as a cut off for acceptable therapeutic intent. NTCP modeling of radiation induced Liver disease was also performed.

Results: Non-GTV Liver mean dose ranged from 13.1 to 17.0Gy, breaching mandatory trial constraint of <15.2Gy in three cases. NTCP ranged from 0.0 to 0.3 assuming an alpha/beta of 1.0 for normal Liver and negligible assuming alpha/beta of 2.0 or more. At D98%, four sets of contours did not achieve 65Gy BED to gold standard PTV, two sets failing to reach 65Gy BED at D90%.

Conclusion: Significant variability exists in contours drawn by different centers/clinicians in the setting of pre-trial QA to the extent where 10% or more of the PTV receives a BED insufficient for local control in a proportion of cases and NTCP is significantly affected. Given this variability, the pre-trial and on-trial RTTQA process is essential if the effect of contour variability on tumour control rates and treatment toxicity is to be mitigated.

EP-1721

Feature extraction from duodenal dose surface maps to predict toxicity in pancreatic chemoradiation

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Purpose or Objective: To use spatial features from dose surface maps of the duodenum to predict acute duodenal related toxicity in pancreatic chemoradiation.

Material and Methods: Dose surface maps were produced for the duodenum describing the spatial surface dose distribution. Traditional metrics were extracted including mean and max dose, surface area receiving 25, 35, 45 and 55 Gy as absolute and fraction of the surface. Spatial metrics extracted include the length of the duodenum which received less than 25, 35, 45 and 55 Gy to at least 10-90% of the circumference (in 10% intervals). Different thresholds for the length of the duodenum achieving these constraints were tested in order to find the best predictor of toxicity. Toxicity results from 19 patients from the ARCII clinical trial (EudraCT: 2008-006302-42) were used as a proof of concept. 6 and 11 patients had grade (Gr)and Gr ≥2 toxicity respectively.

Results: The best predictors for patients with grade (Gr)≥3 toxicity were at higher doses of 55 Gy. While restricting the dose < 55 Gy to at least 10% of the circumference for at least 10% of the length of the duodenum, or at least 20% of the circumference for at least 20% of the length accurately predicted toxicity for 74% of the patients studied, this only had a sensitivity of 17% and 33% respectively (specificity of 100% and 92%). Figure 1 indicates a better predictor may be restricting dose < 55 Gy to at least 20% of the circumference for at least 70% of the length which, although only accurately predicts toxicity for 58% of the patients, has a sensitivity and specificity of 67% and 54%. It was found that the relative percentage of the circumference spared was a better predictor than absolute circumferential length spared. However, similarly to the spatial metrics, predictions of patients with at least Gr 3 toxicity was seen in the higher dose regions such as mean dose of 60 Gy, maximum dose to a pixel of 62 Gy and when 70% of the surface area receives 55 Gy. Gr 2 toxicity could not be predicted.

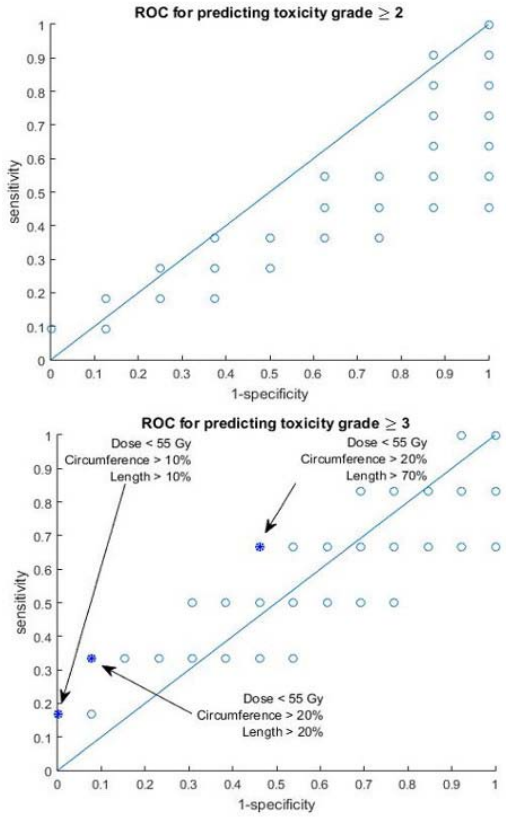

Figure 1: ROCs for grade ≥ 3 and grade ≥ 2 toxicity. Each point represents a different dose-surface feature and threshold that was tested.

