pat. one, in further 14 pat. two and in 11 pat. three and more organs were involved. An average of 1.77 cycles was applicated. The systemic side effects corresponded to a toxicity WHO grade 1 in 6 pat., grade 2 in 27 pat. and grade 3 in further 6 pat.

Results: In 6 pat. (15.4%) a complete remission and in 2 pat. (5.1%) a partial remission was achieved. In further 11 pat. (28.2%) a stable disease and in 20 pat. (51.3%) a progressive disease during the IC was noted. The highest response rate (r.r.) of 44% was found in pulmonary lesions. Metastases of the bones were resistant to the therapy. After a mean followup time of 15.3 months, 3 pat. are alive with no evidence of disease (1 pat. due to IC and 2 pat. due to surgery of metastases after IC), 19 pat. are alive with tumor. Further 16 pat. are dead of disease and 1 pat. died of a tumor unrelated cause.

Conclusion: In contrast to recent reports in the literature, this study demonstrates, that a IC with IL-2, IFN-a and 5-FU is only of limited benefit for patients with metastatic RCC.

166 POSTER

Results and prognostic factors after surgical treatment of lung metastases in renal cell carcinoma

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Purpose: Metastatic renal cell carcinoma has a poor prognosis. In a retrospective study we examined the prognostic factors and the influence of an adjuvant therapy after resection of pulmonary metastases in renal cell carcinoma (RCC).

Methods: Between 1975–1996 42 patients (pts.) with pulmonary metastases of RCC were admitted to our department, 39 underwent surgical treatment, while 3 were not suitable for surgery. 6 pts. (14.3%) had synchronous metastases. The mean disease free interval (DFI) after nephrectomy was 32 (SD 41.3) months. Of the pts. surgically treated, 33% presented with a single lesion, 39% had two to five lesions and 28% had more than five lesions. In 61% the lesions were unilateral. 31 (82%) pts. had thoracotomy (24 pts. one stage and 7 pts. two stage), and 8 pts. (18%) had median sternotomy. With 66% atypical resection was the technique mainly used.

Results: The 5-year-survival rate of the pts. after pulmonary metastasectomy of RCC was 14%. Multivariate analysis (COX-model) for survival of preoperative risk-factors showed, that time of diagnosis (synchronous/metachronous) of the metastases ($p = 0.05$) and the number of metastases ($p = 0.01$) were of prognostic significance. Age ($p = 0.9$), localisation (uni-/bilateral) ($p = 0.36$), DFI ($p = 0.1$) and adjuvant therapy ($p = 0.7$) as a postoperative prognostic factor were of no prognostic significance.

Conclusion: In pts. with metachronous and not more than five metastases after RCC pulmonary metastasectomy should be performed. Because presence of synchronous metastases or more than 5 pulmonary metastases after RCC are unfavourable prognostic factors, indication for metastasectomy should be restricted in such cases.

167 POSTER

Intensified salvage therapy for germ cell cancer using sequential cycles of high dose carboplatin/etoposide/cyclo-phosphamide (CEC)

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The prognosis of germ cell cancer patients failing initial, cisplatin based chemotherapy is poor with an expected three years survival of approximately 20%. To improve on these results, patients were entered on a phase II protocol of sequential cycles of high dose chemotherapy. Patients received two cycles of conventionally dosed cisplatin/etoposide/ifosfamide (PEI) and peripheral blood stem cells were mobilized by GM-CSF (5 μg/kg/d s.c.). After stem cell collection, two cycles of high-dose CEC (Carboplatin 500 mg/m^2 d1–3; etoposide 400 mg/m^2 d1–3; cyclophosphamide 2500 mg/m^2 d4+5) followed by stem cell retransfusion on day 7 and GM-CSF from day 8 until hematologic recovery were administered. 28 patients have been entered; 21 in first and 7 pts in second relapse. Medium number of prior cisplatin containing cycles was 4.5 (2–10). One pt showed progressive disease while receiving PEI and was not considered for HD-therapy. 27 pts received the first cycle of CEC and 20 received both cycles. Reasons for terminating therapy after the first CEC cycle were: progression 2 pts; therapy related death 2 pts; patients refusal 2 pts; antiplatelet antibodies 1 pt. Median interval between first and second cycle of CEC was 35 days. Severe to lifethreatening toxicities, mainly infections and mucositis, were seen in all patients but did not increase in severity after the second CEC cycle. Three patients died during treatment (2 after cycle 1 and 1 after cycle 2). After a median follow up of 22.9 months (6–46 mos), 17 pts (61%) are cwithout signs of tumor progression; 3 (11%) are alive with progressive tumor and 8 (29%) have died (3 treatment-related deaths; 5 deaths from progressive tumor). These data show that two cycles of high-dose chemotherapy given 5 weeks apart are feasible in patients with relapsing germ cell tumors. Early survival data are encouraging.

