often achieved after optimal primary surgery followed by platinum-based chemotherapy. Monoclonal antibodies (Mabs) may be used to consolidate these responses: we are conducting studies using both radiolabelled MAb (single, intraperitoneal dose for patients in first pathological CR) and unlabelled MAb (multiple intraderma) doses for patients in 2nd CR or with residual peritoneal disease). The MAb used in both trials is the murine Mab HMFG1, which is directed against the tumour associated antigen MUC1. Methods have been developed to assess the generation of anti-idiotypic (Ab2) and anti-anti-idiotypic (Ab3) antibodies in patients receiving HMFG1.
The induction of both Ab2 and Ab3 has been shown in both groups of patients by ELISA. We have also used a biosensor to demonstrate affinity maturation of the Ab2 response as patients progress through the multiple-dose MAb vaccination regimen, the first time that this has been shown using this technique.
MAb therapy is most likely to find clinical application in the treatment of minimal residual disease. Traditional clinical and radiological assessments of response have no value in this setting. Assessments of immunological response can be correlated with survival and thus used to modify MAb treatment strategy: we have used this information in modifying our unlabelled MAb regimen.

OP 175

PHARMACOKINETIC (PK) STUDY OF A COMBINED PACLITAXEL (P) AND EPIDOXORUBICIN (E) REGIMEN.

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PK analysis of E and its metabolites epirubicinol (EOL) and 7-deoxyaglicone (7d-AONE) was performed in 12 pts with node positive breast cancer treated with a combination of P (175 mg/m² in a 3-hour IV infusion) and E (90 mg/m² as an IV bolus). Four pts received their first CT course with single-agent E 24 hours before P, for baseline E PK studies. All subsequent pts (n=8) were treated with E either immediately before or after P, in the first course. The opposite sequence was adopted in the second. Heparinised blood samples were obtained before treatment, at the end of E injection and 5, 15, 30 and 60 min, 2, 3, 4, 6, 24, 48 and 72 h after E administration. Parent E and metabolites were measured by HPLC with fluorimetric detection. A triexponential equation provided the best description of plasma E elimination for all pts examined. The main PK parameters for E alone and in combination with P are listed in the table.

		E	E --> P	P --> E
C_0	mg/l	2118 ± 366*	1693 ± 712	4840 ± 2478*
Terminal half-life ($t/2_\gamma$)	h	20.4 ± 4	15.0 ± 2.0	13.0 ± 1.0*
Total plasma exposure ($AUC_{0-\infty}$)	mg/l h	1758 ± 226	1520 ± 137	1735 ± 227
Volume of distribution (Vss)	l/m²	1146 ± 109	1117 ± 310	671 ± 198*
Total-body Clearance (Cl_{TB})	l/h/m²	50 ± 6	58 ± 8	46 ± 9

* mean ± s.d. * p<0.05 vs E->P (Wilcoxon Signed Ranks test)

The PK parameters of parent E were not significantly influenced by P in the E-P sequence. E $t/2_\gamma$ was 25% lower than baseline when administered immediately before P, but the difference did not reach statistical significance (p=0.066). In contrast, in the P-E sequence C_0 values were approximately twice the baseline and the E-P values. Of note is the significant decrease in the $t/2_\gamma$ and Vss in the P-E sequence compared to the reverse one, with no difference in the AUC and Cl_{TB}. In all pts, EOL appeared quickly after E administration and its terminal half-life was close to that of the parent drug (18.2±5 and 13.9±3 h in pts treated with E alone and in combination with P, respectively). EOL AUC increased 1.6-fold from baseline when E was administered with P (1528±128 vs 981±205 mg/l h). A similar pattern was noted for 7d-AONE. Both metabolites increased during P infusion and the plasmatic peak was reached at the end of P infusion. These findings suggest that concurrent administration of E and P can cause an altered metabolic or PK behaviour of E in man. However, although P affects the metabolic profiles of E regardless of the sequence used, differences in the PK of parent E from baseline were observed only when P was given before E. The possibility of a faster release from tissues or an increased elimination rate of E when this sequence is used warrants further study.

