7, or 5 equispaced IMRT fields gave similar benefits, but dose distributions deteriorated with 3 equispaced fields. A computerised optimisation algorithm was designed which, for selected tumour sites, customised the IMRT beam directions allowing both coplanar and non-coplanar beam arrangements. This produced novel techniques that maintained the advantages of multi-field IMRT but using only 3-4 beams. This should reduce the time required for IMRT delivery, and verification. Treatment plans were delivered to humanoid phantoms using a dynamic multi-leaf collimator technique, and the delivered doses were found to be accurate to within 1-2% using photographic film and BANG gels. A Phase 1 clinical protocol was designed to evaluate dose escalated IMRT (50-65 Gy) to pelvic lymph nodes while sparing small bowel. The main end-points will be clinician and patient assessments of acute and late toxicity, recruitment starting in April 2000.

Conclusions: IMRT represents a significant advance in conformal radiotherapy. The benefits are greatest for tumours with a concave PTV where normal tissue structures within the concavity can be spared. For non-concave tumours, dose homogeneity is improved compared to current techniques, and for all tumour sites some normal tissue sparing was observed. Treatment delivery is possible with 3-5 optimised beam directions, and clinical assessment of this technique is underway.

1010 ORAL

Increasing specificity of Clostridium mediated protein transfer via radiotherapy: the use of bacterial radio-induced promoters

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Purpose: Ionizing irradiation can be used to activate cytokine production by clostridia to obtain genes encoding for cytotoxic agents under control of a radiation-inducible promoter. Gene therapy can thereby be targeted and localized by x-rays leading to spatial and temporal control of gene expression.

Methods: Northern blot hybridizations and reporter gene analysis were used to investigate if the recA-gene, belonging to the SOS-repair system of bacteria, was induced by radiotherapy. In the next step, the recA promoter was cloned upstream of the TNF-cDNA. Recombinant bacteria containing this construct were irradiated (2 Gy), and TNF production was quantified at different time intervals after radiotherapy using ELISA. A second dose of 2 Gy was given at a later time-interval to see if repetitive gene activation was feasible.

We also deleted the LexA binding site in the recA promoter to prove this was the radio-responsive element. In a next step, we incorporated a second LexA binding site in the promoter to increase radio-responsiveness.

Results: Northern blots and reporter plasmid analysis proved that the recA gene was induced already at a dose of 2 Gy. At TNF-level, a 44% significant increase in secretion was seen, 3.5 hours after a single dose of 2 Gy ($p<0.05$). A second dose of 2 Gy was also capable of repeating gene activation and gave a significant increase of TNF production of 42% ($p<0.05$).

The construct without the LexA binding site showed no induction after irradiation, where as the construct with a second LexA binding site gave even higher induction levels of 412%.

Conclusion: These results show evidence that spatial and temporal control of gene expression can be achieved using a radio-inducible promoter. The recA promoter is already induced after a single dose of 2 Gy and repetitive gene activation was feasible with a second dose of 2 Gy, indicating that fractionated radiotherapy could lead to repeated gene induction resulting in prolonged and enhanced gene expression. Gene targeting by ionizing radiation could provide a new means of increasing the therapeutic ratio in cancer treatment.

1011 ORAL

The effect on local control of the time interval between surgery and radiotherapy in patients with head and neck squamous cell carcinomas. An empirical approach using Monte Carlo simulation

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Purpose: To analyze the influence of the time delay in the irradiation after surgery on the disease local control in head and neck cancer patients.

Methods: Computer simulation tools which allow us to include the variations, from patient to patient, in the growth kinetic and tumour clonogenic survival characteristics have been used. As a novelty, a proliferation kinetics model which depends on the number of clonogens in the tumour in a given time have been introduced in the analysis. The tumour growth is described in terms of the Gompertz equation: $n(t_1) = n(t_0) \exp\{[A\text{-}\ln(n(t_0)/n_{norm})][1\text{-}\exp(-a(t_1\text{-}t_0))]\}$.

To reproduce the actual variability we consider the initial number of clonogens in each tumour uniformly distributed between 10^6 and 10^7. The normalization number n_{norm} is taken to be unity. The parameters $A = 25 \pm 1$ and $a = 0.004 \pm 0.001$ days^{-1} are supposed to be normally distributed around their mean values. A total dose of 60 Gy (5 fractions of 2 Gy per week) was given in 40 days. Finally, a surviving fraction of 0.5 ± 0.025 (normally distributed) is considered constant along the treatment. The clonogen growth and survival are obtained by means of a binomial statistics. To evaluated the uncertainties in the Monte Carlo procedure we have analyzed 10 series of 50000 tumours each.

Results: We have obtained a control probability of 85% in the case of no delay, with a absolute mean reduction of 2.5% per week of delay in the beginning of the irradiation. The maximum of this reduction is obtained for a delay of around 40–50 days, where the control probability is of around 60%. In this point the absolute mean reduction per day is 0.5%. An increase of around 1 Gy per week is needed in the first three or four weeks in order to maintain the control probability for no delay. The ratio of the probabilities of local-regional failure for delays larger and shorter than 50 days is found to be around of 2. These results are in agreement with the clinical results observed for patients with head and neck cancer following surgery plus postoperative radiotherapy with variable delay times in the beginning of the irradiation.

1012 ORAL

Superposed images of FDG-PET and CT in a commercially available 3-dimensional radiation treatment planning system in patients with non small cell lung cancer

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Purpose: Positron emission tomography (PET) with 18F-fluoro-deoxy-glucose (FDG) provides physiological images on the basis of glucose metabolism as an additional information to CT or MRI based conventional therapy planning. In different attempts to delineate radiation fields in patients with non small cell lung cancer (NSCLC) using FDG-PET several indirect techniques were already employed. We investigated the usefulness of a commercially available radiation treatment planning system for the integration of PET.

Methods: During the superposing process the PET-information of 12 patients with NSCLC is transferred to reconstructed computed tomography (CT) scans and later on visualized on the original CT slices.

Results: A median tumor volume of 118 cm3 [range: 40-197 cm3] in conventional measurement and of 94 cm3 [range: 33-257 cm3] in PET was determined. We observed an intraindividual variability of 8 cm3 [range: 4-26 cm3] during three matching procedures. In five patients we found FDG-activity slightly outside the conventionally derived target volume. In two patients an improved differentiation between atelectasis and tumor seemed to be possible.

Conclusion: The discrepancies of the maximal tumoral volumes indicate the clinically promising value of adding metabolic imaging into the target definition. Although the procedure is time consuming it is successfully demonstrated to include PET images into a routinely available planning system.