Results: Sensitivity and specificity of A. O. fluorescent staining in phase I study, were 80% and 100%, respectively, and all the cells from 10 healthy volunteers stained negative. Those in phase II study were both 100% in 16 patients with TCC, and all the cells from 13 healthy volunteers stained negative. p53 IMC and IMH were identical in 95% of the patients with TCC, and all the cells from 9 healthy volunteers did not expressed p53. mdm2 IMC and IMH were identical in 70% of the patients, and all the cells from 20 healthy volunteers did not expressed mdm2.

Conclusions: Our results confirm the usefulness of IMC as a non invasive method for diagnosis and intensive follow-up of TCC. A.O. fluorescent analysis of primary urine derived cell cultures is a promising non-invasive diagnostic technique.

128 POSTER

Ifosfamide (IFO) in the treatment of metastatic hormone refractory prostate cancer

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Purpose: There is no good chemotherapy available for hormone refractory prostate cancer. To evaluate efficacy, schedule and toxicity of IFO fifteen patients (pts) with metastatic hormone refractory prostate cancer were treated.

Methods: IFO was given every third week at a dose of 5 gr/m^2 per 24-hour infusion on day one or at a dose of 1.5 gr/m^2 on days 1–4 as a short infusion with concomitant mesna uroprotection. Treatment was continued until disease progression (PD), untoward side effects or maximum 6 cycles.

Results: The mean age of the pts was 63 years (range 49 to 74 years). The mean time from diagnosis to the beginning of IFO was 21 months (range 5 to 46). All pts had bone metastasis and PSA from 16 to 1270. Nine (60%) pts received all six cycles with a cumulative IFO dose from 8 to 96 gr. Five pts responded with an over 50% decrease in PSA, and one with an over 45% PSA response and PR in his bone metastasis yielding a response rate of 40%. In three pts PSA remained stable and in six pts PSA increased (PD). The median survival has not yet been reached; the shortest was two months and the longest is 42+. Responses were equal in both treatment schedules, but there were more PD:s in 4-day arm. No serious adverse reactions occurred. Leukopenia grade 1–2 in 6 pts, anaemia grade 1–2 in 5 pts and no thrompocytopenia was reported. Dizziness, fatigue, nausea, vomiting, alopecia and bladder irritation were other adverse events.

Conclusion: IFO seems to be effective in the treatment of prostate cancer (RR 40%) and more pts should be treated to compare the two treatment schedules.

129 POSTER

Enhancement of radiation response of Dunning R3327 prostatic adenocarcinoma by IL-2 and histamine

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Purpose: The purpose of the present study was to investigate whether treatment with histamine alone, Interleukin-2 (IL-2) alone or IL-2 in a combination with histamine affects the result of irradiation (RT) of Dunning R3327 prostatic adenocarcinoma in rats. The growth pattern during treatment, and the effects of the various treatments on the tumours both macroscopically and microscopically at sacrifice were studied.

Method: Rats transplanted bilaterally in the flanks with the syngenic androgen-sensitive Dunning R3327 prostatic adenocarcinoma, were treated with histamine, IL-2 alone or with a combination of both histamine and IL-2. RT was delivered unilaterally to each of the animals, once daily, for 3 consecutive days, to a total dose of 18 Gy. The contra-lateral tumour served as intra-animal control. Treatment with IL-2, histamine and the combination treatment were started one week before RT and continued until the animals were sacrificed, 5 weeks after the RT was finished.

Results: All the tested agents alone but especially the combination treatment with histamine and IL-2 caused considerable reduction of the tumour growth. The effects of RT was potentiated and the most prominent decrease in tumour volume was seen in combination treatment. The microscopical analysis revealed pronounced alterations with e.g. decline in tumour cells and multiple appearance of cysts in the tumour tissue following IL-2/Histamine and RT.

Conclusion: Histamine and IL-2 in clinically tolerable concentrations seems to be a potent combination in enhancing the effects of RT. Further investigation on the underlying mechanisms of action are currently undertaken.

130 POSTER

p53 gene mutations in primary bladder carcinoma

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Transitional cell carcinoma of the urinary bladder is an heterogeneous disease with very different pathologies and clinical outcomes. Superficial lesions recur in 30–80% of patients and 20% of these recurrences become invasives and potentially metastatic. Besides, metastatic diseases appears in 50% of patients with invasive carcinomas after radical cystectomy. Thus, it is very important to identify patients who might benefit from more accurate therapy. To achieve this purpose we studied p53 protein over-expression and the presence of mutations. We evaluated histological sections from 46 patients with bladder cancer using immunoperoxidase technique. p53 was assessed with three different antibodies (PAb 1801, DO-1 and MU-195). TCC tumors were also analysed for p53 mutations using frozen samples by SSCP and direct sequencing analysis of exons 4 through 9. Overall, 20 of the 46 (43%) TCC tumors were positive for at least one antibody. Mutations were identified in 19 of the 41 samples showing a good concordance between positive immunohistochemical staining ($p < 0.05$). Interestingly, p53 mutations occurred more frequently in exons 4.5 and 6. The presence of mutated p53 was correlated with tumor grade ($p < 0.01$) (1 of 15 low-grade tumors vs 18 of 27 high-grade tumors) and stage ($p < 0.01$) (6 of 23 superficial vs 13 of 19 infiltrant tumors). These findings support that mutations in p53 gene appear later in progression and that its presence in superficial and/or low-grade tumors defines a subset of patients with more aggressive tumors which might warrant new strategies of treatment.

