

**P 860****Salvage treatment of recurrent skin cancer of the midface**F L Ampil<sup>1</sup>, C A Nathan<sup>2</sup>, F J Stucker<sup>2</sup>, J C Hardin<sup>3</sup>

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**Background:** The midface contains areas representing embryonic fusion planes and tumors arising in these planes tend to invade deeply. The purpose of this report is to describe our experience of salvage therapy applied for recurrent skin cancer of the midface (RSCM).

**Methods:** During a 23-year period (1976 to 1999), nine patients with RSCM were treated by definitive surgery (with adjuvant radiotherapy in five individuals).

**Results:** RSCM invasion of the adjacent maxilla, orbit, nose or sinus occurred in eight patients. In the remaining person, perineural invasion extended up to the base of the skull. Most of the patients' clinical courses were fraught with subsequent local or regional, recurrent disease. The overall mean survival was 46 months; five patients lived more than 3 years, and three individuals survived more than 5 years.

**Conclusion:** Recurrent midfacial cancers are often locally extensive tumors. Disease control can be elusive despite aggressive salvage therapy. Close long-term follow-up should not be neglected because of the distinct possibility of further locoregional relapses.

**P 861****Cutaneous melanoma: a single portuguese experience of 412 patients over a 21-year period**

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**Purpose:** Melanoma comprises 10% of all skin cancers, yet it accounts for 80% of skin cancer deaths. The clinical characteristics, treatment and survival of melanoma patients (pts) in connection with the use of dacarbazine (DTIC) based therapy was analyzed in a retrospective study. **Materials and Methods:** In this study 412 pts were included. Subsequently they were stratified into 2 groups as follow: (1) 138 pts from 1980 to 1990 and (2) 274 pts between 1991 and 2000. The melanoma was classified according to The American Joint Commission on Cancer. The disease free interval (DFI) and the 10-year survival were calculated using the Kaplan-Meier method. **Results:** There were significant differences in the melanoma histotype and stage between the two subsets. However no differences were observed concerning the age, gender and tumour site and the 10-year survival (56,5% vs 59,9%). Gender, stage and melanoma histotype were identified as significant prognostic indicators for survival. Concerning DFI no significant correlation was found between the two subsets of pts. **Conclusions:** This single center study on a large cohort of unselected pts confirms that the gender, stage and melanoma histotype are the strongest prognostic factors in terms of survival. Analysis also suggested that adjuvant DTIC based chemotherapy did not improve survival.

**P 862****The impact of immunohistochemistry on pathological staging of sentinel nodes for malignant melanoma**G L Ross<sup>1</sup>, D S Soutar<sup>1</sup>, H Gray<sup>2</sup>, R Bessent<sup>2</sup>, T Shoaib<sup>1</sup>, R MacKie<sup>3</sup>

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**Background** Sentinel node biopsy (SNB) has emerged as an accurate means of identifying nodal disease in malignant melanoma. Super selection of pathological nodes has allowed improved pathological staging of disease. The aim of this study was to look at the impact of immunohistochemistry on pathological staging of sentinel nodes. **Methods** The first 100 patients undergoing SNB for primary cutaneous malignant melanoma were included in this study. Sentinel node harvesting was performed using pre-operative lymphoscintigraphy and the intraoperative use of both a gamma probe and blue dye. If the sentinel nodes contained tumour on either routine pathology or immunohistochemistry, patients were offered a therapeutic lymph node dissection (TLND). Patients underwent no other treatment to the primary lymph node basin if the sentinel node was free of metastases. **Results** Ninety-five patients had at least one node identified. Twenty-five patients were staged SNB positive and were offered subsequent therapeutic lymph node dissection (TLND). 76% (19/25) of those SNB positive were staged positive on routine pathology and 24% (6/25) staged with immunohistochemistry. Immunohistochemistry upstaged disease in 8% (6/76). Twenty-one patients staged positive with SNB underwent TLND. No patients (0/5) staged sentinel node positive with immunohistochemistry had disease in the subsequent TLND compared to 50% (8/16) of those patients staged sentinel node positive with routine H+E (p<0.05). **Conclusion** Immunohistochemistry is an essential part of identifying micrometastasis in sentinel nodes, upstaging 8% of patients in our series. Patients with micrometastatic disease may well have a different prognosis than those with occult disease and careful classification delineating between these patients is required to determine the prognostic influence of micrometastasis.

**P 863****Withdrawn****P 864****Does the risk of regional lymph node metastases in patients with melanoma less than 1.0 mm thick justify sentinel lymph node biopsy?**

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**Background-** The administration of adjuvant therapy as well as regional lymphadenectomy in patients with melanoma greater than 1.0 mm thick depends on the identification of early lymph node (LN) metastases by sentinel lymph node (SLN) biopsy. This approach has almost completely replaced elective (prophylactic) lymphadenectomy. Ultra staging of sentinel lymph nodes using PCR (polymerase chain reaction) techniques for identifying tumor antigens or the advent of microarray techniques may further subdivide high-risk melanoma patients who may benefit from further

surgery or adjuvant therapy. However, there are no strict guidelines to identify candidates for SLN biopsy. What is the indication for SLN biopsy in patients with melanoma less than 1.0 mm thick? Methods- A retrospective review of our patient database to identify all patients with 5 or more years of follow-up presenting with melanoma less than 1.0 mm thick.

Results- 313 patients completed 5 or more years of follow-up. Of these patients, 133 had melanoma less than 1.0 mm in thickness, and 13 (10%) of them developed LN metastases. The tumor thickness ranged from 0.3 to 0.99 mm.

Depth of invasion (mm)	0.3-0.4	0.41-0.5	0.62	0.8-0.9	0.9-0.99	Total
# of patients	4	2	1	4	2	13
Deaths	3	1	1	2	0	7
Median DFI (months)	84	69	11	33	52	55

The disease-free interval (DFI), i.e. from the time of surgical treatment to the time of regional LN metastases, varied from 2 to 112 months with a median of 55 months.

Conclusions- As many as 10% of patients with melanoma less than 1.0 mm thick may benefit from upstaging their tumors by SLN biopsy. These data suggest that SLN biopsy is justified provided the technique would detect metastatic disease years before it becomes clinically evident.

## P 865

### Serum levels of interleukin-8 directly correlates with tumor burden, angiogenesis and metastasis in human malignant melanoma cells xenografted in nude mice

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Interleukin-8 has been demonstrated to be an important multifunctional cytokine in melanoma growth, angiogenesis and metastasis. Interleukin-8 can be produced by tumor cells or host cells recruited to the tumor or both tumor and host cells. In this study, we examined whether levels of interleukin-8 (IL-8) in serum produced by tumor cells can be used as a marker to predict the tumor growth, angiogenesis and metastasis in human malignant melanoma. Human melanoma cells with different metastatic potential expressing different levels of IL-8 were xenografted in nude mice. Serum levels of human IL-8 were examined using a human IL-8-specific enzyme-linked immunosorbent assay. Serum samples from non-tumor bearing mice were used as controls. Tumor growth, spontaneous metastases and experimental metastases were analyzed. Tumor neovascularization was analyzed by immunohistochemistry. Correlation analysis between serum levels of IL-8, tumor size, spontaneous and experimental metastases and levels of neovascularization were performed using Kendall's tau<sub>b</sub> and Spearman's rho nonparametric test using SPSS software. We did not detect any IL-8 protein in non-tumor bearing mice. The levels of serum IL-8 were higher in mice bearing tumors from high-metastatic high-IL-8 expressing melanoma cells. We observed a direct correlation between tumor burden and serum IL-8 levels ( $r=0.695$ ,  $p=0.0001$ ). Furthermore, a direct correlation between serum IL-8 levels and numbers of lung nodules in experimental metastases was observed ( $r=0.677$ ,  $p=0.0001$ ). We observed a direct correlation between spontaneous metastatic potential with serum IL-8 levels at the time of primary tumor excision ( $r=0.571$ ,  $p=0.003$ ) but not at the time of sacrifice ( $r=0.235$ ,  $p=0.19$ ). These results suggest that in malignant melanoma release of IL-8 into serum may be used as marker for tumor progression, angiogenesis and metastasis.

## P 866

### A phase 2 trial of neoadjuvant biochemotherapy in stage 3 melanoma

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Background: Novel approaches to the management of stage 3 melanoma need to be explored as historical data suggest that about 70% of patients developing lymph node metastases from malignant melanoma will ultimately die of metastatic disease. In phase II studies of biochemotherapy for stage 4 melanoma response rates have been in the range of 40-60%, with complete responses in approximately 10-15 % of patients. On the basis of this promising activity we initiated this phase 2 study to explore the safety and activity of neoadjuvant biochemotherapy in patients with stage 3 melanoma. Methods: Forty-eight patients with stage 3 melanoma were enrolled between April 1996 and May 1999. The median age was 46 years (range 19-70). Two cycles of biochemotherapy were administered prior to, and following lymph node dissection. Each cycle consisted of cisplatin 20 mg/m<sup>2</sup> days 1-4, vinblastine 1.6 mg/m<sup>2</sup> days 1-4, dacarbazine 800 mg/m<sup>2</sup> day 1, interleukin-2 9 x 10<sup>6</sup> IU/m<sup>2</sup>/day intravenously over 24 hours days 1-4 and interferon alpha 5 x 10<sup>6</sup> IU/m<sup>2</sup>/day subcutaneously days 1-5, every 3 weeks. Thirty-six patients had measurable disease and are evaluable for response. All patients are evaluable for toxicity and survival. Results: Responses were seen in 14 of the 36 patients (38.9%), including 13 (36.1%) PRs and one CR (2.8%). Complete pathological responses were seen in four of these 36 patients (11.1%). The response to treatment was predictive of patient outcomes. Overall toxicity was substantial but manageable and there were no treatment-related deaths. At a median follow-up of 31 months, 38 patients (79.2%) are alive and 31 patients (64.6%) remain progression free. Comparison with historical control groups suggests an impact of neoadjuvant biochemotherapy on overall survival. Conclusion: Neoadjuvant biochemotherapy has acceptable toxicity and may improve the survival of patients with stage III melanoma.

## P 867

### Investigation of the immunocytochemical expression of c-kit oncoprotein (CD117) in malignant melanomas

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Background: The diagnosis of malignant melanoma may be very difficult in cytology and surgical pathology, often complicated by the unpredictable spread of this tumor and its variable histologic morphology. The aim of our study was to investigate the immunocytochemical expression of CD117 in melanomas, in correlation with the traditionally used markers S-100 and HMB-45. The c-kit proto-oncogene encodes a transmembrane receptor with tyrosine kinase activity, c-kit, which is closely related to the platelet-derived growth factor receptor family. c-kit plays a role during haematopoiesis, gametogenesis and melanogenesis. It is expressed in normal melanocytes as well as in melanomas. Methods: FNA biopsies were performed in 20 patients with primary or

metastatic melanomas and the samples were processed according to the ThinPrep method. Routine pap-stained smears of each case were initially evaluated. The residual fluid of the ThinPrep collection tube was used for further smears' and cell blocks' preparation as well as immunocytochemical detection of CD117, S-100 and HMB-45. In addition, some specimens which presented strong reactivity to CD117, were examined by Transmission Electron Microscope. Results: The Thin-monolayer system provided adequate material for the performance of immunocytochemical techniques, with satisfactory results. S-100 was the most sensitive marker, but lacked specificity, while HMB-45 was more specific, but lacked sensitivity. The immunostaining was considered positive for CD117 if the cancer cells showed specific membrane staining and the intensity of staining was evaluated in correlation with clinical data. Reactivity with CD117 was present in a significant number of primary lesions, while metastatic lesions demonstrated positivity in a lower degree. Because of the limited number of literature references, further investigation is required in order to clarify the role of c-kit in malignant melanomas.

## P 868

### Antimetastatic effect of Avemar® in high-risk melanoma patients

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Patients with stage III melanoma have a high risk of relapse and death from the disease, especially if they have clinically detectable lymph-node involvement. As immunotherapy with interferon  $\alpha$  is very expensive and its results are controversial chemotherapy with DTIC still remains an alternative in this category of patients. The objectives of this randomised study was to compare the effect of post-surgery adjuvant DTIC chemotherapy with DTIC plus AVEMAR® in high-risk melanoma patients.

A total of 42 patients with resected regional melanoma metastases were entered into the study by the moment: 23 (Arm I) were allocated to receive 4 cycles of DTIC (2 g per cycle) and 19 (Arm II) - the same plus AVEMAR® - biotechnologically treated, microencapsulated wheat germ extract standardized to substituted benzoquinone derivatives - for 12 months. The arms of the study are well balanced for gender and age. Median follow-up is 10 months. Despite the fact that there was no significant difference in relapse rates we have observed a clear benefit for time to progression in Arm II: 8,9 months as compared with 4,2 months in Arm I. The estimated 1-year relapse free survival rate was 54,5% for patients treated with DTIC plus AVEMAR® versus 38,9% for those treated with DTIC alone. The study is still open.

These preliminary data show that combination of routine DTIC chemotherapy and AVEMAR® may decrease risk of relapse and postpone time of melanoma progression. The published preclinical results suggest that the antimetastatic effect of AVEMAR® is related to its cell adhesion inhibitory, cell proliferation inhibitory, apoptosis enhancing and antioxidant characteristics.

## P 869

### Role of cryodestruction in the treatment of malignant melanoma

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Melanoma is 10 times less common than skin cancer. It constitutes approximately 1% of all malign tumors. Annually, in the Republic of Moldova 75-85 cases of melanoma are registered. Among them in the head and neck area 10-15 cases are registered annually. The majority of patients with malign melanoma apply for medical help late, with III-IV level of invasion by Clark. Between 1977 and 1999, 102 patients were treated using the method of cryosurgery. The disease is more common in person of feminine sex as compared to those of masculine sex, yet the difference is not very big. Morbidity is much higher in the 30-39 age group, after that a slight increase can be observed at the age of 60-69.

Results of cryosurgical treatment for malign melanoma in the area of head and neck

Disease	Sex	Number of patients	Survived after 5 years	
			Absolute number	%
Melanoma of skin in the area of head and neck	Feminine	53	42	79,2
	Masculine	49	39	79,6
Total		102	81	79,4

Survival at 5 years with the method of cryosurgery + 3 courses of polichimiotherapy was 79,4%. We know that melanoma is a very aggressive tumor, radio- and chimoiresistant. The method of treatment used consists in the following: treatment of the operation area with antiseptics, cryodestruction of the tumor at the temperature of the cryoagent -193oC. In the first phase the cryodestruction of healthy skin is performed on a perimeter of 5 cm from the center of the tumor using special double rings. This enables us to block the migration of malign cells during the freezing of the tumor. After that the freezing and melting of the tumor is repeated three times. At the last freezing tumor excision is performed, the wound is treated with 5% KMnO4 and bandaged.

## P 870

### Ultrastructural study of in transit and local satellite foci malignant acral melanoma recurrence, following chemotherapeutic hyperthermic perfusion

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Background. Hyperthermic limb perfusion is a therapeutical method with a very high percentage of success in advanced limb melanoma. Patients with skin primary melanoma, with a thickness of more than 1,5 mm according to Breslow, present possibly local micrometastasis during the time of operation, on the primary focus. Material-Methods. Hyperthermic limb perfusion has an absolute indication as a therapeutical method in acral melanoma or in local recurrence (local satellites, in transit). The method was applied in 94 patients (38 of which had acral limbus melanoma and 56 were high

risk group) as well as a prophylactic method in 101 patients. The aim of the study is to present the results of the action of chemotherapeutic hyperthermic perfusion in metastatic foci of skin melanoma of the limb, using Transmission Electron Microscopy (TEM). Specimens for TEM were taken on the 7th, 14th and 21st postoperational day. Results. The TEM study showed initially necrosis of the area, with some viable melanoma cells, which on the 21st day ended up in augmented fibrosis, with no viable cancer cells (in local satellites and in transit). Conclusions. Hyperthermic limb perfusion is a very efficient method for treating recurrence of acral limb melanoma.

## P 871

### Adjuvant pulsatile high dose interferon-alfa therapy in stage IIb/III malignant melanoma: a pilot study

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Adjuvant high dose IFN-alfa therapy as developed by J. Kirkwood prolonged disease-free survival in 3 out of 3 randomized multicenter trial in patients with stage II/III malignant melanoma and overall survival in 2 out of 3. This effective treatment is unfortunately associated with severe side effects (about 75% of the patients experience grade III/IV toxicities). At present it's unclear, which part of the 12 months treatment schedule is responsible for the observed efficacy. Some evidence such as IFN plasma level, hazard analysis over time etc. suggests that the i.v. phase of the treatment may be most relevant for the survival benefit.

A new i.v. IFN-treatment schedule with a lower side effect profile was developed. The patients received 3 times 4 weeks of i.v. IFN-alfa 2B at a dose of 20 Mio/m<sup>2</sup> Monday through Friday. Between the i.v. cycles the patients were untreated for 3 months. According to this schedule 29 patients were treated (17 male; 20 female; age 25-66 years) and evaluated. Not counting lymphopenia only 7 (24%) patients experienced grade III/IV toxicities (leukopenia, liver enzyme elevation, pancreatitis) demonstrating acceptable tolerability of this treatment regime. Fatigue and depression appeared less often and not intense. The drop in leukocytes, the rise in hepatic enzymes and the increase in IFN-induced proteins were monitored in each i.v. phase. In the 1st cycle the leukocytes significantly dropped from a mean of 8320 to 3100 and gradually improved thereafter. However, at the beginning of the 2nd and 3rd cycle the means of the leukocytes were significantly lower (6480, 6320) than the leukocyte mean at the start of the therapy indicating a long-term effect of IFN-alfa upon the bone marrow. Mx proteins (IFN-induced proteins) increased 10 to 40-fold demonstrating high IFN-activity in vivo. In summary, this treatment schedule is tolerable to most patients at the proposed dose;

The efficacy of therapy needs of course to be tested in a randomized study.

