OC-0546
Minimally ablative dose (MAD) for the treatment of lung cancer using SBRT: Is it such a “MAD” concept?
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Purpose/Objective: To determine whether individualization of dose prescriptions based on tumor size and location is a feasible approach for SBRT-based treatment of non-small cell lung cancer.

Materials and Methods: Treatment plans for 133 NSCLC patients treated using 12 Gy/Fxn x 4, and planned using a pencil-beam (1D-equivalent-path-length, EPL-1D) algorithm were retrospectively calculated with a Monte Carlo (MC)-based algorithm using EPL-1D plan parameters. 4D imaging was performed to generate an ITV. PTV margin was 5 mm. For each plan, generalized equivalent dose (gEUD) and tumor control probability (TCP) with SF=0.28 were computed. Tumors were stratified according to peripheral (island, N=39), lung-wall (attached to the rib-cage, N=44) and central locations (N=50), as well as tumor size and mean plan field size.

Results: gEUD values for the EPL-1D algorithm were based on prescription doses and ranged from 48-49 Gy for all cases. MC-computed gEUD decreased significantly with decreasing tumor size; values in Gy were 41.9±3.6 for average plan field widths (FW) between 3-5 cm; 43.8±3.2 (FW>5 cm); 45.9±3.3 between (7FW-10 cm). TCP's for the EPL-1D algorithm increased with decreasing tumor size with values of 0.88±0.04 (3FW-5 cm); 0.85±0.03 (5FW-7 cm); 0.80±0.05 (7FW-10 cm). On the other hand, MC-computed TCP's remained relatively constant as a function of tumor size; values were 0.77±0.07 (3FW-5 cm); 0.76±0.05 (5FW-7 cm); 0.76±0.05 (7FW-10 cm). Results were consistent for ‘island’, lung wall and Central Tumors. There was no correlation between tumor size and local control rate among the 92% of patients who were controlled locally at 2-years, which is consistent with the MC-calculated TCPs. Note, however, that MC-computed gEUDs were significantly lower for smaller tumor sizes. This suggests that although smaller tumors were receiving much lower doses (on average, 10.5 Gy vs. 12 Gy per fxn), they were being controlled. These findings are consistent with radiobiology; smaller tumors have fewer tumor cells and therefore require lower doses to be controlled relative to larger tumors. Results are also suggestive that dose escalation for smaller tumors, based on the mimimum ablative dose is likely to be clinically relevant for tumors situated close to normal tissue, i.e. one size does not need to fit all. We speculate as well that the concept of minimally ablative dose (MAD) is perhaps not an unreasonable approach to consider for smaller tumors. Dose escalation for smaller tumors, based on the minimum ablative dose is likely to be clinically relevant for tumors situated close to normal organs (e.g. ribs, centrally located airways) and for patients being treated for recurrent disease.

Conclusions: Retrospective dose analysis of 133 NSCLC patients treated with SBRT is suggestive that individualization of doses based on tumor size and location may be a feasible approach toward achieving equivalent local control and possibly reducing toxicity based on the clinical circumstances.

OC-0547
How to identify patient specific rectal sub-region likely responsible of rectal bleeding in prostatic IMRT?
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Purpose/Objective: Current toxicity models in prostate cancer radiotherapy, based on dose/volume histograms, do not enable to identify region in the rectum involved in bleeding. Localize such regions may be crucial in IMRT to decrease rectal toxicity. The goals of this study were:
- firstly to assess the rectal bleeding/local dose correlation using voxel wise statistics on several anatomically different templates (thus avoiding a specific template effect),
- secondly to back propagate the significant regions found on these templates to a specific patient (pts).

Materials and Methods: A total of 93 patients receiving a total dose of 80Gy in the prostate by IMRT were included in the analysis. Rectal bleeding (RB) at two years was analyzed (# grade 1). The series was divided in 2 cohorts: one for training (63 pts) and the other one for testing (30 pts). A total of 63 randomly chosen individuals (12/51 with/without RB) 3D CT scans and planned dose were non-rigidly registered towards 10 templates in a 3 step process: one rigid registration and two elastic registrations (demons algorithm). The registrations were designed to ensure accurate alignments of rectums and dose distributions. Dice scores and Dose-Organs Overlap (DOO) were computed on the rectum for each pt on the 10 templates to assess the accuracy of the registration.

