Methods: Over the last 5 years we investigated 87 patients for the pO2-status of cervical cancer (age 34-80 yrs). All patients were treated with curative intent and the same treatment schedule. The pO2-measurements were done using polarographic needle probes and the Eppendorf-device.The microvessel density was determined in pretreatment biopsies immunhistologically using a CD31-antibody.

Results:. The median- pO2 for all 87 patients was 15 mmHg pooled over 4 measured tracks, so the threshold for classification was set to 15 mmHg. We found only a marginal effect of the pretreatment pO2 in the 3-year-survival (52 +9% vs.69 + 8% p =0,15) Measurements of oxygenation after 11 fractions revealed no changes of pO2 if the group of patients was analyzed as a whole group. The analysis of the pO2-changing after 11 fractions can be classified in 4 groups of pO2-modification: 1. a level >15mmHg at both measured points; 2. a level <15mmHg at both measured points 3. an increased or a decreased pO2 after 11 fractions. In a Cox-model - adjusted to stage -the best clinical results were obtained for patients with a well-oxygenated tumor independent of the time of high pO2-level, the worst results are shown in patients with persistent hypoxic cancers. In 46/87 patients the vasculary density prior to therapy was evaluated. Tumors with a persisting low pO2 showed a significantly higher vessel count in comparison to the 3 other groups (p<0,001).

Conclusiones: Our investigation demonstrated that tumor hypoxia is linked to angiogenesis. This supports the use of hypoxic-modifying strategies.

530 POSTER DISCUSSION

Erythropoietin enhances radiation treatment efficacy in patients with pelvic malignancies.final results of a randomized phase III study

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Purpose: To determine the efficacy and safety of the subcutaneous administration of recombinant human erythropoietin (EPO) to patients with pelvic malignancies receiving radiotherapy(RT).

Patients and Methods: 385 patients underwent conventional RT with 2 Gy daily fraction/5days/week to a total dose of 50-60 Gy+/- EPO 10000U daily 5 times per week. All patients received iron supplements. Primary endpoints were weekly haemoglobin increase and local tumor control. Secondary endpoints were safety, disease free survival and overall survival.

Results: There were no significant differences between the two groups for age, Hb levels before RT, site and stage of disease(P>0.1). The mean Hb levels during RT in the EPO group were 12.9±2.6g/dL versus 10.6±2.5 g/dL in the control group. The mean weekly increase of Hb was 0.54g/dL in the EPO group versus 0.17g/dL in the control group.The 4 year disease free survival was 85.3% in the EPO group versus 67.2% in the control group(p=0.0008).No EPO related side effects were observed.

Conclusion: EPO can be safely administered and improves significantly the local tumor control in patients with pelvic malignancies undergoing RT.

Genitourinary cancer

531 POSTER DISCUSSION

The importance of implant dose on biochemical outcome following I-125 prostate brachytherapy

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Purpose: To determine the effect of implant dose as assessed by CT based post-implant dosimetry on biochemical outcomes following I-125 brachytherapy for prostate cancer.

Methods: 234 patients were treated from 1991 to 1999 with I-125 brachytherapy without hormonal therapy or external beam irradiation for T1-T2 prostate cancer. All patients had Gleason scores < 7. Presenting PSA ranged from 1.3 to 189 (median 6.8). Clinical stage was T1b-T2a in 173 patients and T2b-T2c in 61 patients. All patients were implanted using a real-time ultrasound guided technique. One month post-implant, all patients underwent CT based dosimetric analysis. Implant dose was defined as D90 (dose delivered to 90% of the prostate on dose volume histogram). D90 values ranged from 15 to 256 Gy (median 163 Gy). All values conformed to TG43 guidelines. PSA failure rates were calculated with actuarial methods using the ASTRO definition. Follow-up from date of implant to last seen ranged from 24 to 119 months (median 47).

