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Functional-Guided Radiotherapy Using Knowledge-Based Planning

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Abstract

Background and Purpose—There are two significant challenges when implementing functional-guided radiotherapy using 4DCT-ventilation imaging: 1) lack of knowledge of realistic patient specific dosimetric goals for functional lung and 2) ensuring consistent plan quality across multiple planners. Knowledge-based planning (KBP) is positioned to address both concerns.

Material and Methods—A KBP model was created from 30 previously planned functional-guided lung patients. Standard organs at risk (OAR) in lung radiotherapy and a ventilation contour delineating areas of high ventilation were included. Model validation compared dose-metrics to standard OARs and functional dose-metrics from 20 independent cases that were planned with and without KBP.

Results—A significant improvement was observed for KBP optimized plans in V20Gy and mean dose to functional lung ($p=0.005$ and 0.001 , respectively), V20Gy and mean dose to total lung minus GTV ($p=0.002$ and 0.01 , respectively), and mean doses to esophagus ($p=0.005$).

Conclusion—The current work developed a KBP model for functional-guided radiotherapy. Modest, but statistically significant, improvements were observed in functional lung and total lung doses.

Keywords

Knowledge-based planning; functional-guided radiotherapy

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Introduction

Functional-guided radiotherapy is a treatment strategy that seeks to customize radiotherapy treatment plans based on physiological findings from functional imaging. One exciting, new example that is being increasingly explored is the use of 4DCT ventilation imaging to create treatment plans that preferentially spare areas of high functioning lung in the treatment of lung cancers. Previous studies have demonstrated that dose to areas of high functionality in the lung can be more predictive of radiation pneumonitis[1-3] and/or radiation fibrosis[4] than traditional total lung dose metrics. Additional studies have quantified the dosimetric reductions achievable[5-8] in functional lung with one estimating that the corresponding absolute reductions in radiation pneumonitis to be 4.7% for grade 2+ events and 7.1% for grade 3+ events[9].

Through the use of phase resolved CT images, 4DCT ventilation can calculate pulmonary ventilation on a voxel-by-voxel basis[10-14]. With the use of 4DCT being a commonly used technique for motion management in lung cancer patients, the calculation of ventilation images can be performed at no extra cost to the patient, financial or dosimetric. The methodology[12, 14], validation[12, 14-21], and uses[2, 22-24] of 4DCT ventilation imaging have been extensively covered in the literature. Capitalizing on this momentum, clinical trials aimed at prospectively evaluating functional-guided radiotherapy are underway (NCT02528942, NCT02773238, NCT02002052, NCT02308709, NCT01034514, NCT02843568). Trials include single center and multi-center efforts.

The optimization process of functional-guided radiotherapy planning provides challenges due to the patient-to-patient variation in lung functional distribution and the relative lack of experience with functional avoidance. These challenges make it difficult to predict what functional dose reductions are achievable in individual patients.

Knowledge-based planning (KBP) is a means of improving planning efficiency and reducing variability in plan quality[25]. Through the use of a dataset composed of clinically acceptable treatment plans, an estimation of dose-volume histograms (DVH) is achieved based on the relationship between anatomical and geometric features of the planning site[26, 27]. The estimated DVHs can then be used to automatically generate planning objectives for optimization.

The potential advantages of a KBP model in the context of functional-guided radiotherapy are twofold. It first provides a guiding estimate for the achievable dose metrics helping to mitigate the lack of experience with functional avoidance for treatment planners. The initial estimate in the DVHs are based on patient specific geometry and anatomy and provide valuable feedback for a new form of treatment planning in which dosimetrists do not have the years of experience to draw upon during the planning process. The second area of benefit is reduced deviation in plan quality, an especially important factor in on-going and future multi-institutional clinical trials[28]. Because of these two benefits, KBP models have the potential to be an important tool in realizing the full benefits of functional-guided

radiotherapy. The purpose of this work was to create and validate a KBP model for thoracic functional avoidance radiotherapy.

Methods

Dataset

The patient dataset consisted of 50 previously treated lung cancer patients that had 4DCT imaging performed as a part of their pre-treatment imaging. Inclusion of the patients in a functional-guided radiotherapy dataset was contingent upon the calculated ventilation map meeting a heterogeneity inclusion criterion previously described[29]. Briefly, this criterion considered patients with regional ventilation defects greater than 15% of the mean to be candidates for functional-guided radiotherapy. Among the 50 treatment plans used, 19 were from clinically treated plans as a part of an ongoing functional-guided radiotherapy clinical trial, and 31 patients were retrospectively planned using functional-guided planning techniques. Of the 50 patients, 39 were diagnosed as non-small cell lung cancer (NSCLC) and 11 with small cell lung cancer. Forty eight patients had stage III disease and 2 had stage II disease. All treatment plans were planned as volumetric arc therapy (VMAT) deliveries using standard fractionation (1.8 – 2.0 Gy/fraction, cumulative dose 45-70Gy).