168 POSTER

Paclitaxel (P) and cisplatin (C) as salvage treatment for nonseminomatous germ cell tumor (NSGCT) patients (pts)

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Based on the data that P demonstrated activity in NSGCT pts we used P 175–225 mg/m^2 3 hour infusion followed by C 100 mg/m^2 every 3 wks × 4 cycles. From October 94 to March 96 16 NSGCT pts who did not achieve a CR after C-based chemotherapy (med. number of cycles 4, range 3–6) and surgery and presented disease progression received 44 cycles of PC. From 16 pts included to the trial 13 were assessable for response and 14 for toxicity. Three pts received only one cycle of treatment and have been withdraw from the disease assessment (nephrotoxicity, refusal of the treatment, early death from the undetected brain metastases). One (8%) CR (duration 9+ mo), confirmed by retroperitoneal lymph node dissection (fibrosis and necrosis), and 3/13 (23%) PR (2 mo) were achieved. With a median follow up of 8 (1–11) mo 12 patients died from the disease progression, one is alive disease free, two are alive with disease progression and one has been lost. Median survival for the whole group was 7 mo. The toxicity was moderate: neutropenia gr. III – 29%, gr. IV – 0%, thrombocytopenia gr. I–III – 28%, creatinine >1.5 mg/%–35%, peripheral neuropathy gr. I–II – 50%, nausea and vomiting – 43%. P plus C showed a modest activity (OR rate -31%) in poor prognosis group of pts, who did not achieve a CR on induction chemotherapy.

169 POSTER

TGF-β_1 resistance as a major progression factor in human renal cell carcinoma

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Purpose: Since TGF-β_1 is a potent negative regulator of growth, we analyzed whether defects in the TGF-β_1 system might be involved in the deregulated growth of human renal cell carcinoma (RCC).

Methods: The expression of TGF-β_1 and its receptors (type I, II, III) as well as the functional intactness of the signal transduction pathways were analyzed in 30 human RCC cell lines.

Results: By ELISA, all cell lines secreted TGF-β_1 as a biologically inactive complex. RT-PCR and immunocytochemistry revealed type I ALK-5-receptor in 29 cell lines. Type II-receptor mRNA and protein could be demonstrated in all cell lines, whereas type III-receptor mRNA was observed in only 5 RCCs. Exogeneously added, biologically active TGF-β_1 (1 ng/ml) resulted in a significant ($p < 0.05$) inhibition of proliferation in 14 out of 30 RCC cell lines. In contrast, 16 RCC cell lines proved to be TGF-β_1 resistant. TGF-β_1 resistance could not be explained by mutations in two "hot spot" regions of the type II-receptor gene (bp 622–795 and bp 1868–2019) as shown by DNA sequencing.

Conclusion: A significant proportion of our RCC cell lines showed escape from negative growth control by TGF-β_1. Therefore, the acquisition of TGF-β_1 resistance has to be considered as a major progression factor for human RCCs.

170 POSTER

Bilateral testicular germ cell tumors (TGCT)

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Purpose: To study incidence, characteristics and outcome of patients (pts) with bilateral TGCT.

Methods: The charts of 29 pts with bilateral TGCT were reviewed.