## P 872

### Biochemotherapy of metastatic malignant melanoma (MMM) with CVD-BIO - a phase II study

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To determine activity of biochemotherapy with CVD-BIO, we have assessed response rate toxicity profile and early time to progression and overall survival in MMM patients (pts). Method:

Between September 1999 and September 2001, 27 pts (20/74% female, 7/26% male at average) aged 50 (range 21 - 73), WHO performance status 0-1 according to 20 pts/74% and 2-3 7pts/26%. All tumors have been medicated with CVD-BIO: vinblastine - 1,6 mg/m<sup>2</sup>/d in days 2-5, 24-27 and 46-49; cisplatin - 20 mg/m<sup>2</sup>/d in days 1-4, 23-26 and 45-48; Il-2 - 9 mln U/m<sup>2</sup>/d in days 6-9, 18-21 and 28-31; IFN- $\alpha$  - 5 mln U/m<sup>2</sup>/d in days 6-10, 18-22 and 28-32. Results: Overall response rate 40.7% (11 pts) has been noted. We have recorded within the evolved population: 4 pts/14.8% - CR, 7 pts/25% - PR and 5 pts/18.5% SD. Time to progression 7.25 month (range 4 - 19) and actuarial overall survival 15 months (range 5 - 25 months). WHO morphological toxicity (3rd and 4th grade): leukocytes - 20 pts/74%, erythrocytes - 13pts/48%, platelets - 5 pts/18,5%. WHO other toxicity (also 3rd and 4th grade): fever - 1/3.7%, hypotension - 2/7.4%, nausea - 18/66.6%, vomiting - 14/51.8%, diarrhea - 1/3.7%, skin rash - 2/7.4%, creatinine level - 2/7.4%, transaminases activity - 1/3.7%. Conclusion: Biochemotherapy (CVD-BIO) early results seems to improve activity against metastatic malignant melanoma although as palliative setting and further trials need to be carried out.

## P 873

### The investigation of the immunomodulating effect of retinoic acid in chemoimmunotherapy of patients with metastatic melanoma

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Considering that malignant melanoma (MM) shows poor response to chemotherapy and that it is an immunogenic tumor, combined chemoimmunotherapy is applied. Besides interferon (IFN), retinoic acid (RA) was introduced as a biological agent with antiproliferative, differentiating and immunomodulating potential, although its therapeutic benefit has been controversial. In this study we performed detailed cellular and molecular immunological evaluation of 35 patients with MM receiving DTIC 800 mg/m<sup>2</sup> on day 1 and interferon  $\alpha$ -2a (IFN) 5x10<sup>6</sup> IU/m<sup>2</sup> s.c. day 2-6 (group A) and 35 patients who received the same therapy supplemented with 13-cis RA, 60mg/day, day 1-10, and 39 healthy controls. NK cell activity, PHA-induced in vitro proliferation of peripheral blood lymphocytes and percentage and activation antigens (CD 69, CD38 and HLA-DR) of NK cell and CD4+, CD8+ T cell subsets were analyzed before therapy and on day 1, 6 and 28 of the therapy cycles. NK cell activity was also evaluated after predictive pretherapy in vitro treatments with IFN, RA and IFN and RA for 15 MM patients and 14 controls, as well as the dynamics of transcription of interferon regulatory factor 1 (IRF-1). During therapy immunomodulating effect on NK cell function, expression of CD69 and CD38 was the same in both groups, while the percentage of CD4+T cells and HLA-DR antigen expression was significantly higher in patients in group A. The stimulating effects, except on HLA-DR expression, appeared early and were transitory. In vitro evaluation also showed significantly lower NK cell activity but significantly higher stimulation with IFN and RA in patients compared to controls which appears to be partially realized through IRF-1. Even though the presence of RA significantly enhanced NK cell activity of MM patients in vitro, clinical monitoring of immunological parameters or response rates did not show benefit in patients receiving therapy that included retinoic acid.

**P 874****The addition of adjuvant autologous tumor vaccine treatment of malignant melanoma should not be neglected**

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**Purpose:** For improving the therapeutic effect of combined modality on malignant melanoma, the addition of autologous tumor vaccine (ATV) which was generated by TSPA treated tumor cells lysate was performed and monitored by clinco-immuno-laboratory examination.

**Results:** (1) Each malignant melanoma patient (MMP) and non-tumor subject (NTS) had its individual immune character, but MMP showed the marked tendency of decreased OT skin test reactivity as compared with NTS, the positive OT dilution at  $\leq 1:500$  was 48.6% to 16.9% and at  $\geq 1:2,000$  was 28.9% to 74.0%. However, the ATV treated MMP showed the reaction level of OT was enhanced near to NTS. (2) Before ATV treatment, there were 17.6% (n 34) patients showed positive ATV antigen skin test, after ATV treatment, 38.9% (n 21) patients turned from negative to positive, it demonstrated the potential activity of ATV on patient's immune system. (3) In the long-term followed successfully treated patient showed the positive and enhanced specific and non-specific immune response with better quality of life and long-term disease free survival, but this phenomenon was hardly seen in treatment failure patient.

**Conclusion:** The addition of autologous tumor vaccine to combined modality therapy on malignant melanoma patient could efficiently reactivate the patient's cell mediated immune response which could not be activated in conventional combined modality therapy. It should not be neglected in combined modality therapy.

**P 875****Treatment results of IV stage skin melanoma**H Rymdzionak<sup>1</sup>, I Zalutsky<sup>2</sup>, S Fradkin<sup>3</sup>

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**Purpose:** Study of remote treatment results of IV stage skin melanoma.

**Material and methods:** Treatment results of 77 patients with IV stage skin melanoma including 65 patients with MIIa and 12 patients with MIIb treated at the clinic of the institute in 1977-1997 are presented. Combination approach was applied in 36 patients and multimodality treatment using whole-body hyperthermia and chemotherapy was applied in 41 patients.

**Results:** Overall 5-year-, 10-year-, 15-year-, and 20-year survival of IV stage skin melanoma patients was 20.8 $\pm$ 5.0%, 18.3 $\pm$ 5.0%, 9.2 $\pm$ 6.9%, and 9.2 $\pm$ 6.9%, respectively. In patients who underwent multimodality treatment 5-year-, 10-year-, 15-year-, and 20-year survival was 30.2 $\pm$ 8.4%, 24.7 $\pm$ 8.5%, 12.3 $\pm$ 9.7% and 12.3 $\pm$ 9.7% and combination approach resulted in 5-year- and 10-year survival of 12.9 $\pm$ 5.6% and 12.9 $\pm$ 5.6% respectively, but no one patient was alive at 15 and 20 years.

**Conclusion:** High survival can be achieved with multimodality therapy in patients with IV stage skin melanoma.

**P 876****Cytokines dynamics in the blood, urine and drainage liquid in the earlier postoperative period of kidney cancer patients**

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A comparison of earlier postoperative period and preoperative II-1 $\beta$ ; TNF- $\alpha$ ; II-6 and II-4 levels in the blood, urine and drainage liquid of 26 kidney cancer patients has been done. The cytokines concentration was checked by ELISE before the operation and during the first 10 days after the operation. The postoperative period in the patients from the 1st group (n=9) passed without any problems. The patients from the second group (n=17) had postoperative complications: acute renal failure (n=14) and multiorgan failure (n=3). Before the operation the II-1b level in the blood was: 28  $\pm$  15 pg/ml; II-6 - 26  $\pm$  11 pg/ml; TNF-a - 44  $\pm$  20 pg/ml. After the operation a slight II-1b concentration fluctuations was detected with maximums within 1 hour and in the end of the 1st day after the operation. Beginning from the 2nd day II-1b was not detected in the blood. TNF-a concentration after the rise during the 1st day up to 65  $\pm$  21 pg/ml with some small fluctuation to the initial level. II-6 in the blood decreased to the initial level in 1 hour after the operation. II-4 in the 1st group patients was detected in the blood beginning from the 1st day and was absent in the patients from the 2nd group. II-6 level in the 1st group decreased from 67  $\pm$  28 pg/ml to the initial level in 1 hour after the operation. In the 2nd group it was 124  $\pm$  46 pg/ml and had a trend to growth during 7-10 days. The II-1b and TNF in urine in both groups were practically on the same level. It fluctuated between 130  $\pm$  42 pg/ml and 220  $\pm$  76 pg/ml resp. II-4 in urine was not detected. II-6 concentrations in 1st group patients reached 1240 - 1556 pg/ml at the end of the 1st day. In the 2nd group the urine concentrations were minimal. The cytokines concentrations in drainage liquid was the same as in urine. Some difference was noted in the II-6 dynamics: in the 1st group its maximum was not higher than 3453 pg/ml; in the 2nd group the II-6 level reached 5626 pg/ml.

**P 877****Phase I/II trial of gemcitabine (G) administered every other week plus cisplatin (P) in advanced non-small cell lung cancer (NSCLC): final results**

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**Background:** This phase I/II trial was designed to determine the MTD, activity and toxicity of biweekly G plus monthly P in NSCLC. **Methods:** Chemonaive pts with stage IIIB or IV NSCLC received G (30-min i.v.) on days 1 and 15, escalating in 250 mg/m<sup>2</sup> increments from 1250 to 2250 mg/m<sup>2</sup> (5 levels), plus a fixed dose of P (80 mg/m<sup>2</sup> i.v.) on day 2 every 4 weeks. DLT was defined as WHO Grade (Gr) 4 neutropenia >7 days, febrile neutropenia, Gr4 thrombocytopenia, or Gr3/4 non-hematologic toxicity (except alopecia). All patients gave written informed consent. **Results:** Between 11/99 and 10/00, 50 pts received 162 cycles: male/female: 45/5; median age: 67 (range 30-74); PS 0/1/2: 3/26/21; stage IIIB/IV: 13/37; squamous/adenocarcinoma/undifferentiated histology: 20/27/3. Gr3 non-hematologic DLTs occurred in 4 pts at level 5 (G 2250 mg/m<sup>2</sup>): asthenia in 2 pts (1 of whom also had Gr3 nephrotoxicity), hiccup in 1 pt, non-neutropenic fever in 1 pt; Gr3 nausea/vomiting also occurred in 2 pts in level 5. Gr4 neutropenia occurred only in 1 pt and resolved in a week; no other

hematological DLTs occurred. Thus, a G dose of 2000 mg/m<sup>2</sup> was recommended for phase II study, and a total of 32 pts at this level received 117 cycles. Gr3/4 neutropenia, thrombocytopenia, and anemia occurred in 16 (32%), 5 (10%), and 5 (10%) of 50 evaluable pts, respectively. RBC transfusion was required in 3 pts, but no neutropenic fever or treatment-related deaths occurred. Non-hematologic toxicity did not exceed Gr2. In phase II 27 pts were evaluable, 11 (34.4%) had PR, 12 (37.5%) had SD, and 4 (12.5%) progressed. At a median follow-up of 16 months, the median survival was 9 months and the 1-year survival was 43.7%. Conclusions: This G plus P regimen was well tolerated, with an acceptable response rate and a good median survival time, despite a high proportion of stage IV and PS 2 pts. These results compare favorably with other published phase II studies that tested bi-weekly G plus monthly P.

## P 878

### Adoptive immunotherapy in lung cancer patients

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Objective: To study clinical effectiveness of adoptive therapy of radically operated lung cancer patients by infusion of autologous cytotoxic lymphocytes generated in vitro. Materials and Methods: Antitumor cytotoxicity of lymphocytes, received from regional lymph nodes during surgical operation, was induced in vitro by co-culturing with autologous tumor cells at presence of low concentrations of IL-2 in specially constructed vibration bioreactor. Amount of such cytotoxic lymphocytes infused into the patients as adoptive immunotherapy was at an average - 2 - 108 cells. Adoptive immunotherapy was used in 24 lung cancer patients. Results: Infusion of activated autologous lymphocytes to radically operated lung cancer patients, results in the improvement of 2-year survival (term of follow-up), in comparison to the control group - (87.50±6.75)% and (50.22±2.78)%, respectively. Survival of the patients with metastases into regional lymph nodes after adoptive immunotherapy was (84.62±10.01)%, in control group it was (32.71±4.46)%. Conclusion: Adoptive immunotherapy improves the effectiveness of surgical treatment of lung cancer patients especially with metastases into regional lymph nodes that allows to consider this method promising for further improvement.

## P 879

### Phase III study of prophylactic hange-shashinto treatment of diarrhea following cisplatin and irinotecan combination chemotherapy for non-small cell lung cancer

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Cisplatin (CDDP) + Irinotecan (CPT-11) combination chemotherapy is one of the most effective treatment for stage IV non-small cell lung cancer, while myelosuppression and diarrhea are main adverse effects. Hange-Shashinto, a Japanese herbal medicine containing bicalin, is suggested to be useful to control diarrhea induced by Irinotecan. To evaluate the efficacy of loperamide and Hange-Shashinto combination treatment on diarrhea, comparative study was carried out in 62 patients with advanced or relapsed non-small cell lung cancer treated with CDDP + CPT-11. Patients were treated with more than 2 cycles of CDDP (80mg/m<sup>2</sup>, day 1) + CPT-11(60mg/m<sup>2</sup>, day 1, 8, 15). Patients were assigned alternatively to two groups supported with prophylactic Hange-Shashinto and with only loperamide. In the pro-

phylactic Hange-Shashinto group, 6g/day of oral Hange-Shashinto was administered preventively through the chemotherapy. In the case of diarrhea more than grade 2, 2mg of oral loperamide was administered. Diarrhea was classified into ECOG grade and evaluated with score of grade by days. The result was as follows. 1) In two groups, there were no difference in background of the patients. 2) Severity of diarrhea was significantly (p<0.05) improved in the group with prophylactic Hange-Shashinto compared with the control group. In the prophylactic Hange-Shashinto group, additional loperamide medication was significantly reduced. 3) As adverse effect of Hange-Shashinto, constipation less than grade 2 was observed in 42% cases. 4) Anti-tumor response showed overall response rate at 42% in prophylactic Hange-Shashinto group and at 39% in control group. In prophylactic Hange-Shashinto group, dose intensity was superior significantly (p<0.01 in CDDP, p<0.05 in CPT-11). It is concluded that symptomatic treatment with loperamide and prophylactic treatment with Hange-Shashinto is useful to diarrhea induced by CDDP+CPT-11 combination chemotherapy.

## P 880

### Paclitaxel (P) and carboplatin (C) combination for the treatment of patients with advanced non-small-cell lung cancer (NSCLC): an effective and well tolerated regimen

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Introduction: NSCLC is the number one cause of cancer death; and the prognosis warrants the investigation of new regimens. P in combination with C is an effective combination for the treatment of NSCLC in patients who are not candidates for potentially curative surgery and/or radiation therapy. Material and Methods: 32 patients with advanced NSCLC were treated with a regimen consisted of C AUC 6 d1, and P 175 mg/m<sup>2</sup> d1, q3w. Patients characteristics were as follows: median age 60 years (range 37-74); by sex males (96,9%) and females (3,1%); by clinical stage IIIB (46,9%), IV (40,6%), or non-operable IIIA (12,5%); by histological type squamous (64,6%), adenocarcinoma (28,1%) and non-differentiated (6,2%), all with ECOG2 performance status. Results: The median number of courses administered per patients was 5 (range 3-7), 164 courses were performed. Major toxicity (WHO scale): anemia G-2 (6,3%), neutropenia G-3 (9,4%) and thrombocytopenia G-2 (6,3%), emesis G-2 (6,3%) peripheral neuropathy G-3 (3,1%); G-4 toxicity, toxic neutropenia and fever, hypersensitivity reaction and toxic deaths, was not found. Evaluating the tumour response rate to the treatment after 4 courses of chemotherapy, we have observed 43,8% of partial responses, 37,5% of stable disease, and progressive disease 15,6%. The median survival time was 12 months (15 months in patients with partial responses). Conclusion: The P-C combination is an effective chemotherapy for patients with advanced NSCLC, and well tolerated, with an acceptable toxicity.

## P 881

### Growth inhibition of human pulmonary carcinoma cell lines by cyclosporin A in vitro

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Recently, it is reported that cyclosporin A (CsA) is able to exert a cytostatic activity not only on lymphoid cell malignancy but also on several solid tumors. However, no study has been published regarding a number of human pulmonary carcinoma cells in vitro.

(METHOD) Thirty human pulmonary carcinoma cell lines were examined. All the cell lines were cultured in Ham f12 medium with 5% FBS. The growth inhibitory effect of CsA was examined on the cell lines after exposure with CsA (range:  $10^{-5}$  -  $10^{-8}$ M for 7 days by the MTT assay. (RESULTS) When the cutoff level of potent anticancer effect in clinical use was set at  $5 \times 10^{-7}$ M of ID50 value, the positive rate was 50% (5/10) for squamous cell carcinomas, 40% (2/5) for small cell carcinomas, 20% (2/10) for adenocarcinomas and 20% (1/5) for large cell carcinomas. The growth inhibitory effect on the sensitive cell line was dose dependent manner over a range of  $10^{-8}$ M to  $10^{-6}$ M CsA. When culture medium with  $10^{-6}$ M CsA was replaced every week, the growth of the cells was completely inhibited in the state of cell clusters like islets even after 5 weeks. Furthermore, treatment of the cell lines with CsA caused a dramatic increase in morphologic change as evidenced by the formation of cytoplasmic vacuole. In the presence of  $10^{-6}$ M CsA, a significant increase in the percentage of changed cells should be detected within 48 hours; the maximum extent of morphologic change occurred after 5 weeks treatment. Moreover, when CsA was removed after 5 weeks of treatment at  $10^{-6}$ M, most cells retained the morphologic change included by CsA for at least 10 days. (CONCLUSION) This study demonstrates that low concentration of CsA induces growth inhibition of several human pulmonary carcinoma cell lines in culture. In addition, we have preliminary data that CsA potentiates a synergistic cytotoxicity of several anticancer drugs on the cell lines in vitro. Thus, this study suggests that CsA may be useful in the treatment of human lung cancer.