Two-sampled t-tests were then performed on each template at a voxel-basis leading to the computation of 3D maps for both, the dose differences (and p-values) between the mean dose of pts having or not toxicity. Significant regions (p<0.01) were then characterized in terms of absolute volume, mean dose difference and localization in the rectum. The last one was defined as the distance of the significant region to the prostate and the seminal vesicles surfaces.

The 10 significant regions from each template were then back propagated, using the same registration method, on 30 'test patients' (6/24 with/without RB) leading to the computation of a probability map of the significant region on the rectum for each test patient. The significant regions for toxicity were then delineated using a majority vote approach.

Results:
Median follow-up was 31 months (6 to 64). Two year RB rate were 20%(95% CI: 12-27).
1. Median Dice and DOO were 0.98 (sd 0.01) and 0.97 (sd 0.02).
2. Significant differences of dose related with toxicity were found in large regions on the 10 templates, corresponding to 5.95% of the rectal volume (in average). The anterior wall of the rectum appears involved in RB on the 10 templates (fig): 92.17% (sd 6.3) of the volume of the significant region was localized within the first 15mm of the rectum close to the prostate. In these regions, pts with RB received 6.7Gy (sd 1.3) more than pts without RB.

Conclusions: The anterior wall of the rectum appears strongly involved in RB. Our templates constitute a library of RB correlated region, which can be used to more precisely identify the region at risk of rectal bleeding for a given patient. This new approach opens the way for patient specific treatment by enabling to add IMRT constraints on region likely responsible of RB.

OC-0548
Dose/volume-response relations for rectal morbidity using planned and motion-inclusive dose distributions
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Purpose/Objective: Many dose-limiting normal tissues in radiotherapy display considerable internal organ motion during a course of treatment, potentially deteriorating the relations between dose-volume parameters and morbidity. To address this issue, we have previously developed a motion simulation model and validated it on the rectum geometries in the planning CT scans in a cohort of prostate cancer patients. In this present study we apply this model to compare the associations with morbidity of the planned vs. motion-inclusive dose distributions in two cohorts of patients prospectively followed with respect to a broader spectrum of rectal morbidity endpoints.

Materials and Methods: The patients in the two included cohorts (Clatterbridge: n=192 patients; Cohort II: n=87 patients) were previously treated with RT for localised prostate cancer to prescribed doses of 70 vs. 74 Gy. The dose-response relations for the planned as well as simulated motion-inclusive rectal dose-volume histograms (DVHs) were associated with six rectal morbidity endpoints (Cohort I: RT:Gastro-intestinal (GI) toxicity, stool frequency, mucosal loss, tenesmus, sphincter control and late rectal bleeding (LRB); Cohort II: LRB). The motion-inclusive dose distributions were obtained from simulations of small, moderate and large motion magnitudes applied to the planned dose distributions, using the previously developed and validated model. Additionally, the data was evaluated with a probit NTPC model using the QUANTEC rectal parameters (TDS50=76.9, m=0.13, n=0.09).

Results: Statistically significant associations with the studied endpoints were obtained at high doses (>55 Gy) using both the planned and the simulated motion-inclusive dose distributions, with the strongest associations observed for RT:GI toxicity and stool frequency (Spearman’s rank correlation coefficient, Rs=0.13-0.21 and Rs=0.14-0.16). Within the high dose region the associations with morbidity using the planned or the motion-inclusive DVHs were stronger than the associations seen when simulating large motion. Using the probit NTPC model the strongest associations were observed for tenesmus (Rs=0.14, p=0.03) and LRB (Rs=0.12, p=0.13).

Conclusions: Equally strong associations with rectal morbidity were observed for high doses (>55 Gy), for the planned dose distributions and the simulated dose distributions including small and moderate rectal motion. Using a probit model with the QUANTEC recommended parameters the strongest significant associations were obtained for tenesmus.

OC-0549 Effective alpha/beta concept: normal-tissue fractionation accounting for heterogeneous dose and volume effect
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Purpose/Objective: The Linear-Quadratic (LQ)-based ‘Withers’ iso-effect formula (WIF) is the standard method for deriving a new (tumour) dose prescription such that there is normal-tissue (NT) iso-effect when changing the fraction size and/or number. However, the WIF is invalid unless the NT receives a uniform dose equal to the tumour dose, or, the NT response is solely determined by the maximum NT dose (100% serial). For parallel/quasi-parallel NTs the WIF yields highly conservative hypofractionation prescriptions. Our aim was to find a method to calculate NT iso-effective fractionation schemes which correctly account for arbitrary NT dose distributions and ‘architecture’.