Results: Among 796 pts with TGCT (1979–January 1997) 7 (0.9%) had synchronous bilateral TGCT and 10 (1.3%) developed a metachronous 2nd

TGCT. The incidence of 2nd metachronous TGCT in pts with chemotherapy for their 1st TGCT was only 0.8% (5 of 592). 12 additional pts were referred for treatment of their 2nd TGCT. Of the 7 pts with synchronous TGCT (median 31 years) 2 had discordant and 5 concordant histology. 3 died of disease or toxicity and 4 are alive with NED. In 22 pts with metachronous TGCT median age at diagnosis of the 1st TGCT was 25 years; median time to the 2nd TGCT was 7.5 years. 9 pts had concordant (6 nonseminoma, 3 seminoma) and 13 discordant histology (1st TGCT nonseminoma in 11). 19 of 22 pts (86%) presented with stage I at diagnosis of the 2nd TGCT. 21 of 22 pts (95%) are alive with NED (median 52 months); 1 pt died from a late relapse of his 1st TGCT.

Conclusion: The incidence of 2nd TGCT is low, especially in chemotherapy-pretreated pts. As the vast majority of pts carries a good prognosis, routine biopsy of the contralateral testicle cannot be recommended.

171 POSTER

Nuclear accumulation of wildtype p53 protein cannot be related to complex formation with mdm2 in human renal cell carcinoma cell lines

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Purpose: As little attention has been paid so far to alternative mechanisms of p53 inactivation, a comprehensive characterisation of the structure and expression of p53 and mdm2 was performed in 38 newly established human RCC cell lines of different histological types.

Methods: DNA sequence analysis of all p53 exons was done by direct sequencing the PCR-amplified exons. Expression of p53 and mdm2 was assessed by Northern blot and immunocytochemistry. Southern blot was used for analysis of mdm2 amplification.

Results: *1.* p53 mutations could exclusively be identified in clear cell RCCs: "hot spot" mutations of exons 5 to 8 were found in 3 cell lines, whereas three other cell lines exhibited a microdeletion in exon 9, a loss of exons 2 to 11, and a mutation in the non-coding region of exon 1. *2.* p53 mRNA was detected in only 11 cell lines by Northern blot. *3.* Nuclear wildtype p53 protein accumulation was observed in 15 cell lines. *4.* No amplification or overexpression of mdm2 could be demonstrated.

Conclusion: These findings provide evidence that a significant proportion of human RCCs shows nuclear accumulation of wildtype p53 protein without mdm2 amplification or overexpression. Further studies will have to elucidate the functional significance and molecular mechanisms of wildtype p53 accumulation in human RCCs.

172 POSTER

Germ cell tumors (GCT) in men with HIV infection

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Purpose: To evaluate frequency, treatment and outcome of HIV+ men with GCT.

Methods: The records of all patients (pts.) with testicular and extragonadal GCT diagnosed and/or treated at our institution between 1/86 and 1/97 were reviewed and analysed with regard to HIV seropositivity.

Results: 7 out of 229 pts. (224 with testicular, 5 with extragonadal GCT) were HIV+ at the time of tumor diagnosis. 2 pts. turned out to be HIV+ after completion of therapy for a non-seminoma (NSGCT). 2 pts. had seminoma (SGCT) and 5 pts. NSGCT. 1 pt. with bilateral stage I SGCT received adjuvant radiotherapy and was lost to follow-up. The other pt. (stage III SGCT) was treated with 4 courses PEI and remained in CR for 48 months. 1 pt. with stage I NSGCT is free of disease more than 10 years after diagnosis and retroperitoneal lymphadenectomy (RLA). 1 pt. (Stage IIA NSGCT) refused RLA but 4 courses PEB were applied for progressive GCT 31 months later; he is in CR for 29+ months. Intensified platinum-based chemotherapy (ECBC) was applied to 2 pts. with advanced NSGCT. 1 pt. achieved a markernegative PR and relapsed, the other suffered progressive GCT. Both pts. developed AIDS and died. 1 pt. (stage IIB NSGCT) received 2 courses PEB after RLA and remains in CR for 10+ months. Under therapy for GCT CDC-category deteriorated in 3 pts. and did not change in 4 pts.

Conclusion: Oncological therapy based on the patients individual situation is recommended for HIV+ pts. with GCT.

173 POSTER

Bilateral germ cell tumors of the testis (GCTT): Report of two institutions experience

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Purpose: This study is undertaken to evaluate the incidence of bilateral tumors in patients (pts) treated at two different institutions for GCTT.