## P 882

### Treatment with oral Etoposide for elderly patients with non small cell lung cancer

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From August 1995 to August 2000, 38 elderly patients (pts), 25 males and 13 females, with non small cell lung cancer (NSCLC), received treatment with oral Etoposide (VP-16) 50 mg/m<sup>2</sup>/day for 14 days, every 28 days. The median age of the pts was 73 years, range 65-89. ECOG P.S. 0-9 pts, 1-16 pts, 2-13 pts. Thirty-four pts (89%) had different associated illnesses: cardiac, respiratory, renal, gastrointestinal, and mental. Pts underwent biopsy for diagnosis of the tumor and not radical surgery. The histology, NSCLC, adenocarcinoma 24 pts, squamous cell carcinoma 11 pts, large cell carcinoma 3 pts. Twenty-four pts had local advanced disease, and 14 pts metastatic disease. Pts received between 3 to 16 courses of chemotherapy, median 6 courses. Eight pts (21%) had partial remissions, 5 to 14 months (mos), median 9 mos. Thirteen pts (34%) had no change between 6 to 24 mos, and median 10 mos. Seventeen pts (45%) showed no response. Toxicity: alopecia 35 pts, nausea 22 pts, vomiting 8 pts, leucopenia 8 pts, anemia 7 pts, and mucositis 6pts. Our results suggest that oral Etoposide can be administered to elderly pts with acceptable toxicity and modest activity in advanced NSCLC, on an outpatient basis.

## P 883

### Phase II trial of weekly docetaxel in patients with advanced non-small-cell lung cancer who have failed or relapsed after the frontline platinum-based non-taxanes therapy

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**Background.** This Phase II study was conducted to evaluate the efficacy and toxicity of weekly docetaxel in second-line therapy for patients with advanced non-small-cell lung cancer (NSCLC).

**Methods.** Patients with confirmed and progressive NSCLC during or after one platinum-based, non-taxanes regimens were eligible. A performance status of 0-2 and adequate organ function was required. Patients were treated with docetaxel 40 mg/m<sup>2</sup>/week for 3 consecutive weeks. Cycles were repeated every 4 weeks.

**Results.** Fifty-three patients were eligible for this study. The overall response rate [OOR] was 13%. The median survival time (MST) for all patients was 25.0 weeks and the 1-yr survival was 31%. For patients with PS 0-1, MST was 29.7 weeks and 1-year survival was 36%. Hematologic toxicity was very mild. Non-hematologic toxicities were moderate, grade 3-4 mucositis, diarrhea and peripheral neuropathy occurred in 6-13% of patients and caused dose modifications. Fatigue (48%) was common but not severe.

**Conclusions.** Weekly docetaxel appears to be tolerated and effective as second-line therapy for NSCLC. When compared to other studies, no history of previous taxanes treatment does not increase the response of docetaxel in second line therapy.

## P 884

### A pilot study of concurrent chemotherapy (teniposide and carboplatin) combined with whole brain radiotherapy in non-small cell lung cancer patients with brain metastases

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**Purpose:** Brain metastases will developed in 5-10% of patients with non-small cell lung cancer at the time of diagnosis. The development of brain metastases is associated with considerable morbidity. The mainstay of treatment is palliative whole brain radiotherapy (WBRT). A phase II trial was performed to evaluate efficacy and toxicity of concurrent whole brain radiotherapy with systemic chemotherapy in previously untreated patients with non-small cell lung cancer and multiple brain metastases. Fourteen patients entered the trial between June 1999 and December 2000. The patients received WBRT 30Gy in 10 fractions and carboplatin was administered according Calvert formula (AUC 6) on day 1 of radiotherapy with teniposide 100mg/m<sup>2</sup> on day 1, 3, 5. All the patients finished scheduled treatment regimen and were evaluable for response: one had a complete response (CR) in brain, three achieved a partial response (PR), five had a stable disease (SD) and one progressed while on treatment. The median event free survival time was 14.7 weeks (range: 4-48 weeks). The median overall survival time was 21.3 weeks (range 4 - 68 weeks). The main toxicity was hematological: neutropenia, thrombocytopenia, anaemia. Response rates of treatment

	CR (%)	PR (%)	SD (%)	PD (%)	ND (%)
Central nervous system	1(10)	3 (30)	5 (50)	1(10)	4(28,6)
Lung and chest	0 (0)	1 (8,3)	11(91,7)	0 (0)	2(14,3)
Skin and subcutaneous tissue	1(50)	1 (50)	-	-	-
Liver	-	1(100)	-	-	-

CR - complete response, PR - partial response, SD - stable disease, PD - progression disease, ND - not done

## P 885

### A phase II trial of gemcitabine-cisplatin-paclitaxel (GDT) chemotherapy as neoadjuvant treatment of unresectable stage IIIA(N2)-IIIB non-small cell lung cancer (NSCLC): preliminary results

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**Background:** Recent data indicate high activity of three-drug chemotherapy regimens in advanced NSCLC. Although phase III trials failed to demonstrate any benefit in terms of overall survival in metastatic disease, efficacy of these combinations needs to be tested in earlier stages NSCLC. We conducted a phase II trial to evaluate toxicity and activity of GDT combination in unresectable stage IIIA(N2) and IIIB NSCLC.

**Patients and Methods:** From September 2000 to November 2001, 42 chemo-naive IIIA(N2)-IIIB NSCLC patients have been enrolled into the trial. Therapy consisted in gemcitabine 1000 mg/m<sup>2</sup> IV days 1 & 8, cisplatin 50 mg/m<sup>2</sup> IV days 1 & 8, paclitaxel 125 mg/m<sup>2</sup> (1-hour infusion) IV days 1 & 8, every 21 days for 3 cycles.

We analyzed data from the first 38 patients whose characteristics were: median age 59 years (range 37-71), male/female ratio 28/10, stage IIIA/IIIB 26/12. All patients had PS 0-1 at study entry. Histology was: 22 adenocarcinoma, 8 squamous-cell, 7 undifferentiated and 1 with mixed histology.

**Results:** Response rate was evaluated on the first 36 patients. We observed 25 PR (70%) and 1 CR (2%) for an overall clinical response rate of 72%. 4 patients (11%) progressed while on treatment. 21 responding patients (58%) including 6 IIIB cases, received radical surgery. Pathological CR has been obtained in 3 cases (8%). 11 patients (30%) were not considered eligible for radical surgery and received external radiotherapy. Grade 3-4 neutropenia and thrombocytopenia were 27%/0% and 9%/3%, respectively. Non-hematologic toxicity consisted in grade 3-4 nausea/vomiting (6%/0%), diarrhea (0%/3%), and neurotoxicity (3%/0%).

**Conclusions:** These preliminary data suggest that this combination is active and well tolerated in locally advanced NSCLC. Accrual up to 50 evaluable patients is ongoing.

## P 886

### Holoxan (ifosfamide), mitomycin and cisplatin chemotherapy in NSCLC-report from India

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Holoxan (ifosfamide), Mitomycin, and cisplatin combination chemotherapy has been demonstrated as one of the best active regimens in patients with non-small cell lung cancer (NSCLC). We evaluated this regimen in a group of Indian patients with advanced unresectable NSCLC (stage IIIB or IV). A total of 242 patients were enrolled. About a third of them did not continue therapy after the first course either because of toxicity, lack of affordability, or death. The remaining 162 patients (136 males and 26 females) received 2 or more cycles of chemotherapy. Nearly half of all followed up patients showed a partial or complete radiological response. Overall performance status (Karnofsky scale) worsened in 36 (22.2%) and improved in 54 (33.3%). While 60 patients (37.0%) gained weight, 75 (46.2%) lost weight during follow-up. Overall median survival of the patients was 22 weeks (95% confidence interval, CI, 16-24 weeks) irrespective of the number of chemotherapy cycles. However, overall survival improved progressively with the number of chemotherapy cycles administered. Median survival in patients receiving at least 3, 4 and 5 chemotherapy cycles was 23.5 (95% CI, 19-27); 27.5 (95% CI, 24-30) and 36 (95%CI, 28-42) weeks respectively. Survival at the end of 3, 6, 9 and 12 months was 65%, 30%, 16% and 12% respectively. Survival had no association with age of the patient, but was significantly correlated with baseline performance status (Pearson's correlation coefficient 0.290, p<0.01). The cost of each course of chemotherapy was a little over US\$ 100 only. The regimen was tolerated well by all and the side effects were minimal and acceptable. Thus, we concluded that the ifosfamide regimen containing mitomycin and cisplatin is a good chemotherapeutic combination in patients with advanced NSCLC.

## P 887

### Our experience of chemotherapy (CT) with vinorelbine (V) alone and vinorelbine (V) plus cisplatin (C) for non-small-cell lung cancer (NSCLC) patients (pts)

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From 1992 through 2000, 75 chemotherapy-naive pts with stage IIIB and IY NSCLC (histologically confirmed) were treated. 31 pts received V (25 mg/ m<sup>2</sup> days 1, 8, 15 and 22) - Group A. 44 pts received V (the same regimen) plus C (100 mg/m<sup>2</sup> day 1) - Group B. Both regimen were repeated every 4 weeks. The characteristics of the pts in the both groups were comparable, except for the proportion of pts with ECOG performance status 2, which was greater in Group B (38,6% vs. 5,7%). We compared the efficacy and toxicity 3 and 4 grade of the both groups. These data are presented in the table below.

	Group A, n=31	Group B, n=44
CR	0	1 (2,3%)
PR	6 (19,4%)	18 (40,9%)
ORR	6 (19,4%)	19 (43,2%)
SD	15 (48,4%)	10 (22,7%)
PD	10 (32,2%)	15 (34,1%)
Median survival	45,0 weeks	46,0 weeks
1-year survival	35,5%	38,6%
Neutropenia	7 (22,6%)	34 (77,2%)
Anemia	3 (9,6%)	10 (22,7%)
Thrombocytopenia	0	2 (4,5%)
Renal failure	0	1 (2,2%)
Peripheral neurotoxicity	1 (3,2%)	2 (4,5%)
Nausea / Vomiting	0	3 (6,8%)

Our results showed that the rates of response with combination of V plus C were close to double those with V alone (43,2% vs. 19,4%), but response rate in Group B was not accompanied by improvement in survival (46 weeks vs. 45 weeks). The combined CT was associated with more frequent hematological toxicity. Besides we observed severe renal failure and nausea / vomiting in Group B.

## P 888

### Porphyrin metabolism and radiosensitivity of squamous-cell lung carcinoma

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**Purpose:** To study the feasibility of correlation between the values of porphyrin metabolism and individual tumour radiosensitivity.

**Materials and methods:** The study enrolled 112 male patients with T2-4N0-3M0 squamous-cell lung carcinoma (SCLC). The content of porphyrins in the 24-hours' urine (coproporphyrin (CP) and uroporphyrin (UP)) and blood erythrocytes (protoporphyrin (PP) and CP) was measured before the treatment, immediately after it and 1.5 month after radical regimen radiotherapy at a total dose isoequivalent to 64-66 Gy. The values of the porphyrins content were compared with SCLC radiosensitivity assessed by the extent of primary tumor response.

**Results:** It was found that:

- the concentration of CP in the urine and PP in blood erythrocytes of SCLC patients was significantly decreased in comparison with the normal values ( $p < 0.05$ ) before the treatment;
- UP values did not significantly differ from the normal ones before the treatment; there was a statistically significant increase ( $p < 0.05$ ) of CP content in the urine of SCLC patients in the cases of complete (100%) and significant (>50%) response to radiotherapy;

- a significant difference ( $p < 0.05$ ) existed between CP content in SCLC patients with complete response (100%) and those with insignificant effect (<50%) of radiation treatment;

- the study of the role of PP and CP values required further accumulation of data.

**Conclusions:** On the whole, the investigation demonstrated the existence of correlation between the concentration of endogenous porphyrins (CP) in the urine of SCLC patients and the antitumour effect of radiotherapy, which makes it advisable to take into account the values of endogenous porphyrins content in the urine when creating the prognostication model of tumour (SCLC) response to radiation treatment.

## P 889

### The effect of complementary radiotherapy in lung cancer patients with partial response of the tumor after the primary radiotherapy course

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**Purpose of the study:** Evaluation of the impact of complementary radiotherapy in inoperable squamous-cell lung carcinoma patients.

**Materials and Methods:** The study included 28 inoperable (owing to metastatic involvement of mediastinal lymph nodes or severe concomitant pathology) squamous-cell lung carcinoma patients administered unconventional split-course radiotherapy (RT) (a 3-4-week interval in the middle of the treatment). At the first stage of RT the single target dose (STD) was 4 Gy ' 7 fractions, the total target dose (TTD) being 28 Gy; at the second stage - STD 2 Gy ' 15 fractions, TTD 30 Gy. The total dose of the whole RT course was isoequivalent to 64-66 Gy. One to 1-1.5 month period after the completion of RT, continuation of tumor growth was ascertained in this group of patients, which was detected as a result of radiologic, bronchoscopic and morphologic check-up. Complementary RT was delivered in the conventional fractionation mode, the TTD, taking into account the time interval after the primary course of RT, amounted to the dose isoequivalent to 80 Gy, i.e. being 20-30 Gy.

**Results:** The complementary RT course brought about an objective improvement in 64% of the patients, the significant one being in 54%. Complete response of the primary tumor occurred in 36%. No improvement was achieved in 36% of the patients with the size of primary tumor more than 5 cm in the diameter before the start of the special treatment. After the complementary RT course 68% of the patients presented with radiation pneumosclerosis of different intensity, and destruction foci in the residual tumor appeared in 18%.

**Conclusions:** The beneficial effect of the complementary RT makes it advisable to administer it in the cases of partial tumor response 1-1.5 month after the completion of the primary RT course, with subsequent antiinflammatory and rehabilitation therapy to prevent prostradiation damage of the lung tissue.

## P 890

### Mediastinal lymphadenectomy improves survival in surgically treated patients with non-small cell lung cancer

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Between 1960-1999, more than 3000 operations for non-small cell lung cancer (NSCLC) were performed and the clinical course of the disease was studied. The paper deals with the analysis of 2523 curative operations: 916 performed in the 60th-70th, 942 – in the 80th and 665 in the 90th. The operations performed in the 60th-80th were mostly "standard", and those of the 90th were "extended" i.e. – supplemented with complete mediastinal lymph nodes dissection (MLND). There were more elderly patients and more widespread disease in the group of the 90th. Combined treatment (with radio- and/or chemotherapy) was used among 7.0; 10.5; 12.0% of patients only in the analyzed groups. There were 8.3;5.2;4.8% of patients died within the first postoperative month.

Actuarial 1-3-5-year survival was: 74.7; 76.9; 79.1%; 45.1; 46.5; 55.3% and 30.9; 35.2; 40.3%. ( $p < 0.05$ ; log-rank test). The

improvement of treatment results turned to be not due to the use of combined treatment, but through the implementation of MLND. This conclusion is proved by the decrease of the incidence of tumor progression, including local metastases in the mediastinum. Also is of importance the increase of survival in patients with stage I (T1-2 N0M0) of disease: 5-year survival rate constituted: 39.4; 49.3; 56.7%. ( $p < 0.01$ ; log-rank test). Mediastinal metastases hadn't been diagnosed at thoracotomy without MLND, thus misleading the staging of the tumor. The removal of lymphatic pathways en block with potential (clinically undetected) metastatic lesions contributed more precise staging, decreased the progression rate and increased survival.

## P 891

### Surgical treatment for multiple primary non-small cell lung cancer cases

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**Patients and Methods:** From 1986 to 2001, 34 patients have been diagnosed as having multiple primary non-small cell lung cancer, in our Institute. These patients were divided into those with multiple synchronous tumors (ST) and those with multiple metachronous tumors (MT). These were then investigated clinically and histopathologically, and the survival curves from the date of diagnosis were calculated according to the pathological stage, histological type, and disease-free interval, using the method of Kaplan and Meier. **Results:** The incidence of multiple lung cancer cases over all lung cancer cases was 3.7% (33/884) in this ten-year period. There were 16 cases of ST, and 18 cases of MT. Overall, the histological type of these cases was Ad./Ad. (in 17 cases), Sq./Sq. (in 10 cases), and Ad./Sq. (in the other 7 cases). Various operations were performed in ST (single lobectomy in 5 cases, bi-lobectomy in 2 cases, single lobectomy with partial resection of the other lobe in 4 cases, partial resection of both lobes in 2 cases, and both single lobectomy or partial resection with endobronchial laser irradiation in 2 cases). Seventeen cases of MT underwent resection of the second primary tumor in the remnant lung (4 cases underwent completion pneumonectomy). The five-year-survival rate of the 16 ST cases was 83%. The operative morbidity in the MT cases was 35% (6/17) (including 3 of hospital death). **Discussion:** It is important to discriminate clinically between multiple primary lung cancer and intrapulmonary metastasis, because a good prognosis can be achieved after resection of early stage synchronous multiple lung tumors. However, present study found not so favorable outcome after resection (especially after completion pneumonectomy) for metachronous primary lung cancer. Therefore the oncological radicality and prediction of residual cardio-pulmonary function of these cases must be considered prudently in making an attempt to resect the metachronous tumors.

## P 892

### Central bronchopleural fistulae closed by bronchoscopic injection of absolute ethanol

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Bronchopleural fistulas (BPF) after pulmonary resection is one of life-threatening complications and usually treated surgically. We have developed a new unsurgical method. [Material & Method] Five patients, mean age of 69, were diagnosed with BPF after pneumonectomy or lobectomy. The treatment procedure was initiated by scratching intramural mucosa of the fistula using a brush or curet under bronchoscopic observation (2T20; Olympus; Tokyo, Japan). These five consecutive BPF were treated by injecting 0.1 ml aliquots of absolute ethanol directly to the submucosal layer of the fistula 6 - 25 times using an injection needle (NM-21L; Olympus) through a fiberoptic bronchoscope. Ethanol injection was stopped when it was confirmed that the surrounding mucous closed the fistula. The bronchoscopic treatment was repeated until each orifice of BPF was closed. [Result] Fistulas in five consecutive patients were successfully closed, leading to the healing of aspiration pneumonia, empyema, or mediastinitis. The closure of each BPF was bronchoscopically confirmed without any complication. The mean survival time after fistula formation was 40.4 months. [Conclusion] Our unsurgical treatment suggests to keep the patient's quality of life well and to reduce costs and duration of hospitalization. This is the first report of the bronchoscopic closure of BPF by injecting absolute ethanol, and we would recommend this treatment as a first-line therapy for post-operative BPF.