Conclusion: In this small sample we have shown that spatial features can be extracted from dose surface maps to aid toxicity prediction, and that high doses to the duodenum appear to be correlated with Gr 3 toxicity. An improved understanding of how these spatial features correlate to toxicity can improve traditional constraints on the duodenum. Further work is required to build a more complete picture of this result, and the analysis will now be extended to a larger patient cohort.

EP-1722

Simulation of the radiation response of a hypoxic prostate tumor in the rat

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Purpose or Objective: In a previous work a model which simulates the radiation response of hypoxic tumors was developed. The task of this work is to validate the model by using preclinical experimental dose response data of rat prostate tumors for single and multiple irradiations.

Material and Methods: The model is voxel-based and simulates the spatio-temporal behavior of tumors considering six radio-biological processes. Important input data are the oxygenation levels of each tumor subvolume at the time of irradiation, which are given as pre-calculated oxygen frequency histograms.The experimental data for validation include growth curves, dose response curves and TCD50s for 1, 2 and 6-fraction (Fx) experiments. A very high α/β value of 84.7 ± 13.8 Gy was determined.A strategy of adjustment was

defined to fit the model to the experimental data in terms of growth curve, dose response curves, TCD50 and α/ß value.

Results: The experimental data are well described for an O2-independent response. For this case an α/ß of 74.7 ± 5.5 Gy was obtained.
When including the effects of O2, we aimed to reproduce this high experimental value starting from smaller intrinsic α/ß values. Unexpected shifts towards lower doses of the 2-Fx curves with respect to the 1-Fx curves were observed. This effect could be explained by a strong reoxygenation between the 1st and the 2nd Fx. Known reoxygenation mechanisms in the model include shrinkage, angiogenesis and the increase of available O2 due to the presence of dead cells. The latter was found to be the dominant mechanism of the three. When switching off these mechanisms, the unexpected shifts were still observed. A fourth reoxygenation mechanism, which is inherent to the original model, was identified. It implicitly arises by assuming that the distributions of cells at specific O2 levels remained the same after irradiation. To eliminate this effect, the histograms were updated to consider the actual O2 levels of the surviving cells. After doing so, the unexpected shifts of the curves were no longer observed and higher simulated values of α/ß were obtained.

Conclusion: This work constitutes the first stage of experimental validation with preclinical data of a computer model which simulates the radiation response of hypoxic tumors. It was confirmed that reoxygenation plays an important role in the dose response of tumors. Additionally, important information on how to further improve the model was gathered.

EP-1723

Radiobiological analysis of rib fracture incidence in lung SABR

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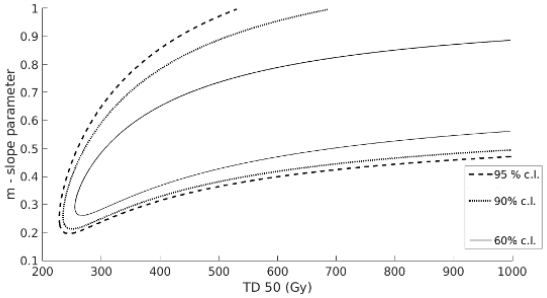
Purpose or Objective: SABR (Stereotactic Ablative Radiotherapy) is only possible in a subset of patients with small tumors and favourable anatomy as the very high BED increases the risk of complications. Lung SABR is often delivered to tumors that are more peripheral thus; the ribs are structures now exposed to significantly higher doses than historically has been the case. The first fifty-two SABR (Stereotactic Ablative Radiotherapy) patients treated at our centre were monitored for rib fracture and chest pain. In this study, we fit the data to the LKB model of normal tissue response.

