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

Results: The experimental data are well described for an O2-
independent response. For this case an a/B 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 a/B
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 a/B 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 5f (40 patients), 60 Gy in 8f (6 patients) or
54 Gy in 3f (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 a/B = 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 parameter volume.

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 by 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 RILT 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), normally randomly distributed in the proton
arm with mean 4.2 Gy and s.d. 2 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 data 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).

### Table 1: Standard trial design (log-rank statistics) compared to model based Cox regression. Risk factors included were: pre-existing pulmonary co-morbidity (HR = 3.271), mid or inferior tumour location (HR = 1.87), current smoker (HR = 0.62), and age (HR = 0.66). The consequences of a misspecified effect metric were examined for correlations ranging from 0 to 1.5; example results are shown.

<table>
<thead>
<tr>
<th>Population</th>
<th>Estimated trial size</th>
</tr>
</thead>
<tbody>
<tr>
<td>High benefit population</td>
<td></td>
</tr>
<tr>
<td>Model-based (Cox regression to JMLD)</td>
<td>494 patients</td>
</tr>
<tr>
<td>Model-based (misclassified effect metric, correlation 0.80)</td>
<td>164 patients</td>
</tr>
<tr>
<td>Model-based (misclassified effect metric, correlation 0.50)</td>
<td>743 patients</td>
</tr>
<tr>
<td>Low benefit population</td>
<td></td>
</tr>
<tr>
<td>Model-based (Cox regression to JMLD)</td>
<td>218 patients</td>
</tr>
<tr>
<td>Model-based (log-rank)</td>
<td>106 patients</td>
</tr>
<tr>
<td>Standard population</td>
<td></td>
</tr>
<tr>
<td>Model-based (Cox regression to JMLD)</td>
<td>744 patients</td>
</tr>
<tr>
<td>Standard (log-rank)</td>
<td>409 patients</td>
</tr>
</tbody>
</table>

**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 ∆ MLD 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-naïf 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 symptoms after WP-IMRT, affecting importantly patients' quality of life. The aim of this study was to identify predictors of diarrhea in a cohort of chemo-naïf patients treated with WP-IMRT after prostatectomy.

**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