Results: Implant dose had a significant effect on freedom from PSA failure (FFPF) rates. Patients with D90 values of < 140 Gy (71), 140 - < 160 Gy (97), 160 - < 180 (100) and > or equal to 180 Gy (97) had FFPF rates at 7 years of 63%, 85%, 95% and 88%, respectively (p=0.0025). Overall, patients with D90s > or equal to 140 Gy had a FFPF rate at 7 years of 90% versus 63% for those with D90s < 140 Gy (p=0.0003). In addition, pretreatment PSA also significantly affected PSA failure with FFPF rates at 7 years of 82%, 83% and 24% for PSA levels of < or equal to 10, >10-20 and > 20, respectively (p=0.0001). A dose response cutpoint of 140 Gy was seen in both patients with initial PSA < or equal to 10 (190) and those with PSA > 10 (44), p=0.001 and p=0.04, respectively. The median follow-up was 48 months and 46 months for patients with D90 < 140 Gy and > or equal to 140 Gy, respectively. A multivariate analysis testing the effect of dose, PSA, score and stage on FFPF rates found dose to be the most significant predictor of outcome with p values of <0.0001, 0.03, 0.31 and 0.58, respectively.

Conclusions: Implant dose is the most significant predictor of PSA failure following I-125 prostate brachytherapy. Based on this analysis, optimal D90 values from the post-implant CT analysis should be > or equal to 140 Gy. Current data reveal no significant improvements with values > 180 Gy.

532 POSTER DISCUSSION

Inhibition of 20S Proteasome results in serum IL-6 and PSA decline in patients (pts) with Androgen-Independent Prostate Cancer (AIPCa) treated with the Proteasome Inhibitor PS-341

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Purpose: Assessing surrogate markers of NFkappaB activity in patients with androgen-independent prostate cancer(AIPCa) treated with proteasome inhibitors is of great importance for drug development. Preclinical studies indicate that PS-341, a specific proteasome inhibitor, inhibits NFkappaB, which is implicated in the progression of PCa in bone and resistance to therapy. Serum IL6 concentration can serve as a surrogate of NFkappaB activity.

Methods: We studied 43 pts (age: 64 (45-78), PS:0/1: 43) with metastatic AI PCa treated on a Phase I trial of PS-341, administered intravenously weekly x 4 every 6 wks over 14 dose levels (0.13-1.6 mg/m2) for evidence of anti-tumor activity, serial serum (s) IL-6 concentration (by ELISA) and 20S proteasome inhibition (20S-PI). 20S-PI is measured ex vivo in peripheral blood (PB) using a fluorogenic substrate.

Results: 4/15 pts with 45-55% 20S-PI (0.75-1.21 mg/m2) and 16/18 pts with > 70% 20S-PI (1.32-1.6 mg/m2) had serum available for analysis. Patients with 45-55% 20S-PI had 40% suppression in median sIL-6 but no change in PSA slope or concentration, while pts with >70% 20S-PI had 80% decline in median sIL-6 with parallel decline in PSA slope (63% of pts) and PSA concentration (19% of pts). We also observed radiographic partial response (PR) in 2 patients.

Conclusions: Our data demonstrate a dose dependent decline in sIL-6 and PSA slope and concentration in pts treated with weekly PS-341. The biologic effect occurs within a tolerable dose range of PS-341. This data suggests that weekly PS-341 may be active in prostate cancer and supports the view that its action may be mediated through the inhibition of NFkappaB.

533 POSTER DISCUSSION

Pronounced radiosensitization of estramustine phosphate in the treatment of locally advanced prostate cancer

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Purpose: Since the potential of Estramustine phosphate (EMP) as tumor radiosensitizer has been shown extensively by us and others in animal models, a clinical study was designed to test the hypothesis that EMP would preferentially enhance the anti-tumor effects of radiation therapy for the treatment of prostate cancer. A prospective phase II trial was carried out to determine whether the combined EMP and external beam radiotherapy (EBRT) would increase the tumor control rate of locally advanced prostate cancer with no enhanced normal tissue toxicity.

