consequently reduce chances of survival. Models to predict acute dysphagia are available. However, these models were based on limited amounts of data and the performance of these models needs improvements before implementation into routine practice. Furthermore, Bayesian network models are shown to perform better than conventional modeling techniques on datasets with missing values, which is a common problem in routine clinical care. In this work, we train a Bayesian network model on a large clinical datasets, originating predominantly from routine clinical care, to accurately predict acute dysphagia in NSCLC patients during and shortly after (C)RT.

Material and Methods: Clinical data from 1250 inoperable NSCLC patients, treated with radical CRT, sequential chemo-radiation or RT alone were collected. The esophagus was delineated using the external esophageal contour from the cricoid cartilage to the GE junction. A Bayesian network model was developed to predict severe acute dysphagia (Grade 3 according to the CTCAEv3.0 or v4.0). The model utilized age, mean esophageal dose, timing of chemotherapy and N-stage to make predictions. Variable selection and structure learning was done using the PC-algorithm. The model was trained on data from 1250 patients. The model's performance was assessed internally and on an external validation set (N=218) from the United Kingdom. Model discriminative performance was expressed as the Area Under the Curve (AUC) of the Receiver Operating Characteristic (ROC). ROCs were compared using the method proposed by DeLong and colleagues. Model performance was also assessed in terms of calibration. Calibration refers to the agreement between the observed frequencies and the predicted probabilities and is expressed as the coefficient of determination (r2).

Results: One-hundred forty patients (11,2%) developed acute dysphagia (≥ Grade 3 according to the CTCAEv3.0 or v4.0). The model was first validated internally, by validating on the training cohort (N=1250, AUC = 0.77, 95% CI: 0.7325-0.8086, r2 = 0.99). Subsequently, the model was externally validated on a UK dataset (N = 218, AUC = 0.81, 95% CI: 0.74-0.88, r2 = 0.64). The ROC curves were not significantly different (p = 0.28).

Conclusion: The Bayesian network model can make accurate predictions of acute dysphagia (AUC = 0.77, 0.81 in the internal and external validation respectively), making it a powerful tool for clinical decision support.

OC-0258

Linear-quadratic modeling of acute rectum toxicity in a prostate hypo-fractionation trial

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Purpose or Objective: In the Dutch prostate hypo-fractionation trial (19x3.4Gy versus 39x2Gy) a higher incidence of acute gastro-intestinal toxicity was observed in the experimental arm. We performed model estimations using various alpha/beta ratios to determine whether this difference can be explained according to the linear-quadratic model.

Material and Methods: Patients with localized prostate cancer were randomized between standard fractionation (SF=5x2Gy per week, N=293) and hypo-fractionation (HF=3x3.4Gy per week, N=285). Proctitis (grade 2+) was defined as moderate to severe mucous or blood loss, or mild mucous or blood loss combined with at least 2 other complaints: diarrhea, incontinence, tenesmus, cramps, pain. Peak incidences over treatment weeks 4 and 6 were available from prospectively collected patient reports. Normalized Total Dose (NTD, 2Gy equivalent) was accumulated per week for alpha/beta ratios of 3, 5, 10, and∞ (=physical dose), and used to derive relative Dose-Surface Histograms (DSHs) of the delineated anorectum for each patient. Maximum likelihood logistic regressions were performed using a DSH point as variable. Univariate (UV) models and multivariate (MV) models with fractionation schedule as factor were constructed.

Results: Acute proctitis incidences were highest for hypo-fractionation (SF: n=67; 22.9%, HF: n=98; 34.3%, p<0.01). The 7Gy/week DSH point correlated well with proctitis, and was used for subsequent modeling. Figure 1 illustrates the models for the various alpha/beta ratios, and incidences for five (roughly) equal size patient bins. Note that the NTD correction decreases the surface areas that receive <2Gy per day, and increases surfaces receiving >2Gy. The central NTD values of the patient bins therefore lie at higher values for HF than for SF. The MV models have higher likelihood than the UV models, but likelihood for different alpha/beta ratios is similar. All MV models have odds ratios >1.5 (p<0.05) for HF versus SF, i.e. fractionation remains a factor.

Conclusion: Linear-quadratic dose correction cannot explain the observed acute rectum toxicity difference between hypo-fractionated and standard treatment in patients with prostate cancer. Subsequent modeling will concentrate on alternative mechanisms.

