Radiotherapy and radiobiology

466 POSTER

A treatment planning comparison of conventional, 3D conformal, intensity modulated photon - and proton irradiation therapy in the treatment of paranasal sinus carcinoma

U. Mock[1], J. Bogner[1], D. Georg[1], T. Auberger[2], R. Pötter[1]. [1] *University Hospital Vienna, Department of Radiotherapy and Radiobiology, Vienna, Austria;* [2] *University Hospital Innsbruck, Department of Radiotherapy, Innsbruck, Austria*

Purpose: To determine potential improvements in patients with paranasal sinus carcinoma by comparing proton and intensity modulated photon radiotherapy (IMRT) with conventional– and conformal photon treatment techniques.

Methods and Materials: In 5 patients with paranasal sinus carcinoma comparative treatment planning was performed. Dependent on indications prescribed total doses varied from 60-70Gy (fraction size: 2Gy) with the 95% isodose including the PTV. Patient related proton plans (2-3 fields) were compared with corresponding standard (2-3 fields)-, conformal (7 fields)- and IMRT (6 fields, step and shoot technique, max. 12 segments) photon plans. All treatment plans were evaluated by DVH analyses of the target volumes and the organs at risk (OAR). Dose distributions within the PTV were analyzed with regard to mean– and maximum values, conformity indices and dose inhomogeneities. DVH analysis of the OAR (i.e. ipsi– and contralateral bulbus occuli, retinae, optic nerves, chiasm, hypophysis, glandulae lacrimales, brain) referred to the mean doses and the percentages of volumes receiving more than defined tolerance doses (i.e. glandular lacrimalis: 30Gy, lens: 10Gy, retina: 45Gy, optical pathway structures: 50Gy, hypophysis: 20Gy, brain: 50Gy). Dose exposures to non-target tissues were estimated by calculating respective volumes receiving 10%, 30%, 50%, 70%, 90% and 95% of prescribed PTV doses.

Results: Mean doses of 100% for all planning modalities were determined and maximum doses of 107% (conventional), 105% (conformal), 108% (IMRT) and 111% (proton) were assessed. Conformity indices and dose inhomogeneities were comparable for the different treatment planning techniques with values of 1,5 and 9% (conventional), 1,2 and 7% (conformal), 1,1 and 12% (IMRT), 1,2 and 9% (proton), respectively. Photon plans resulted in higher volumes of irradiated normal tissues to the 10%-70% dose levels when compared to corresponding proton plans. Volumes thereby increased by factors of 1,0–3,2 (conventional), 1,2–4,1 (conformal) and 1,1–3,8 (IMRT), respectively. In comparison to conventional techniques both conformal- and IMRT photon techniques reduced the mean doses to OARs. No additional benefit in dose reduction was found for the IMRT technique. Usage of protons further reduced the mean doses to the OARs by up to 65% and 62% in comparison to the conformal– and IMRT techniques, respectively.

Conclusion: In comparison to conventional treatment techniques conformal- and IMRT techniques similarly enabled dose reductions to non target tissues. Even relatively simple proton based techniques further reduced doses applied to the OAR and appeared superior to all photon based treatment options. Acknowledgment: This work was supported by the Government of Lower Austria and the Federal Ministry for Education, Science and Culture.

467 POSTER

The radiosensitising effect of difluorodeoxyuridine, a metabolite of gemcitabine, in vitro

B. Pauwels[1], A.E.C. Korst[1], G.G.O. Pattyn[1], H.A.J. Lambrechts[1], C.M.J. de Pooter[2], F. Lardon[1], J.B. Vermorken[1]. [1] *University of Antwerp (UIA/UZA), Department of Medical Oncology, Wilrijk, Belgium;* [2] *St Augustinus Hospital, Department of Radiotherapy, Wilrijk, Belgium*

Introduction: Gemcitabine (dFdC) is an active antitumour agent with radiosensitising properties. dFdC is rapidly metabolised, intracellularly as well as extracellularly, by deoxycytidine deaminase to difluorodeoxyuridine (dFdU), a compound with little antitumour activity. However, plasma concentrations are maintained for a prolonged period (> 24 h) at levels known to cause growth inhibition. In this study, we investigated the radiosensitising potential of dFdU *in vitro*.

Materials and methods: ECV304, a human epidermoid bladder cancer cell line was treated with dFdU (0-0.15 mM) for 24 h prior to radiotherapy (RT) (γ -Co^{60}, 0-8 Gy, room temperature). Cell survival was determined 7 days after RT by the sulforhodamine B test. Experiments were performed at least three times. ID50, radiation dose resulting in 50% cell kill, was calculated from the survival curves, fitted according to the linear-quadratic model: survival=exp(-α D-β D^2). The radiosensitising effect was represented by the dose enhancement factor (DEF): ID50 /ID50. Synergism was determined with combination index (CI) analysis.

