plans, respectively. With 3D-CRT, six fields (laterals and obliques) were used to deliver 76 Gy at 2 Gy/fx to isocenter, ensuring complete target coverage with the 95% isodose line. With IMRT, the prescribed dose was 70 Gy (2 Gy/fx) at the 85% isodose line, limiting only 15% of rectum and 33% of bladder to exceed 68 and 65 Gy, respectively. Radiobiological response probabilities for 3D-CRT and IMRT plans were calculated using Niemierko's Equivalent Uniform Dose (EUD) model for targets and the Burman-Kutcher-Lyman model for normal tissues. TCP and NTCP between 3D-CRT and IMRT plans were compared by Student's paired T-tests.

Results: Prostate mean EUD was significantly higher for 3D-CRT plans (75.19 Gy) compared to IMRT (73.19 Gy, p=0.017), while the mean EUDs for seminal vesicles were comparable between the two techniques (74.87 Gy for 3D-CRT and 74.72 Gy for IMRT, p=0.74). Insignificant differences in TCP values were observed between 3D-CRT and IMRT plans for prostate (0.9952 and 0.9792, respectively, p=0.017) and seminal vesicles (0.9994 and 0.9995, respectively, p=0.740). IMRT resulted in significantly reduced NTCP compared to 3D-CRT for upper rectum which anatomically corresponds to the level of the seminal vesicles, (0.018 and 0.034, p=0.025) and for femurs (<.0001 and <.001, p=0.021). However, insignificant NTCP differences were observed between 3D-CRT and IMRT for both the lower rectum (p=0.939) and the bladder (p=0.137).

Conclusion: Biological response models indicate that target dose escalation by both 3D-CRT and IMRT result in comparable TCPs in the treatment of patients with prostate cancer. Moreover, IMRT also achieves superior avoidance of normal tissues as evidenced by the decreased NTCP values for upper rectum and femurs. Clinical trials are currently conducted to evaluate outcomes of patients treated with both techniques.

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Rapamycin increases the efficacy of fractionated radiation in malignant glioma cells

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Purpose: Repopulation of tumor clonogens during fractionated radiotherapy may adversely affect local tumor control. This suggests that pharmacologic inhibition of tumor proliferation during fractionated radiotherapy may enhance overall efficacy of treatment. As a preliminary test of this concept, we evaluated the effects of rapamycin, a novel cytostatic agent, on the proliferation of U87 and SK-MG3 malignant glioma cell lines and its efficacy when given concurrently with fractionated radiation.

Methods: Cell proliferation was evaluated by the MTS assay, which is a colorimetric assay that measures viable cell number. Cell cycle distribution was evaluated by flow cytometry after staining with propidium iodide. Cell survival was evaluated by standard clonogenic assay.

Results: Incubation with 10 nM rapamycin reduced the S-phase fraction of the SK-MG3 and U87 cells by 38 and 28%, respectively. Moreover, in an MTS assay, incubation of U87 cells with 10 nM rapamycin for six days resulted in a 41% decrease in the relative cell number compared to an untreated control. Despite the inhibition of proliferation and increased fraction of cells in G1, a 24 h incubation with 100 nM rapamycin prior to irradiation had no effect on the clonogenic survival of either SK-MG3 or U87 cells. However, when SK-MG3 cells were treated with five fractions of 3 Gy over a 96 hour period, concurrent treatment of cells with rapamycin resulted in the exclusive formation of abortive colonies containing < 20 cells. In contrast, treatment with rapamycin alone resulted in 'normal' colonies that were the same size as those treated with fractionated radiation alone. These data are consistent with the inhibition of proliferation during and after radiation. We are now testing the possibility that inhibition of proliferation by rapamycin in a U87 xenograft animal model will improve the efficacy of fractionated radiation, and the results from these ongoing animal studies will be presented.

Conclusions: Rapamycin is a promising novel therapeutic agent that is currently being investigated as a single agent in clinical trials with malignant CNS tumors. Our data suggest that concurrent administration of rapamycin may enhance the efficacy of fractionated radiation therapy and that the clinical evaluation of this combination in patients with malignant gliomas may be warranted.

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Epidermal growth factor as a potential early indicator of late radiation damage to the kidney

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Background and purpose: This study was designed to evaluate the proliferative response of epidermal growth factor (EGF) gene expression as an early indicator of late renal radiation damage.

Materials and Methods: EGF gene expression was measured in the irradiated left kidneys of C3H/HeSlc mice using RT-PCR 24 hours after radiation doses of 9, 12, or 15 Gy. In a second experiment, the same radiation doses were administered to the right kidney plus the lower half of the left kidney. The partly irradiated left kidneys were harvested and EGF gene expression was measured. The irradiated whole right kidneys were subjected to immunohistochemical staining for EGF protein. In a third experiment, 12 Gy was administered to the right kidney plus the lower half of the left kidney. The mice underwent left nephrectomy 24 hours after radiation, and the EGF gene expression in the kidney was correlated with blood urea nitrogen (BUN) level representing late renal functional damage.

Results: EGF expression increased in 1 of 10 control mice and in 9 of 10 mice that received 15 Gy. The extent of increase of EGF was dependent on radiation dose. In mice having an increased BUN level after irradiation, 7 of 10 had EGF positive irradiated kidneys. All six mice whose BUN levels were unchanged had EGF-negative irradiated kidneys. EGF protein staining was observed in tubule cells only, not in glomerular cells. The amount of EGF protein staining correlated with radiation dose to some extent.

Conclusions: EGF gene expression seems to be a very early indicator of late radiation damage to the kidney.

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Intercellular adhesion molecule-1 (ICAM-1) knockout (KO) reduces radiation induced intestinal inflammation

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Introduction: The aims of the study were to characterize the role of ICAM-1 as a mediator of radiation-induced inflammatory response.

Methods: Endothelial ICAM-1 expression were determined by the radiolabeled antibody technique (ng mAb/g tissue) in control mice or at 24 hours and 14 days following irradiation with 10 Gy. Leukocyte endothelial cell interactions (rolling and firm adhesion) were assessed using intravital microscopy in intestinal venules, in wild-type and ICAM-1 KO mice. Inflammatory infiltration was evaluated by myeloperoxidase activity. Additional survival experiments were performed in wild-type and ICAM-1 KO mice irradiated with 10 or 20 Gy; weight loss, stool consistency, occult blood, and mortality were examined daily.

Results: In wild-type and ICAM-1 KO mice, there was a similar flux of rolling leukocytes under baseline conditions, 24 hours and 14 days after radiation. In wild-type mice, leukocyte adhesion significantly increased 24 hours after radiation and was reduced at 14 days (0.6 +-0.05, 4.3 +- 0.7, 2.1 +- 0.2). Expression of ICAM-1 (829 +- 67, 2120 +-173, 881+- 39 cells/100um) and mieloperoxidase activity (46 +- 33, 263 +- 63, 9 +- 2 u/gr tissue) on the intestine was significantly increased 24 hours after abdominal radiation and returned to normal values at 14 days. Compared to wild-type mice ICAM-1 KO mice had a significantly lower number of adherent leukocyte at 24 hours and 14 days (1.9 +- 0.3, 1.2 +-0.2) and mieloperoxidase activity (111 +- 55, 4 +- 2). Irradiation with 20 Gy induced a loss in body weight and mortality that was significantly higher in wild-type than in ICAM-1 KO. No differences were observed between these two groups of animals when radiation was delivered with 10 Gy.

Conclusions: ICAM-1 plays an important role in radiation- induced intestinal injury. Modulation of ICAM-1 may protect normal tissue to radiation damage.