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

collections/questionnaires per patient varied from 1 to 11 (median: 6). In both the pre-RT and post-RT settings, there was strong correlation between saliva flow rates, RTOG toxicity scores, and most questionnaire responses. There was no measured correlation between flow rates (stimulated or unstimulated) and pilocarpine use. The relationship between speech toxicity and saliva flow rates was variable: In the pre-RT time period, there was strong correlation between toxicity and both stimulated ($p = 0.04$) and unstimulated ($p<0.01$) saliva flow rates. In the post-RT follow-up period, there was weak correlation between stimulated saliva flow rates and toxicity ($p = 0.06$), and no correlation between unstimulated flow and toxicity ($p = 0.3$).
Conclusion: There is strong correlation between most quality of life endpoints, RTOG toxicity, and stimulated and unstimulated saliva flow rates, which makes the sparing of salivary tissue a worthwhile planning goal in head and neck IMRT treatments. We did not observe a statistically significant relationship between post-RT saliva flow rates and speech toxicity.

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Dose reduction to the heart with respiratory gated radiotherapy

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Purpose/Objective: Because there are hints for an increased risk of cardiovascular diseases after radiotherapy of the left chest wall the dose to the heart should be reduced as far as possible. With respiratory gating technique irradiation can be restricted only in the inspiratory plateau phase and so the distance between heart and chest wall will be increased. As a result the dose to the heart, in particular to the anterior wall, can be reduced. We investigated in all patients with left sided breast cancer dose reduction to the heart when treated only in the inspiration phase compared with not gated treatments.
Materials and methods: Between Sep. and March 2005 32 patients with left sided breast cancer were treated with respiratory gating technique based on a retrospective 4D CT scan. With this technique we irradiate only in maximum inspiration with a range between 10%-20%. For the investigation of real dose reduction to the heart we performed for all of these patients a normal and a respiratory gated planning CT. Planning was done with the same treatment parameters in both CT. DVH for the entire heart and the anterior left ventricle wall were calculated. All of these patients were treated with 2 Gy single dose to a total dose of 50 Gy to the entire left breast/chest wall. 18 patients had an additional boost of 10 Gy. The PTV was in 36 patients after breast conserving surgery the left breast, in 6 patients after mastectomy the left chest wall.
Results: The mean dose to the entire heart was 1.7 Gy (0.5 Gy-3.2 Gy) without and 0.8 Gy (0.5 Gy-2.0 Gy) with respiratory gating ($p = 0.03$). To mean dose to the anterior ventricle wall was 7.1 Gy (0.9 Gy-15.3 Gy) without and 2.4 Gy (0.7 Gy-6.0 Gy) with respiratory gating ($p = 0.003$). The mean maximal dose to the anterior wall was 40.6 Gy (27.3 Gy-53.6 Gy) without and 24.9 Gy (1.9 Gy-42.3 Gy) with respiratory gating ($p = 0.001$). For the 26 pat after breast conserving surgery the mean doses to the anterior wall was 7.5 Gy in the non gated compared to 2.4 Gy in the gated group. After mastectomy the doses were 6.5 Gy (non-gated) and 3.1 Gy (gated).
Conclusions: Respiratory gating and irradiation only in the inspiratory phase reduce radiation dose to the heart and especially to the anterior wall of the heart significantly.

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To pee or not to pee? A randomized study of Full vs. Empty Bladder instructions during prostate radiotherapy and its impact on organ motion and targeting accuracy