Methods: The medical records of 815 pts with GCTT [395 Seminoma (S) and 420 non-seminoma (NS)] successfully treated between 1/82 and 12/95 have been reviewed. All pts had been treated for their GCTT according to the stage of disease with standard regimens: 328 irradiation, 421 pts chemotherapy (CT) and 66 surveillance. 374 pts received platinum (P)-based CT, whereas 47 pts some other form of CT. Contralateral biopsy at diagnosis of GCTT was not performed in any of these pts.

Results: The median follow-up of these pts was 9.4 yrs (range 1–13 yrs). 3 pts (0.42%) had bilateral synchronous GCTT (2S, 1S/NS). 16 pts developed metachronous GCTT (1.97%). 14 of 805 pts had a testicular primary site at diagnosis of 1st GCTT, 2 of 7 pts initially had an extragonadal (retroperitoneal) tumor ($p < 0.01$). The median interval between 1st and 2nd GCTT was 45 months (mos) (range 5–242 mos). The tumor in the contralateral testicule occurred more frequently if the 1st tumor was NS ($p < 0.01$). In 5 pts (31.25%) histological differences (S and NS) between 1st and 2nd GCTT were found, whereas in 11 pts (68.75%) occurred the same histology (NS 9, S 2). 2 of 421 pts (1.7%) were treated with CT for the 1st GCTT, whereas 5 of 66 pts (7.6%) were on surveillance ($p < 0.05$). 4 of 328 pts (1.22%) had radiotherapy for the 1st GCTT ($p < 0.01$). The median interval between 1st and 2nd GCTT, according to applied primary treatment, was 49, 54 and 67 mos, respectively. After treatment for the 1st GCTT 13 pts are alive NED after median follow-up of 12 mos (range 25–245 mos).

Conclusion: The incidence of bilateral GCTT in our series is less than expected according to the series assessing contralateral carcinoma in situ at the time the 1st tumor is diagnosed. On the bases of these results it is difficult to recommend contralateral biopsy at diagnosis of GCTT in our population. Although CT and irradiation reduce the development of the 2nd GCTT, the risk apparently is not completely eliminated. pts with primary retroperitoneal GCT need a close and careful follow-up, as they appear to be at increased risk for developing a GCTT.

174 POSTER

Interferon-gamma (IFN-g) and interleukin-2 (IL-2) is a feasible and effective out-patient regimen for advanced renal cell cancer

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We designed a phase II study for pts with advanced RCC to study the feasibility, toxicity, and efficacy of out-patient IFN-g+IL-2.1 cycle consisted of 100 mcg IFN-g sq 3 x/week for 2 wks, 4.5 MIU IL-2 sq for 4 consecutive days for the next 2 wks followed by a 2 wk rest period. At least 3 cycles were given and in the case of response therapy was to be continued until PD. Data of 67 pts (39 m/28 f) with a median age of 60 yrs (range: 44–81) are now available. A median of 3 cycles (r: 1–15) have been applied (median observation time [mot]: 22 mos, r: 7–36) and all patients are eligible for feasibility and toxicity evaluation, and 51 patients for response. 45 pts were trained in self-application of the cytokines. No WHO-grade III/IV toxicity has been documented. Side effects consisted of flu-like syndrome grade I/II in 35 pts (56%) despite prophylactic paracetamol and local erythemas after IL-2 application in 11 pts (18%). Only mild myelotoxicity was observed (leucopenia grade I only and no thrombocytopenia). Anemia grade I/II occurred in 25 pts (40%). Response data of 51 patients (mot: 10 mos, r: 5–16) are: CR:n = 2 (4%), PR:n = 4 (8%), SD:n = 19 (37%), PD: n = 26 (51%). This preliminary data shows that IFN-g/IL-2 is a feasible regimen with acceptable toxicity which can be easily applied on an out-patient basis. The objective remission rate (CR + PR) with 12% and the response rate (CR + PR + SD) of 49% proves the activity of this therapy in RCC. This data are comparable with other cytokine regimens which usually need hospitalization, are more toxic, and are less cost-effective (e.g. infusional IL-2).