131 POSTER*

Correlation between PSA, post-treatment biopsy and clinical outcome in irradiated prostate cancer patients

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Purpose: The role of PSA in the detection of local recurrence after radiotherapy (RT) is unclear. The main objective of this study was to examine the correlation between post-treatment PSA values and histopathologic finding in the prostate after definitive external beam RT.

Methods: 61 transrectal ultrasound (TRUS) guided biopsies were performed on 57 asymptomatic patients during routine clinical follow-up after RT for prostate cancer. Median follow-up from conclusion of RT was 26 months.

Results: Out of 61 biopsies 33% showed normal prostatic tissue, 40% showed dysplasia and 26% were positive for cancer. The median PSA value for the negative biopsy group was 1.6 μg/ml. For the positive biopsy group it was 8.4 μg/ml. Only 25% of the patients with positive biopsies developed a clinical recurrence during a 5-year follow-up.

Conclusion: A low PSA value does not exclude a positive biopsy. There is no rationale for routine post-irradiation biopsies in prostate cancer as they rarely reflect therapy outcome.

132 POSTER

High-dose rate interstitial brachytherapy followed by percutaneous irradiation for prostate cancer – First results of a prospective trial

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Aim: To test the effectiveness and side effects of a combined high dose rate brachytherapy and percutaneous irradiation (RT) for localized prostate cancer in a prospective phase II trial.

Material: Between 10/92 and 6/96 58 patients (pts.) were treated. All pts. were node negative. 4 pts. had T1 tumors, the others T2/T3 tumors. Two

times 9 Gy each (until 10/93: 10 Gy) ^{192}Iridium brachytherapy was given, followed by 40 Gy percutaneous RT (grom 10/95: 45 Gy).

Results: The median follow up is 27 months. The median PSA before start of treatment was 11.4 ng/ml and 0.72 ng/ml 12 months and 0.4 ng/ml 24 months after RT. 17/26 pts. (60%) had negative biopsies 12 months after RT, 4 were positive and 5 showed regression grade II/III. 24 months after RT 10/17 biopsies were negative and only 3 were positive. 5 pts. showed a PSA > 3 ng/ml. Severe side effects occurred in 2 pts., both had additional biopsies from the rectal wall.

Conclusions: The early results are encouraging. The rate of severe side effects (4%) is tolerable and seems to be lower with 9 Gy HDR-brachytherapy. The dose to the ant rectal wall is now limited to 6 Gy.

133 POSTER

Potential doubling time (T_{POT}) in adenocarcinoma of the prostate

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Purpose: To relate the T_{POT} with grade of differentiation and clinical stage in prostate cancer.

Methods: A hybrid T_{POT} was determined as a combination of the S-phase time (by FCM) and LI (by histology) after *in vivo* labelling with iododeoxyuridine in 45 patients with adenocarcinoma of the prostate. The histological LI was determined in hot-spots. Tumours were classified according to the UICC 1992 classification and graded according to the WHO grading system.

Results: The median histological LI was 7.5% (0.7;31.9) and the median hybrid T_{POT} 2.1 days (0.5;27.0). They were significant different from the FCM LI of 2% (0.0;10.0) and the FCM T_{POT} of 27.8 days (5.8;304.4). There was a statistical significant relation between grade of differentiation and the histological LI ($p = 0.02$) and hybrid T_{POT} ($p = 0.002$). Tumour stage >T2 and/or M1 were related with a significantly higher histological LI ($p = 0.02$) and lower hybrid T_{POT} ($p = 0.005$). FCM LI and T_{POT} correlated with differentiation, but not clinical stage.

Conclusions: Results of the study indicate that hot-spot LI and hybrid T_{POT} are related with the aggressiveness in prostatic cancer.

The study was supported by the Danish Cancer Society.

134 POSTER

Local intratumoral immunotherapy of prostate cancer with interleukin-2 reduces tumor growth significantly

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Purpose: This study was designed to determine effectiveness and toxicity of local continuous immunotherapy of prostatic cancer.

