

times 9 Gy each (until 10/93: 10 Gy) ^{192}Ir brachytherapy was given, followed by 40 Gy percutaneous RT (from 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 I/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.

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POSTER

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

M. Borre¹, M. Høyer², F.B. Sørensen³, B. Neerstrøm¹, J. Overgaard².

¹Department of Urology; ²Department of Pathology; ³Danish Cancer Society, Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark

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.

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POSTER

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

S. Hautmann, E. Hülndt, H. Hülndt. Department of Urology, University Hospital of Hamburg, Germany

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

Methods: 60 juvenile male Copenhagen 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.

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POSTER

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

A. Caty, S. Oudard, Y. Humblet, M. Beauduin, E. Suc, Th. Gil, F. Rolland, Ph. Houyau, X. Sun, Ph. Montcuquet, J. Breza, E. Favreau, P. Tresca, D. Chopin. Centre Oscar Lambret, Lille, France

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/m² 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, hormone therapy 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.

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POSTER

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

P. Pęczkowski, M. Pilichowska, G. Madej. Department of Urology-Oncology, The Maria Skłodowska-Curie Memorial Cancer Center, Warszawa, Poland

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.

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POSTER

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

F. Joly^{1,3}, D. Brune², J.E. Couette², J.F. Héron¹, M. Henry-Amar³.

¹Department of Oncology; ²Department of Radiotherapy; ³Department of Epidemiology, Centre Régional François Baclesse, Caen Cedex 5, France

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,

statistical differences were observed concerning interest in sex ($p = 0.016$) and sexual activity ($p < 0.001$), urinary incontinence ($p < 0.001$) and cystitis ($p = 0.01$). No major digestive complications were observed among patients. When morbidity was reported by patients, physicians generally underestimated it (from 69% for incontinence to 96% for pelvic pain).

Conclusion: The study demonstrates that survivors from LPC treated with an association of EBI and brachytherapy have good global health status. Major problems that persist are sexual disorders, urinary incontinence and cystitis without severe digestive complications. The association of EBI and brachytherapy could be considered an alternative to exclusive EBI. The exact benefit that can be expected from this technique should be explored in randomized trials.

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POSTER

Fibronectin is a prognostic factor in malignancy: An ultrastructural and immunofluorescence study of carcinoma of the bladder

H.A. Yehia, S.S. Mansy¹, L.M. El-Baz², H.N. Tawfik³, N.M. El-Badrawy¹.

¹Electron, Microscopy Department, Theodore Bilharz Research Institute; ²Department of Pathology, Al-Azhar University; ³Department of Pathology, National Cancer Institute, Egypt

Purpose: Fibronectin (FN) is a major adhesive glycoprotein of extracellular matrix that is implicated in neoplasia. FN expression in benign and malignant lesions of the bladder were studied, as a trial to assess the value of FN staining in relation to grading and staging of bladder tumours, for the prediction of their biological behavior.

Material and Methods: 60 cases of carcinoma of the bladder, 23 cases of benign inflammatory lesions and 7 normal control specimens were subjected to indirect immunofluorescence staining using antifibronectin monoclonal antibody and were also studied ultrastructurally in addition to routine histopathology.

Results: The FN distribution pattern found in squamous and transitional cell tumours, was eminently different from that observed in benign lesions. Immunofluorescence staining for FN revealed a prominent intracellular reaction in grade I tumours both squamous (Sq.C.C.) and transitional cell carcinoma (Tr.C.C.). This could be attributed to the early damage of Golgi complex noticed ultrastructurally. This intracellular FN accumulation in grade I tumours decreased significantly with the increase of tumour grade ($p < 0.05$). This could be explained by the marked decrease in amount of rough endoplasmic reticulum revealed by electron microscopic examination in grade II & III tumours. The diffuse stromal FN decreased significantly with the increase of tumour grade ($p < 0.05$) in cases of Tr.C.C. Whereas in Sq.C.C. the pericellular stromal FN increased significantly with increase of tumour grade ($p < 0.05$).

Conclusion: We suggest that FN expression in the stroma of Sq.C.C. and Tr.C.C. cell carcinoma may have clinical prognostic implications regarding their invasive behavior and their radio and chemotherapeutic resistance.

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POSTER

Strong correlation of basement membrane degradation with up-regulation of metalloproteinases by functional p53 loss

E. Özdemir^{1,2}, Y. Kakehi¹, O. Yoshida¹. ¹Department of Urology, University Hospital of Kyoto; ²Department of Urology, University Hospital of Dicle, Japan

Purposes: We investigated the relationships between the degradation of basement membrane underlying superficial urothelial carcinomas and functional p53 loss.

Methods: Nuclear accumulations of p53 and mdm2, and up-regulation of metalloproteinases (MMPs) were examined immunohistochemically for 60 transitional cell carcinomas and 13 concomitant CIS lesions. Degradation of the basement membrane was defined as the reduction or total loss of type IV collagen expression.