Material and Methods: Fifty-two patients were treated with either, 55 Gy in 5# (40 patients), 60 Gy in 8# (6 patients) or 54 Gy in 3# (6 patients) depending on the size and location of the tumor. For each patient a chest wall volume was delineated. The chest wall volume encompassed the rib and chest wall between the ribs. Data were fitted to the Lyman-Kutcher-Burman (LKB) model, a model using the normal cumulative density function to produce a sigmoidal dose response curve. The model consists of three parameters TD50, which determines the dose at which 50% of treatments will result in a complication, m which governs and slope and the volume parameter, n. We assumed α/ß = 3 Gy.

Results: Of the 52 patients there were 5 occurrences of rib fracture (NTCP = 9.6% -6.4%/+11.4%). Leaving the volume parameter free in the fit produced best-fit parameters of n = 0.01, TD50 = 370 Gy and m = 0.45. Due to the small NTCP it is difficult to extrapolate to find TD50. This is shown graphically in Figure 1; a small change in the slope will have a very large effect on the point at which the NTCP is equal to 50%. Consequently, the uncertainties were large, n could not be constrained although very small values were preferred. At 95% confidence TD50 > 220 Gy and m>0.2, assuming that rib fracture is approximately a serial complication. Figure 1 shows the correlation between TD50 and m at the best-fit value of the volume parameter.



Conclusion: We conclude that the rate of rib fracture is relatively low (<10%) in SABR patients. NTCP modelling suggests that a very low volume parameter is most consistent with the data. This is in agreement with what might be naively expected. Due to small number of patients and events analysed to date it is not possible to constrain parameters tightly. This may be helped be re-parameterising the curve. We are now studying the effects of low absolute NTCP values and physically bounded parameters on the confidence intervals.

EP-1724

Model-based effect estimates reduce sample-size requirements in randomized trials of proton therapy

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Purpose or Objective: Standard power calculation methods for randomized trials do not account for patient-to-patient differences in effect of novel radiotherapy (RT) techniques. The expected advantage of a new technique can often be related to heterogeneous dose metrics in individual patients. Here, we investigate if model-based outcome assessment can affect sample size requirements for a randomized trial of proton versus photon RT for lung cancer with reduction of severe radiation-induced lung toxicity (RILT) as primary endpoint.

Material and Methods: We estimated the number of patients needed to demonstrate an advantage of proton versus photon RT in a randomized trial, with α=0.05 and 80% power. We simulated outcomes using Weibull survival distributions with baseline probability of freedom from RITL at 2 years of 85% for patients without clinical risk factors. Heterogeneous gain from proton therapy was quantified by change in mean lung dose (ΔMLD), randomly normally distributed in the proton arm with mean 4.2 Gy and s.d. 2.1 Gy. ΔMLD values were translated into hazard ratios (HR) using the QUANTEC dose-response relationship, adjusted for clinical prognostic factors (comorbidity, tumour location, smoking status, age) evenly distributed between the trial arms. Simulated follow-up was distributed over a time period of 2 years. Monte Carlo simulations (3000 per data point) were used to assess trial power. Sample size estimates were calculated as follows: *Standard:* Comparison of treatment arms using log-rank statistics; and *Model-based:* Cox proportional hazards regression fitted to the change in dosimetric predictor, here ΔMLD. The consequence of a misspecified dose metric was assessed by assuming an underlying true effect metric that was correlated to, but not equal to, ΔMLD.

Results: Sample size estimates differed considerably for the two approaches; see **Table 1**. 744 patients were needed to show the advantage of proton versus photon RT with standard comparison of trial arms, while superiority of protons based on a direct fit to the effect metric (ΔMLD) required only 549 patients. The advantage of using the model-based method