OP 176

SEQUENCE-DEPENDENT PHARMACOKINETICS (PK) OF IFOSFAMIDE (I) COMBINED WITH DOCETAXEL (D).

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The PK of different sequences of the combination of D and I were studied in a phase I study in cancer patients. D was given as a 1-hour infusion followed by a 24-hour infusion of I (schedule A). After reaching maximum tolerated dose (MTD)(D:85mg/m²;I:5g/m²), I was administered as a 24-hour infusion followed 24 hours later by a 1-hour infusion of D (schedule B). Both schedules were given every 3 weeks. Schedule B was more toxic (MTD:D:75mg/m²; I:5g/m²). Plasma concentrations of D and I were determined by HPLC. Twenty seven patients were treated with schedule A, 6 with B. Combining D and I did not alter their plasma half live ($t_{1/2}$) compared to single agent data in the literature (D:$t_{1/2}\alpha$: 4.4-11.6 min; I:$t_{1/2}$: 3.8-7.1 h). The area under the curve (AUC)of D increased with increasing doses (2.8-3.7 µg.h/ml). Sequence of administration did not alter AUC or clearance (CL) of D. The AUC of I increased with dose (322-792 mg.h/L). AUC of I was higher in schedule B (1330 + 610 mg.h/L) compared to A (792 ± 324 mg.h/L) at equal dose related to a higher CL in B.
D PK are not influenced by combination with I regardless the sequence but I PK are schedule dependent resulting in a higher clinical toxicity when I is given before D.

PP 177

MONOCLONAL ANTIBODY-BASED THERAPY

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Monoclonal antibodies have been developed for cancer therapy because they specifically target tumour related antigens. The current design of antibodies and delivery strategies seek to overcome the obstacles encountered in delivering antibodies to their target. Protein engineering techniques to humanize murine antibodies diminishes to immune response, which develops against murine monoclonal antibodies, allowing for multiple doses. Antibodies linked to vasoactive substances or conjugated to liposomes increase antibody and drug localization to tumours. Tumour growth factors increasingly are bein targeted by antibody-based therapeutics. To enhance immune activation of cytotoxic effector cells, bispecific antibodies and antibodies linked to superantigens are being examined. Prodrugs are being converted to their active compounds at the tumour site by antibodies conjugated to enzymes.

OP 178

ADENOVIRUS-MEDIATED HSV-tk GENE THERAPY FOR BT4C RAT GLIOMA

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Introduction: Gene therapy is a novell approach for the treatment of malignant glioma. In the present study we evaluated the efficacy of adenovitus-mediated Herpes Simplex virus-thymidine kinase (HSV-tk) gene therapy in rat malignant glioma.
Methods: BDIX rats received stereotactic adenovirus (AdV-tk) injections (20µl; titer 1.6 10^{∞} pfu/ml) into the tumour or healthy brain tissue either once (n=26) or three times (n=25), followed by GCV medication. The growth of the tumours were confirmed with MRI. Animals (n=31) were sacrificed after GCV treatment. 26 rats were left for long term follow up. Hematoxylin-eosin (HE) staining was performed to show brain tumours. Astroglia and microglia responses were evaluated with GFAP and CD68 immunohistochemical stainings.
Results: HE-stainings showed large glioma tumours in the control group. Animals with BT4C glioma tumour and AdV-tk gene therapy showed large tumours with small necrotic areas which were probable due to the treatment effect. GFAP reactivity was positive at the injection site and surronding the large tumours. No or very little CD68 reactivity was shown. The survival study is going on.
Conclusion: Adenovirus-mediated HSV-tk gene therapy may offer a new additional tool for treatment of malignant glioma.

PP 179

ECTEINASCIDIN-743 (ET-743), A MARINE NATURAL COMPOUND, SHOWS ANTITUMOR ACTIVITY AGAINST HUMAN OVARIAN CARCINOMA XENOGRAFTS.

