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THE PROGNOSTIC VALUE OF PSA MEASUREMENTS AFTER RADICAL IRRADIATION OF LOCALISED PROSTATE CANCER PATIENTS WITH SURGICAL LYMPH NODE STAGING

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Since January 1990 a conservative therapeutic approach was used with surgical staging of lymph nodes for selection of patients eligible for radical radiotherapy. A selected group of 85 pN0M0 pts was irradiated with curative intent (66 Gy in 33 fractions, four-field isocentric technique on the prostatic loge). Clinical T-staging was T1: 5 pts, T2: 54 pts, T3: 26 pts.

Fifteen % of the patients had a normal PSA value (< 4 ng/ml) at the end of radiotherapy and 85% had not. Their mean initial PSA values were 8.31 ng/ml (range 2.3–20.9 ng/ml) and 22.6 ng/ml (range 3.2–161 ng/ml), respectively. The difference was statistically not significant ($P = 0.074$).

Eighty-eight % had a normal PSA value 12 months after the end of radiotherapy and 12% (6 patients) did not. Their mean initial values were 16.03 (range 2.3–89.2 ng/ml) and 64.93 (range 27.2–161 ng/ml), respectively. The difference was statistically significant ($P < 0.000$). Since the initial PSA values of these 6 pts were $\geqslant$ 27.2 ng/ml, it seems that only initial PSA values under $\pm$ 25 ng/ml can be normalised with radical radiotherapy.

The PSA clearance (% decrease of PSA/week) during radiotherapy was not predictive of PSA normalisation one year after treatment.

Lymph node sampling allows to select patients for small prostate field irradiation. However, whether patients with an initial PSA < 25 ng/ml actually need a lymph node sampling remains to be established. The present series suggests that they would be better treated with palliative hormonal therapy only.

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THE TREATMENT OF LOCALIZED PROSTATE CANCER BY EXTERNAL BEAM IRRADIATION: LONG-TERM FREEDOM FROM BIOCHEMICAL RECURRENCE

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The outcome for 1044 men with T1-4NxM0 prostate cancer treated by conventional external beam radiation therapy at the Massachusetts General Hospital between 1977 and 1991 was assessed using strict biochemical criteria of disease eradication. Median follow-up was 49 months. Failure was defined as: two sequential rises in serum prostate specific antigen (PSA) level; a PSA > 1 ng/ml 2 or more years after radiation; or any clinical failure. The 10 year actuarial freedom from PSA failure for T1–2 patients was 40%. Those with Gleason grade 1-2/5 tumors exhibited a 53% actuarial 10-year disease-free survival, Gleason 3/5 42%, and Gleason 45/5 20%. Pretreatment serum PSA was available in those treated after 1988 and was a strong predictor of outcome independent of grade in a multivariate analysis. Those with a pretreatment serum PSA of $\leqslant$ 4 ng/ml showed an 89% 4 year freedom from biochemical recurrence, those 4–10 ng/ml 63%, and those >10 ng/ml 33%. The 10 year actuarial freedom from PSA failure for T3–4 patients was 18% (Gleason 1–2 33%, Gleason 3 20%, and Gleason 4–5 10%).

Less than half of the T1-2NxM0 and less than one-fifth of the T3-4NxM0 patients receiving conventional radiation therapy were biochemically disease free at 10 years. Pretreatment serum PSA and Gleason grade were independent predictors of outcome.

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CLINICAL SIGNIFICANCE OF BCL-2 PROTEIN EXPRESSION IN RENAL CELL CARCINOMA: AN IMMUNOHISTOCHEMICAL STUDY

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The bcl-2 protein has been related to the inhibition of programmed cell death (apoptosis), and its overexpression has been reported in several malignant tumors. In order to elucidate the clinical significance of the bcl-2 protein in renal cell carcinoma, seventy-five renal cell carcinomas were investigated by immunohistochemistry using an anti-human bcl-2 antibody. Moreover, the bcl-2 immunoreactivity was also compared with PCNA and p53 immunoreactivities as well as clinico-pathological findings. In all cases, the bcl-2 immunoreactivity was detectable in not only cancerous areas but also normal renal tubules. The bcl-2 immunoreactivity significantly correlated with M category ($P < 0.05$), whereas it did not with histological grade, T and N categories. On the other hand, the bcl-2 immunoreactivity inversely correlated with both PCNA and p53 immunoreactivities ($P < 0.01$ and $P < 0.05$, respectively). In addition a lower bcl-2 immunoreactivity significantly correlated with an unfavorable clinical outcome ($P < 0.005$), and was proved to be an independent prognostic factor using a multivariate analysis ($P < 0.05$). These findings suggest that the bcl-2 immunoreactivity seems to be related to the aggressive attitude of the tumor, and is one of the pivotal factors affecting prognosis in patients with renal cell carcinoma.

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THE EFFICACY AND SAFETY OF LINOMIDE IN THE TREATMENT OF RENAL CELL CARCINOMA [RCC]. AN EORTC PHASE II STUDY

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Linomide [L], a new immunomodulator, acting partly by activation of lymphocytes (also NK-cells), was investigated in an EORTC phase II study. *Patients and Method:* From 03.91 until 07.92, 72 patients with metastatic RCC were treated. L. was given orally, twice weekly, 3 mg/m^2 in week 1, with dose escalation to 6 mg/m^2 in week 2 and 9 mg/m^2 thereafter. Treatment was conducted until disease progression or unacceptable toxicity. Two patients (pts) were ineligible. *Results:* No haematological toxicity was observed. The most often reported non-haematological side-effects were: flu-like syndrome (54%), nausea/vomiting (40%) and neurotoxicity (34%). Most of the side-effects were of mild or moderate intensity (WHO grade 1 or 2). L. overall response rate was 4%: CR—1 pt (1%), PR—2 pts (3%). NC was reported for 28 pts (40%) and PD for 30 pts (42%). Nine pts (12%) were inevaluable for response. The duration of response was 17, 22 and +30 months for the 3 responders [RP] respectively. Median time to progression (TTP) was 12 weeks (range 2 weeks–32 months). TTP calculated for RP and pts with stable disease [RP + NC] (44% of pts) was 5 months (range 1–32 months). A L. related phenomena observed in lab values were an increase in WBC's and a drop in LDH.

Conclusions: Linomide is a well tolerated drug, but with a low overall response rate. A hint of activity could be derived from the median 5 months TTP in 44% of pts who showed progression 3 months prior to entry in the study.

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HETEROGENEITY IN RENAL CELL CARCINOMA, PROGNOSTIC SIGNIFICANCE

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Genetic instability is the basis for the evolution of tumor cell clones with different genotypic and phenotypic characteristics. Intratumoral heterogeneity concerning DNA ploidy was analyzed in 192 renal cell carcinomas using flow cytometry after propidium iodide staining. DNA ploidy pattern and its influence on clinicopathological parameters was analyzed. Eightyfive tumors (45%) were homogeneously concerning ploidy. Heterogeneous tumors contained in most cases (79%) both diploid and aneuploid cell clones. Patients with homogeneously diploid tumors had a significantly lower incidence of local tumor spread and survived longer than aneuploid tumors ($P < 0.001$) but the frequency of distant metastases at time of diagnosis was similar. The study demonstrates a frequent heterogeneity in renal cell carcinoma but the heterogeneity itself did not influence survival. The occurrence of aneuploidy in one or several samples of a renal cell carcinoma seemed to be important for the malignant potential, demonstrating that multiple samples must be investigated in order to properly evaluate the malignant character in renal cell carcinoma. Based on our results a model with different pathways for the evolution of renal cell carcinoma is suggested.