122 POSTER

The polymorphic enzymes *N*-acetyltransferase 2 and glutathione *S*-transferase M1 in bladder cancer patients

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Purpose: Shifts of *N*-acetyltransferase 2 (NAT2) and glutathione *S*-transferase M1 (GSTM1) which are involved in metabolism of carcinogenic aromatic amines and polycyclic aromatic hydrocarbons (PAH) resp. were to investigate.

Methods: 179 bladder cancer in-patients were interviewed for possible bladder cancer risk factors. All patients were phenotyped for NAT2 by HPLC using molar ratios of urinary caffeine metabolites. A subgroup of 89 patients was genotyped for GSTM1 by PCR of lymphocyte DNA.

Results: 64% of the 179 bladder cancer patients had a low acetylating capacity ("slow" acetylators). In 70% of the 89 genotyped bladder cancer patients GSTM1 gene was lacking. The distribution of NAT2 and GSTM1 in office personnel (59% slow acetylators, 54% GSTM1 negative) did not differ from normal population. Slow acetylators were overrepresentated in smokers (72%), occupationally exposed to colorants (71%) and in coke oven workers (5 out of 6). 16 out of 19 coal miners (84%), 10 of 13 exposed against fumes (77%), 5 of 8 exposed against tar and all four genotyped coke oven workers were GSTM1 negative.

Conclusion: The results are consistent with the view that "slow" acetylator status and the lacking of GSTM1 gene are genetically determined risk factors for bladder cancer in persons exposed to aromatic amines and PAH.

123 POSTER*

High precision conformal radiotherapy (RT) (HP-CRT) of patients with prostatic cancer

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Purpose: Biopsies two years after RT-treatment for prostate cancer indicates remaining tumour cells in 20–60% of biopsies. Higher doses (>70 Gy) with large fields increases the risk for serious side-effects Due to day-to-day set-up variation and movement of the prostate, a margin of less than 1.5–2 cm is always inaccurate since it might miss the tumour. Visualisation of the prostate on the treatment machine has not been possible. New technical improvements are needed to accurately localise the prostate during RT.

Methods: We have developed a new technique to accurately position the prostate during RT. The method only needs a simple fixation set up. The technique is used clinically during CT planning, field simulation and when RT is delivered.

Results: With this new treatment technique the day to day variation is this less than ±1 mm. The technique has been tested on 7 patients with conventional dose level (70 Gy) and 15 patients in the first Scandinavian dose escalation study with external beam radiotherapy. Side effects are evaluated weekly by the doctor (according to EORTC/RTOG) and by the patient with a daily diary and a self assessment questionnaire (QUFW-94). The new technique will be presented together with evaluation of side-effects.

Conclusion: With the new HP-CRT we have developed a technique that allows us to increase the dose to the prostate without excessive side-effects. The need of margin will decrease from 1.5–2 cm down to 1–2 mm.

124 POSTER

Results of conformal radiotherapy in prostate cancer

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Purpose: Results of conformal radiotherapy in prostate cancer were evaluated in terms of toxicity, local control, biochemical control and survival.

Methods: From January 1992 to June 1995 curative radiotherapy was planned with a 3D-system in 52 patients. 45 patients were treated for primary tumor and 7 patients for local recurrence. 34 patients received hormonal treatment additionally. The prostate was irradiated with total doses up to 70 Gy, dose per fraction of 1.8–2.0 Gy, 5 f./w.. Individual risks were estimated by dose volume histograms for normal tissues.

Results: The mean follow-up is 32 months. Actuarial local control, biochemical (PSA) control and survival are 95% (3 Yrs.). There were no severe acute or late effects. Only two local recurrences occurred.

Conclusions: Conformal radiotherapy is a safe and an effective treatment for patients with localized carcinoma of the prostate.

125 POSTER

Prostate cancer below 60 years of age: Increasing incidence and worsening prognosis?

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Purpose: Increased awareness of prostate cancer and improved diagnostic techniques have led to earlier and increased detection resulting in improved overall prognosis, mainly in elderly patients. We investigated if improvement of prognosis has also occurred in young prostate cancer patients.

Methods: European standardized incidence rates and relative survival rates were calculated for patients aged 40–59, diagnosed and registered in the cancer registries of Southeastern Netherlands and East Anglia, UK.

Results: The incidence increased by 42% in the Netherlands and by 66% in East Anglia. The 5-year relative survival rate declined from 65% in 1975–1979 to 48% in 1985–1989 in Southeastern Netherlands and remained largely unchanged in East Anglia. The proportion poorly differentiated tumours increased from 15 to 25% in Southeastern Netherlands.

Conclusion: The unfavourable trends in prognosis are remarkable because an improvement would have been more plausible. Similar findings from other European countries suggest an increasing risk of lethal prostate cancer at young age.

126 POSTER

P53 nuclear reactivity and the prognosis and response to chemotherapy in patients with metastatic bladder cancer

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Purpose: We investigated the relationship between p53 nuclear immunoreactivity in bladder tumors and the response and outcome following chemotherapy in patients with metastatic bladder cancer.

Methods: Fifty patients with metastatic bladder cancer were evaluated by P53 nuclear reactivity. Immunohistochemical analysis of P53 nuclear reactivity was detected by PaO 1801 in archival paraffin embedded tissue sections from primary tumor. The patients received combination chemotherapy including cisplatin, methotrexate, together with either carboplatin or doxorubicin and vinblastine.

Results: Twenty-four patients had tumors with a positive reaction to P53. The median survival after chemotherapy was 5.9 months and the overall response rate was 38%. The survival of the patients, with a positive P53 reactivity was 8.4 months, whereas patients without reactivity survived 5.2 months ($P = 0.38$). Response to chemotherapy was achieved in 50% of patients with P53 positive tumors compared to 27% of the patients with P53 negative tumors ($P = 0.14$).

Conclusion: Patients with P53 positive tumors can respond to chemotherapy, allowing adjuvant treatment to be considered in these patients.

127 POSTER

Fluorescent and immunocytochemical stainings of primary urine derived cell cultures from patients with TCC

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Purpose: For successful treatment of TCC, early diagnosis by non-invasive means is important. Sensitivity of conventional cytology is limited. We reported that (Jpn. J. Cancer Res, 87; 718–23, 1996) p53 IMC is useful for early detection and intensive follow-up of patients with TCC. To develop more sensitive methods, we further analyzed p53, mdm2 IMC and acridine orange (AO) fluorescent stainings of primary urine derived cell cultures.

Methods: p53 and mdm2 IMC was performed in 20 patients and 20 healthy controls. AO fluorescent staining was performed in 26 patients, and 23 healthy controls, divided in two step.

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