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ET-743 is a tetrahydroisoquinoline alkaloid of marine origin which has shown activity *in vitro* and *in vivo* against a variety of human tumor cell lines. Although it is known that ET-743 binds to DNA and modifies the microtubule network, its actual mechanism of action is not yet fully elucidated. The antitumor activity of ET-743 was studied on three human ovarian carcinoma xenografts transplanted s.c. in nude mice: HOC22, HOC18 and MNB-PTX1, sensitive, marginally responsive and resistant to cisplatin, respectively. ET-743 was given i.v., at various schedules and doses. At the optimal schedule of Q4x3 and maximum tolerated dose (MTD) of 0.2 mg/kg/inj, ET-743 induced long-term complete regressions in 83% of mice bearing HOC22 tumors and caused a significant growth inhibition (T/C=6%) of HOC18 tumors, while it had almost no activity on MNB-PTX1 tumors (T/C=72%). On the intraperitoneal ovarian carcinoma xenograft model, ET-743 significantly increased the survival time of mice bearing HOC22 tumors with complete tumor remissions. These results, showing that ET-743 is active on ovarian carcinoma xenografts, further support clinical assessment of this drug.

OP 180

HYPOXIC PERFUSION OF PELVIS, ABDOMEN AND LIVER WITH TNF-α MELPHALAN AND MITOMYCIN C USING NEW BALLOONCATHETER TECHNIQUES : PHARMACOKINETICS IN PIGS

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The promising clinical results of isolated extremity perfusions with TNF-α and Melphalan for melanoma and soft tissue sarcoma have initiated efforts to translate this success to other perfusion settings. The aim of this study was to investigate pharmacokinetics of TNF-α, Melphalan and Mitomycin C during hypoxic pelvic (HPP), hypoxic abdominal (HAP) and isolated hypoxic hepatic perfusion (IHHP) using an innovative minimally invasive balloon catheter technique in pigs.
Pelvic and abdominal vascular beds were isolated by retrogradely inserted balloon catheters in aorta and caval vein with balloons positioned at the level of bifurcation (HPP) or diaphragm (HAP). IHHP was performed by inserting a double balloon catheter in the caval vein, canulating the hepatic artery and clamping the portal vein. Marked regional drug concentration advantages were observed during all three procedures. During HAP and HPP, however, regional drug levels steadily declined and significant systemic drug levels were measured due to leakage through collaterals. Throughout and after IHHP no significant systemic drug levels were measured, indicating complete isolation and an efficient wash-out procedure.
The results demonstrate that when performing HPP, HAP and IHHP with described balloon catheter techniques, marked regional concentration advantages of perfused agents can be achieved, while keeping systemic exposure minimal.

OP 181

CT AND MRI IN 3D-CRT PLANNING OF PROSTATE CANCER

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3D-CRT (three-dimensional conformal radiotherapy) uses sophisticated computerized treatment planning to accurately conform the distribution of a prescribed radiation dose to the anatomy of the prostatic target volume in its 3D configuration. One of the problems encountered in 3D-CRT is the exact delineation of the target volume. At present, MRI is not routinely used for prostate 3D-CRT planning because of the lack of tissues density information required for the correction of inhomogeneities used in dose calculation algorythms. However, prostate anatomy is very well defined by T2-weighted images, and some uncertainties usually inherent to CT-imaging could be solved using MRI. With CT-scan the precise localisation of the prostate apex is perhaps the greatest area of uncertainty, and the adequate coverage of this region with high-dose radiation is likely to be important (up to 75-85% of prostate cancers involve the apical portion of the gland). CT images on the other hand have the advantage of providing density data necessary for RT planning, together with rather good definition of the taget, but they usually result in a delineation of a target which is larger than the gland itself, and which often includes seminal vesicles, bladder base, venous plexus, fibromuscular stroma, neurovascular bundles and anterior rectal wall. The interest of MRI in 3D-CRT planning of prostate cancer is increasing, since software for CT-MRI image fusion has become available, combining the advantages of both image modalities. Authors are performing at the University Hospital in Leuven a study on the argument.