## P 893

### The remote results of chemo-radiotherapy in patients with small cell lung cancer brain metastases

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We have analyzed the results of chemo-radiotherapy 106 patients with SCLC metastases in the brain. This group of patients was divided into 2 parts: I - patients receiving brain irradiation  $\pm$  chemotherapy (CAV, CAM, EP) - 71, II - patients receiving chemotherapy AVP - 35. The regimen of AVP was as follow: Nidran (ACNU) 2-3 mg/kg i.v. day 1 + Vepesid 100 mg/m<sup>2</sup> i.v. day 4,5,6 + Cisplatin 40 mg/m<sup>2</sup> i.v. day 2,8 every 6 weeks. The survival from the start of the treatment for brain metastases constituted in the group I -  $7.4 \pm 0.8$  months, in the group II -  $8.8 \pm 0.7$  months. The improvement of neurological clinic in the group I after the beginning of the treatment was 1-2 months and in the group II - 2 weeks. Objective response rate in the brain (registered by means of CT) in the group with AVP was 62% (18/29): 15 complete responses (52%) and 3 partial responses (10%). The main toxicity of AVP chemotherapy was hematological. It was as follow: anemia G2/G3 - 17,1%; neutropenia - G3/G4 - 23%; thrombocytopenia G3/G4 - 34,3%. Chemotherapy with AVP was well tolerated and about 50% patients received the treatment in the outpatient department. Results showed high activity of AVP chemotherapy in patients with brain metastases.

**P 894****Phase II study of vinorelbine and cisplatin with concurrent radiotherapy for unresectable stage III NSCLC. A preliminary analysis**

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Background: Combination of cisplatin with new drugs (topoisomerase inhibitors, taxanes) and concurrent radiotherapy have a promising effect on outcome. Purpose: We conducted a phase II study to determine the response rate (RR), toxicity and survival of concurrent vinorelbine (Navelbine) and cisplatin (2 cycles) with radiotherapy (RTE), followed by 2 more cycles of the same drugs for advanced stage III NSCLC. Patients and methods: Between 16.11.2000 to 17.07.2001, 22 previously untreated patients with inoperable stage III NSCLC were enrolled: median age: 59 (45-67), male/ female = 19/3, PS1/2: 7/11, IIIA/IIIB1/21, squamous cell carcinoma: 18, adenocarcinoma: 2, adenoid chistic carcinoma: 1, large cell carcinoma: 1. Treatment consisted of 2 cycles of vinorelbine 15 mg/sqm d1, 8 and cisplatin 80 mg/ sqm d1, with Ethylol 740 mg/sqm d1, 8, q 21 d, concurrently with RTE 60Gy/ 30 fr, followed by 2 cycles of the same drugs: vinorelbine 25 mg/sqm d1,8 and cisplatin 100mg/sqm d1, with Ethylol 740 mg/sqm d1, 8, q 21 d. Results: 22 patients were evaluable for response and toxicity. 76 cycles were given, median number of cycles/ patients= 3,6; 20 patients completed RT, 16 patients completed treatment. Grade 3-4 neutropenia was present in 18%, grade 3-4 gastrointestinal toxicity in 18%, and esophagitis grade 3-4 in 9 % of the pts. One patient developed G4 neutropenia with septic death. One patient with G4 gastrointestinal toxicity, which needing parenteral rehydration abandoned treatment. One patient achieved a complete response (4%) and 8 patients achieved partial response (36%), for an overall response rate of 9/22= 42%. Conclusion: Preliminary analysis indicate that concurrent chemoradiotherapy with vinorelbine and cisplatin (2 cycles with thoracic RTE, followed by 2 more cycles of the same drugs) for advanced stage III NSCLC is feasible, well tolerated and has a positive effect on the response rate.

**P 895****Continuous hyperfractionated accelerated radiotherapy week-end less (CHART-WEL) omitting elective nodal irradiation (ENI) in stage III (SIII) non-small cell lung cancer (NSCLC) patients (pts)**

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Purpose: In an intent to improve local control reducing radiation induced acute toxicity, we evaluated prospectively CHART-WEL omitting ENI with neoadjuvant chemotherapy (NACT) on SIII NSCLC pts. Method: Thirty-one pts were included since 04/98. Adenocarcinoma 11; squamous 16; undifferentiated 4. Male 25; Female 6. Mean age 61.3 years (r45-80). SIIIA 10; SIIIB 21. Performance Status (PS) = <1 23; >2: 8. Weight loss (WL) = <5%: 21, >5% 10. Mean follow-up 12.1 months (r3-33).

NACT, generally 2-3 cycles of Cisplatin+Vinorelbine, was followed by CHART-WEL. Radiotherapy delivered 3 daily fractions of 1.5 Gy with 6 hours interval between fractions from Monday to Friday. Only the tumor and any node >15 mm on CT were included in the CTV. Kaplan-Meier method was used to estimate OS, PFS and illustrate the effect of S, PS, WL and response on both parameters. Cox-test was used to find the difference between curves. Results: Twenty-five pts received NACT, six didn't due to medical reasons, and 28/31 pts completed CHART-WEL (90.3%). Fourteen pts received 54 Gy in 16 days and 14 pts 60 Gy in 18 days. Tumor response (31 pts): CR 7 (22.5%). PR 18 (58%). OR 25 (80.5%). SD 4 (13%). PD 2 (6.5%). Isolated elective nodal failure 0%. CHART-WEL acute toxicity: G3 esofagitis 4 (13%); G3 anemia 1 (3.25%). Late toxicity: G2 radiation pneumonitis 1 (3.25%). NACT was well tolerated. OS(12 m)59% (CI 40-76), OS(24 m) 10% (CI 3-32). PFS(12 m) 46% (CI 29-64), at 24 months 0%. Responding patients OS 13 months, non-responders 4 months (p 0.01). S, PS and WL didn't show predictive value. Conclusions: CHART-WEL, omitting ENI, is well tolerated as ambulatory treatment, no ENI failures were seen. Its association with NACT is tolerable and results, in terms of tumor response, seem promising. Taking into account that we were able to escalate the dose from 54 to 60 Gy without increasing toxicity, we are considering a dose escalation protocol in this group of patients.

**P 896****Induction chemotherapy with the TIP regimen (paclitaxel/ ifosfamide/cisplatin) in stage III non-small-cell lung cancer**

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Background: Induction chemotherapy has shown promising results in non-small-cell lung cancer (NSCLC) stage III. Methods: Thus the Austrian Association for the Study of Lung Cancer (AASLC) has performed a multi-center phase II trial with TIP induction chemotherapy (paclitaxel 175 mg/m<sup>2</sup> over 3 hours on day 1 after standard premedication, ifosfamide 1000 mg/m<sup>2</sup> per day on days 1-3, cisplatin 60 mg/m<sup>2</sup> on day 1, and prophylactic G-CSF 5 µg/kg daily on days 4-13). Treatment cycles were repeated every 3 weeks for 3 cycles. Then patients were re-staged and selected for local treatment. Results: Forty-three patients (29 male, 14 female; median age 58 years, range 36-78; 22 IIIA, 21 IIIB; 24 adeno, 12 squamous cell, 4 large cell, 3 undifferentiated carcinomas) have been treated in this trial. Forty-two patients are evaluable for response and toxicity. An overall clinical response rate of 50% was achieved. Complete remission and partial remission were observed in 2 (5%) and 19 (45%) patients, respectively. Stable disease and progressive disease were seen in 14 (33%) and 7 (17%) patients. No significant differences in response rates were seen between stage IIIA and IIIB. The toxicities of the chemotherapy were mild and included mainly arthralgia, myalgia, neurotoxicity and alopecia. No severe hematological toxicity was observed. No dose reductions due to neutropenia were necessary. Surgery was performed in 21 (49%) patients (12 IIIA, 9 IIIB) and complete tumor resection was possible in 19 patients. Those patients for whom complete tumor resection was not anticipated received local radiotherapy. Median overall survival was not reached yet. Conclusion: The TIP regimen is active and well tolerated and, therefore, should be further evaluated as induction chemotherapy in NSCLC.

**P 897****Survival in lung cancer patients with brain metastasis; comparison among surgery, radiation and chemotherapy**E Budisin<sup>1</sup>, V Canak<sup>1</sup>, N Budisin<sup>2</sup><sup>1</sup>Institute of Lung Diseases, Department of Bronchology, Sremska Kamenica, Yugoslavia; <sup>2</sup>Institute of Oncology, Department of Surgery, Sremska Kamenica, YugoslaviaContact e-mail: [nikbu@eunet.yu](mailto:nikbu@eunet.yu)

Forty lung cancer patients with diagnosed brain metastasis were evaluated at the Institute of Lung diseases at Sremska Kamenica in the period from 1997-1999. Duration of survival in such patients was evaluated and compared according to the treatment employed as well as to the histology, number of metastasis and presence/absence of synchronous other visceral metastasis. Treatment modalities included: irradiation, surgery, and chemotherapy for chest tumor, and for the brain metastasis, and symptomatic treatment. There were 34 male (85%) and 6 female (15%). 72.5% have had solitary metastases, while 27.5 % presented with multiple metastasis. Mean survival was 3.2 months from the diagnosis of brain metastasis (range 0-14 months). Irradiation of thorax underwent 57.5%, chest operation 15% and chemotherapy 22.5%. Irradiation of brain metastasis underwent 42.5% of patients, chemotherapy 7.5% patients, while 12.5% were operated for brain metastasis. 37.5% were treated only symptomatically. Sixty percent were without other visceral metastasis. Statistical significance in terms of longer survival was found in patients who had solitary compared to multiple metastasis  $p < 0.026$ , in patients with irradiated brain metastasis  $p < 0.015$  and in patients operated for brain metastasis  $p < 0.003$ . Although prognosis of patients with lung cancer and brain metastasis is gloomy, our investigation suggests longer survival with employed brain surgery or brain irradiation.

**P 898****Clinical evaluation of HER-2/neu protein in malignant pleural effusion-associated lung adenocarcinoma and as a tumor marker in pleural effusion diagnosis**W C Su<sup>1</sup>, T L Hung<sup>2</sup>, F F Chen<sup>2</sup>, W W Lai<sup>3</sup>, A L Hsiao<sup>4</sup>, W T Huang<sup>1</sup>, H H W Chen<sup>5</sup><sup>1</sup>National Cheng Kung University Hospital, Internal Medicine, Tainan, Taiwan; <sup>2</sup>National Cheng Kung University Hospital, Pathology, Tainan, Taiwan; <sup>3</sup>National Cheng Kung University Hospital, Surgery, Tainan, Taiwan; <sup>4</sup>National Cheng Kung University, College of Medicine, Microbiology, Tainan, Taiwan; <sup>5</sup>National Cheng Kung University Hospital, Radiotherapy, Tainan, Taiwan  
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Purpose: Lung adenocarcinoma presenting as malignant pleural effusion (MPE) is common in Taiwan. Microscopically, the involved pleurae are infiltrated by numerous tumor foci, which suggests that the cancer cells are highly invasive. Overexpression of HER-2/neu has been related to proliferation, anti-apoptosis, and the high invasiveness of various cancer cells. We therefore were interested in studying the role of HER-2/neu in MPE-associated adenocarcinoma cell lung cancer (ADCLC). Experimental Design: The expression of HER-2/neu in pleural effusion was measured by enzyme linked immunosorbent assay (ELISA) and the expression on tumor cells was evaluated by immunohistochemical staining (IHS). Results: The mean value of HER-2/neu in pleural effusions of patients with ADCLC and other non-malignant lung diseases was 9.9 and 2.7 ng/ml, respectively. The difference is statistically significant ( $P < 0.001$ ). Compared with CYFRA 21-1, the performance of HER-2/neu as a tumor marker in pleural effusion diagnosis was better. Overexpression of HER-2/neu in tumor tissues was found in 70% (23/32) patients with MPE-associated ADCLC, 30% (13/43) stage I/II non-small cell lung cancer (NSCLC), and

44% (14/32) with stage III NSCLC. The incidence of HER-2/neu overexpression in tumor tissues of patients with MPE-associated ADCLC is significantly higher than that of patients with stage I-III NSCLC without MPE. The correlation of HER2/neu expression between ELISA and IHS is highly significant. Conclusions: These findings indicate that HER-2/neu is important in the pathogenesis of MPE-associated ADCLC and is a potential tumor marker for pleural effusion diagnosis.

**P 899****Prognostic significance of mutant p53 determination in patients with differentiated squamous cell lung cancer (DSCLC), T2N0M0**

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Tumor growth suppressor p53 is the key protein regulating the cell cycle. P53 expression is necessary for activation of several forms of apoptosis, whereas mutations of this marker associated with severe forms of the disease and resistance to chemotherapy and radiotherapy. The purpose of the investigation is to evaluate the significance of p53 determination in order to improve the individual prognostification of surgical treatment results in patients with DSCLC, T2N0M0. 49 patients with SCLC operated on in CRC RAMS were enrolled in this investigation. Expression of VEGF by immunohistochemical study of 49 paraffin blocks was determined. In the test group the distribution of patients was as follows: central cancer (78,57%), upper lobe involvement (61,5%), endobronchial and mixed growth forms, the dimensions of tumor were  $4,28 \pm 0,35$  cm. The patients were divided into two groups: I group (25) included patients with p53 expression, II - without expression of this marker. The analysis has shown statistically true differences of relapse-free survival in these groups:  $25,56 \pm 4,43$  months and  $49,62 \pm 4,47$  months ( $p < 0,001$ ), respectively. Conclusions: results of investigation has shown the correlation between expression of mutant p53 and surgical treatment results in patients with DSCLC, T2N0M0 and allow to consider it to be a significant factor of individual prognosis of the disease.

**P 900****VEGF in the prognosis of results of surgical treatment of patients with squamous cell lung cancer, T2N0M0**

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VEGF is the main factor inducing angiogenesis in the tumor by stimulating proliferation and migration of endothelial cells of nearby vessels. The purpose of the investigation is to determine the prognostic significance of VEGF for evaluation of results of surgical treatment in patients with SCLC, T2N0M0 49 patients with SCLC operated on in CRC RAMS were enrolled in this investigation. Expression of VEGF by immunohistochemical study of 49 paraffin blocks was determined. In the test group the distribution of patients was as follows: central cancer (78,57%), upper lobe involvement (61,5%), endobronchial and mixed growth forms, the dimensions of tumor were  $4,28 \pm 0,35$  cm. The patients were divided into two groups: I group (25) included patients with VEGF expression, II - without expression of this marker. The analysis has shown statistically true differences of relapse-free survival in these

groups:  $25,56 \pm 4,43$  months and  $49,62 \pm 4,47$  months ( $p < 0,001$ ), respectively. Conclusions: results of investigation have shown that VEGF expression is independent prognostic sign, which correlates with survival of patients with SCLC, T2N0M0.

## P 901

### Expression of mutant p53 and VEGF in prognosis of the treatment results in patients with differentiated squamous cell lung cancer (DSCLC), T2N0M0

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One of the contemporary ways of improvement of the lung cancer course prognosis and, therefore, optimization of the post-operative follow-up and treatment of patients is to investigate several individual molecular and biologic tumor characteristics, influencing its growth, differentiation and propensity to metastasize. The purpose of the investigation is to apply nowadays molecular and biologic prognostic factors to the prognosis of clinical course of the stage I SCLC. 50 patients with DSCLC operated on in CRC RAMS were enrolled in this investigation. As a result of molecular biological and immunological study poor prognosis factors were determined such as expression of mutant p53 and positive VEGF. The patients were divided into two groups with respect to the clinical course of disease and were comparable in relation to composition, age and advance of the disease. The significance of appropriate factors was determined in each group. In the group with favorable prognosis (which included 5-year survivors), the mutant p53 expression was 2,790,59 and in the II group - 4,390,44, respectively ( $p < 0,001$ ). In the group I positive VEGF was revealed in 25%9,02 and 76%8,71 in the group II ( $p < 0,05$ ). Conclusions: the results of this investigation have shown the informativeness of the studied factors in prognosis of results of surgery in patients with DSCLC, T2N0M0.

