cancer. However, the long-term results and the late toxicities are still unknown.

Methods: Between 8/89 and 9/95, 150 patients with a median age of 31 years (range: 18 to 55 years) with refractory or relapsed germ-cell tumors received HDCT containing carboplatin (1,500 to 2,000 mg/m^2), etoposide (1,200 to 2,400 mg/m^2) and ifosfamide (0 to 10 g/m^2). Thereafter patients were re-evaluated every three months during the first year and every 6 months during subsequent years.

Results: After a median follow up time of 50 months (range: 17 to 88), 149/150 patients were assessable, one patient was lost for follow up. In November 1996 all patients were censored; 60/149 (40%) patients were still alive. Among the survivors 35 (24%) patients were in CR or had become free of tumor after additional surgery, 18 (12%) patients achieved an unresectable markernegative partial remission, and 7 (5%) patients were in markerpositive partial remission or had progressive disease. Nephrotoxicity was observed in 17 (28%) patients, peripheral nervous toxicity in 24 (38%) patients, auld hearing impairment in 16 (26%) patients. Three patients acquired a hepatitis B or C during HDCT, one patient is alive with hemodialysis and another patient developed aseptic necrosis of the right femoral head after HDCT.

Conclusion: The short- and long-term evaluation data demonstrate the efficiency of HDCT as well as acceptable chemotherapy induced late toxicities in patients with refractory or relapsed germ cell cancer.

157 ORAL

Long-term effects of testicular cancer treatment on sexual functioning

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Purpose: To evaluate the influence of combined treatment modalities on sexual functioning and fertility potential in patients cured from testicular cancer.

Methods: Aspects of sexuality and fertility were assessed by questionnaires in 98 testicular cancer pts being in CR for at least 12 months. 19 pts (19%) had seminomatous, 79 (81%) non-seminomatous germ cell tumors, median age 28 years (19–53). Treatment included surgery alone in 17, platin-based chemotherapy (ctx) alone in 30, radiotherapy (rtx) alone in 5, combination of ctx ± rtx ± surgery in 46 pts. Median time interval between time of interview and end of treatment was 78 mon (18–169).

Results: *Fertility:* 39 (44%) were parents before therapy. No pregnancy occurred during treatment. 22 (25%) farthered children at a median of 54 mon after the end of treatment (3–108). In 19 pts pregnancy was not achieved with 15 of 19 pts having pathological semen analysis, 2 pts suffering from psychosocial distress, 1 pts with dry ejaculation and in one case the spouse did not want children. *Sexual problems/emotional distress:* The frequency of intercourse significantly decreased during the treatment, but afterwards recovered almost completely. 8% of pts reported dissatisfaction with sexual life before diagnosis of testicular cancer and 4% had experienced reduced libido and erectial difficulties. At the time of the interview significantly more pts (24%) reported an unsatisfactory sexual life and libido or erectial difficulties (19%) compared to the pretreatment situation. Increased age at the time of diagnosis, psychological distress before diagnosis and using of more than one treatment modality tended to correlate with a higher incidence of sexual problems.

Conclusion: Long-lasting sexual problems after therapy for testicular cancer are found in nearly a fifth of pts. From 41/98 testicular cancer pts wishing children 22 (54%) became parents. 19 pts were identified to be infertile and in 16 of these possibly treatment-related alterations were detectable.

158 POSTER*

Telomerase activity and telomere length in testicular cancer tissues and residual tumor mass after cisplatin based chemotherapy

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Activation of the ribonucleoprotein enzyme telomerase has been associated with immortalization and cancer. Thus, telomerase has emerged as a novel target for chemotherapy. We have previously shown that the antineoplastic agent cisplatin is capable of inhibiting telomerase activity in testicular cancer cells *in vitro* and proposed that the effect might contribute to cisplatin's marked efficacy against germ cell derived tumors. In this study, we examined whether the hypothesis might be operative in a clinical case scenario. The telomeric repeat amplification protocol and mean terminal restriction fragment (TRF) length analysis were used to study telomerase activity and telomere length in normal testes, testicular tumors, and residual mass after cisplatin therapy. Tissues were microdissected prior to enzyme extraction to investigate enzyme activity and TRF-length in relationship to different pathologies. Telomerase activity was measured in concentrations between 6–0.06 μg of total cellular protein and teratoma cell line SUSACP used as positive control to allow quantification. Eighteen of 25 samples had telomerase activity, 16 of which were germ cell tumors and 2 were normal testes. Activity was high in tumors, but only moderate in normal tissue. Telomerase was not detected or very low in necrotic testicular germ cell tumors and lymph node metastases after therapy and in differentiated teratomas. Accordingly, telomeres were significantly shorter in such cases compared with untreated seminomas or undifferentiated teratomas. Our data demonstrate that clinical response to cisplatin based treatment regimens is paralleled by telomere shortening and absence of detectable telomerase activity. Measurement of telomerase activity may be a useful predictor of response to therapy.

159 POSTER*

Germ cell tumor (GCT): Staging and therapy control with ^{18}FDG-PET. First results of German multicenter trial

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Purpose: We have studied the value of PET as a staging method in pts with GCT before and after therapy in a prospective multicenter study.

Method: 54 pts with seminoma (18) and non-seminomatous tumor (36) were included in the study. In total 77 FDG-PET were performed, 27 at diagnosis, 50 after therapy, with a median of 34 days after treatment (range 13–122). So far 28 pts are validated, 28 with tumor marker profil, 23 with both, PET and tumor marker. Follow up for more than 6 months (11) (median 13 months, range 8–23) or histological examination (12) or was used for validation.

Results:

	True positive	False positive	True negative	False negative	Sensitivity	Specificity
PET	13	3	6	1	93%	66%
AFP/HCG	4	0	6	9	30%	100%

Conclusion: PET is a sensitive but non-specific method for predicting vital tumor, while tumor marker are more specific. The reason for the low specificity of PET is not yet fully understood, but might be due to an inflammatory process after chemotherapy. Perhaps this problem can be solved by extending the interval between the end of therapy and PET.

160 POSTER*

Prognostic risk factors in low stage testicular nonseminomatous germ cell tumors (NSGCT)

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Purpose: Since optimal therapy for clinical stage I (CS I) NSGCT still remains controversial, we examined the clinical utility of histopathological and biological prognostic markers to stratify the risk of occult retroperitoneal disease.

Methods: Orchiectomy specimens of 149 CS I NSGCT (86 PS I, 63 PS II) were chosen for immunohistochemical analysis of p53, bcl-2, MIB-1, cathepsin D and e-cadherin expression and specimens were also reviewed for presence of vascular invasion (VI) and percentage of embryonal carcinoma (%EC). Uni- and multivariate logistic regression models were used for statistical analysis.

Results: Combination of VI and % EC was the most significant prognosticator to predict path. stage II ($p < 0.0001$) by multivariate analysis. Using cut-off values of <45% EC and VI– path. stage I was correctly predicted in 88% (68/77) with a negative predictive value of 92%. Cut-off values of >80% EC and VI+ correctly predicted path. stage II in 85% (41/48) with a

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