positive predictive value of 88%. Overall, path. stage was correctly predicted in 131/149 (88%) CS I NSGCT. Immunohistochemical expression of p53 ($p < 0.03$) and e-cadherin ($p < 0.04$) was statistically different between path. stage I and II by univariate, but not by multivariate analysis.

Conclusion: % EC and VI are clinically useful parameters to identify CS I NSGCT both at low risk and at high risk for retroperitoneal disease and biological markers do not seem to be of additional prognostic value. CS I NSGCT should be evaluated for quantitative histology and presence of VI to stratify the therapeutic approach.

161 POSTER*

BOMP/EPI intensive chemotherapy in poor-prognosis Germ Cell Tumors (GCT)

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Introduction: Patients (pts) with poor-prognosis GCT by IGCCCG classification had a expected 3-year survival of 50%.

Methods: In a multicenter study, 43 of these pts were treated with an intensive alternating chemotherapy regimen between Sept. 1985 and Dec. 1995. Primary site was testis in 32, retroperitoneum in 6 and mediastinum in 5. Treatment consisted of bleomycin 30 mg, vincristine 2 mg, methotrexate 300 mg/m^2 and cisplatin 100 mg/m^2 (BOMP), alternating at 14 day interval with etoposide 120 mg/m^2 d1–4, ifosfamide 1.3 gr/m^2 d1–4 and cisplatin 25 mg/m^2 d1–4 (EPI). BOMP was administered at 21 day interval from EPI. The median of cycles administered was 6 (1–10 cycles). Ten patients received additional chemotherapy after BOMP/EPI.

Results: Response to BOMP/EPI was complete response 8, partial response with negative markers 19, partial response with positive markers 8, growing teratoma 3, and no response 2. Twenty-three pts underwent surgical resection of postchemotherapy masses, including 4 pts with residual cancer. Twenty-seven pts (63%) achieved NED status after chemotherapy ± surgery and, in addition, 5 pts were marker negative but had non-resected residual masses (12%). There were an early death and a drug-related death. Toxicity grade 4 was: granulocytopenia 21 pts (49%), thrombocytopenia 1, anemia 3, lung toxicity 1, mucositis 1 and nephroxicity 1. Eighteen pts had granulocytopenic fevers. After a median follow-up of 25 months (12–135), the actuarial 2-year overall survival and progression-free survival were 67% and 62%, respectively.

Conclusion: BOMP/EPI is active enough in poor-prognosis GCT pts, when comparing with the reported IGCCCG results, to warrant comparative trials in this subset of pts.

162 POSTER*

Secretion of immunomodulating GM-CSF and M-CSF by human renal cell carcinoma of different types

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Purpose: GM-CSF and M-CSF have been shown to affect tumor-directed immune response in human renal carcinomas in phase I/II trials. So far, however, little is known about the synthesis of these growth factors by human renal cell carcinomas (RCCs).

Methods and Results: 38 newly established human RCC cell lines of different histological types were analyzed for the expression of hematopoietic growth factors and their corresponding receptors. ELISA revealed secretion of GM-CSF in 38 cell lines (max. concentration: 90 pg/ml per 10^5 cells) and of M-CSF in 37 cell lines (max. concentration: >2000 pg/ml per 10^5 cells). 14 cell lines showed secretion of G-CSF (max. concentration: 4.2 pg/ml per 10^5 cells) and IL-3 was found in 14 cell lines (max. concentration: 3 pg/ml per 10^5 cells). Secretion of IL-5 and EPO was not detected in any cell line. Using FACScan or RT-PCR, only 2 cell lines were shown to express receptor for M-CSF, whereas receptors for GM-CSF and G-CSF were not detected. Exposure to exogenous M-CSF, GM-CSF and G-CSF (concentrations: 0.1–100 ng/ml) did not affect the growth of our RCC cell lines as shown by MTT-assay.

Conclusion: Our study demonstrates that human RCCs of different histological types secrete significant amounts of GM-CSF and M-CSF, thereby supposedly being able to modulate the host's tumor-directed immune response.