## P 902

### The value of soluble selectin levels in the management of lung cancer patients

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Increased expression of selectins has been found on endothelial cells of venules and capillaries in the tumor stroma of human neoplasms. E-selectin is also thought to participate in angiogenesis, based on the observation that its levels correlate with angiogenesis in hemangiomas. This suggests that the elevated levels of sE-selectin found in advanced stages of some human cancer may reflect adhesion processes of circulating tumor cells and/or neovascularization. Thus, this study was aimed to analyze the behavior of plasma soluble (s)E-selectin and sP-selectin levels in 154 patients with either benign (38) or malignant (116) lung diseases and 59 healthy donors. The association with CEA levels and clinicopathological variables was also analyzed. The results obtained showed that sP- ( $F=4.3$ ,  $p < 0,02$ ), sE-selectin ( $F=6.0$ ,  $p < 0,005$ ) and CEA ( $F=11.9$ ,  $p < 0,001$ ) levels

were higher in patients with lung cancer. CEA levels correlated with sP- ( $r=0.25$ ,  $p < 0,01$ ), but not sE-selectin levels, in the overall population. Increased levels of sP-selectin, sE-selectin and CEA were significantly associated with advanced squamous lung cancer ( $p < 0,05$ ), but not adenocarcinoma. To further analyze the relationship among these variables, a multiple regression analysis including age, sex, CEA, sP- and sE-selectin levels was also carried out. The final model obtained by stepwise regression analysis revealed that elevated CEA [ $\beta=0.41$ ,  $p < 0,001$ ], sE-selectin [ $\beta=0.34$ ,  $p < 0,01$ ], sP-selectin [ $\beta=0.24$ ,  $p < 0,05$ ] levels, and male gender [ $\beta=0.26$ ,  $p < 0,03$ ] were independently related to the stage of squamous lung cancer, whereas only elevated sE-selectin levels were independently related to the presence of distant metastasis [ $\beta=0.35$ ,  $p < 0,01$ ] in the same histotype. These results suggest that measurement of plasma soluble selectins might represent an useful laboratory parameter in the management of patients with squamous lung cancer. *Partially supported by P.F. Ministero della Sanita 1999*

## P 903

### Expression of 90K (Mac-2 BP) can predict distant metastasis and survival in stage I non-small-cell lung cancer patients

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Background: 90K, also known as Mac-2 binding protein, is a secreted glycoprotein involved in immune response mechanisms and in cell-cell and cell-extracellular matrix adhesion. Moreover, it has been shown that 90K serum levels hold prognostic value in several neoplasms. Objective: We aimed to investigate the role of 90K as a prognostic indicator in pathological stage I Non-Small-Cell Lung Cancer (NSCLC) patients. Method: 90K expression was assessed by immunohistochemistry, and confirmed by ELISA assay, on 72 stage I NSCLC specimens, obtained from complete surgical resections of the lesions. 50% of stained cells was chosen as cut-off point between low and high expression samples. The median length of follow up care was 54 months. Results: 28% (20/72) of tumors showed high levels of 90K expression, and this was associated with a poorer prognosis. In fact, in high 90K-expressing patients, both disease-free and overall survival rates were significantly lower than those same rates in patients with low 90K expression ( $p=0.0001$  and  $p=0.003$ , respectively). Moreover, the incidence of distant metastases in patients with high 90K expression levels (60%, 12/20) was significantly higher than that of patients with low expression (21%, 11/53;  $p=0.0038$ ). The results of multivariate analysis showed that a high level of 90K expression was a significant factor to predict poorer prognosis. Conclusions: 90K expression, assessed immunohistochemically, could be an useful prognostic factor in patients with pathological stage I NSCLC, likely as an indicator of the metastatic propensity of the tumor.

**P 904****Soluble vascular endothelial growth factor levels in lung cancer. Relationship with coagulation and platelet activation markers**

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Vascular endothelial growth factor (VEGF) is a potent angiogenic factor essential for tumor growth and metastasis. Lately, it was shown that thrombin activation of platelets causes VEGF release, and that VEGF-stimulated endothelial cells promote adhesion and activation of platelets through the generation of thrombin. Therefore, the present study was aimed to analyze plasma soluble (s)VEGF levels in 65 patients with non-small cell lung cancer (NSCLC)[32 adenocarcinomas (ADC), 33 squamous cancer (SC)] and 33 age- and sex-matched healthy donors. Furthermore, a correlation analysis between sVEGF and markers of platelet activation (sP-selectin) or thrombin generation [thrombin-antithrombin complexes (TAT)] was performed to test the hypothesis of a role of haemostatic abnormalities in tumor growth and metastatization in NSCLC. Median plasma sVEGF levels were higher in NSCLC (68.2 pg/ml) compared to controls (28.6 pg/ml;  $p < 0.005$ ). Similarly, sP-selectin (55.5 vs. 48.8 ng/ml,  $p < 0.05$ ) and TAT (9.6 vs. 2.1  $\mu\text{g/l}$ ,  $p < 0.001$ ) were higher in NSCLC than controls. Median sVEGF ( $F = 6.3$ ,  $p < 0.005$ ) and sP-selectin ( $F = 3.7$ ,  $p < 0.03$ ) levels were higher in SC than either ADC or controls. A correlation analysis among the variables showed that sVEGF correlated with sP-selectin ( $r = 0.57$ ,  $p < 0.001$ ) and TAT ( $r = 0.52$ ,  $p < 0.005$ ) only in SC. sP-selectin correlated with TAT complexes ( $r = 0.39$ ,  $p < 0.05$ ) in the same histotype. Multiple regression analysis including age, sex, diagnosis, sVEGF, sP-selectin and TAT revealed that sP-selectin ( $\beta = 0.41$ ,  $p < 0.002$ ), TAT ( $\beta = 0.34$ ,  $p < 0.02$ ), and SC ( $\beta = 0.22$ ,  $p < 0.05$ ) were independently related to sVEGF. In particular, mean sP-selectin and TAT levels were approximately 2-fold higher in SC patients with sVEGF levels above the median value. These results suggest that haemostatic abnormalities are strictly related to the presence of elevated sVEGF levels in patients with lung SC. *Partially supported by P.F. Ministero della Sanità 1999 and 60% Facoltà 1998/00*

**P 905****Markers of tumor invasion as predictors of survival after resection of non-small cell lung cancer in stage I**

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Background: Surgical resection is widely accepted as the treatment of choice for stage I of non-small cell lung cancer (NSCLC). A recurrence will develop in approximately one-third all resected patients in this stage. The different markers of tumor invasion were

identified as the predictors of high risk of recurrence and shorter survival. Matrix-metalloproteinases (MMP) play a crucial role in the breakdown of vascular barriers and tumor cell invasion. Tumor induced angiogenesis is necessary for both tumor growth and metastatic spread. Method: The aim of the study was to compare expression of different matrix-metalloproteinases (matrix-metalloproteinase 2, matrix-metalloproteinase 9, matrix-metalloproteinase 11) and two markers of neoangiogenesis (microvessels density-MVD, vascular endothelial growth factor-VEGF) to the survival in patients in pathological stage I NSCLC, who have undergone a curative resection. Result: Formalin-fixed and paraffin-embedded specimens from 50 surgically treated patients were used for the indirect immunoperoxidase detection of the above-mentioned MMP, MVD and VEGF. Relationship between overexpression of the selected markers and the survival was statistically analyzed. Conclusion: Overexpression of some cancer invasion markers in tumor tissue may serve as an indicator of poor prognosis in surgically treated patients with NSCLC and could provide a key to select patients for possible adjuvant therapy. This work was supported by grant MZCR 6615-3.

**P 906****Cytotoxicity of factors secreted by macrophages for transformed rat mesothelial cells**

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Macrophages strongly inhibited asbestos-induced transformation of rat pleural mesothelial cells in vitro and such inhibition was caused by preferential depletion of malignitized cells. The aim of this work was to investigate cytotoxic action of macrophages and asbestos on transformed mesothelial cells, to characterize its specificity and the nature of factors mediating it. The viability of cells of different lines after asbestos exposure was studied in co-culture with macrophages. Mesothelioma cell lines obtained from tumors developed in vivo were the most sensitive to the cytotoxic action of these conditions. Mesothelium cells of late passages and ras-transformed cell lines IAR2 and Rat1 were somewhat less sensitive, whereas untransformed cells of IAR2 and Rat1 lines and early passage mesothelium were low sensitive to that toxic action. In experiments performed on Petri dishes with inserts which allowed to treat with asbestos only one of two cell populations it was shown that asbestos treatment of mesothelioma cells was necessary and sufficient for manifestation of cytotoxic effect (in the absence of macrophages asbestos showed very low toxicity). The medium conditioned by macrophages was not cytotoxic by itself but it strongly enhanced toxic action of asbestos on transformed mesothelial and mesothelioma cells but not on normal mesothelial cells and IAR2 and Rat1 cells (both normal and ras-transformed). Media conditioned by human peripheral blood monocytes but not by granulocytes and lymphocytes can cause this augmenting effect also. The specificity of that effect for different toxicants was investigated. It was shown that medium conditioned by macrophages enhanced cytotoxicity of asbestos, hydrogen peroxide and sodium azide but not that one of nonfibrous silicon dioxide, ethylmethanesulfonate and sodium dodecylsulfate. The factor mediating this effect is thermolabile, non-dialyzable and protease-sensitive. Its m. w. is approximately 3 - 5 kD.

**P 907****Malignant mesothelioma in Europe and the Mediterranean region**

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**Background** During the last decades mesothelioma has become a major health problem in various countries. Asbestos is recognized as the principal etiologic factor in the genesis of the tumor. The present study was aimed to obtain an outline of mesothelioma epidemiology in Europe and the Mediterranean region.

**Methods** A questionnaire was sent to 264 researchers of 45 different European countries, and extra-European countries facing on the Mediterranean Sea. Information about the approximate annual number of mesotheliomas diagnosed in the country was requested. In addition, the recent literature on mesothelioma epidemiology was reviewed.

**Results** For some large industrialized countries (e. g. Russia, Ukraine) data are not available. In Europe, estimated annual crude incidence rates of malignant mesothelioma ranged between 2 cases per million in Portugal, and 29 in Belgium. In general, incidence was lower in Central and Eastern Europe than in the Western part of the continent. In the Mediterranean region estimated annual crude incidence rates ranged from low values in Northwestern Africa (0.6 and 0.7 cases per million respectively in Tunisia and Morocco), to intermediate values in Israel and Slovenia (3 cases per million), and to high values in France and Italy (17 cases per million).

**Conclusions** In explaining the very wide variations in mesothelioma incidence, various points have to be considered, including: 1) the demographic features: the percentage of people aged 60 years or more is 4.3% in Libya, and 22.5% in Italy; life expectancy varies markedly from one part to another of Europe as well as in the Mediterranean countries; 2) differences in the history of industrialization; for instance, asbestos-cement industry started in 1907 in Italy, in early 1920s in Croatia, and in 1952 in Israel. These characteristics are very relevant for a tumor with long latency periods (frequently 50 years or more).

**P 908****Comparative study regarding the efficiency of the cytological and histopathological examination in diagnosis of bronchopulmonary cancer**

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**Objective.** The goal of our study was to demonstrate the efficiency of the cytological and histopathological examination in patients with suggestive clinical manifestations and radiological aspects for bronchopulmonary cancer. **Material and method.** Our study was performed on 620 patients, aged between 32-84 years, 551 (88.8%) male and 69 (11.24%) female. 535 (86.2%) patients among these were smokers. Bronchoscopy was performed in all cases, drawing of pathologic samples by bronchial lavage was made in 543 cases and bronchial biopsy in 454 patients, and cytological examination on smear and by marks (impressions) was made parallel with histopathological one. **Results.** Cytological examination was positive in 86.8% cases and histopathological one in 92.4% patients. The histological type of pulmonary cancer was established in 83.8% patients with positive cytology. In 13 patients (4.3%) non-differentiated carcinoma with small cells and in 289 cases (95.6%) non-small cancer were diagnosed, among which: 64.5% squamous carcinoma, 21.8% non-differentiated carcinoma

with big cells, 5.9% adenocarcinoma and 2.9% adenosquamous carcinoma. The results of the histopathological examination are the same with those of cytological one but the cases of carcinoma with small cells were diagnosed with 7.1% times more by this method. **Conclusion.** The cytological examination by lavage and by marks (impressions) cannot replace the histopathological one but may be necessary in many cases in which the biopsies cannot be made by bronchoscopy or these are on small size.

**P 909****Diagnostic methods in lung cancer: evaluation of bronchoscopy and trans thoracic needle aspiration: an Indian experience**

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Contact e-mail: [soumil\\_v@yahoo.com](mailto:soumil_v@yahoo.com)**Introduction:**

The Tata Memorial Hospital is a tertiary referral center for the treatment of Cancer and allied diseases; a premier cancer center in this part of the world. We see about 800 new cases of lung cancer every year and perform about 100 pulmonary resections for cancer every year.

**Materials and Methods:**

A total of 431 thoracotomies were performed in our unit over a four-year period. The case records of these patients were scrutinized for the diagnostic methods employed in these patients. A total of 313 patients were completely staged for cancer. All these patients had a routine diagnostic bronchoscopy performed as an out patient procedure. 135 (43.13%) patients had central lesions while 178 (56.86%) patients had peripheral lesions.

**Results:**

A positive diagnosis of cancer was correctly obtained in 68.37% of the patients while 31.63% had an inconclusive diagnosis. The overall accuracy of a diagnostic bronchoscopy in our center was 74.95% which correlates well with that reported in the world literature. A chi squared test conducted showed bronchoalveolar lavage to be highly significant to diagnose correctly central lesions. ( $p=0.00001$ )

A trans thoracic needle aspiration was performed in 91 pts. The procedure had a sensitivity of 74.72% with an overall accuracy of 89.01%. Other indices such as sensitivity, specificity, positive predictive value, negative predictive value and accuracy were also calculated in both groups. (not presented here due to paucity of space)

The complication rate in both groups of patients was negligible.

**Conclusions:**

Our results show that diagnostic bronchoscopy and TTFNA; are effective and safe methods in the preoperative diagnosis of lung cancer.

**P 910****Imaging guided fine needle aspiration cytology of thoracic lesions**

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**Objective of the Study:** The objective of our study is to assess the efficacy, reliability, simplicity & safety of Image guided aspiration cytology of thoracic lesions. **Materials/Methods/Procedures:** Needle aspiration was performed in 590 patients from Feb. 1989 to Nov. 2001 using Fluoroscopy, Ultrasound & CT as Image guid-

ance. After reviewing the patient and coagulation profile, a plan is formulated to adopt the safest approach to the thoracic lesion. A fine needle (22G L.P. or Chiba) is guided to the thoracic lesion with an Image technique and material is aspirated with 20 cc plastic syringe and smeared on slides. Immediately after the technique, puncture site is put on dependent position (Roll-over technique) to reduce the risk of pneumothorax. Results: There were 500 male and 90 female in the range of 15 to 91 years. Results were obtained in 489 patients (82.9%). Malignant cases were 454 (76.9%). Maximum no. of malignant cases were in 6th decade (39%). Of the rest 136 cases, Non-malignant lesion-35 and Inconclusive result-101. Complications included haemoptysis (two) and pneumothorax in 12 (2%). 54 patients (9.2 %) needed repeat aspiration. Conclusions: Image guided aspiration is a safe, swift, easy and reliable method in tissue diagnosis of thoracic lesions. Morbidity is very low. Accuracy is very high. Procedure can be performed without any special preparation. Risk of pneumothorax can be very significantly reduced by meticulous planning and Roll-over technique.

## P 911

### Reassessment of GSTM1 and GSTT1 cancer predisposing roles: comparison of genotypes in elderly tumour-free smokers and non-smokers vs. healthy donors vs. lung cancer patients

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**Objective:** To reassess the controversial evidence for the role of GSTM1 and GSTT1 deficiencies in cancer susceptibility, we included in the molecular epidemiological study the group of apparent cancer resistance, namely elderly tumour-free subjects ("elderly donors", ED).

**Method:** PCR genotyping was used in the study.

**Results:** Comparison of ED smokers and non-smokers vs. healthy donors (HD) vs. lung cancer patients (LC) confirmed a modest unfavourable impact of GSTM1 but not GSTT1 null genotypes. In particular, GSTM1(-) variants were underrepresented in ED vs. HD (146/324 (45%) vs. 184/339 (54%); OR = 0.69 (0.51 - 0.94), P = 0.018). The prevalence of GSTM1 deficiency in LC (91/167 (54%)) did not statistically differ from the one observed in HD, however showed a significant increase when ED served as a non-affected control (OR = 1.46 (1.00 - 2.12); P = 0.048). Furthermore, in agreement with mechanistic considerations, an excess of GSTM1(-) genotypes was more pronounced in squamous cell carcinoma (SCC) cases (51/88 (58%)) as well as in LC patients with seemingly low cumulative carcinogen exposure dose (non-smokers: 12/19 (63%); patients aged below 50 years: 13/17 (76%)). Contrary to GSTM1, GSTT1 polymorphism did not display regular deviations between the studied groups. In conclusion, the results of this study are in good agreement with the body of literature data, including several published meta-analyses.

**Conclusions:** The suggested study design involving additional "cancer resistant" group of non-affected subjects may provide highly demonstrative data and seems to be suitable for pilot investigations as well as resolving of controversial issues.

## P 912

### Phallus impudicus in treatment of Lewis lung carcinoma

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**Objective:** The present study is aimed to examine the possibilities of inhalant immunotherapy of Lewis lung carcinoma using *Phallus impudicus* concentrated extract (Ph.i.ex) 30% w/w in small particle spray and to investigate the mechanism of action and the possible targets of this remedy.

**Method:** The experiments were carried out on C57BL/6 strain male mice (n=80) with Lewis lung carcinoma after surgical ablation on 14<sup>th</sup> day after carcinoma inoculation. Ph.i.ex was injected subcutaneously in a dose of 5,0 mg/kg on the 7<sup>th</sup> day after inoculation of tumor cells and inhaled for 28 days in concentration 50 ppm with pH 6,5 starting from day 5 after injection. Alveolar macrophages were extracted by Fidler method (1980). Adenosine deaminase (AD) and 5' nucleotidase (5'N) activity was estimated in lysate by ascending paper chromatography.

**Results:** Surgical ablation of the primary tumor resulted in a sudden increase of the volume and number of metastases in the lungs compared to nonoperated animals. 5 days inhalation after subcutaneous injection of Ph.i.ex was beneficial for reducing the number of metastases by 7,4 times, depressing the metastases volume by 14 - 15 times. The studies of the enzyme activity of adenosine metabolism in alveolar macrophages, directly contacting metastatic cells in mice lungs reveal that by spray inhalation the activity of AD deaminase increased while that of 5 nucleotidase decreased against the values in nontreated animals.

**Conclusion:** The obtained results suggest that the action of Ph.i.ex. gives rise to restoration of the disordered function and activation of alveolar macrophages as affected by stress reactions and tumor cells spreading in organism. The features noted make it possible to offer Ph.i.ex for antimetastatic therapy, including preoperative and postoperative correction of alveolar macrophage function.

