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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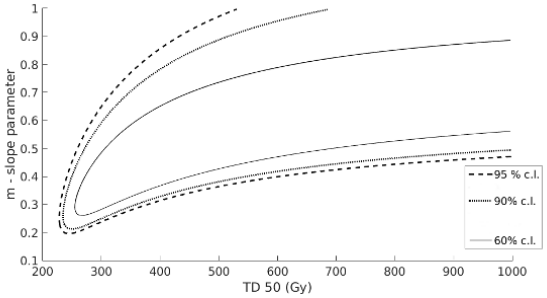
Purpose or Objective: SABR (Stereotactic Ablative Radiotherapy) is only possible in a subset of patients with small tumors and favourable anatomy as the very high BED increases the risk of complications. Lung SABR is often delivered to tumors that are more peripheral thus; the ribs are structures now 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

was maintained as long as the effect metric used for Cox regression had a linear correlation with the true effect metric of at least 0.50. The conclusions held if the trial cohort consisted of an expected high benefit population (22% reduced sample size), but the effect was even stronger if the cohort was a population with modest expected benefit (31% reduced sample size).

	Estimated trial size
Standard population	
ΔMLD=4.2 Gy, s.d. 2 Gy, normal risk factor prevalence	
Standard (log-rank)	744 patients
Model-based (Cox regression to ΔMLD)	549 patients
Model-based (misspecified effect metric, correlation 0.80)	614 patients
Model-based (misspecified effect metric, correlation 0.50)	743 patients
High benefit population	
ΔMLD=5.8 Gy, s.d. 2 .7 Gy high risk factor prevalence	
Standard (log-rank)	218 patients
Model-based (Cox regression to ΔMLD)	169 patients
Low benefit population	
ΔMLD=2.6 Gy, s.d. 1.3 Gy, low risk factor prevalence	
Standard (log-rank)	2300 patients
Model-based (Cox regression to ΔMLD)	1587 patients

Table 1: Standard trial design (log-rank statistics) compared to model based Cox regression. Risk factors included were: pre-existing pulmonary co-morbidity (HR = 2.27), mid or inferior tumour location (HR = 1.87), current smoker (HR = 0.62), and old age (HR =1.66). The consequences of a misspecified effect metric were examined for correlations ranging from 0.95 to 0.45; example results are .shown.

Conclusion: We have demonstrated that the required patient sample size for randomized trials in radiation oncology may be considerably reduced by taking heterogeneous dose-effect into account. Dual planning provides support for the statistical outcome modelling that increases trial power even if the dose-response model is moderately misspecified. The outcome of a trial in the example studied would be a randomized measure of 'benefit per Gy ΔMLD' with confidence interval.

EP-1725

Predictors of diarrhea after whole-pelvis post-prostatectomy radiotherapy

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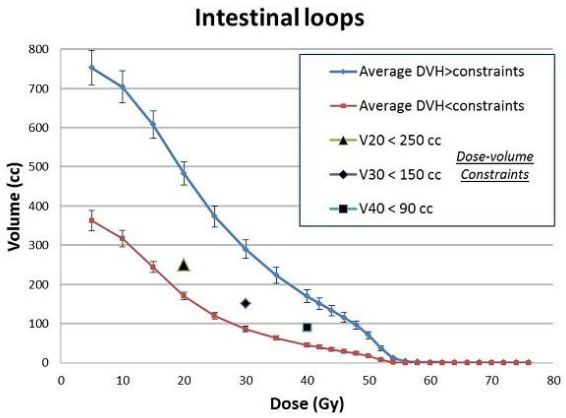
Purpose or Objective: Gastrointestinal (GI) toxicity is a side-effect induced by whole pelvis intensity modulated radiotherapy (WP-IMRT), affecting importantly patients' quality of life. The aim of this study was to identify predictors of diarrhea in a cohort of chemo-naïve patients treated with WP-IMRT after prostatectomy.

Material and Methods: The Inflammatory Bowel Disease questionnaire (IBDQ) was used to assess the degree of GI symptoms after WP-IMRT, investigating 4 distinct areas: bowel and systemic symptoms, emotional and social functions. This study focused on the most clinically relevant item 5 relative to the bowel domain, in order to evaluate the frequency of liquid defecation. Patient-reported scores at baseline, at RT mid-point and end, and every 3 months after RT end were prospectively collected . The responses are scored on a 7-point scale where 7 corresponds to the best function and 1 to the worst. Clinical/dosimetric data in 115 patients treated with adjuvant (n=65) or salvage (n=50) WPRT in a single Institute were available (static field IMRT:19; VMAT:55; Tomotherapy:41). Dose-volume histograms (DVHs) for intestinal loops and sigmoid colon were calculated. The 25th percentile of the score variation between baseline and half/end RT was considered as end-point (Δ -IBDQ5≤-3). Associations between diarrhea and clinical/DVH parameters were assessed by logistic uni- and backward multi-variable analyses. A previously introduced method based on DVH differences between patients with/without diarrhea toxicity was used to select the most discriminative DVH parameters.

Results: No significant correlation emerged for sigmoid colon, then the analysis was focused on intestinal loops. Patients without basal score and with -IBDQ5≤-3 were excluded from the analysis: 23/77 pts showed acute GI toxicity. At univariate analysis, volumes receiving 5 to 40Gy (V5-V40) were correlated with -IBDQ5≤- 3 ($p<0.03$). Multivariate analysis confirmed a leading role of dosimetric variables, while no significant correlation for clinical parameters was found. Best cut-off values (assessed by ROC) discriminating patients with/without -IBDQ5≤-3 were: V20<250cc, V30<150cc and V40<90cc. The overall incidence equal to 10% and 50% resulted for the group of patients with DVH parameters lower/higher than thresholds, respectively ($p=0.0028$, OR=4.9, AUC=0.68).



Conclusion: Low-medium IMRT doses to intestinal loops were correlated to diarrhea symptom at half/end of RT. This study proposed new dose volume constraints, that may be used to prevent much radiation-induced GI morbidity.

EP-1726

Biological modelling to identify proton therapy candidates in focal boosting of prostate tumours

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Purpose or Objective: MRI-based focal tumour boosting is currently under clinical investigation for prostate cancer patients, e.g. in the FLAME trial. These highly conformal, focal dose distributions can be difficult to achieve with photons, depending on the size and location of the boost volume (i.e. proximity to critical organs at risk). Selected patients might therefore be candidates for proton therapy. In previous work we have established an MRI-based tumour control probability (TCP) model. Combined with published rectum and bladder normal tissue complication probability (NTCP) models we have in this study explored the use of biological (TCP and NTCP) models to identify prostate cancer patients that might be suitable candidates for proton therapy if treated according to FLAME-like trial protocols.

Material and Methods: CT scans of seven patients from a prospective trial in our institution were used for planning. To obtain realistic boost geometries, MRI-based index tumours from a different cohort were used (matched on prostate volume), propagated with rigid registration on the prostate volume. VMAT plans (Eclipse, Varian Medical Systems) with and without a boost to the index lesion (95 Gy / 35 fx) were created; both plans delivered a conventional dose (77 Gy / 35