OP 182

NUMBER OF CD34+ CELLS INFUSED IS RELATED TO COMPLICATIONS AND MORTALITY OF HIGH-DOSE CHEMOTHERAPY. **A Yubero, A Sáenz,, JI Mayordomo, R Cajal, M Alonso, P Bueso, J Herráez, MD García-Prats, P Escudero, D Isla, A Tres. Division of Medical Oncology. Hospital Clínico Universitario. Zaragoza, Spain.**

Infusion of peripheral blood stem cells (PBSC) following high-dose chemotherapy (HD-Cht) results in shorter aplasia than bone marrow (BM), and this translates into less extrahematologic complications and lower mortality. There is an inverse correlation between the number of CD34+ cells and the duration of aplasia. There is little information as to the clinical correlates of this observation, that is, are the severity of complications and the mortality affected by the number of CD34+ cells infused?. Complications in 45 consecutive patients (pts) treated with HD-CHT+PBSC in our institution was evaluated by an investigator unaware of the CD34+ counts, and subsequently correlated with the number of CD34+ cells infused. Pts with mild complications were those with fever lasting <48 hours, grade 0-2 mucositis and diarrhoea and no need of total parenteral nutrition. Pts with severe complications were those with grade 4 diarrhoea plus either peritonitis or sepsis of intraabdominal origin, and those who required admission in the Intensive Care Unit. All others were labeled intermediate complications. 18 pts had mild complications, 19 intermediate and 8 severe. The median numbers of CD34+ cells$x10^{-6}$/Kg infused were 4.3(range 2.3-18.5), 3.7(2.2-16.5) and 2.9(2-5.3) respectively($p<.05$ mild vs severe). Since the evaluation of complications is subjective, we then compared CD34+ cell numbers in pts with toxic death (5 pts) vs those who survived (40 pts). Medians were 2.6(2-5.3) and 3.7(2.2-18.5) ($p<.05$). None of 12 pts receiving $>5.5x10^6$ CD34+ cells had severe complications vs 24% for <5.5. Infusion of high numbers of CD34+ PBSCs not only results in shorter aplasia but also in milder extrahematologic complications and lower mortality.

Palliative and Supportive Care

OP 183

THE EFFECT OF TWO DIFFERENT DOSES OF ORAL CLODRONATE ON PAIN IN PATIENTS WITH BONE METASTASES

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There are few studies in the literature related to the effectiveness of oral clodronate in pain palliation of bone metastases (BM) and optimal dose is not clear. The aim of this study was to evaluate the efficacy of low dose oral clodronate in palliation of pain arising from BM and to determine the optimal oral clodronate dose which inhibits osteolysis caused by the tumor.
Fifty patients with bone pain caused by BM and using narcotic and non-narcotic analgesics were included in this study. All were receiving antitumor chemo or hormonal therapy. These patients were randomised into three groups according to the dose of clodronate. Groups A and B were given 800 mg/day and 1600 mg/day of oral clodronate respectiveley for 3 months. Group C was the control group. The effect of clodronate in pain palliation was evaluated with pain score, performance status and changes in analgesic use. The effect on osteolysis was examined with urinary calcium, hydroxyproline (OHP) and serum cross-linked carboxyterminal telopeptide region of type I collagen (ICTP) levels.
Group A contained 16 patients, and groups B and C contained 17 patients each. After a 3 months use of oral clodronate, significant decrease in the pain score of groups A and B was noted when compared to group C (p values were 0.024 and 0.007, respectively). The analgesic use of 11 patients in group A (69%) and 8 patients in group B (47%) was decreased, but only the decrease in group A was statistically significant (p: 0.038). Pain score was increased in 5 patients in group C (29%), 3 patients in groups A (19%) and B (18%) each. Therapy increased urinary calcium, OHP ve serum ICTP levels in group C and decreased in groups A and B, but only the decrease of urinary calcium levels of group B was significant (p= 0.003). There was no grade 3-4 toxicity secondary to clodronate use, but gastrointestinal side effects were more frequent in group B than A.
In conclusion, low dose (800 mg/day) oral clodronate seems to be as effective as standart dose (1600 mg/day) in palliation of bone pain secondary to BM.