## P 913

### Gender differences in postoperative complications and length of stay in surgical thoracic patients with poor, intermediate and normal pulmonary function

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**Background:** Our objective was to compare postoperative complications (PC) rates and length of stay (LOS) in men and women after pulmonary resection. Men are known to have higher rates of PC than women. Various preoperative parameters were employed in the past to predict PC. Our earlier study found Predictive Respiratory Quotient (PRQ = ppoFEV1% x ppoDLCO%<sup>2</sup>/A-a PO2) to be a sensitive and specific indicator for the occurrence of PC. We employed PRQ to categorize patients and evaluate gender differences. **Methods:** Postthoracotomy cancer patients were evaluated. LOS and PC rates were compared between genders in 3 equisized groups with low, intermediate and high PRQ (cutoff points: 5200, 14400) with univariate tests. The power of the PRQ and other cofactors to predict LOS and PC and to categorize patients into groups with or without PC was tested with regression and discriminant analyses. **Results:** 167 patients were included: 77

men, 90 women. Mean age was  $64.4 \pm 10.9$  and did not differ significantly between genders. Mean LOS was  $6.9 \pm 3.7$ ; men stayed on average 1d longer than women ( $7.4 \pm 3.5$  vs.  $6.4 \pm 3.5$ ,  $p = .07$ ). PC occurred in 40.6%. LOS and PC rates did not differ significantly between genders in both high and low PRQ groups, while in the intermediate PRQ group, they were significantly higher in men than in women:  $7.8 \pm 3.2$  vs.  $5.9 \pm 2.6$  and 19/29 vs. 7/27 respectively. Based on age, sex and PRQ, a regression model predicted only 27% of variance in LOS and discriminant analysis showed moderately good separation between groups with or without PC. Conclusions: There was no difference in length of stay and postoperative complications rates between genders on both extremes of pulmonary function. In the intermediate pulmonary function group, men had more complications and stayed in the hospital longer.

## P 914

### Imaging evaluation and staging of bronchial carcinoma

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**Introduction:** The bronchial carcinoma is a major cause of cancer deaths in man with incidence, which is increasing permanently. Purpose: To demonstrate the value of Computed Tomography of the Lung and Mediastinum in preoperative evaluation and staging of bronchial carcinoma. Material and methods: We demonstrate 43 cases of bronchial carcinoma with preoperative CT staging. The patients are in age of 45 to 77. The disease afflicts man over the age of 60. 34 (79%) are males and 9 (21%) are females. All patients underwent on CT of lungs and mediastinum after standard patient preparation. Results: With CT staging we find: T1 in 6, T2 in 20, T3 in 13 and T4 in 4 patients, N0 in 7, N1 in 19 and N2 in 17 patients, M0 in 36 and M1 in 7 patients. The patients according to TNM classification are divided in IV stages: stage I (includes tumours T1, T2 without lymph node metastases) - 7 cases, stage II (includes tumours T1, T2 with intrapulmonary and hilar lymph node metastases) - 10 cases, stage III (includes tumours T2, T3 and ipsilateral positive mediastinal lymph nodes N2) - 15 cases and stage IV (includes tumours T3, T4 with lymph node metastases and distant metastases) - 11 cases. This is the margin on surgical treatment accepted by many authors. The most common were squamous cell carcinoma in 29 patients and adenocarcinoma in 14. The comparison is been made between the CT findings and the operative finding according to TNM classification. The sensitivity of CT in tumour estimation according to operative finding is 61%, while the specificity is 69%. The sensitivity of CT in node estimation according to operative finding is 60%, while the specificity is 67%. Correct CT staging has in 56%, under staging in 37% and over staging in 7%. Conclusion: CT is valuable diagnostic method in tumour and node estimation, particularly on N2 category, which is very important in planning the radically of surgical treatment.

## P 915

### CYFRA 21-1, SCC-Ag, CEA and selected biochemical factors of cachexia in patients with squamous cell lung cancer

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In assessment of prognosis of lung cancer patients, apart from classical predictive and prognostic factors such as: stage, type of histology, an grade, results of biochemical examinations were also analyzed, especially of tumor markers. In many of cancer patients develops syndrome of cancer cachexia caused by deficiency of energy and structural substrates. Nutritional depletion is one of causes of this state, but it is mainly generated by tumor induced activation of the host immune system. Cachexia is a result of the malfunction of many metabolic processes which are expressed by changes of concentration of biochemical factors, among other hypoalbuminemia and tendency to elevated levels of alpha-1 and alpha-2 globulin.

The aim of study was estimation of dependencies between levels of tumor markers: CYFRA 21-1, SCC-Ag, CEA and concentration of fractions of electrophoretical proteins in serum, in respect of selection squamous cell lung cancer patients with a very poor prognosis.

In squamous cell lung cancer patients, in comparison to the refernc group were found significantly higher concentrations of CYFRA 21-1, SCC-Ag, CEA, alpha-1, alpha-2 globulin and significantly lower concentration of total protein and albumin. In this patients, the diagnostic sensitivity of CYFRA 21-1 results was significantly higher than for other tumor markers. An univariate analysis indicated that, apart from stage of disease, albumin, alpha-1 globulin and all assessed tumor markers were the most influential prognostic factors for survival. Especially poor prognosis is demonstrates by patients having hypoalbuminemia and elevated level of CYFRA 21-1 and a group with elevated levels of CYFRA 21-1 and alpha-1 globulin. In multivariate analysis, apart from stage of disease, independent prognostic factors were high concentrations of CYFRA 21-1 and alpha-1 globulin.

## P 916

### Fish consumption as a protective factor in lung cancer

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Male age-adjusted lung cancer mortality rate is high in Rosario City, Argentina (62.7 %000). The purpose of this investigation was to evaluate the possible protective effects of certain dietary habits in the development of primary lung cancer in male smokers. A case-control study involving interviews with 65 histologically confirmed lung cancer male patients, and 85 controls, admitted to three medical institutions of Rosario, was done. Controls were selected from patients admitted for a non-smoking related disease. A standardized questionnaire including age, smoking characteristics, lifetime occupations, and dietary habits was applied. Cases and controls were classified as follows: 1) Occupation: a) workers non-exposed to occupational contaminants (e.g.: lawyers, teachers), b) workers in metallurgic industries, c) workers exposed to other contaminants (e.g.: farming, drivers); 2) Smoking intensity: a) ? 20 cigarettes/day, b) >20 cigarettes/day; 3) Fish consumption: a) none, b) less than the median, c) more than the median. The odds ratios (OR), crude and adjusted by age, medical institution,

smoking intensity and occupation, were calculated using exact logistic regression analysis. CP risk was lower in subjects consuming fish more than four times a month (OR=0.41; CI=0.17–0.97). When considering fish origin, a protective effect was found in subjects eating more than two monthly portions of river fish (OR=0.34; CI=0.12–0.94). In conclusion, while smoking and occupational contaminant exposures are the most important CP risk factors, fish consumption could be protective.

## P 917

### Caffeine-potentiated chemotherapy for high-grade soft tissue sarcoma

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**Background:** In order to improve patient's survival and enhance the safety of limb-sparing surgery, we introduce caffeine-potentiated chemotherapy for high-grade soft tissue sarcomas. **Methods:** Forty-four patients were treated with caffeine-potentiated chemotherapy. The group consisted of 24 men and 20 women ranging in age from 12 to 77 years (mean, 49 years). Sixteen patients had malignant fibrous histiocytoma, 5 had synovial sarcoma, 8 had liposarcoma, 4 had epithelioid sarcoma, 6 had leiomyosarcoma, 2 had rhabdomyosarcoma, and 3 had other tumor types. Eleven patients were at stage III with lung metastasis and the other 33 were at stage IIB without metastasis. For intra-arterial preoperative chemotherapy, we administered 2-5 courses of cisplatin, doxorubicin, and caffeine. Surgical margins were wide for 22 patients, additional wide for 11, marginal for 4, additional marginal for 1, and intralesional for 6. **Results:** Five patients had a local recurrence. Of the 33 stage IIB patients, 7 developed lung metastasis. Following preoperative chemotherapy, radiography confirmed a complete response in 2 patients, partial response in 26 and no response in 16. Histologic results showed grade III (no viable cells) in 9 patients, grade II (90% necrosis) in 11, grade I (50-90% necrosis) in 6, and grade 0 (no response) in 18. Overall response rate was 76% (32 out of 42). The mean follow-up period was 56 months (range: 1-136 months). Ascertained by the Kaplan-Meier method, the five-year survival rate of stage II patients was 86%. **Conclusion:** Caffeine-potentiated chemotherapy provided excellent response rate and 5-year survival to patients with high-grade soft tissue sarcoma since caffeine, which is a xanthine analogue, has a DNA-repair inhibiting effect enhances the cytotoxic effects of anticancer drugs. Caffeine-potentiated chemotherapy contributed to the improvement of the patient's prognosis with high-grade soft tissue sarcomas and the safety of limb-saving surgery.

## P 918

### Effect of a novel somatostatin analog (tt-232) combined with cytostatics on the growth of human tumour xenografts and metastasis number of b16 mouse melanoma

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A novel somatostatin analog, TT-232 possessing inhibitory activity on the proliferation of various cell cultures and transplantable mouse tumors was examined regarding its action on human melanoma and lymphoma xenografts as a single treatment or in combination with DTIC (dacarbazine) (Lachema, Brno, Czech Republic) or with Etoposid (EVA, Haarlem, Netherlands). Antimetastatic effect of TT-232 treatment combined with DTIC was studied using the B16 mouse melanoma muscle-lung metastasis model. TT-232 inhibited the growth of HT-18 melanoma xenografts, 5 mg/kg being the most effective. Combination of 1 mg/kg TT-232 with 30 or 60 mg/kg DTIC (daily administration) resulted in a stronger effect compared to TT-232 or DTIC alone. The lung metastasis number of B16 melanoma could be decreased by daily administration of 1 mg/kg TT-232 or 60 mg/kg but not of 30 mg/kg DTIC. TT-232, combined with 30 or 60 mg/kg DTIC decreased the lung metastasis number to a value, which was significantly lower compared to the control. Nearly 50% growth inhibition of HT-58 lymphoma was achieved by daily treatment with 1 mg/kg TT-232. Five mg/kg Etoposid administered daily, resulted in a similar effect. The combination of 1 mg/kg TT-232 and 5 mg/kg Etoposid was significantly more effective than the two compounds alone. The very strong tumor growth inhibitory effect of 10 mg/kg Etoposid could even be increased by combination with TT-232. TT-232 may be considered as an effective new tool in combination chemotherapy of malignant tumors like melanoma and lymphoma.

## P 919

### The response of chemotherapy and radiotherapy in high grade glioma in relation to p53 protein expression

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**Background and Objective-** Malignant glioma constitute 50% of primary brain tumors and is responsible for 2.5% of cancer death. Main modalities of treatment are surgery followed by radiotherapy. The addition of chemotherapy improves the survival. **Material and Methods-** Thirty patients with high-grade glioma were included in this study. p53 protein expression was studied in histological embedded tissue. All patients were treated with 2 cycle of neo-adjuvant chemotherapy followed by radiotherapy. This was again followed by 2 cycle of chemotherapy (Inj Cisplatin 50mg D1-D3 and Inj Etoposide 150mg D1-D3). External radiotherapy was given to a total dose of 66Gy/33fractions with initial 50Gy/25fractions including 2-3cm margin around primary tumor and edema followed by boost of 16Gy/8fractions. **Result-** Twenty patients were evaluable at the end of the study. The p53 protein was over-expressed in 50% of the patients. The toxicities of chemotherapy were mild (RTOG Grade I-III) and all were managed conservatively. There were no chemotherapy related deaths. The

mean survival duration was 17 months for whole group with median survival of 19 months. Median survival at 6 months and 12 months was 95% and 65% respectively. Conclusion-The improvement of survival as evident by both clinically and radiologically, which suggest that chemotherapy regimen is active in high-grade glioma. There was no significant correlation with p53 protein expression and survival of the patients. However the patients with high percentage of p53 protein expression had aggressive course.

## P 920

### Neoadjuvant chemotherapy with cisplatin and docetaxel for stage IIIA non-small cell lung cancer (NSCLC) based on in-vitro findings. A pilot study

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Patients (pts) with stage II or III NSCLC have tumors that are considered marginally resectable because of the high incidence of local treatment failure with surgery alone. Several recent studies suggest that neoadjuvant (induction) chemotherapy can convert pts with marginally resectable tumors to pts with curatively resected tumors and improve the cure rate. In this case, it is important to choose most effective combination chemotherapy. We chose a combination of cisplatin and docetaxel based on in-vitro findings: 1) This combination was synergistic or additive in all nine human NSCLC cell lines tested, that were sensitive to cisplatin and docetaxel. 2) Docetaxel dramatically inhibited cancer cell migration. Eleven pts with stage IIIA NSCLC, 9 men and 2 women, median age 65.5 ± 5.7 (mean ± SD), without prior chemotherapy, with measurable disease and good hematological, cardiac, hepatic and renal function, were treated with 80 mg/m<sup>2</sup> cisplatin and 60 mg/m<sup>2</sup> docetaxel every 28 days for 2 cycles. Of 11 pts, 6 pts were PR, and 5 pts were NC; proportions of tumor reduction were 57.8 ± 25.0% (16%-91%). Grade 3-4 neutropenia was observed in 2 pts. Other mild toxicities were diarrhea (1 pt), nausea & vomiting (3 pts), mild liver dysfunction (2 pts), anemia (5 pts), thrombocytopenia (4 pts), and skin rash (1 pt). Eight pts were curably resected, 1 pt received only exploratory thoracotomy, and 2 pts offered continuous chemotherapy. Stages based on pTNM were I (2 pt), IIA (2 pt), and IIIA (4 pts). Immunohistochemical studies of the resected cancer lesions showed no excessive appearance of multi-drug resistance-relating proteins. Thus, cisplatin and docetaxel regimen was effective to stages IIIA NSCLC and relatively safe. From results of our pilot study, we recommend to conduct randomized trial.

## P 921

### 5-FU-Levamisol vs 5-FU-Levamisol-Leucovorin in patients with colorectal cancer in stage II-III. Final results

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Purpose To present the results of a randomized study comparing the administration of 5-FU plus Lev versus 5-FU and

Lev plus LV in a group of patients with colorectal cancer in stages II and III.

Materials and Methods Between 1991 and 1997 two hundred patients were randomly to receive: Group A: 5-FU 370mg/M<sup>2</sup> day 1 every four weeks during a year and Lev 50mg/3 times a day every 15 days during one year. Group B: 5-FU and Lev at the same dosages as Group A, plus LV 200mg/M<sup>2</sup> one hour before 5-FU day 1 monthly during one year. Results One hundred and eighty-four patients were evaluated for statistical analysis. The two groups, presented a homogeneous distribution as to age, sex, location of the tumor, type of surgery, state and modality of treatment. With an mean of follow-up of 85 months (Range: 2-120 months), in Group A there were 30/91 relapses and 28/91 deaths and in Group B there were 33/93 relapses and 34/93 deaths. The 10 years disease free survival (DFS) and overall survival (OS) for Group A was 67% and 69% and for Group B 64% and 63%, with a p that was insignificant.

The analysis of the multivariate survival rate based on the localization of the tumor (colon or rectum) showed that for the stage in relation to the DFS there was a risk estimation of RR=2.75 (IC 95% 1.59 - 4.77), for the ganglia affection >4 vs 0 an RR=6.46 (IC 95% 3.38-12.3) and for 1-3 vs 0 an RR=2.37 (IC 95% 1.29-4.35). For the stage, in relation to the OS, there was an estimated risk of RR=2.46 (IC 95% 1.42-4.28), for ganglia affection n4 vs 0 an RR= 5.1 (IC 95% 2.68 - 9.88) and for 1-3 vs 0 an RR=2.03 (IC 95% 1.11-3.69). The modality of complementary treatment did not affected the clinical behavior of the patients. The treatments were well tolerated, with mucositis and diarrhea I and II. Conclusions In our study the addition of Leucovorin to the combination of 5FU-Levamisol did not appear to improve the disease-free and overall survival rates of the patients.

## P 922

### Surgical results of gastric cancer with positive washing cytology without peritoneal dissemination

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The background of the study

Intraoperative peritoneal washing cytology is an established prognostic factor and considered to detect latent peritoneal dissemination in general. This study examined the efficacy of surgical resection with chemotherapy for patients with gastric cancer with positive washing cytology without peritoneal dissemination (POCY1).

The method used

We carried out a retrospective study of 26 patients with positive washing cytology without peritoneal dissemination from 1992 to 2000. Survival rates were compared between POCY1 patients and patients with peritoneal dissemination (n=111). We divided POCY1 patients into three groups : (1)surgery alone, (2)surgery with adjuvant chemotherapy, (3)surgery with chemotherapy after recurrence. We have administered to these patients TS-1 or 5-fluorouracil(5Fu)+methotrexate(MTX) or cisplatin(CDDP)+irinotecan(CPT11). Survival rate was compared between patients who received chemotherapy and those who did not, and between those who received TS-1 and those who received 5-Fu+MTX and those who received CDDP+CPT11.

The results obtained

Median survival time of 26 patients with positive washing cytology without peritoneal dissemination was 14 months. The POCY1 patients had a significantly better survival rate than that of the patients with peritoneal dissemination (p=0.001). There was no survival advantage with adjuvant chemotherapy or chemother-

apy after recurrence when compared with surgery alone. When chemotherapy was examined, there was no difference in survival between those who received TS-1 and those who received 5-Fu+MTX and those who received CDDP+CPT11.

The conclusion reached

The prognosis of POCY1 patients was better than that of P (+) patients, but it remains very poor. Although partial response were obtained in 4 patients, adjuvant chemotherapy and chemotherapy after recurrence did not improve survival rates for POCY1 patients.