Methods: Between January 1991 and March 2000, 75 patients (pts), stage T2 through stage T4, were entered into the study. Forty-seven (63%)

pts were given EMP and VBL. Twenty-eight (37%) pts were given EMP only. Gleason pattern scores ranged from 4 (n=3), 4-7 (n=49), and 8-10 (n=23). Pre-treatment prostate specific antigen (PSA) was as follows: < 20 in 25 pts (33%), 21 to 50 in 28 pts (37%), and > 50 in 22 pts (29%). 47 pts (62%) were T2, 21 pts (28%) T3, and 7 pts (10%) T4. The median age was 77 years. All pts were treated with mega-voltage external beam radiation with a dose of 65 to 70 Gy in 7-71/2 weeks. Oral EMP 450 mg/m2 daily and VBL 3 mg/m2 weekly were given concomitantly in 47 pts. The remaining 28 pts received EMP only.

Results: Pronounced tumor regression was achieved in all pts at 6 weeks following the completion of the combined treatment. The serum PSA fell to an undetectable level in 81% of pts (61 out of 75) in 6 weeks. The long-term results with the median follow-up time of 63 months show that 80% of T2, 50% of T3 and 40% of T4 pts are free from the biochemical relapse (PSA > 4 ng/ml). In particular, the tumor control rate was impressive for those with the serum PSA 21-50, achieving a 74% freedom from the biochemical relapse. Importantly, there was no increased acute and late normal tissue morbidity from the combined regimen.

Conclusion: The long-term follow-up study of the combined EMP and EBRT confirms our earlier findings that the combined regimen is highly effective in achieving a durable tumor control in pts with locally advanced prostate cancer. Unlike other cytotoxic chemotherapeutic drugs, the combined treatment did not produce any disproportionately enhanced normal tissue toxicity.

534 POSTER DISCUSSION

External beam radiotherapy with high dose rate (HDR) brachytherapy boost in localised prostate cancer

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Purpose: To retrospectively analyse the outcome for patients (pts) with localised prostate cancer treated with conformal external beam radiotherapy (EBRT) in combination with HDR brachytherapy (BT).

Patients and Methods: Since 1988, 290 pts with localised prostate cancer (T1a-3b) have been treated with a combination of EBRT and BT in our hospital. EBRT was given with 2 Gy fractions to a total dose of 50 Gy. BT was given in two 10 Gy fractions. A remote afterloading technique was used with a HDR Ir-192 source. From 6 to 21 needles were inserted transperineally guided by transrectal ultrasound.

Data from 128 pts treated from 1988 to 1997, were analysed: The mean as well as median age was 64 years (range 50-77). Median follow-up time was 57 months (range 12-155). Preirradiatory androgen ablation therapy was given to 68 pts (50%). The tumour was classified as T1 in 16 pts (12%), T2 in 90 (70%), and T3 in 22 pts (17%). Pre-treatment PSA was available in 125 pts (98%) (range 1.2-93). PSA was <10 in 67 pts (52%), 10-20 in 29 (23%), and >20 in 29 pts (23%). Tumour pathological grade was low (Gleason score 2-4) in 37 pts (29%), intermediate (5-7) in 76 pts (59%), and high (8-10) in 15 pts (12%).

Results: At three years, the biochemical no evidence of disease rate (bNED) was 90%. Overall bNED was 83%. The bNED for pts with T1, T2, and T3 tumours was 81%, 86%, and 72% respectively. The overall bNED for pts with pre-treatment PSA <10, 10-20, and >20 was 90%, 79%, and 69% respectively. According to the histological grading the bNED was 86%, 83%, and 73% for low, intermediate and high grades. Disease progression was seen in 22 patients (17%). Local recurrence developed in 3 pts and metastatic disease in 9 pts. Eleven pts had biochemical failure only. Late severe complications were few. Urethral strictures requiring surgical intervention were seen in 9 pts.