PP 185

CLINICAL AND EMOTIONAL EVALUATION OF THE ONCOLOGIC PATIENT ON ANTINEOPLASTIC THERAPY.

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The aim of this study are to evaluate the Quality of Life (QL) of patients on antineoplastic therapy (AT) attended at Day Hospital and to assess the relationship between AT and anxiety and depression.
Psyco-oncological clinical sheet has been written which studied general aspects (age, sex, job), clinical and therapeutic aspects (site of the cancer, metastases, type of therapeutical intervention, presence of Port - a -Cath).
We have included some of psychometric tools to evaluate the following aspects: for physical condition we included WHO scale (for adverse effects), for Pain the Italian Questionnaire Of Pain (QUID) and the Visual Analogic Scale (VAS), for coping the MINI-MAC scale, for the quality of life we included the Functional Living Index for Cancer (FLIC) and for Anxiety and Depression the Hospital Anxiety and Depression Scale (HAD).
We have reclutated 114 pts (67 F and 47 M, mean age 60.1 ± 10.6)treated by the Oncologic DH, Independent Section of Oesophageal and Oncological Surgery, of Turin University, during June and July of 1997 to be treated with AT. We have not included follow - up pts.
Multivariate analysis between HAD scale and general and clinical - therapeutical aspects has been shown that there is not relation between the information given to the pts regarding his/her disease and HAD scale, nor between the family living and single status and Had scale, nor between the mutilant surgery and HAD scale. Has been shown a relation between pts with Port - a - Cath and depression pointed out by HAD scale ($P < 0.001$).
A lesser number of pts follow depression therapy than the expectation could be due to the pt's conviction that this therapy is for psychiatric pts. We have found low pain
levels probably because DH pts are not terminal pts. The results of multivariate analysis could be determinated by high number of non responders (78% of n.r. at QUID).

OP 184

NURSING MANAGEMENT OF IRINOTECAN (CPT-11)-INDUCED SIDE-EFFECTS

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To define management policies for nursing personel, side-effects were monitored in patients (pts) receiving CPT-11, an inhibitor of topoisomerase I. Patients failing prior first-line therapy with Fluorouracil combined with Leucovorin for metastatic disease were entered in a Fase II trial of CPT-11 as single agent: CPT-11 350 mg/m2 as a short infusion of 30-90 min. day 1 q 21 days. A median no. of 5 cycles (range 1-9) were given to 25 metastatic colon cancer pts (17 males, 8 females) with median age 63 years (range 36-69). All pts received prophylactic antiemetic treatment with an antiserotonin and steroids. Atropine sulfate was not given at baseline. Side effects were as follows: Grade 3 diarrhoea in 6 pts (24%) all requiring hospitalization; acute cholinergic-like syndrome in 5 (20%); neutropenia, Grade 3-4, 2 (8%) and Grade 2-3 alopecia in 100% of pts. Diarrhoea (there is no known prophylactic treatment) is unpredictable and possibly life-threatening. No. of stools/ day and presence of gross blood should be carefully monitored. Grade 1-2 diarrhoea requires a hypercaloric, low-fibre diet with $\geq$ 2 l liquids/day and loperamide. For acute cholinergic symptoms: slow infusion and atropine 0.25 mg s.c.. For neutropenia: in addition to antibiotic therapy, inform pts and family of importance of temperature and hygenic rules. New drugs require specific nursing procedures.