## P 923

### Venous invasion as a prognostic indicator in TNM-II colorectal carcinoma

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**Background:** In Israeli colorectal carcinoma (CRC) patients (pts) after surgery with curative intent, venous invasion (v.i.) +/- has been shown to define two subsets in each Dukes and Astler-Coller stage, that differ significantly in recurrence and survival (Europ J Cancer, vol. 29A, Supp 6, p S99, 1993). This study assesses if v.i. defines two prognostically distinct subsets among Japanese TNM-II CRC pts as well. **Method:** Retrospective study of 504 Japanese CRC pts. Minimal follow-up: 5 years after surgery with curative intent. Sources of data: Japanese cancer registry forms, inpatient and outpatient files. 151 pts (30%) had TNM-II tumors; v.i. was identified in 56 (37.1%) of them. Disease-free, observed and CRC-related survival curves (Kaplan-Meier) were calculated for TNM-II v.i.(+) and for TNM-II v.i.(-) pts, and compared for statistical significance (Breslow). Results: V.I.(+) was associated with an increase in local/regional as well as in distant recurrence in TNM-II CRC following surgery with curative intent. Disease-free, observed and CRC-related survival of v.i.(+) pts were significantly worse than those of v.i.(-) pts ( $p=0.0129$ ,  $p=0.0077$ ,  $p=0.0141$  respectively); DFS at 5 years was 78% versus 93%. **Conclusions:** As in Israeli pts, substaging Japanese TNM-II CRC pts by v.i. +/- defines two patient subsets that differ significantly in recurrence and survival. Consequently, it is suggested that selection of TNM-II CRC pts for adjuvant therapy may be based on the presence of v.i. This method requires no sophisticated or expensive equipment or tests, and it is immediately applicable in any health-care system worldwide. We believe that a clinical trial is justified to assess if this method produces a survival benefit. \* This study was partially funded by a UICC fellowship (ICRETT no. 99/1999).

## P 924

### Two schedules of CPT-11 in patients with advanced colorectal cancer (ACC)

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In our clinic we usually use two schedules of administration CPT-11: once-every-three week schedule and weekly-times-four every six weeks (wks) in patients (pts) with ACC. Purpose: To evaluate the efficacy and toxicity profile of two dosing regimens of CPT-11. Patients and Methods: Group A - 44 pts were treated CPT-11 250-350 mg/m<sup>2</sup> every 3 wks as a 90 min infusion (171 cycles). Group B - 20 pts were treated CPT-11 100-125mg/m<sup>2</sup> weekly every 6 wks (34 cycles). The started dose was chosen according to risk factors at baseline for diarrhea and neutropenia

(Performance Status 2, age > 65, abnormal bilirubin level, prior abdominopelvic radiotherapy). Pts characteristics in the both groups were comparable except for the proportion of the pretreated pts, which was greater in Group B (90% vs 41%). Group A: 40 pts evaluated for efficacy: 6 PR (15%), 18 SD (45%) and 16 PD (40%). Median survival was 41,6 wks. 1-year survival - 27%. Group B: 19 pts were evaluable for efficacy: 3 PR (15,8%), 9 SD (47,4%) and 7 PD (36,8%). Median survival was 51 wks. 1-year survival - 25%. Toxicity gr 3+4 by pts/cycles of two groups are given in the table below:

Side effects	Group A% pts ( % cycles)	Group B%pts ( % cycles)
Neutropenia	20,4 (10,5)	25 (14,7)
Febrile neutropenia	16 (5)	5 (3)
Diarrheac	15,9 (4,7)	5 (2,9)
Nausea	4,5 (1,8)	0
Vomiting	9,1 (2,3)	0
Hospitalisation	7% pts	0

**Conclusion:** Our data showed comparable results in either groups of efficacy. But weekly schedule administration of CPT-11 had better safety profile and it seems to be preferable for pts with high risk factors and for outpatient use.

## P 925

### Hyaluronidase improves the distribution of liposomal doxorubicin in human osteosarcoma xenografts

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**Background:** Liposomal drug administration might improve the antitumour effect and reduce toxicity compared to administration of the free drug. The high interstitial fluid pressure (IFP) is, however, a major obstacle to successful delivery of large molecules such as liposomes. The antitumour effect of free doxorubicin has been reported to be enhanced by preadministration of hyaluronidase, which disintegrate the polysaccharide gel of the interstitium. We therefore studied the effect of hyaluronidase on IFP and tumour uptake and distribution of liposomal doxorubicin. **Methods:** IFP was measured after intratumoral injection of 50µl hyaluronidase in orthotopic (around femur) human osteosarcoma in athymic mice. Liposomal doxorubicin (Caelyx®), 16 mg/kg, was injected i.v. 60 min after injection of 1500U of hyaluronidase. The uptake and distribution of doxorubicin was measured on frozen tumour sections using confocal laser scanning fluorescence microscopy, and quantified by measuring the average fluorescence intensity per image. **Results:** Hyaluronidase (150U, 500U, 1500U) reduced IFP in a dose-dependent manner, and maximum reduction of approx. 50% was obtained 60 min after injection of 1500U. Increasing the dose up to 3000U, however, induced a smaller reduction in IFP of about 25%. The reduced IFP might cause a transvascular pressure gradient. Consistent with this, hyaluronidase increased the tumour uptake of doxorubicin approx. 4 times, and the heterogeneous distribution of the drug was improved, as doxorubicin was located further into the tumour. In untreated tumours the most intense doxorubicin fluorescence intensity was found at the rim and 200-400µm into the tumour, and the uptake was here 5 fold higher compared to central areas. **Conclusion:** Pretreatment of hyaluronidase might enhance the antitumour effect of liposomal doxorubicin by improving the distribution of the drug.

**P 926****Hepatic artery infusion chemotherapy (HAI) for metastatic liver tumor from gastric cancer**

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Metastatic liver tumor from colon, hepatic arterial infusion has important role as topicl therapy. However role of hepatic arterial infusion chemotherapy (here after we will call HAI) for gastric cancer is not clear. We have evaluated the result of HAI for patient with gastric cancer who had metastatic liver tumor. Since 1993 12 cases of gastric cancer who had synchronous multiple liver metastasis were treated by HAI. Among those 10 cases were underwent resection of primary lesion, the rest 2 cases were treated by HAI alone. HAI therapy (20mg of CDDP in 4 hours and 750mg of 5FU in 5 hours) was administered for four days starting from 2weeks after surgery. Average 2.4 times of HAI were given during hospitalization. Nausea was most frequent complication accompanied by HAI. The effect of HAI was evaluated by CT scan of liver. Mean survival duration of responder group (n=7) who had demonstrated complete or Partial response to HAI were 17.7 months while those of non-responder group (n=5) were 5.2 months. The duration of survival after treatment was different between these two groups. Among seven cases of responder, 4cases developed AFP producing tumor and five cases were positive for NSE. Two patients are still alive including one surviving 56 months after initial treatment with liver recurrence, the rest 5 cases were died of liver recurrence, peritoneal dissemination, lymph node metastasis. By histo pathological evaluation in the non-responder group extensive lymph node involvement was more common than responder group. HAI itself could not control tumor progression in the liver and lymph node for those who had extensive lymph node involvement. HAI therapy using CDDP and 5FU could demonstrate satisfactory result for AFP producing tumors and NSE positive tumors. In order to improve survival, treatment for extra hepatic lesion such as peritoneum and lymph node should be considered. On the other hand, the effect of HAI for common type of gastric cancer was insufficient. Another regimen (drug, dose, duration) should be established.

**P 927****Phase 1 study of CPT-11 plus S-1 for patients with metastatic gastric cancer**

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Background and Objectives: CPT-11 is one of key agents in the treatment of gastric cancer. S-1 is a novel oral fluroropyrimidine agent containing both DPD and ORTC inhibitors. The Phase 1 study was conducted on combination of CPT-11 with a fixed dose of S-1. Patients and Methods: The eligibility was as follows; histologically proven gastric cancer with measurable metastatic lesions, PS 0-1, life expectancy of more than 3 months, age 20-75, normal organ functions, and written informed consent. No prior chemotherapy, except for adjuvant setting completed 30 days before registration, was allowed. S-1 was administered orally (80 mg/m<sup>2</sup>/day) twice a day for 21 consecutive days. CPT-11 was injected intravenously for 90 minutes (level 1,2,3,4: 40,60,80,100 mg/m<sup>2</sup>) on day 1 and 15. This schedule was repeated every 4 weeks. Dose limiting toxicities (DLT) were determined as grade 4

hematological and grade 3 non-hematological. Critical toxicity was defined as the observation of DLT, or more than 7 days delay or cessation of the 2nd CPT-11 during the first course. MTD was defined as a dose with 33.3% (2/6) critical toxicities. Results: Nineteen patients were enrolled in this Phase I study from April 2000 to June 2001. At level 1 (n=6), one patient developed DLT (grade 3 non-hematological). At levels 2 and 3, no patients developed DLT. At level 4 (n=6), one patient developed critical toxicity (skip of the 2nd CPT-11) and two developed DLT (grade 3 rash and diarrhea). Level 4 was determined as the MTD and the dose at level 3 was recommended. Overall response rate was 56% and the response rate of above RD was 70%. No grade 4 toxicities were observed in any patients. Median number of courses administered was 4 (range: 1-8). Conclusions: The MTD of CPT-11 in this combination is 100mg/m<sup>2</sup>, and the RD is 80mg/m<sup>2</sup>/day. The response results of this combination are promising. These results warrant further investigation and a Phase II study is currently ongoing at OGSG.

**P 928****Phase I studies of Xeloda Plus chemotherapy and radiation in head/neck or gastrointestinal cancers**

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Objective: To define the toxicities and response of Xeloda (X) given in escalating doses when combined with standard radiation (RT) and either taxol (T) or CPT-11 in patients with head/neck (H/N) gastrointestinal (GI) cancers. Methods: All doses of X were given as mg BD not mg/m<sup>2</sup> on days RT delivered only. This report is a summary of 3 Phase I studies (S1, S2, S3). S1: 14 pts with locally advanced stage III/IV H/N receiving 70.2Gy plus T 45mg/m<sup>2</sup> iv weekly. X given in cohorts of 3 pts at 650 or 1150. S2: 18 pts with locally advanced upper abdominal GI cancers, 14 pancreas, 2 gall bladder and 2 bile duct receiving 54 Gy plus T 45 mg/m<sup>2</sup> iv weekly. X was given to cohorts of 6 pts each at 650, 1150, and 1500. S3: 10 pts with T3, N0-1 rectal cancer given preoperative RT at 50.4 Gy plus CPT-11 40mg/m<sup>2</sup> weekly x 4. X was given at 500 (6 pts), 650 (3 pts), and 1150 (1 pt). CTC scoring was used for toxicity. Results: S1: 1 pt died day 2 not treatment related. Gr III skin and mucositis toxicities occurred in 2/3 pts X 650, RT 70.2 Gy; 3/4 pts X 1150, RT 70.2 Gy (Dose limiting toxicity, DLT); 2/3 pts X 650, RT 72.6 Gy DLT; 2/3 pts at X 650, RT 72.6 Gy with chemotherapy held during boost (DLT). All pts achieved CR without surgery and at 13+ months (mos) follow-up 1 pt has recurred and died. Study open to explore lower chemotherapy doses during RT 72.6 Gy. S2: Gr III/IV toxicities occurred in 4/6 pts X 650, 2/6 pts X 1150 and 2/6 pts X 1500 and included dysphasia, anorexia, fatigue dehydration, diarrhea. Progression during RT 1 pt all others stable. 11pts alive at 11+ mos. S2 continues at highest X level with addition of celecoxib. S3: no Gr III/IV toxicities. At surgery all pts down staged 1-3T, 1N, colostomy avoided 1 pt, pathologic CR1 pt. S3 remains open with all pts alive without recurrence at 17+ mos median follow-up. Conclusions: Xeloda is safe and highly active when combined with chemoradiation therapy in head / neck, and upper / lower GI cancers.

**P 929****Combined treatment ( RT + ChT) in malignant glioma adults - acute adverse events**

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Malignant Glioma have a very bad prognosis. The main treatment in these cases are surgery followed radioterapy (RT). Additional chemotherapy (ChT) can prolonge time to recurrence. CCNU, BCNU, Procarbasine, Vincristine are the most common agents in these cases. The aim of this paper is the evaluation of acute adverse event (AAE) in the adults undergone combined treatment (RT + ChT) after operation of Malignant Glioma between 1987- 2000 years in our Department. The material: there were treated 151 Malignant Glioma pts. Fifty six of pts were begun RT +ChT. Median age in these group was 46 years. All pts were undergone conventional RT to 60 Gy. Thirty one of pts were applied CCNU (120mg/m<sup>2</sup> every 6 weeks), 25 pts were applied PCV (CCNU 120mg/m<sup>2</sup>+ Procarbasine 100mg/m<sup>2</sup> x 14 days + Vincristine 1mg once a week - every 6 weeks). The first cycle of ChT was given before RT. The results: In the PCV group 16 of pts appeared hematological AAE 2-4 degree after the 2-3 cycles more than 10 weeks. Allergic reaction degree 2 was manifest in one case. One of pts have had gastro-intestinal AAE degree 3. These pts finished ChT after the second or third cycle. In the CCNU group 2 of pts have had hematological AAE degree 2- 4 more than 10 weeks. These pts finished ChT after the second cycle. The remaining of patients finished ChT after 5 - 9 cycles and have had hematological AAE degree 1-2. The vomiting was not observed because all of pts received Zofran during whole treatment. Conclusions: - Unequal groups of CCNU and PCV pts could not compared the frequency of AAE. - Chemotherapy PCV and CCNU are well tolerated.

**P 930****Role of paclitaxel as a radiosensitizing agent in advanced stages of head & neck cancers: head & neck**R Vashistha<sup>1</sup>, J S Sethi<sup>1</sup>, H Singh<sup>1</sup>, N Jain<sup>1</sup>, R Arora<sup>2</sup>, A Verma<sup>1</sup>, M Aggrawal<sup>1</sup>, R Aggrawal<sup>1</sup>, V Gupta<sup>1</sup><sup>1</sup>M.D.Oswal Cancer Hospital, Radiation Oncology, Ludhiana, India; <sup>2</sup>M.D.Oswal Cancer Hospital, Medical Oncology, Ludhiana, India

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**Background:** Head & neck malignancies constitute 5% of all cancers worldwide. Surgery & radiotherapy which were traditionally used for treatment have shown poor results because of local recurrence (up to 50%) and metastatic spread (10-30%). Addition of Chemotherapy has shown to improve results in these malignancies. Chemoradiation when given simultaneously has shown to improve survival significantly when compared to surgery and/or radiotherapy alone. The aim of the study was to find the effect & toxicity of paclitaxel in advanced cases of head & neck. **Materials & Methods:** Thirty-five patients were given concomitant paclitaxel, 30mg/m<sup>2</sup>, 6 cycles & external radiotherapy 68-72 Gy. Eligible patients had Stage II, III & IV, histo-pathologically proven squamous cell carcinoma, with no distant metastases. Only previously untreated patients were taken up in the study. Pre-treatment evaluation included a complete blood count, kidney function test, liver function test, chest X-ray, ECG, CT scan of head & neck region wherever patient was affording, direct laryngoscopy. In the study there were 29 males & 6 females with age group between 30-70 years. Primary sites included oral cavity-13, oropharynx-7, Hypopharynx-7, larynx-5 and nasopharynx-2. Stage-wise distribu-

tion was Stage II- 10, Stage III- 17, Stage IV- 8. **Results:** A complete response was seen in 25(71%) patients and a partial response was seen in 9(26%) patients and stable disease was seen in 1(3%) patient. The commonest toxicity encountered was mucositis observed in 90% of cases, Grade II accounting for 40%, Grade III- 37%, & Grade IV- 13%. Radiation skin reactions Grade II-III were seen in 3 (10%) patients. Myelo-suppression was seen in 1(3%) cases. **Conclusion:** Early results show that 97% patients achieved a clinical response to the treatment. There is significant toxicity attached to the treatment but it is less traumatic to the patient & is cosmetically more acceptable.

**P 931****Capcitabine and concurrent radiation therapy in GI and head and neck cancers: phase I studies at the university of Maryland**D A Van Echo<sup>1</sup>, A S Kennedy<sup>2</sup>, M Suntha<sup>2</sup><sup>1</sup>University of Maryland School of Medicine, Medical Oncology, Baltimore, United States; <sup>2</sup>University of Maryland School of Medicine, Radiation Oncology, Baltimore, United States

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Phase I studies were performed combining capecitabine with paclitaxel + RT (cap+pac+RT) in pts with upper GI cancers, and cap with CPT-11 in pts with rectal cancers (cap+cpt-11+RT) as separate phase I studies. Methods: Eligible pts had cancers of the pancreas, bile duct or gallbladder for the cap+pac+RT protocol, or distal rectum for the cap+cpt-11+RT protocol. RT 54 Gy was given to primary tumor and nodes. Cap was given in fixed-dose increments; for cap+pac+RT: 650mg, 1150 mg, 1500 mg p.o bid on RT days. For cap+cpt-11+RT: cap was given 500mg bid, 650mg bid, and 1000mg bid, on RT days. Results: Since 01/99, 27 pts have been treated. For the upper GI protocol, 18 pts, median age 67 yrs (range 53-81yrs), had the following primary tumors: 15 pancreas, 2 gallbladder, and 1 cholangiocarcinoma. Median follow up is 9+ months with an overall survival of 9.5+ months (4+-20+ mo.). The MTD was determined to be 1500mg of cap p.o. bid on days with RT when combined with pac 45mg/m<sup>2</sup> weekly via 1 hour i.v. infusion based on grade 3,4 enteritis related to study treatment. For the rectal tumor trial, 9 pts have completed therapy with a median age of 66 yrs (38-90 yrs). All pts experienced downstaging of at least one T-stage, with 1 pathologic CR. All had been ultrasound staged uT3 or uT4 prior to chemoradiation. There has not been any increase in perioperative or postoperative complications. The MTD has not yet been reached when cap is combined with weekly i.v. infusions of CPT-11 50mg/m<sup>2</sup> during pelvic radiotherapy. Conclusions: Cap combined with RT and other chemotherapy agents is a promising and safe approach for GI malignancies. We have determined the MTD is 1500mg p.o. bid given on RT days with weekly pac for pancreas and biliary tree malignancies. The MTD of cap combined with pelvic RT and weekly CPT-11 for preoperative treatment of uT3-T4 rectal cancers has not been achieved (current level at 1000mg bid).