Conclusion: Treatment results after conformal EBRT combined with HDR BT in patients with localised prostate cancer are promising.

535 POSTER DISCUSSION

Oncologists' perceptions and treatment practice variations in the treatment of hormone-refractory prostate cancer (HRPC): a pilot multinational study

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Purpose: To examine differences in the treatment practices, and perceptions of hormone-refractory prostate cancer therapy in different countries worldwide.

Methods: A written questionnaire was sent to medical oncologists and urologists in 21 countries (Canada, USA, Austria, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Slovak Republic, Spain, UK, Australia, Argentina, Brazil, Japan, Russia, South Africa) to assess aspects of HRPC including: current national guidelines and screening programs, clinical management of HRPC, historical trends, and reimbursement issues. All data were stratified by country and major geographical location and analyzed using the Fisher's Exact Test.

Results: Fifty-three oncologists from the 21 surveyed countries completed the questionnaire. The oncologists were categorized by major geographic location: North America (n=12), Europe (n=26), Australia (n=4), South America (n=5), Japan (n=3), and Other (n=3). In most cases, guidelines and screening programs are not nationally regulated or mandated. In Japan primary screening for prostate cancer is commonly performed through the health check-up system. Secondary hormone therapy is the current standard therapy for HRPC in all groups. Pain control was rated the most important parameter in first-line treatment option decisions in most groups. Most notably exceptions to this were Japan where patient satisfaction was rated the highest, and North America where median survival benefits was considered the most important. However, in both cases, pain control was the next most important parameter identified. For second-line treatment option decisions, all groups, except for Japan where patient satisfaction was again rated highest, ranked pain control most important. Moreover, 92% of the clinicians surveyed reported that quality of life evaluations were not routinely conducted. Doctors/prescribers were identified as having the most influence on the introduction and use of a new treatment in all groups, except for Japan in which health care organizations were identified as most influential.

Conclusions: For the majority of parameters assessed in this survey, the data collected from each groups was homogenous. However, Japan consistently differed from all other groups, especially in terms of importance of patient satisfaction and pain control in their treatment decision process.

Breast cancer: New drugs/regimes

536 POSTER DISCUSSION

An eight weeks dose-dense versus a 24 weeks sequential adriamycin/docetaxel combination as preoperative chemotherapy (CHT) in operable breast cancer (T2-3, N0-2,M0)

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In a previous phase II b - trial including 248 patients (P) we demonstrated that dose-dense CHT in the preoperative setting (ADOC: adriamycin 50mg/m2 + docetaxel 75 mg/m2 q 14d x 4 + G-CSF + Tamoxifen) results in a pathological complete response (pCR) - rate of 9.7%. In this current randomized study in P with cT2-3, cN0-2,M0 untreated breast cancer we want to demonstrate that this dose-dense schedule obtains a similar pCR - rate as a sequential schedule (AC-DOC: adriamycin 60 mg/m2 + cyclophosphamide 600 mg/m2 q 21d x 4 followed by docetaxel 100 mg/m2 q21d x 4) prior to surgery. Tamoxifen (20 mg/d for 5 years.) was given simultaneously in all P.

Within 22 months 728 of 1000 planned P have entered this trial. Median age was 52 years; median initial tumour diameter by palpation and by best appropriate imaging method was 4 cm and 2.8 cm, respectively; 60.7% had no palpable axillary lymphnodes. So far data on toxicity are available for 197 pts (ADOC 101, AC-DOC 96), i.e. the 4 or 8 cycles have been given completely.

Grade III/IV Toxicity	ADoc (% of P)	AC (% of P)	AC-Doc (% of P)
Anaemia	2	2	2
Neutropenia	32	61	55
Thrombopenia	0	2	1
Nausea	4	10	2
Skin	4	2	9
Nail	1	0	7
Alopecia	91	92	99
Infections	5	2	0
Neurotoxicity	1	0	4