OP 186

The clinical effect of high doses (HD) metroxiprogesterone acetate (FARLUTAL) in patients with advanced colorectal cancer and cachexia

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Purpose: To evaluate the clinical effect of HD MPA in cancer cachexia pts. - weight gain (weight increase, appetite, serum proteins) and QL (mood, energy).
Patients: 34 recurrent or advanced colorectal cancer pts. with cachexia - anorexia syndrome, Karnofsky performance status >60; average age up to 65; no metastases in CNS; no concomitant treatment -chemotherapy, radiotherapy, corticosteroids or anabols.
Methods: Pts. receive 1500 mg MPA (FARLUTAL) daily for six weeks. At entry into the study and after 3 and 6 weeks, pts. were assessed as follows: weight; blood tests; biochemistry blood analysis etc. QL questionnaires were used.
Results: 30 pts. were eligible for evaluation at week 6. There was significant improvement in appetite (87%) and the body weight (79%) - 1 to 3 kg. QL improvement in 72%.
Discussion: MPA is an effective agent in cancer cachexia with minimal side effects, easy for outpatient treatment. The results are preliminary and the study is still ongoing.

PP 187

BETWEEN SUFFERING AND REDEMPTION

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This study is based on transdisciplinary approach to the religious interpretation of their illness by Jewish and Christian cancer patients. Phenomenology, hermeneutics as well as the interpretative-biographical method were combined to investigate the religious motives patients use to frame their experiences of suffering and in coping. The results not only show that suffering from cancer is to large extent a religious experience but also that Jews and Christians principally do not differ in the motives they choose to overcome their situation. An historical analysis showed that the motives they use are rooted in their respective traditions. Finally it was found that there is an interdependence between patients' way of suffering and their religiousness.

PP 188

PSYCHOTHERAPY AS A SUPPORTIVE CARE IN ONCOLOGICAL PATIENTS

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This paper presents „creative imagery" and „symbol drama" as a forms of psychotherapy techniques in supportive care of oncological patients. „Creative imagery" and „symbol drama" are diagnostic and therapeutic projective procedures in basic individual psychotherapy, evolved by C.H.Leuner.

These techniques were used in 17 patients(lymphoma). Seances (3 days each) were performed during every course of chemiotherapy. For evaluation of emotional status of patients we choose depression level because those syndromes were present in each case of neoplasm. Depression symptoms were examined using Beck Inventory before and after psychotherapy.

Depression symptoms were less intensive after psychotherapy in the patients with applied „creative imagery" than in the patients without psychotherapy. Thereby quality of life was better during and after treatment.

OP 189

WHOLE BODY HYPERTHERMIA AT TEMPERATURES OVER 43.5°C IN THERAPY OF CANCER

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Introduction: Whole body hyperthermia (WBH) at temperatures over 43.5°C uses temperature as a factor directly damaging cancer cells and considerably increases efficacy of chemotherapy. WBH at 43.5°C improves prognosis in cancer patients having advanced metastatic diseases.
Objectives: 60 cancer patients with advanced metastatic diseases (melanoma, lipocarcoma, breast cancer, etc.), underwent WBH at temperatures over 43.5°C and have been under observation.
Methods: Patients under general anesthesia, pulmonary high-frequency jet ventilation and special heat shock protection were heated up to 43.5°C in a special bathtub, the temperature was measured in patient's rectum, esophagus and throat. During WBH reduced dose chemotherapy was conducted. After the procedure chemotherapy was continued at usual doses. The procedure was repeated 2 to 3 times as necessary with 2-3 months breaks.
Results: Immediate effects such as pain syndrome regression and tumour and metastases mass reduction were demonstrated in all patients. Average remission duration after the procedure was 1 year. 15 patients have been in remission over 2 years.
Conclusion: 43.5°C WBH improves prognosis and life quality in patients with advanced cancer, and in a number of cases causes a complete remission.