**P 932****Phase I study of KW-170, a novel pyrazoloacridone compound against solid tumors**

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KW-2170 is a novel pyrazoloacridone compound with DNA intercalating and topoisomerase II inhibitory activities. KW-2170 showed a broad spectrum of antitumor activity against human

tumor xenografts and exhibited non-cross resistance to P-glycoprotein expressed tumors. Furthermore, KW-2170 showed less cardiotoxic than doxorubicin in animal studies. Phase I study of KW-2170 was conducted in Japan. KW-2170 was given as 30 min iv infusion in patients with refractory solid tumors. Objectives were 1) to determine dose limiting toxicity (DLT), maximum tolerated dose (MTD) and recommended dose for phase II study and 2) to analyse pharmacokinetic parameters. The initial dose level was 1.0 mg/m<sup>2</sup> and dose escalation followed a modified Fibonacci method. 41 patients (26 male, 15 female) with median age 55 (range 33-73 years) and performance status 0-2 were treated at 13 dose levels up to 53 mg/m<sup>2</sup>. Tumor types included lung (19), breast (8), colon (3), H&N (2), cholangiocarcinoma (2) and others (7). DLT was neutropenia (febrile neutropenia or grade 4 neutropenia lasting 3 days or longer) and was observed at 32 mg/m<sup>2</sup> (2 patients out of 6) and at 53 mg/m<sup>2</sup> (2 patients out of 2). No DLT was seen at 41 mg/m<sup>2</sup>. As the first two patients at 53 mg/m<sup>2</sup> developed DLT, further patients accrual was stopped with this dose determined as MTD. Recommended dose for phase II study was decided to be 41 mg/m<sup>2</sup>. Other hematological toxicities ( $\geq$ grade 3) were leucopenia, lymphopenia and decrease of hemoglobin. Major non-hematological toxicities included nausea/vomiting, fatigue, anorexia, and stomatitis. They were all grade 1 to 2. Tumor reduction in metastatic lesions was seen in two patients (one with Cholangiocarcinoma and one with H&N) treated at low doses but no CR/PR was achieved. After end of infusion, plasma concentration of KW-2170 decreased triexponentially with the terminal elimination half life between 23 and 42 hr. Total clearance was ranged from 1.1 to 1.5 L/h/kg. C<sub>max</sub> and AUC<sub>0-∞</sub> increased almost proportionally to the dose.

## P 933

### Weekly paclitaxel for the second-line treatment of recurrent and advanced gastric cancer (RAGC)

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Paclitaxel induces p53-independent apoptosis in a number of chemotherapy-resistant solid tumors. The aim of this study is to elucidate the toxicity and efficacy of weekly paclitaxel for the second-line treatment of RAGC. [Patients and Methods] In 7 months (6-12/2001), a total of 15 patients with recurrent (n=4) and remnant metastatic (n=11) gastric cancer after resection were treated with paclitaxel for the second-line (n=9) or the third-line (n=6) treatment. 14 out of the 15 patients received TS-1 in the previous treatment. Paclitaxel was administered once weekly in a dose of 80 mg/m<sup>2</sup> per day for 3 weeks followed by 1-week rest as one cycle. The numbers of target organs were 6 for liver metastases, 8 for peritoneal metastases, 5 for lymph node metastases, 1 for lung metastasis, respectively. Pharmacokinetic study was also performed in 2 patients with peritoneal metastasis and collectable ascites. [Results] Response rate: A total of 35 cycles of treatment was delivered for 15 patients. Of the 15 patients, 5 had non-measurable lesions. Overall response rate was 27.3% (CR 0/11, PR 3/11, SD 2/11, PD 6/11). Improvements of symptoms were observed in 2 patients: one for abdominal discomfort and the other for back pain. For peritoneal metastases, the response rate was 25% (2/8) and 3 of them failed in 1 cycle due to disease progression. Toxicity: The adverse events occurred in 27 cycles in 13 patients. The frequency of alopecia was 73.3%, followed by leucopenia and infection (20% for each), neutropenia, stomatitis and peripheral neuropathy (13.3% for each). Grade 3 toxicity occurred in 3 patients. Pharmacokinetic study: The intra-abdominal drug

delivery of paclitaxel was maintained over minimal effective concentration (10nM) for 48 hours after drug administration. [Conclusion] Weekly paclitaxel is an active and well-tolerated regimen for the second-line treatment of RAGC.

## P 934

### Dihydropyrimidine dehydrogenase activity in peripheral blood mononuclear cells is not a useful indicator of 5-fluorouracil clearance in patients with liver dysfunction

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**Background:** Dihydropyrimidine dehydrogenase (DPD) is the rate-limiting enzyme of 5-fluorouracil (FU) catabolism, which occurs mainly in the liver. It has been shown that DPD activity in the peripheral blood mononuclear cells (PBMCs) is correlated with systemic 5-FU clearance. Based on these findings, PBMC-DPD has been used as a reliable indicator to estimate 5-FU clearance and to detect DPD deficient cancer patients prior to 5-FU treatment. However, it remains unknown whether PBMC-DPD activity may indicate 5-FU clearance in the patients with liver abnormalities, though liver metastases are frequent occurrence in various cancers, and also the majority of hepatocellular carcinoma develops from cirrhotic liver. The purpose of the present study was to investigate whether DPD activity in PBMCs may be influenced by the liver dysfunction.

**Material and Methods:** This study was performed on 32 patients, including 7 patients with terminal hepatic failure who died within a year from the measurement of DPD activity (group A), 7 cases of decompensated liver cirrhosis with ascites (group B), 9 cases of compensated liver cirrhosis (group C) and 9 control subjects with normal liver function (group D). DPD activities in PBMCs were measured, and the correlation between liver function and PBMC-DPD activity was analyzed.

**Results:** PBMC-DPD activities in group A (mean $\pm$ SD; 715 $\pm$ 212 pmol/min/mg protein) were higher than those in group B (484 $\pm$ 127), C (536 $\pm$ 94) and D (358 $\pm$ 84).

**Conclusion:** In patients with liver dysfunction, DPD activity measured in PBMCs was not depressed, suggesting that it may not show systemic 5-FU clearance. Therefore, it must be essential to examine the liver function itself prior to 5-FU treatment to avoid unexpected 5-FU toxicity in those cases.

## P 935

### Relationship between the survival outcome with CDDP-based chemotherapy and the expression of reticulocalbin-1 detected by two-dimensional electrophoresis in cases with non-small cell lung cancer

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**Objective:** We attempted to detect a polypeptide related to drug resistance and investigated its clinical effects in cases of primary lung cancer. **Study Design:** Comparing the two-dimensional polyacrylamide gel electrophoresis (2-DE) patterns of the parent strain and CDDP-resistant cultured lung cancer cells (H69 and PC14), we detected a polypeptide in which the expression levels clearly changed. Measurement of clinical materials in 2-DE was successful in 80 patients with primary lung cancer between 1994 and 1998. We evaluated the relationship between the expression levels

of this polypeptide, clinicopathological factors and outcome. Results: We detected a polypeptide (molecular weight 44.0 kDa) which significantly decreased in expression level in CDDP-resistant cells. The amino acid sequence suggested that this polypeptide might be homologous with reticulocalbin-1. We could not recognize any statistically significant relationship between the expression of reticulocalbin-1 and any clinicopathological factors. However, only in cases with adjuvant chemotherapy using platinum-based drugs with positive expression of reticulocalbin-1 was a better outcome obtained compared with cases without reticulocalbin-1 expression. Conclusion: These results suggested that the reticulocalbin-1 molecule might have some kind of involvement in the chemical tolerance mechanism of platinum-based drugs.

## P 936

### Expression of ABC-transporters' functional activity in human solid tumors

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ABC-transporters' functional activity associated with MDR mechanism was studied in human solid tumors by a new method developed in this laboratory. The index is determined as a decrease of doxorubicin fluorescence in incubation medium with and without an inhibitor of Pgp, MRP and all ABC-transporters' activity namely: verapamil, genisteine or sodium azide. The following new data are the result of more than 200 tumor specimen investigation (breast, colon and cervix carcinoma). 1. Activity of various ABC-transporters, including well-known Pgp, MRP and other transporters different from Pgp and MRP, was revealed in human solid tumors investigated. There were no specific combinations of different ABC-transporters' expression characteristic for a certain tumor or type of drug resistance - inherent or acquired. 2. No MDR phenotype (no expression of activity of any ABC-transporter) was shown in half of primary breast cancer. Such cases were not observed in colon and cervix carcinomas, which are characterized by inherent MDR. 3. Pgp and MRP activities are important determinants of inherent MDR in colon cancer (were expressed in about 60 and 80% of tumors respectively). 4. Pgp activity in cervical carcinoma was expressed in 25% of tumors only. 5. Activity of ABC-transporters different from Pgp and MRP and specifically sensitive to taxol and taxoter inhibitory action was observed in about 40% of breast cancer. Conclusion. "Severity" of MDR phenotype of solid tumors can be determined not so much as by the manifestation of different ABC-transporters' expression but mostly by the number of expressed ABC-transporters. Due to the observed heterogeneity in expression of MDR markers clinical attempts to overcome MDR using specific inhibitor of only one ABC-transporter (mainly Pgp) may not be sufficient to overcome resistance. Using a combination of several specific inhibitors or blocking some "common point", for example, energy dependence of ABC-transporters' function can be more promising.

## P 937

### Studies on copper-transporting P-type adenosine triphosphatase (ATP7B) expression in gastric carcinoma

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The recent search for new marker of chemoresistance has identified that copper-transporting P-type adenosine triphosphatase (ATP7B), copper-transporter by energy-dependent system, was involved in cisplatin-resistance. In this study, we investigated the hypothesis that ATP7B is expressed in certain gastric carcinomas. Fresh frozen surgical specimens from 51 patients with gastric carcinoma were studied. ATP7B protein could be detected in 41.2% (21/51) of gastric carcinoma by immunohistochemical analysis. ATP7B expression in poorly-differentiated/undifferentiated carcinoma was significantly higher than that in well/moderately-differentiated carcinoma (p=0.0278). These findings suggested that ATP7B expression might be a chemoresistant marker against cisplatin in some patients with poorly-differentiated/undifferentiated gastric carcinoma.

## P 938

### Glutathione-S transferase and O6-methylguanine DNA methyltransferase activities in patients with gastric carcinoma

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Background: Alkylating agents which are metabolized by glutathione-S transferase, have important role in the etiology of cancer by forming mutagenic DNA adducts. Most harmful DNA alkylation damage is O6 -methyl guanine. A relation between consumption of the smoked-dried meat and fish, which contain considerable amount of alkylating agents, and gastric cancer has been suggested. Previous studies have shown that DNA repair protein, O6 -methyl guanine DNA methyl transferase (O6 -MGMT), repairs these mutagenic DNA adducts by transferring the alkyl group to itself at a specific cysteine residue. As a result of this autoalkylation O6 -MGMT becomes inactivated and, is not regenerated. O6 -MGMT activity is correlated with the resistance of human tumors to alkylating agent-based anti-cancer drugs. On the other hand GST have been shown to play an important role in multiple drug resistance in cancer chemotherapy. We measured the activities of GST and O6 -MGMT in tumor tissue from patients with gastric carcinoma and in normal tissue, adjacent to tumor, in the same patient. Methods: Activities of GST and O6 -MGMT were measured by spectrophotometric and scintillation counting assays, respectively. Results: We determined that both GST and O6 -MGMT activities were significantly increased in tumor tissue as compared to adjacent normal tissue. Conclusion: This increase in the GST and O6 -MGMT activities may be evaluated as a compensation. Increased O6 -MGMT in tumor tissue may also derived from lack of time for DNA repair, because of increased cell proliferation during malign transformation which causes O6 -MGMT to accumulate. We conclude that GST and O6 -MGMT activities in gastric tumors may be considered as an important factor for determination of the most suitable chemotherapy for these patients.

**P 939****CD95-deficient cell line resistance to death receptors activation and other apoptotic signals**

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Apoptosis can be induced by a multitude of stimuli, including depletion of growth factors and hormones, heat shock,  $\gamma$ -irradiation, intracellular mediators of signal transduction pathway, stimulation of death factors receptors such as TNF and Fas receptor. It has been proposed that CD95 signalling pathway plays a critical role in drug-induced apoptosis and the absence or diminished expression of CD95 on the surface of tumour cells is associated with resistance to cytotoxicity drug treatment.

CD95-deficient cell line Jurkat/A4 was generated from the parental wild type (Jurkat/wt) cells by serial treatment with apoptosis-inducing anti-CD95 mAb (clone IPO-4, IgM). Apoptotic cells was detected by flow cytometry (FACSCalibur) after stain with propidium iodide or/and Annexin V-FITC.

Comparative studies showed that Jurkat/A4 acquired CD-95 negative phenotype, but both lines equally expressed DR5 and DR4 receptors. However, Jurkat/A4 line was highly resistant to induction of apoptosis by both agonistic anti-Fas mAb and TRAIL. Surprisingly, Jurkat/A4 was also highly resistant to apoptosis induced by anti-cancer drugs (doxorubicin, etoposide, cis-DDP, cycloplatin, staurosporin), X-rays, UV-light, hydrogen peroxide, while all these treatments induce the apoptosis on parental Jurkat/wt cells in time- and dose-dependent manner.

We have created multiresistant leukemic cell line, by selection on continuous stimulation of Fas(CD95) death receptor. Its resistance bases not only on the deficiency of CD95 expression, but mainly contributed by the defects of other molecular targets, which are involved in the execution phase of programmed cell death (apoptosis) as well. The model can reflect usual clinical situation when selection under pressure of strong immune system of young patients yields of highly malignant multiresistant tumors.

**P 940****Results of multimodality therapy in poor risk non-seminomatous germ cell tumors (NSGCT)**

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Objective: To review our experience of multimodality therapy in patients with poor risk NSGCT. Patients: Ten patients with NSGCT and poor risk according to the IGCCCG classification were treated at Tokyo Metropolitan Komagome Hospital from 1993-2001. The male/female ratio was 9/1, and the median age was 21 (range 17-42). Yolk sac histology was the most predominant (50%). Bulky tumor, as defined larger than 10cm in diameter, was present in 6 patients (60%). Poor risk factors were: mediastinal primary (60%), non-pulmonary visceral metastasis (60%), serum markers (80%). Therapy: All patients received initial chemotherapy (CT) with BEP (bleomycin, etoposide, and cisplatin). The median number of CT cycles was 5 (range 3-9). After initial BEP only one of 10 patients (10%) achieved radiological complete

response (CR), six of 10 patients (60%) partial response (PR) and 3 of 10 (30%) serum marker remission. Nine of 10 patients (90%) had residual tumors. High Dose Chemotherapy (HDCT) with autologous peripheral blood stem cell transplantation (PBSCT) was administered as salvage therapy to 8 patients. Four patients received multicycles of HDCT. The median number of HDCT cycles was 2.5 (range 2-5). Only after multicycles of HDCT serum marker remission was achieved in 2 patients. Surgical resection of residual tumors after CT was performed in 6 patients. Three patients received Radiation to the mediastinal residual tumor. The median follow-up was 36 months (range 8-91). Currently Nine patients are alive. One patient with progressive disease died. Seven of 10 patients (70%) achieved continuously disease-free (NED) after multimodality therapy. Conclusion: Poor risk NSGCT patient even who failed to attain CR after initial BEP could achieve continuously NED with multimodality therapy.

**P 941****High dose chemotherapy (HDC) followed by autologous peripheral blood stem cell transplantation (auto-PBSCT) in solid/lymphoid tissue tumors - toxicity and early results**

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21 patients (8 females, 13 males) in age 26 to 61 years underwent HDC with auto-PBSCT (July 1999 - December 2001). The procedure was introduced in 7 patients with germ cell tumors, 7 women with breast cancer, 2 patients with multiple myeloma, 3 patients with B-cell lymphoma, 1 with ovarian and 1 with anaplastic cancer of thyroid gland. HDC with auto-PBSCT was the second, the third or the fourth line treatment (n=13, n=9 and n=1 respectively). 9 patients were enrolled in complete remission, 6 - in partial, 3 in stable and progressive disease. Cyclophosphamide in dose of 60mg/kg and 10  $\mu$ g/kg/day of G-CSF were used as the mobilization. The mean  $3.14 \times 10^6$  CD34(+) cells/kg were collected. The conditioning regimen differed according to the diagnosis. We analyzed number of leukapheresis necessary for graft collection (range 1-7, mean 3), than assessed tolerance and system/organ-profiled toxicity of HDC, treatment related mortality (TRM) and patients d+100 status (4/23 deaths caused by PD; n=12 in CR, n=4 in PR, n=1 SD, n=1 PD, n=1 in d+28). There were no treatment-related deaths observed in our patients. Most frequent chemotherapy side effects occurred in gastrointestinal tract (18/23 patients, usually with WHO grade III) and consisted of nausea, vomiting, diarrhea and mucositis. Hepatotoxicity was mild (n=7) as only transient aminotransferases elevation and hiperbilirubinaemia appeared. Others non-hematologic side effects were rare. Neutropenic fever was diagnosed 10 cases. All patients developed WHO grade IV leukopenia with neutropenia and trombocytopenia. Mean Neu < 500/mm<sup>3</sup> period lasted 9 days (range 4-16 days) with mean Plt < 20.000/mm<sup>3</sup> period of 8 days (range 1-23 days) and Hgb < 8,5 g/dL - 8 days (range 0-35). The mean follow-up period was 425 days (range 28-842 days). Till date 17 patients were alive and we have found progressive disease (PD) to be responsible for all deaths that have occurred. Medium progression free survival (PFS) was 89 days (range 34-165 days).