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Interval between preoperative radiotherapy and surgery influences postoperative mortality in rectal cancer patients: the sooner the better

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Purpose: In a prospective randomized multicenter trial the value of preoperative radiotherapy (5x5 Gy) in combination with TME surgery was evaluated for rectal cancer patients. Treatment related toxicity is of major concern in such multimodality approaches. Anxiety for an increase of surgical complications after preoperative radiotherapy was the basis for the recommendation to keep the interval between radiotherapy and surgery as short as possible. This study was undertaken to assess the influence of the interval between radiotherapy and surgery on local recurrences and surgical complications.

Methods: We analyzed 690 preoperatively irradiated patients entered in a randomized trial and compared them with the patients treated with surgery alone. Patients were divided in two groups with either a very short interval between radiotherapy and surgery (< 3 days) or a longer interval (>3 days). Surgical complications, postoperative morbidity and mortality as well as local recurrence rate were compared.

Results: There was no difference in surgical complications or postoperative morbidity between patients with a short interval compared to patients with a long interval. A significant increase in the postoperative mortality rate at 180 days was observed in the patients operated after an interval of more than 3 days (4.1% vs. 8.4%, p=0.02). This difference was mainly observed in patients above 75 years of age. Patients with an short interval had similar mortality rates compared to patients that were treated with surgery alone (4.1% vs. 5.4%). There was no difference in local recurrence rate between the two interval groups.

Conclusion: Extension of the interval between preoperative radiotherapy and surgery leads to a significant increase of postoperative mortality. We suggest that this might be explained by a radiation-induced increase of systemic cytokines.

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Phase II study of raltitrexed in combination with oxaliplatin as second line treatment in refractory advanced colorectal cancer

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Raltitrexed ("Tomudex") is a specific thymidylate synthase inhibitor with comparable efficacy to 5-fluorouracil (5-FU)/folinic acid (FA) regimens in advanced colorectal cancer (aCRC). Recent phase II studies have demonstrated that the combination of raltitrexed and oxaliplatin is active in the first line treatment of aCRC. The aims of this multi-center phase II study were to determine the efficacy and tolerability of the combination of raltitrexed and oxaliplatin as second line therapy in patients with refractory aCRC. Patients received raltitrexed 3 mg/m² (15 min) followed 45 min later by oxaliplatin in 130 mg/m² (2h) every 3 weeks. Fifty patients (M/F: 26/24; mean age 61 years (38-75); performance status 0/1/2: 20/26/4) have been included. All patients had a documented progression while on 5-FU/FA ± irinotecan or within 3 months after stopping first line treatment. Nineteen patients received adjuvant chemotherapy prior to entering the study. Six patients had a relapse on adjuvant treatment and did not receive first line treatment prior to entering the study. In total 260 cycles were administered. The mean time on treatment was 97 days and the median number of cycles per patient was 5.0 (1-11). The objective response rate was 16% (n=8). The median duration of response was 6.4 months (mo) (range 2.1-8). In addition, disease stabilisation was observed in 26 patients (52%). The median TTP was 4.6 mo (0.7-8.5). The median survival amounted 7.1 mo. Hematologic toxicity was: neutropenia gr 3-4: 7.4% of courses; thrombopenia gr 3-4: 2.1%; febrile neutropenia: 0.8%: 45 patients (90%) had signs of polyneuropathy (gr 1-2-3: 48-36-6%); diarrhea gr 3-4 was present in 12% of patients; vomiting gr 3-4: 16%; severe fatigue 16%. One patient died due to neutropenic sepsis and diarrhea.

Conclusion: The combination of raltitrexed/oxaliplatin is active as second line treatment in refractory aCRC with acceptable toxicity.

Radiotherapy

1009a ORAL

Modelling the impact of two forms of hypoxia on novel radiotherapy approaches

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Purpose: One of the aims of this project was to investigate the clinical implications of using two theoretical models for predicting the tissue response to radiation. The choice of the appropriate model is a very important issue in the theoretical estimation of the biological response to radiotherapy. The models investigated are the two most likely to be included in treatment planning algorithms: the linear quadratic model (LQ) and the linear quadratic model with inducible repair (LQ/IR). A second aim of the project was to make a realistic tumour model with respect to the micro-environmental conditions on which to investigate the clinical implications of different treatment strategies. The focus was on the availability of oxygen and other nutrients to cells in tissue.

Methods: Computer modelling was used throughout the whole project for calculating the tissue response to radiation. The most important aspect of the simulation was the inclusion in the tumour model of the relationship between cellular energy reserves and DNA repair ability. Low energy reserves usually determine a loss of repair capacity and thus a loss of radioresistance. This is a quite important fact, since it will affect the starved chronically hypoxic cells but not the acutely hypoxic ones that exibit only an increased radioresistance compared to the oxic cells. It is the first time that this aspect of tumour radiosensitivity has been incorporated into a theoretical model.

Results: The modelling performed in this project has shown that the LQ model cannot accurately predict the response of oxic and hypoxic cells for low doses and that the LQ/IR model should be used instead for predictive purposes in the clinically relevant dose range. It has also shown that the postulated radiobiological differences between acute and chronic hypoxia could explain why a curable treatment does not give irreparable damage to the normal tissue.

Conclusion: The results suggested that it is important to distinguish between the two types of hypoxia in predictive assays and other treatment simulations.

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Intensity-modulated radiation therapy (IMRT) for tumours of the head and neck, pelvis and thorax: pre-clinical evaluation and implementation

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Purpose: To evaluate the potential benefits of IMRT compared to current radiotherapy techniques, and to implement clinical trials of IMRT for appropriate tumour sites.

Methods: 30 patients with head and neck, pelvic and thoracic tumours underwent treatment planning for conventional radiotherapy (RT), 3-dimensional conformal RT (3DCRT) and inverse-planned IMRT. Dose distributions were compared using dose-volume histograms for tumour and normal tissues, and normal tissue complication probabilities were calculated. Methods were developed to optimise beam number and direction to determine the most efficient delivery techniques, and for pelvic tumours a clinical dose escalation trial protocol was designed.

Results: IMRT treatment plans for thyroid carcinoma and pelvic lymph nodes (tumours with a concave PTV) showed the greatest improvements compared to conventional and 3DCRT. There was 12% reduction in maximum spinal cord dose ($p<0.01$), and a 70% reduction in pelvic small bowel treated above 45 Gy ($p<0.01$) respectively. PTV dose homogeneity was improved, and other normal tissues also spared. Oesophageal, parotid, and para-nasal sinus tumours (with moderate or no concavities in the PTV), showed statistically significant but smaller improvements in normal tissue sparing of lungs, oral cavity and cochlea, and optic nerves respectively. 9,

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.

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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.

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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.

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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.