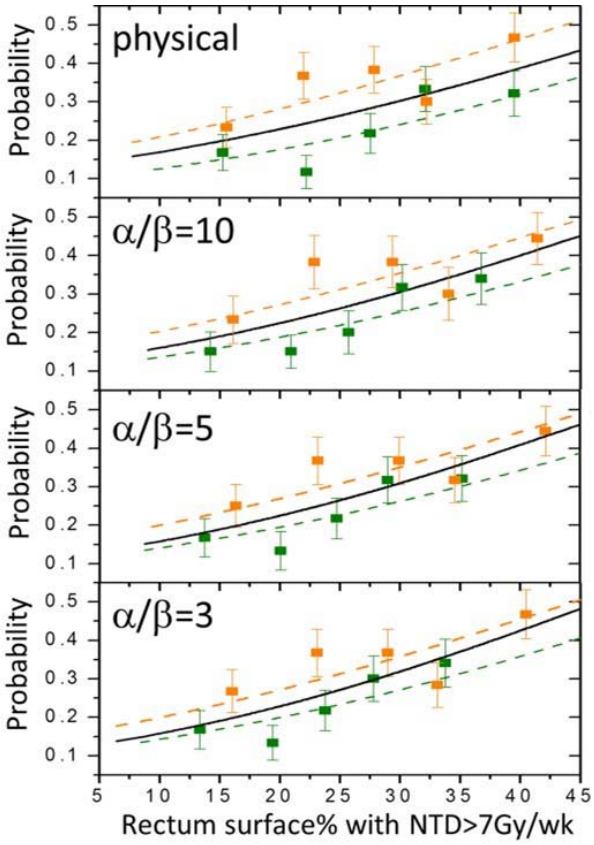

Figure 1 Acute proctitis models (UV solid, MV dashed) for standard (green) and hypo-fractionation (orange)

OC-0259

Spatial rectal dose-response for patient-reported leakage, obstruction, and urgency in prostate RT

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Purpose or Objective: To explore whether spatial dose measures explain the occurrence of rectal leakage, obstruction, and urgency after radiotherapy (RT) for localized prostate cancer.

Material and Methods: Spatial dose measures were extracted for 210 patients treated with RT in 2005-2007, and who all completed patient-reported outcomes (PROs) at a median of 3.6 years post-RT. The rectum was digitally unfolded and 2D maps were created for each patient by interpolating across 25 points for 45º-sectors of each contour. The areas and extents (lateral and longitudinal) were calculated for dose thresholds between 35 and 75 Gy in 5 Gy steps over 9 equally distributed segments over the 2D maps (Fig. 1A), and their lateral and longitudinal combinations, resulting in a total of 216 spatial dose metrics. Univariate (UVA) followed by multivariate (MVA) analysis using logistic regression with 50 times iterated 5-fold cross-validation was applied to investigate the relationship between the spatial measures and 'at least a moderate severity' of five symptoms related to defecation urgency, fecal leakage, or obstruction. The prevalence for all investigated symptoms was ³ 25%. The UVA and MVA were first conducted in 70% of the data, and the performance of the most frequent MVA model, judged by the area under the receiver-operating characteristics curve (AUC), was investigated in the complete cohort.

Results: On UVA 3-11 metrics (mean±SD: AUC=0.58±0.11) were suggested as potential predictors for the investigated symptoms (Table 1). The AUC of the final MVA models was 0.57-0.62 (Fig. 1B). Defecation urgency was explained by metrics related to high doses (>55 Gy), fecal leakage was governed by medium to high-dose extensions in the anterior part of the rectum, and obstruction by metrics related to the lower part of the rectum, as well as extents of the high dose (>75 Gy).

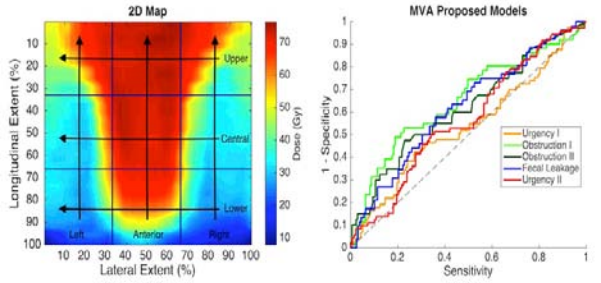

Figure 1. Left Panel: 2D map extracted from one of the patients; Right Panel: ROC plots for the five studied symptoms suggested by the final MVA models.

