Oral presentations (Wed, 2 Nov, 9.15–11.15) **Radiotherapy II**

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Improvement of local tumour control after simultaneous fractionated irradiation and EGFR inhibition by C225 in FaDu hSCC in vivo is caused by the combined effect of decreased repopulation and increased reoxygenation

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Background: Specific targeting of the EGFR by C225 mAb during fractionated irradiation has recently been demonstrated to improve local control of head and neck squamous cell carcinoma (hSCC) in preclinical experiments and in a randomised clinical trial. It has been suggested that inhibition of repopulation and enhanced reoxygenation contribute to this effect, however, so far this hypothesis has not been rigorously tested. The present study addresses this question in FaDu hSCC. For this tumour marked repopulation and incomplete reoxygenation during fractionated irradiation has been demonstrated. Furthermore C225 has been shown to significantly improve the results of fractionated irradiation in this tumour.
Material and methods: Using the same experimental design as in our previous study on repopulation and reoxygenation, FaDu tumours in nude mice were irradiated with 18 fractions in 18 days (18f/18d) or 18 fractions in 36 days (18f/36d). 3 Gy fractions were given either under ambient or under clamp hypoxic conditions. C225 or carrier was applied 4 times during the course of treatment. Fractionated irradiations were followed by graded top-up doses to obtain complete dose-response curves for local tumour control. Tumour control dose 50% (TCD50) was determined at day 120 after end of treatment. A total of 8 TCD50 assays were performed.
Results: Significant repopulation and reoxygenation occurred during fractionated irradiation of FaDu tumours (p values between 0.028-< 0.001). Application of C225 significantly decreased TCD_{50} for 18f/36d under ambient conditions ($p = 0.04$). Bootstrap analysis revealed decreased repopulation and increased reoxygenation after application of C225, however these effects were not significant when considered separately. The impact of C225 on the combined effect, i.e. decreased repopulation plus increased reoxygenation, approached statistical significance ($p = 0.06$) in two separate comparisons. This was further corroborated by a significant effect of C225 on the "repopulated" dose under ambient conditions which is influenced by both, reoxygenation and repopulation ($p = 0.012$).
Conclusion: Our study provides evidence that both decreased repopulation as well as increased reoxygenation contribute to the improvement of local control after targeting of EGFR by C225 during fractionated irradiation of FaDu tumours

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Interaction between accelerated repopulation and angiogenesis might be a determinant of the response to continuous hyper-fractionated accelerated radiotherapy in head and neck cancer

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Background: Previous studies have suggested that the benefit from strongly accelerated radiotherapy could be a balance between countering accelerated repopulation after irradiation on one hand and reducing tumour re-oxygenation potential on the other. Here, the specific hypothesis of a higher order interaction between CD31, as measure of angiogenesis, EGFR, which has been previously related to accelerated repopulation after radiotherapy, and randomization to the CHART trial was tested in a loco-regional control model.
Methods: Immunohistochemistry was used to measure EGFR, CD31, Ki-67 and cyclinD1 expression. Loco-regional tumour control was considered for 402 patients entering the head and neck CHART randomized trial. Interaction between CD31, EGFR and randomization to CHART was tested alone and in a multivariate Cox regression with stepwise likelihood selection. Furthermore, interactions between CHART and a larger panel of markers of proliferation and angiogenesis were tested in this model iteratively.
Results: CD31, EGFR and Ki-67 showed significant interaction with treatment when considered in univariate analyses stratified by the biomarkers. Among these, only CD31 interaction with treatment was retained in an iterative stepwise Cox multivariate analysis; Hazard Ratio (HR) was 0.66 with $p = 0.048$ (HR<1 means that there is a benefit from CHART). This agrees with previous studies. The specific hypothesis that tumours with both high-EGFR and high-CD31 expression will be the most likely to benefit from CHART was tested using the reduced multivariate Cox model including CD31 interaction with treatment. When tumours were stratified by EGFR the significance of the CD31 interaction increased ($HR = 0.58$, $p = 0.02$). After grouping tumours by EGFR expression, this model gave a HR of 0.85 for CD31 interaction with treatment in the low-EGFR expression group, whilst $HR = 0.39$ was seen in the high-EGFR group; this difference was significant with $p = 0.05$.
Conclusion: Concomitant high EGFr and CD31 expression in head and neck tumours correlated with a benefit from CHART. This provides support for the hypothesis that the interplay between accelerated repopulation and vascularization/angiogenesis is a major determinant of the response to accelerated radiotherapy.

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Radiation response of parotid glands examined by dynamic 11C-methionine PET

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Purpose: To investigate the individual radiation dose-function relationship of parotid glands by dynamic ^{11}C-methionine PET in head and neck cancer patients.
Material and methods: Fourteen head and neck cancer patients were examined after RT by dynamic ^{11}C-methionine PET. Functional PET images, quantifying parotid gland function by the net metabolic clearance, *K*, were generated, co-registered and compared voxel by voxel with the 3D radiation dose plan within the parotid gland volume for assessing the individual radiation dose-function relationship of parotid glands.
Results: Voxel-to-voxel comparison of the radiation dose demonstrated that *K* decreased with increasing radiation in each case. Individual data points were fitted better by a sigmoid logistic curve than a linear curve. Data points from all patients were fitted by a sigmoid logistic curve, estimating a mean TD50 of parotid gland tissue at 33.5 Gy with a 95% confidence interval from 26.5 to 40.4 Gy. Further, we estimated the γ_{50} of parotid gland tissue to 2.0 Gy from the slope of the fitted logistic curve.
Conclusions: 3D comparison of radiation dose and parotid gland function supported the existence of a threshold radiation dose beyond which serious damage occurs. Results suggested a mean TD50 of 33.5 Gy with a 95% confidence interval of 26.6 to 40.4 Gy, indicating the range of inter-individual variation of parotid gland radiosensitivity. Co-registration procedures and shrinkage of the parotid glands after RT pose potential pitfalls for correctly matching radiation dose and parotid gland function on a voxel-to-voxel basis.

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Xerostomia toxicity grading scores and saliva flow rates are highly correlated in head and neck cancer patients treated with IMRT

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Purpose: To investigate the strength of correlation between measured saliva flow rates and various toxicity endpoints commonly used in Head and Neck cancer (HNC) treatment.
Methods: All patients enrolled in a phase II study using IMRT for HNC treatment underwent saliva flow measurements (stimulated and unstimulated) before RT and at various intervals post-RT. They also were also assessed for salivary gland toxicity using RTOG late toxicity grading and nine patient-graded toxicities from two questionnaires (Eisbruch xerostomia questionnaire and University of Washington quality of life). The scores for each instrument were correlated using Pearson and Spearman correlation coefficients.
Results: A total of 266 sets of co-registered data were obtained for 42 patients over a period of approximately 3 years. The number of serial saliva