163 POSTER*

Autoimmunity induced by Interleukin-2 and Interferon-α is associated with long-term survival in patients with metastatic renal cell carcinoma

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Interleukin-2 based immunotherapy has been shown to induce thyroid dysfunction and synthesis of thyroid autoantibodies. To assess the prognostic implication of immunotherapy-associated thyroid autoantibodies, we studied 329 unselected patients with metastatic renal cell carcinoma treated with s.c. IL-2 based immunotherapy since May 1989 at our institution. We evaluated antithyreoglobulin (ATA), antimicrosomal thyroid (AMA), and thyreo-globulin-receptor (TRAK) autoantibodies, thyroid dysfunction, and various known predictors of survival (*J Urol* 155: 19, 1996) prior and concurrent to IL-2 based immunotherapy in relation to overall survival. For statistical analysis, we used both univariate and multivariate Cox proportional-hazards models, and two-tailed Fisher's exact test. ATA and/or AMA were detected in 60 patients (18%), of whom 25 (8%) had pre-existing ATA and/or AMA titers as expected from the prevalence in caucasian population (*J Int Med* 239: 517, 1996). Ten of the latter patients showed rising titers concurrent to IL-2 based immunotherapy. We observed thyroid dysfunction in 125 patients, whereas 21 out of 60 patients with thyroid autoantibodies and 183 out of 269 autoantibody negative patients remained euthyroid ($p < 0.0001$). By univariate analysis, the presence of thyroid autoantibodies (ATA and/or AMA) ($p = 0.002$) and of dysthyroidism ($p = 0.04$) was statistically associated with favorable outcome. The mean overall survival in thyroid autoantibody positive patients was significantly prolonged (59 months) when compared to thyroid autoantibody negative patients (29 months; $p < 0.0001$). Upon multi-variate analysis, detection of thyroid autoantibodies was a statistically independent predictor of survival in patients with metastatic renal cell cancer receiving s.c. IL-2 based immuno-therapy. The presence of thyroid auto-antibodies may specifically indicate an altered immune-responsiveness of a subgroup of patients predisposed to a longlasting tumour control, while other cytokine induced autoimmune phenomena (including rheumafactor, antimitochondrial, antinuclear, antiheart, anti-skeletal muscle and anti-smooth muscle autoantibodies) are not associated with an effective antitumor immunity.

164 POSTER

Single agent carboplatin or radiotherapy as adjuvant in stage I seminoma – Results of a prospective trial

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Aim: To investigate the role of single agent carboplatin versus radiotherapy in stage I seminoma.

Material: From 1991–1993 58 patients with stage I seminoma received either 400 mg/qm carboplatin (one course) (n = 31) (group 1) or radiotherapy for the paraaortic lymphatics (26 Gy) (n = 97) (group II) as adjuvant following orchiectomy. All tumors were β-HCG negative. All patients of group II had T1-tumors compared with 29/31 patients of group I.

Results: All patients were scored prospectively. With a median follow up of 35 months in group I and 30 months in group II, all together one tumor progression was seen (group I). No late side effects were seen until yet. Acute side effects were mild and consisted of nausea in 30% of group II and 25% in group I.

Conclusions: No significant differences were seen for both groups. However, longer follow up is necessary. The late treatment results of radiotherapy are well known, but not for patients treated with carboplatin.

165 POSTER

Immunochemotherapy (IC) in patients with metastatic renal cell carcinoma

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Purpose: A response rate of 39% with a IC including Interleukin-2 (IL-2), Interferon-α (IFN-α) and 5-Fluorouracil (5-FU) was reported (J. Urol. 155, 1996) in patients (pat.) with metastatic renal cell carcinoma (RCC).

Methods: We analyzed the results of this regimen in an unicentric study, including 39 pat. (30 men) with a metastatic RCC, who were treated between 8/92 and 8/96. The mean age of the pat. was 56.7 years. In 14

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