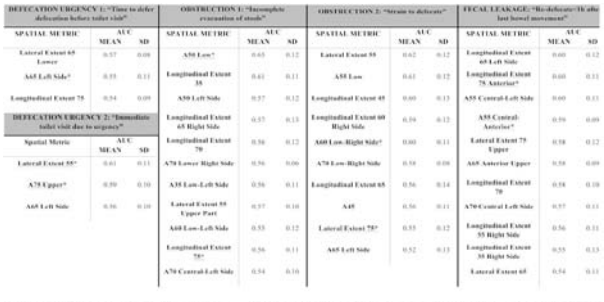

Table 1. Proposed metrics as predictors of the different studied endpoints. These metrics where extracted from the UVA performed over the 70% of the data set, and all of them were not correlate (Pearson Coefficient < 0.7). LogOdds > 0.01 and the highest AUC (> 0.54). Underlined metrics were included in the final predictor model using a MVA. "Ax" is the percentage area of the 2D map enclosed by the isoline of "X Gy" in a specific segment; the "Extent X" is the extension of the largest pixel aggregate above "X Gy" for the different segments.

Conclusion: Our analysis suggests that spatial dose metrics explain symptoms of the gastrointestinal tract such as defecation urgency, fecal leakage and obstruction, and that these symptoms present spatial-specific relationships. The robustness of these results will be explored in other available cohorts (N>500) to evaluate whether these findings, and spatial dose metrics in general should be taken into account in the RT planning and treatment for localized prostate cancer.

OC-0260

Local dose predictors of acute urinary toxicity after RT for prostate cancer

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Purpose or Objective: To investigate the relationship between patient-reported acute urinary (GU) toxicity (tox) and bladder local dose distribution in patients (pts) treated with radical RT for prostate cancer (PCa) by a pixel-wise method for analysis of bladder surface dose maps (DSMs).

Material and Methods: Analyses were performed on the final cohort of pts of a multi-centric study, consisting of 539 pts with PCa treated with conventionally (CONV: 1.8 – 2Gy/fr) or moderately hypo-fractionated RT (HYPO: 2.2-2.7 Gy/fr) in 5 fx/week. GU tox was evaluated by the International Prostate Symptoms Score (IPSS) given to the pts at the beginning and at the end of RT, comprising 7 questions relating to different symp: feeling of incomplete emptying (EMP), frequency (FRE), intermittency (INT), urgency (URG), weak stream (WST), straining (STR) and nocturia (NOC). We here considered the seven symp separately and moderate/severe tox for each item was selected as endpoint (score≥4 at RT end), including only pts who had no disturbs before RT (IPSS at basal < 4). As different fractionation schemes were allowed, DSMs of all pts were corrected into 2Gy-equivalent maps using the LQ model, converting the dose in each pixel with an α/β equal to 10 Gy and a repair factor =0.7 Gy/day. DSMs of all pts were generated by unfolding the bladder: its contour was cut anteriorly at the points intersecting the sagittal plane passing through its centre of mass, normalised in the axial direction and aligned at the bladder base, at the posterior central point, generating a common frame for all pts. For each endpoint average DSMs of pts with/without tox were compared pixel by-pixel by two-sided t-tests, separately analyzing HYPO and CONV pts: the resulting p-value maps were used for identifying the regions better discriminating between pts with/without tox, considering a threshold of p<0.01.

Results: DSMs of 437/539 pts (81%) were available (185 CONV and 252 HYPO). EMP was reported by 28/358 (8%) pts, FRE by 60/361 (17%), INT by 35/366 (10%), URG by 50/357 (14%), WST by 66/341 (19%), STR by 29/377 (8%) and NOC by 63/348 (18%) pts. For HYPO pts, areas significantly correlated with GU tox were found for all endpoints (excepting WST) in the posterior region at 5-17 mm from the base of bladder, consistently with the bladder trigone, with evidence of a threshold effect around 85 Gy (2Gy equivalent). For CONV pts, only 2 endpoints (FRE and URG) showed significantly predictive areas, robustly summarized in the % surface receiving >50-70Gy at 5mm from the base and the vertical extension of 50-70Gy isodoses along the bladder central axis. In the figure, the results concerning FRE and URG are shown.