Methods: 60 juvenile male Kopenhagen rats with Dunning adenocarcinoma of the prostate, implanted subcutaneously into both flanks after proven tumor growth, were treated with either human interleukin-2 (IL-2) depot preparations (n = 30) or albumin (placebo) depot preparations (n = 30) implanted directly in one tumor site. IL-2 depots released IL-2 reliably for more than 24 days. Rat serum was tested during treatment for human IL-2, possibly absorbed from depots, and for rat interferon gamma.

Results: IL-2 treatment reduced tumor growth significantly ($p < 0.001$) compared with albumin treated sites or untreated contralateral sites. No toxicity was observed during treatment. That neither human IL-2 nor rat interferon gamma was detected in serum indicates an exclusively local IL-2 effect.

Conclusion: IL-2 depot preparations reduce tumor growth in Dunning adenocarcinoma of the prostate significantly without toxicity.

135 POSTER

Phase II study of vinorelbine in patients with hormone refractory prostate cancer

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Forty seven patients with hormone refractory prostatic cancer (HRPC) were treated with vinorelbine, a hemisynthetic vincaalkaloid. The objectives were to determine time to progression, specific survival, PSA response and toxicities. **Entry Criteria:** Patients with proven adenocarcinoma of the prostate with metastatic disease clinically progressing after endocrine deprivation based on parameters derived from NPCP criteria. **Treatment:** Vinorelbine was given at 25 mg/m^2 weekly for at least 8 weeks or until progression or toxicity.

Patient Characteristics: Median age 69 yrs (50–81), modal PS = 1, prior surgery 35, prior radiotherapy 29, hormonotherapy 43 pts. 37/43 had bone metastases, 22 local prostate tumors, 13 lymph nodes, 4 lung metastases and 6 liver metastases. Median PSA at inclusion was 82.5 (10–3790). It appear that 21 patients/43 had more than one line of classical hormonal deprivation. At entry duration of hormonal treatment were 20 months for LH-RH, 16 months for antiandrogens.

Results: Median number of cycle administered per patients: 7 (1–21) with a dose intensity of 17.8 mg/m2/w. Median time to progression was 11.7 weeks (5–55) and median overall survival was 32 weeks (6–59+). PSA decrease was observed in 19/43 patients, 3 partial response of measurable lesions were observed. There was no treatment related death. The main event was neutropenia CALGB grade III–IV (48.8%) without severe infection and rapid recovery (one week). Non hematological toxicity was mild.

Conclusion: This study suggest activity of vinorelbine in HRPC and provide data for future selection of patients and optimization of treatment schedule.

136 POSTER

Morbidity of external beam irradiation in patients with locally advanced prostate cancer: Analysis of our experience

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Objectives: To study the risk of developing bladder and bowel complications after radiotherapy (RT) in patients (pts) with prostate cancer T1-T4NxM0.

Material and Methods: In the period 1984 to 1991 125 pts received RT. Mean follow-up was 41.5 months (10–99 m.) The mean total was 63.6 Gy (55–71 Gy) ICRU to the prostate and 47 Gy (26.6–55.2 Gy) ICRU to the pelvis. Acute as well as late complications were evaluated according to EORTC grade.

Results: Mild and moderate cystitis (1–2 grade) were observed in 105 (84%). 7 pts had severe cystitis (grade 3). Grade 1–2 late bladder morbidity was presented in 31 (25%) pts. Only 1 patient (0.8%) developed severe cystitis (grade 3). The actuarial (5 year) bladder complication rate for all grades was 40%. Acute mild and moderate (grade 1–2) bowel complications were observed in 99 (74%) pts. There was no incidence of severe acute bowel complications (grade 3). Grade 1–2 late bowel complications were found in 26 (20.8%) pts. One patient (0.8%) required colostomy because of rectal bleeding (grade 3). The actuarial (5 year) incidence of total bowel complications was 30%. We observed that irradiation of larger pelvic volumes is associated with significantly increased only acute bowel complications.

Conclusion: Our experience shows that the external beam irradiation is the safe method of treatment in patients with locally advanced prostate cancer. In our series the incidence of severe (grade 3) late urinary and intestinal complications was very low.

137 POSTER

Health-related quality of life and sequelae in patients treated with external beam irradiation (EBI) and brachytherapy for localized prostate cancer (LPC)

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Purpose: To evaluate late physical and psychosocial sequelae in patients treated with an association of EBI and brachytherapy for LPC.

Methods: 71 patients free of disease, treated from 1988 to 1992, were matched on age and residency with 71 healthy controls. The French translation of the Nottingham Health Profile questionnaire and that of the EORTC QLQ-C30 core questionnaire were used to evaluate physical-, role-, emotional-, cognitive- and social functioning, global health status as well as tonus and sleep disturbance. Specific problems related to prostate cancer were explored using the prostate specific module developed by the EORTC Genito-Urinary Tract Cancer Cooperative Group. Concordance between clinical complications reported by patients and those reported by physicians was also analyzed.

Results: General health quality of life scale and general symptom scale scores did not significantly differ between patients and controls, However,