Results: The frequency of the degradation of basement membrane underlying grade 1 pTa tumors was 0%, grade 2-3 pTa tumors 57.1%, and primary CIS lesions 83.3%. Nuclear over-accumulation of p53 was found in 48.3% and of mdm2 in 23.3% of the primary tumors. In pTa-pT1 carcinomas, nuclear staining of p53, mdm2, or both was highly correlated with degradation of the basement membrane ($p = 0.00002$). In the CIS lesions, the association of p53 nuclear staining with the destruction of type IV collagen expression was of borderline significance ($p = 0.03$). When mdm2 overexpression was considered as a molecular abnormality together with p53 inactivation, the correlation with the degradation of the basement membrane was highly significant ($p = 0.00006$). Moreover, the functional p53

loss was strongly associated with the up-regulation of MMPs ($p = 0.0005$). This finding was well correlated with the strong association of basement membrane degradation with up-regulation of MMPs ($p = 0.000004$).

Conclusion: Degradation of basement membranes was significantly related to functional p53 loss.

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POSTER

Role of radical radiotherapy (RRT) in the treatment of inoperable invasive bladder cancer in the elderly

G. Toscano, R. Maisano, S. Pergolizzi, P. Spadaro, N. Settineri, A. Santacaterina, G. Chiofalo, A. Scimone. *Istituto Nazionale per la Ricerca sul Cancro, Genova. Sez. Dec. Messina, Italy*

Introduction: currently the standard therapy for muscle invasive bladder cancer is cystectomy, but in elderly unfit pts. alternative therapies are required. In the bladder cancer treated with RRT we achieve an overall survival between 0-59% at 5 years in relation to stage disease. Numerous prognostic factors have been shown to affect treatment results: T-N status; grading; papillary vs solid tumor; presents of ureteral obstruction; pretreatment hemoglobin level; TURB radicality; total dose. We have reviewed the records of 24 pts with age > 65 yrs., unfit for surgical approach because of coexistent illness. Overall survival was the only endpoint.

Patients and Methods: from 5/90 to 12/94, 24 pts. (19 M, 5 F), median age 71 yrs. (range 65-83) with bladder cancer stage 2-4 (MO) were treated with RRT using an isocenter box technique with shrinking field at 46 Gy. Minimal dose at T was 50 Gy (range 50-54).

Results: the overall actuarial survival of 24 pts: was 9.5% at 5 yrs., with a cause specific survival of 17.2%. Complete response was achieved in 15 pts. (62.5%). At our multivariate analysis there were no apparent differences in the outcome of pts. treated with total dose < 60 Gy. Only hemoglobin level > 12 gr% vs < 12 gr% ($p = 0.02$) and complete response vs. partial response ($p = 0.0004$) had statistical significance. Our data show high initial response rate with a very poor overall actuarial survival at 5 yrs. Therefore, on this set of pts., we believe that before planning RRT it is necessary evaluate carefully the prognostic factors in order to personalize the management.

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POSTER

Loss of E-cadherin expression has a prognostic value for bladder carcinoma patients

A. Torregrosa¹, X. Garcia del Muro², M. Verdú¹, E. Condom³, J. Muñoz⁴, F. Vigués⁴, A. Coma⁵, A. Fabra¹, J.R. Germá². ¹Institut de Recerca Oncològica (IRO); ²Servei d'Oncologia; ³Servei d'Anatomia Patològica; ⁴Servei d'Urologia, Hospital Princeps d'Espanya; ⁵Servei d'Epidemiologia, Institut Català d'Oncologia (ICO) Hospital Duran i Reynals, Ciutat Sanitària Bellvitge, Barcelona, Spain

Loss of E-cadherin-mediated cell-cell adhesion (E-CD) is associated with the progression of many carcinomas. Indeed, the invasion of the surrounding tissues and metastatic spread require the detachment from the primary lesion which is favoured by reduction of E-CD expression.

In the present study we have studied the expression of E-CD in human bladder cancer by immunohistochemistry. Tissue samples ($n = 46$) from superficial ($n = 23$) and invasive ($n = 19$) tumors and corresponding normal urothelium were obtained from surgical resections. E-CD expression was evaluated at the invasive front and found reduced or absent in 66% of the tumor samples tested compared to normal urothelium. Reduced expression was also significantly correlated with tumor grade ($p < 0.01$) and stage ($p < 0.01$). Immunostaining was divided into three tiles (positive, positive focally and negative) and when comparing them significant differences in overall survival were found ($p < 0.01$; log rank test). Proportional hazard regression analysis (Cox's multiple variant regression analysis) showed that loss of E-CD has an independent predictive value. In conclusion, we show that E-CD expression has a prognostic value for patients with bladder cancer and its effect on prognosis will be discussed in comparison to other known factors such as the presence of p53 mutations. The expression of a- and b-catenin which couple E-CD molecules to the cytoskeleton is currently under investigation.