14.
SEARCH FOR IMPROVEMENT OF THE THERAPEUTIC RATIO IN RADIOTHERAPY FOR NON-SMALL CELL LUNG CANCER (NSCLC)

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There are several approaches under investigation in view of improvement of the therapeutic ratio of NSCLC radiotherapy in our Department:

1/ Dose escalation above 70 Gy using conformal radiotherapy techniques, 2/ accelerated radiotherapy with or without induction chemotherapy addressed to III stage tumours, 3/ conformal postoperative radiotherapy to total minimum dose in PTV of 50 Gy addressed to completely resected III stage tumours.

Ad 1/ From XI 1998 to XI 2000 43 patients were included in dose escalation study. Doses from 70 to 74 Gy were delivered. Apart from one toxic death, due to radiation pneumonitis, toxicity was acceptable. Since 1999 for N0 patients the study of omission of elective irradiation is conducted. By the time being 10 patients were irradiated with omission of elective fields. There was no relapse in non-treated "elective areas". The actuarial 1-, 2- and 3-year survival were respectively 84-, 64-, and 42%. There were 14 local relapses in 19 progressions observed in the entire group. In spite of encouraging results a high level of local relapses shows the limits of moderate dose escalation using conformal techniques and conventional fractionation in improvement of local control of NSCLC.

Ad 2/ From III 1999 two different accelerated radiation therapy schedules are investigated for III stage tumours. Forty patients were enrolled in the study: 26 were irradiated according to accelerated hyperfractionated radiotherapy (57 Gy in 40 fractions [first week: elective fields - 1.2 Gy x 2 per day, 3 remaining weeks 1.8 Gy to elective fields and 1.2 Gy boost to tumour] during 26 days), 14 were irradiated according to accelerated conformal radiotherapy with concurrent boost (56.7 Gy in 21 fractions and 26 days: all treatment was conformally planned and delivered: 1,9 Gy per fraction to the limited elective field and 0.8 Gy as a concurrent boost to the GTV). There was no difference on compliance with treatment plan, toxicity and response rate (80- and 72%) in the both investigated groups.

Ad 3/ From I 1999 eleven patients were enrolled in the phase II study of postoperative conformal radiotherapy of the region of the highest probability of microscopic invasion by the disease to the minimum dose of 50 Gy in PTV. The study is conducted in view of the future design of randomised study addressing question of the value of postoperative radiotherapy using modern techniques in management of NSCLC.

15.
RADIATION SURVIVAL AND COLONY SIZE OF HUMAN EPIDERMAL KERATINOCYTES IN THE PRESENCE OF KERATINOCYTE GROWTH FACTOR (rhKGF)

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The capacity of recombinant human keratinocyte growth factor (rhKGF) to ameliorate the radiation response of mouse oral mucosa and other epithelial tissues was recently reported. However, the exact mechanisms of action of KGF remain unclear. The aim of the present study was to investigate the effect of rhKGF on survival and colony size of normal human epidermal keratinocytes in vitro. Primary human neonatal keratinocytes (HEKn) were irradiated with doses of 0 Gy and 2 Gy (200 kV X-rays) and incubated in the presence or absence of 100ng/ml rhKGF. Plating efficiency (PE) and surviving fraction (SF2) were determined in a clonogenic assay. In cell cultures without rhKGF the mean PE was 4.6%. Irradiation with 2 Gy resulted in a SF2 of 51%. In cell cultures with rhKGF, the mean PE was identical (4.6%). After irradiation with 2 Gy, a similar SF2 of 54% was observed, indicating that KGF did not change the survival characteristics of HEKn keratinocytes. Individual colony size, however, in all cultures incubated with rhKGF was significantly increased compared to incubation without rhKGF. The number of extremely large colonies (□2 mm) was clearly higher (p=0.0000) with rhKGF-

containing culture medium. In conclusion, rhKGF does not affect keratinocyte survival after irradiation, but stimulates proliferation of surviving cells.

16.
TOLERANCE OF RADIOTHERAPY (3D-CRT) AND ANDROGEN ABLATION FOR PATIENTS WITH PROSTATE CANCER

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Purpose: evaluation acute tolerance of combined treatment (XRT and HT). Material/methods: Between April 1999 and September 2000, 22 patients with prostate cancer (T1-T3NXM0) were treated with 3D-CRT and HT. Median age of patients was 68 years.EBRT was administered daily fraction of 1.8Gy,total dose 70.2Gy. Planning target volume (PTV) was defined as clinical target volume CTV(prostate and seminal vesicles) with 10mm margins around prostate except posterior margin where 5mm were used to decrease risk of rectum morbidity.Acute toxicities were evaluated using RTOG scoring scale. Median follow-up was 11 months. Results: Acute effects in gastrointestinal tract (GI) noted were; rectal discomfort and mild diarrhea. Acute genitourinary (GU) symptoms included urgency, nocturia and dysuria. GI toxicity was observed in 75 % of patients (grade 0 and 1), and 25% of patients (grade 2). GU toxicities were as follow: grade 0 and 1 –80% of patients) and grade 2 – (20% of patients). No grade 3 or 4 GI and GU toxicities were observed. Conclusions: Preliminary results of treatment with 3D-CRT suggested that such modality is well tolerated. HT did not exacerbate radiation toxicity.

17.
GENE THERAPY OF CANCER

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Number of gene therapy clinical trials and patients enrolled increases exponentially. Today there are more than 400 trials and over 4000 patients involved all over the world. However, most of the trails are in the early clinical phases. About 67% of trials are related to cancer. Most of the cancer gene therapy strategies are based on various forms of gene-immunotherapy which include genetically modified tumor vaccines (GMTV), direct intratumoral administration of genes encoding immunostimulatory factors or insertion of these genes into tumor infiltrating lymphocytes (TIL). Other strategies include suicide gene therapy, direct intratumoral administration of genes encoding anti-oncogenes, gene anti-angiogenic therapy or bone marrow cells protection against high dose anti-cancer chemotherapy using MDR genes. Various gene carries are employed in above strategies. Retroviral vectors or Adenoassociated virus vectors are used for GMTV construction, TIL and bone marrow cells modifications. Adenoviral vectors and liposomes are employed for direct intratumoral gene administration. Other carriers such as lentiviral vectors (based on HIV) or SV40 based vectors are in the preclinical studies.

In January 1996 we have initiated melanoma gene-immunotherapy clinical trial using GMTV comprising of irradiated autologous melanoma cells admixed with cells of two allogeneic melanoma cell lines modified to secrete interleukin 6 (IL-6) and agonistic soluble IL-6 receptor (sIL-6R). Until now more than 180 patients were enrolled into study. Phase I trail demonstrated that GMTV is not toxic and possesses therapeutic potential. Phase II trial has shown that in melanoma stage IV with measurable metastatic disease GMTV significantly extended patients' survival. In 16 out of 45 patients (36%) response to the GMTV was observed (4 CR, 4 PR and 8 mixed responses including SD). More than 60% of responding patients survived 2 years while none of non-responders survived that period (rank-log test $p<0.0001$). CD4+/CD8+ T cells ratio, antibody response, soft tissue metastases and performance status correlated with clinical response. Above results allowed the design of the phase III randomized double blind study which is about to be initiated.

18.
DO WE GAME ANY BENEFIT FROM ACCELERATED IN RADIOTHERAPY FOR HEAD AND NECK TUMOR CANCER – WEEKEND'S MYSTERY?

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