Materials and Methods: We propose a generalized WIF (gWIF) which retains the tumour prescription doses but replaces the intrinsic fractionation sensitivity measure (α/β) by a new concept: the normal-tissue effective fractionation sensitivity, (α/β)eff, which takes into account both the dose heterogeneity in, and the volume effect of, the late-responding normal tissue in question. Assuming a power-law dose-volume response model, we have derived a closed-form analytical expression for (α/β)eff which ensures exact NT iso-effect, for an arbitrary dose distribution and arbitrary volume-effect parameter n.

Results: As n is varied, (α/β)eff increases from its intrinsic value at n = 0 (100% serial NT) to values close to or even exceeding the tumour dose (α/β) at n = 1 (100% parallel NT), with the highest (α/β)eff corresponding to highly conformal dose distributions. Assuming an intrinsic (α/β)2Gy = 3 Gy, for two IMRT plans for non-small-cell lung tumours with radiation pneumonitis as endpoint (n = 1), in the moderately conformal case (α/β)eff = 4.5 Gy, whereas for the highly conformal plan we obtained (α/β)eff = 8.5 Gy. For three typical SABR plans, we obtained values of (α/β)eff of 7.0 to 8.9 Gy depending on the DVHs for the non-involved (paired) lungs. Note that our (α/β)eff is independent of the choice of fractionation scheme.

Conclusions: The (α/β)eff from the expression for the volume response model, we have derived a closed-form analytical expression for (α/β)eff which retains the tumour prescription doses but replaces the intrinsic (α/β) by a new concept: the normal-tissue effective fractionation sensitivity, (α/β)eff, which takes into account both the dose heterogeneity in, and the volume effect of, the late-responding normal tissue in question. Assuming a power-law dose-volume response model, we have derived a closed-form analytical expression for (α/β)eff which ensures exact NT iso-effect, for an arbitrary dose distribution and arbitrary volume-effect parameter n.

OC-0550 Overestimation of gross tumor volume of laryngeal/hypopharyngeal cancer on MRI in clinical radiotherapy practice
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Purpose/Objective: To compare gross tumor volume (GTV) of laryngeal and hypopharyngeal carcinoma delineated on MRI with the tumor volume of pathology in laryngectomy specimens.

Materials and Methods: From 22 patients (mean age, 62±3; range, 52-79 years; 20 males and 2 females) with T3 (n=5) or T4 (n=17) squamous cell carcinoma of the larynx (5 transglottic-, 6 supraglottic-, 1 glottic carcinoma) or hypopharynx (n=10), the specimen was obtained after total laryngectomy. The sliced specimen was processed and 3-D reconstructed according to our pathology validation protocol and registered to in vivo MR-images with an accuracy of 3 mm in the cartilage skeleton. Hematoxylin-eosin (H&E) stained sections were obtained and tumor volume on these sections was delineated by a pathologist.

Prior to laryngectomy, a high-resolution 1.5 Tesla MRI-scan was performed in a head-and-shoulder mask with a two-element surface receiver coil. T2w images and T1w images before and after injection of gadolinium were obtained. The mean time interval between the MRI-scan and operation was 10.8 days, range 2.3-34 days.

Three experienced head-and-neck specialists (2 radiation oncologists, 1 radiologist) delineated the GTV on MRI after consensus about guidelines according to delineation of the GTV in clinical practice.

Results: The mean tumor volume (27.1 ml, SD 18.2) delineated by the observers was almost doubled compared to tumor volumes delineated by the pathologist (15.5 ml, SD 15.3). For all patients, the GTV of the observers exceeded the tumor volume of the pathologist (Figure 1). The GTV’s delineated on MRI included tumor tissue as well as non-tumorous tissues e.g.; edema and necrosis, enlarging the GTV compared to pathology. To increase accuracy in tumor delineation, a study is currently performed in our institute to develop MRI-based guidelines for interpretation and delineation of head and neck cancer.

Conclusions:

Figure 1. The GTV of a T3 hypopharyngeal carcinoma delineated on transversal MRI image (1a: T1-weighted-gadolinium, 1b: T1-weighted coronal 1c: T2-weighted) by three observers. MR-images are registered to the transversal gross-pathology photos (2a) and transversal H&E-stained sections (2b) of the same tumor on which true tumor is indicated.