OP 190

"THE EDUCATION SCHOOL FOR BREAST CANCER PATIENTS" - ONE OF THE WAYS IN PSYCHIC HEALTH PROMOTION IN CANCER PATIENTS

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The risk from psychiatric morbidity is increased during diagnosis and treatment of cancer. To etimate benefit of "information about disease" and benefit of psycho-social support in self-help groups we started weekly meeting for breast cancer patients and their husbands. To estimate social functioning and psychological functioning we used EORTC - QL - 30 - BR - 23 - instrument. Most of Breast Cancer patients are under adjuvant treatment or follow-up. The group is functioning on oppen modality. The meeting sessions are structured in two parts: 1. Small lectures about different medical, social and psychological problems, concerning Breast Cancer treatment and follow-up and 2. Question - answers part.
Our current results suggesting, that Breast Cancer Patients who are members of these meetings have greater levels of social functioning (p=0,003) and psycho-social adaption comparing with no-members.

OP 191

METHYLENE BLUE (MB) IN THE TREATMENT AND PREVENTION OF IFOSFAMIDE (I) ENCEPHALOPATHY

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I is an alkylating agent used in the treatment of a variety of tumours. 10 to 15% of patients develop some form of encephalopathy. MB may be used in the treatment of I encephalopathy.
52 patients (age 16 - 77 years) with a solid tumour were treated between 1993 and 1997 with I. The majority had a sarcoma (32%), lung (17%) or cervical cancer (13%). I was used as single agent or in combination therapy. Dosage of I ranged from 3-5 g/m^2 in the combination schedules to 12 g/m^2 as single agent.
Twelve patients (23%) developed significant depression of the central nervous system (CNS), ranging from somnolence to stupor. Eight patients were treated with MB in a dose of 6 x 50 mg/d IV. Four of them showed complete recovery within 24 hours (3 within the firs 12 h.). Two had partial recovery after 24 hours and complete recovery after 48 hours. Two recovered after 72 hours. Four patients did not receive treatment with MB because the CNS depression was not judged to be severe. All of these patients recovered within 48 hours.
Three patients received prophylactic treatment with MB (4 x 50 mg/d orally) for the subsequent cycles of I. Two of them developed a less severe CNS depression, one had no CNS depression at all.
Conclusion: MB is an effective treatment for I induced encephalopathy. Our findings suggest that it may be used as a prophylactic agent.

PP 192

CONFRONTATION OF BREAST CANCER PATIENTS OF PROGRESSIVE AND TERMINAL STAGE AT HOME, BY HOME CARE SERVICES (Y.K.O.N.) OF "AGII ANARGIRI" CANCER HOSPITAL

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The main purpose of the present study was the nursing evaluation of the services provided to breast cancer patients living at home.
During the ten years of existence of our service, 634 breast cancer patients were treated at home. Of these patients, 5 were men and 629 were women. From the total number of patients, 27% are still alive, 26% died at home, 28% died in the hospital, while 13% completed therapy and left our service.
The problems that were managed by Y.K.O.N. included:
* Wounds, caused by dermal metastasis and bedsores: 20%
* Pain: 47%
* Catheter settlements with monthly changes: 5%
* Patients underwent chemotherapy: 28%

and in all breast cancer patients we did blood tests according to the instructions given by the medical doctor.
Observation, interviewing and completion of structured assessments forms, were used in data collection, that indicated the efficacy of Y.K.O.N. services.
In conclusion Y.K.O.N. is able to provide medical care to breast cancer patients at home, to the same high standards as are available in the hospital and also can meet the emotional needs of cancer patients and their family.

OP 193

OPERATIVE STABILISATION OF SKELETAL METASTASES FROM 217 PATIENTS

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Objective: As a result of improved local and systemic tumour control, the operative stabilisation of skeletal metastases is becoming progressively more important. Here we report our experiences with special remark on endoprosthetics.

