The use of image guidance is unlikely to result in an unacceptable increase in second cancer risk.

**OC-0077**

Towards individualized dose constraints: The QUANTEC radiation pneumonitis model with clinical risk factors

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**Purpose/Objective:** Understanding the dose-response of the normal lung in order to minimize the risk of radiation pneumonitis (RP) is of critical importance for optimization of radiotherapy for lung cancer. In this study, we propose a method to combine the dose-response relationship for RP from the landmark QUANTEC paper with clinical risk factors in order to improve individual patient risk prediction. The approach is validated in an independent dataset of 103 patients.

**Materials and Methods:** The prevalence of risk factors (pulmonary comorbidities, smoking history, age and chemotherapy) in the patient populations underlying the QUANTEC analysis was estimated, and a previously published method to adjust the dose-response relationship for clinical risk factors was employed. Estimates of effect size (odds ratios, OR) for clinical risk factors were drawn from a recently published meta-analysis. Baseline values for $D_{50}$ (the dose resulting in a 50% complication probability) and $y_{50}$ (the normalised slope of the dose-response curve at $D_{50}$) were established. Confidence intervals were estimated using random sampling. The method was tested in an independent dataset (103 non-small cell lung cancer patients), comparing the predictive power of the dose-only QUANTEC model and the model taking risk factors into account. Subdistribution cumulative incidence functions for RP were compared in stratified analyses for patients with high / low risk predictions, based on group medians, from the two models, and concordance indices (c-indices) for the prediction of RP were calculated. C-indices were compared using a Student t-test for paired samples.

**Results:** The logistic relationship between mean lung dose and the risk of RP was described in the QUANTEC paper by $D_{50}$ = 30.8 Gy, $y_{50}$ = 0.97. From this, a reference dose-response relationship for a patient without pulmonary co-morbidities, no history of smoking, below 63 years old, and not treated with sequential chemotherapy was estimated as $D_{50}^{0}$ = 32.3 Gy (95% CI: 28.9, 36.5), $y_{50}^{0}$ = 1.10 (95% CI: 0.92, 1.31). ORs for each risk factor were then used to calculate individual patient risk estimates. The cumulative incidences of RP in the validation dataset were not significantly different in high / low risk patients stratified according to the QUANTEC model ($p=0.11$), but were significantly different using the individualized model ($p=0.0046$, see Figure 1). The c-indices were significantly different between the dose-only and the individualized model ($p=0.004$ using binary risk allocation, $p=0.04$ using continuous NTCP as predictor).

**Conclusions:** This study presents a method to combine a dose-response function with known clinical risk factors, based on data from large, published meta-analyses. We demonstrate that the predictive power of the combined model is greater than a dose-only model in an independent dataset. This method, although not taking correlations between risk factors into account, allows for individualization of dose constraints and risk estimations, and it can easily be extended to include additional risk factors.

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Sparing the contralateral submandibular gland in oropharyngeal cancer patients: dose-response analysis

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**Purpose/Objective:** (1) To prospectively determine the prevalence of patient-reported xerostomia after sparing the contralateral submandibular gland (cSMG) in oropharyngeal cancer patients without contralateral lymph node metastases. (2) To construct a normal tissue complication probability (NTCP) curve for submandibular gland (cSMG) function after radiotherapy (RT) based on mean dose and selective flow measurements.

**Materials and Methods:** 50 oropharyngeal cancer patients (cT1-4N0-2bM0) were treated with an optimized IMRT-technique with the intention to spare both parotid glands (PGs) and the cSMG (aim cSMG <40 Gy; cSMG-sparing cohort). They were compared with a historical cohort of 52 patients that received only PG-sparing IMRT (PG-sparing cohort). cSMG- and PGflow rates were measured 6 weeks and 1 year post-RT and converted into the percentage of baseline. Patient-reported xerostomia was recorded using the EORTC QLQ-HN35 single item xerostomia and sticky saliva. For NTCP-analysis, cSMG flow data from a large patient cohort were fitted to the Lyman-Kutcher-Burman model with a complication defined as cSMG flow ratio <25% of pre-RT flowrate (RTOG/EORTC grade 4 xerostomia).

**Results:** cSMG mean dose could be reduced below 40 Gy in 50% and 21% of the patients in the cSMG-sparing and PG-sparing cohorts (mean cSMG dose 39.1 vs 50.4 Gy) respectively. cSMG flow ratio, complication rate and xerostomia scores 1 year post-RT were slightly better in the cSMG-sparing cohort (ns). At 1 year, 56% of the patients from the cSMG-sparing cohort still reported grade 2-3 xerostomia. Post-hoc, patients were re-grouped according to mean cSMG dose above (n= 66) or below (n= 36) 40 Gy. All patients but one in the <40 Gy group had a small (T1-T2) tumor and 53% received only unilateral neck-RT. Significantly higher cSMG flow ratios at 6 weeks and 1 year post-RT in the <40 Gy group translated into lower xerostomia scores at both time points (at 1 yr: 67 vs. 42% grade 2-3 xerostomia, p= 0.07). PG function (1 yr) was similar in both groups. LKB-modelling showed substantial shift of NTCP-curve between 6 weeks and 1 year post-RT. The TD50 (mean dose leading to 50% NTCP) was 23 and 35 Gy, resp. Above 40 Gy mean cSMG dose, NTCP worsened between 6 weeks and 1 year post-RT. See figure for the 1 year NTCP-curve.

**Conclusions:** This study concerns the largest group of patients published, for which a dose response curve for cSMG-flow rate after radiotherapy was analysed. cSMG mean doses below 40 Gy resulted in improved cSMG function and reduced patient-reported xerostomia. Above 40 Gy submandibular function worsened in time. cSMG-sparing in oropharyngeal cancer patients(N-stages sN2b) is still challenging.