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Objective: To determine whether bladder filling (full vs. empty) instructions during radiotherapy (RT) affects inter-fractional prostate motion and targeting precision during a 7-week course of radical conformal RT.
Method: 34 patients with T1-T2 prostate cancer undergoing routine 3D RT (4-field, 70 Gy/35#/7 weeks) were randomized to either full bladder (500 mL water 1 hr before treatment) or empty bladder instruction for the entire treatment course. TRUS-guided insertion of three gold markers into the prostate was done prior to treatment planning. Routine patient set-up by bone-anatomy verification and correction was performed during first week of treatment. Thereafter, twice-weekly orthogonal aSi-EPI images were taken to measure set-up error (image mismatch on bone) and targeting error (mismatch by gold markers). Prostate motion was determined as the arithmetic difference between set-up error and targeting error. All images were analyzed by one expert user of Varian Vision software.
Results: Eighteen and 16 patients were randomized to full and empty bladder set-up respectively. No significant difference in inter-fractional prostate motion and targeting error was observed (Table 1). However, absolute prostate motion >5 mm in the sup-inf direction was seen in 13% of 422 images analyzed for all patients. Targeting error >5 mm was observed in 19% of 424 images. Prostate motion and set-up error both contributed to targeting variability, which remained constant during the 7-week course treatment. No difference in treatment-related bladder or rectal morbidity has been observed (median F/U 12 months).

Table 1: Measurements of prostate motion and targeting accuracy on patients treated with either full or empty bladder instructions

Measurement	Bladder Instruction	Median Standard Deviation		
		Right-Left	Ant-Post	Sup-Inf
Prostate motion	Full (n = 18)	0.7 mm	1.9 mm	1.9 mm
	Empty (n = 16)	0.5 mm	1.7 mm	1.7 mm
Targeting variability	Full (n = 18)	2.0 mm	2.6 mm	2.3 mm
	Empty (n = 16)	1.9 mm	2.6 mm	2.2 mm

Conclusions: Inter-fractional prostate motion and targeting accuracy were not influenced by bladder filling instructions given to patients. Improvement of treatment precision to within 5 mm will likely require daily pre-treatment target-imaging with table adjustments.

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A randomised study to investigate the role of abdominal compression in prostate intrafraction motion

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Background: Intrafraction prostate motion may contribute to target volume underdosage when using small PTV margins. Abdominal compression may decrease intrafraction motion by reducing respiratory effect. Therefore, to evaluate the role of abdominal compression in prostate intrafraction motion we performed a randomized study using 2 different immobilization devices, one of which incorporated a component to reduce abdominal movement (Bodyfix).
Methods: 32 patients receiving conformal radiotherapy (RT) for localized prostate cancer (PTV = 7 mm post and 10 mm elsewhere) provided informed consent and were assigned to Vac Lok (n = 16) or Body Fix (n = 16). All patients had daily on-line correction of interfraction errors of $\geqslant$3 mm using electronic portal imaging (EPI) of implanted fiducial markers (at the apex, posterior and base) as a surrogate for prostate position. During every 4th fraction of RT, EPI's were also taken at the start and end of the first and last lateral beams. Absolute maximum displacements from the planned position for each EPI were measured for centre of mass (COM) and individual markers.
Results: A total of 1242 images were reviewed, taken an average of 10 fractions per patient, distributed over their course of treatment. The mean time between the first and last EPI was 6.5 min (range 3.5 to 14.5). The displacements measured from the EPI's are shown in table 1. There were no statistical differences in displacements of the COM or markers with or without abdominal compression at the 5% confidence level (Mann Whitney U-test).
With current PTV margins, absolute maximum displacements from the planned position would have resulted in target underdosage in $\leqslant$1.6% of fractions analysed. Absolute maximum displacements from the planned position incorporate both intrafraction prostate motion and the residual displacements after the application of online correction strategies. When these residual errors were mathematically eliminated from the measured displacements, intrafraction prostate motion would have resulted in target underdosage in $\leqslant$1.4% of treatment fractions.
Conclusions: When using the Bodyfix system, abdominal compression produced no statistically significant effect on intrafraction motion of the prostate. Our current PTV margins appear to adequately encompass both inter and intrafraction prostate displacements in more than 98% of patients. With daily online image guidance and correction protocols, intrafraction prostate motion appears to be the major contributor to residual errors and possible target underdosage.