Material and Methods: Between 1980 and 1997, 217 patients, 125 female and 92 male, with bone metastases from primary extraskeletal tumours were operatively stabilised. The age of the male patients lay between 36 and 85 years, mean 58.2 years, the age of the female patients between 32 and 82, mean 58.9 years. Of the primary tumours the renal cell carcinoma was most frequently found with 32%, followed by breast cancer with 24% and bronchial carcinoma with 10%. In 18% of the cases the primary tumour remained unknown. 29% of the patients were hospitalised with pathological fractures.

Results: Of the 217 bone metastases 115 were treated by endoprostheses. Replacement of the proximal femur predominated with 62 cases, followed by replacement of the distal part of the femur, 10 cases, and total femur replacement, 7 cases. In 32 cases an excochleation of the metastases followed by patacos refillment was done. 31 patients were treated by osteosynthesis. In 39 patients an amputation were necessary.

Conclusion: The goal of the operative therapy of skeletal metastases is to achieve weight-bearing stability, or at least exercising stability and relief of pain of the affected limb. In our experience endoprosthetics has the advantage of allowing a really radical resection of the metastases and further permits the full stability of the affected limb.

OP 194

MANAGEMENT OF MALIGNANT PERICARDIAL EFFUSION AND CARDIAC TAMPONADE BY BLEOMYCIN AS A SCLEROSING AGENT

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The incidence of symptomatic malignant pericardial effusions (MPE) is increasing, because of longer survival of neoplastic patients. The goals of therapy of neoplastic cardiac tamponade are prompt symptoms relief, etiologic confirmation and recurrence prevention. Preventing MPE recurrence improves survival and quality of life. We evaluated the effectiveness of intrapericardial Bleomycin for tamponade recurrence prevention. Since 1994 we treated 12 pts (8 women and 4 men) with MPE due to solid neoplasms, with overt or impending cardiac tamponade: 5 pts had breast carcinoma, 4 non-small cell lung cancer, 1 gastric carcinoma, 1 unknown origin carcinoma and 1 sarcoma. All complained of dyspnea and tachycardia, 4 (33%) had cough, 4 (33%) orthopnea, 5 (42%) paradox pulse. In all pts the echocardiogram documented a massive pericardial effusion, in seven cases (58%) with tamponade signs. We treated all pts with drainage by echoguided subxiphoid pericardiocentesis and subsequent 20 IU Bleomycin intrapericardial instillation. All pts had a pericardial fluid cytology positive for neoplastic cells. In all cases we obtained a significant and lasting symptoms relief. During the follow-up there was a significant MPE relapse in only one case (breast carcinoma) (92% of therapeutic success). To date the overall median survival from MPE diagnosis is 7.3 months (SD 7.4), with 13.6 months (SD 8) for breast carcinoma and 3.5 months (SD 2) for non-small cell lung cancer. Side effects of intrapericardial instillation were fever in 3 pts (25%) and atrial fibrillation in 1 (8%).

Conclusions. We confirm the effectiveness of intrapericardial Bleomycin for MPE control. Survival is related to the primary neoplasm.

OP 195

STATUS OF CANCER PAIN MANAGEMENT IN GERMANY - AN INPATIENT AND OUTPATIENT PERSPECTIVE -

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The undertreatment of cancer pain has been reported from a number of countries. We assessed the standards of cancer pain management in a large outpatient population and an inpatient population of a university hospital.

The computerized patient records of 1.104.435 patients in the former West-Germany were screened for patients with cancer who received strong opioids. Additionally, the charts of 100 inpatients with cancer (University of Freiburg) were reviewed.

Of 16.630 outpatients with cancer only 322 (1.9%) received strong opioids. The majority of those patients received very few strong opioid prescriptions over the three years' period (only 99 patients received more than 3 strong opioid prescriptions). A wrong time interval or 'PRN' schedules were commonly used. Sustained release morphin and Buprenorphine were most commonly prescribed.

The data from the inpatient population is compared to the outpatient data.

From the data retrieved in this survey it can be concluded that cancer pain patients in Germany are not treated in accordance with well founded standards of cancer pain management. The WHO guidelines are not adequately applied. Basic principles of opioid prescribing and pain management are disregarded.