Results: dFdU caused a clear radiosensitising effect. DEFs increased with an increasing concentration dFdU: DEFs were 1.70 ± 0.35, 2.15 ± 0.23 and 2.83 ± 0.33 after treatment with 0.05, 0.1 and 0.15 mM dFdU, respectively, concentrations with moderate cytotoxicity (IC50=0.29 ± 0.09 mM). The CI analysis showed synergism with 0.1 and 0.15 mM and moderate synergism with 0.05 mM dFdU. The radiosensitising effect of dFdU was observed at the initial part of the dose-response curve, shown by an increase of the α value of the linear quadratic model ranging from 0.23 to 0.75. The increase in α value is statistically significant at dFdU concentrations of 0.1 and 0.15 mM.

Conclusion: dFdU, the main metabolite of dFdC, caused a clear radiosensitising effect *in vitro*. Since the metabolite is present in plasma for a long period (> 24 h) after treatment with dFdC, it might be partly responsible for the interaction between RT and dFdC. This observation might have important consequences for the optimal schedules of dFdC during radiation therapy in order to obtain the maximal radiosensitising effect.

468 POSTER

Transfection of human cell lines with the human multi-drug-resistence (MDR-1) gene supresses radiation-induced apoptosis and increases radioresistence

J. Schaefer[1], K. Fleckenstein[1], S. Fruehauf[2], K.J. Weber[3], F. Wenz[1]. [1] *Mannheim Medical Center, University of Heidelberg, Department of Radiation Oncology, Mannheim, Germany;* [2] *University of Heidelberg, Internal Medicin V, Heidelberg, Germany;* [3] *University of Heidelberg, Department of Radiation Oncology, Heidelberg, Germany*

Introduction: Radiation-induced apoptosis has only a minor influence on clonogenic survival of tumor cells from most solid tumors. However, several normal tissue cells, e.g. of hematopoietic origin, undergo apoptosis after exposure to therapeutic agents. Suppression of radiation induced apoptosis in normal tissue may therefore be a potential mechanism to increase the therapeutic gain and therefore improve tumor control rates. We studied a novel mechanism to suppress radiation induced apoptosis by transfecting human cell lines which are susceptible to radiation-induced apoptosis with the human multi-drug-resistance 1 (MDR1) gene.

Methods: The human ovarian cancer cell line A2780 and the MDR1 transfectant cell line A2780/M250 were used. The transfected cells stably overexpressed P-glycoprotein (P-gp), as monitored by flow cytometry after immunostaining, when maintained in 250 nM vincristine which was isotoxic to about 0,1 nM vincristine with the A2780 cells. Additionally, the human lymphoblastoid cell lines TK6, TK6E6, WTK1 were retrovirally transfected, followed by selection for vincristine resistance. The cell lines were irradiated with increasing X-ray doses (0-6 Gy), apoptosis was measured using the Nicoletti-assay and clonogenic survival was determined.

Conclusion: P-glycoprotein overexpression from MDR-1 gene transfer suppresses radiation-induced apoptosis. Corresponding findings were recently reported with a conditional P-gp expression system (Ruth and Roninson, 2000). With the cell systems used, MDR-1 gene transfer also increases clonogenic radioresistance, similar to the effects of PMA or caspase inhibition (in human lymphoblasts).

The P-gp inhibitor Cyclosporin A, which restores vincristine toxicity, does not prevent apoptosis suppression, indicating different pathways.

P-glycoprotein not only protects cells against chemotherapeutics but may also induce clonogenic radioresistance. This may become a novel approach to protect (hematopoetic) stem cells in cytotoxic combined modality therapy.

469 POSTER

Dose - dysfunction relationships within the parotid gland after radiotherapy

A. Maes[1], B. Bussels[1], P. Lambin[2], P. Flamen[3], K. Erven[1], R. Hermans[4], S. Nuyts[1], C. Weltens[1], W. Van den Bogaert[1]. [1] *UH Gasthuisberg, Radiation Oncology Departement, Leuven, Belgium;* [2] *UH Maastricht-RTIL, Radiation Oncology Department, Maastricht, The Netherlands;* [3] *UH Gasthuisberg, Department of Nuclear Medecine, Leuven, Belgium;* [4] *UH Gasthuisberg, Department of Radiology, Leuven, Belgium*

Purpose: To determine salivary dysfunction of different areas within the parotid gland after radiotherapy (RT) and to evaluate dose-dysfunction relationships within the parotid glands and between patients.