Ventilation Imaging and Ventilation Contours

Ventilation images were calculated using pre-treatment 4DCTs acquired for each patient. The lungs were segmented out and the trachea, main-stem bronchi, pulmonary vasculature, and the gross tumor volume were excluded for both inhale and exhale phases[14]. The voxels in the peak inhale and peak exhale images were linked through deformable image registration[30]. The ventilation in each voxel was then calculated using a density change based algorithm[5, 14]. Manual inspection of the ventilation maps was then performed to ensure no artifacts were present.

The delineation between functional and non-functional lung was determined from a heterogeneity algorithm developed and previously published by our group[29]. Briefly, the algorithm identifies regions of the lung that show a decreased-deviation greater than 15% from a theoretically homogeneous functional distribution. Ventilation values above the threshold are included in the ventilation contour using auto-thresholding methods. Post-processing on the contour removes segments less than 0.50cm³.

Model Training

A KBP model was generated using Varian's RapidPlan (Varian Medical Systems, Palo Alto, CA) module. The model training consisted of 30 treatment plans. Structures for which the model was trained were total ventilation (the structure representing functional portions of lung), total ventilation minus the planning target volume (PTV), esophagus, heart, left lung, right lung, total lung, lung minus the PTV, and the spinal cord. Regression plots of the model training results were visually assessed and coefficient of variation values (R^2) for individual structures were used to evaluate the goodness of fit for each structure in the model. The average chi squared from Pearson's chi-squared test was used as measure of the difference

between the original data and generated estimation (with values closer to 1 representing a better fit).

In addition to providing DVH estimations, the KBP model is capable of generating optimization objectives for trained structures. Automated objectives allow for KBP generated priorities, doses, and/or volume (as a percentage of the structure). The model trained in this study included objectives for the PTV, esophagus, heart, lungs minus PTV, spinal cord, and ventilation minus PTV. A combination of maximum, volume, and line objectives were used. For the ventilation minus the PTV structure, volume based objectives were chosen based off of a previous study[3] that examined the dose-function metrics most predictive for radiation pneumonitis. A complete list of the automatically generated objectives is presented in Table 1. A consistent, manually set Normal Tissue Objective was used to minimize dose to healthy tissue, increase dose conformity, and maximize the dose fall-off.

Validation

Model validation was performed on the 20 remaining patients from the original 50 patient dataset. An experienced treatment planner, following standard planning techniques, generated functional-guided treatment plans and user defined optimization objectives. Functional-guided plans were then made using the KBP model and auto-generated optimization objectives. No changes were made to the KBP functional-guided plans after running through the optimization with auto-generated objectives.

Dose-function metrics for the ventilation contour and standard dose metrics for all other structures were compared between the plans optimized by the human treatment planner and the plans that were optimized using the KBP model. A paired Wilcoxon Signed Rank test assessed significance of any differences in dose-metrics where significance corresponded to a p-value ≤ 0.05 . The dose metrics chosen for comparison were based off our own institutional constraints used for clinical plans.

Results

Coefficient of determination and average coefficient of variation results for each trained structure are reported in Table 2. All modeled structures exceeded Varian's suggested coefficient of determination value of 0.7. Structures with the highest coefficient of determination, corresponding to improved model fit for the structure, were the right, left, and total lung (0.98, 0.92, and 0.94, respectively), lung minus PTV (0.93), and total ventilation (0.90). A regression plot of the ventilation contour is presented in Figure 1.

Validation of the KBP model compared dose metrics to the modeled structures for plans generated with the KBP model to those that were user-generated. The average dose metrics for each of the structures are reported in Table 3 along with a p-value quantifying if the difference is significant. Briefly, significant differences between user optimized plans and KBP plans were observed in V20Gy and mean dose to functional lung ($p=0.005$ and 0.001), V20Gy and mean dose to the total lung minus the GTV ($p=0.002$ and 0.01), and mean dose to the esophagus ($p=0.005$).

Discussion

Our results indicate that a KBP model can be successfully generated in the setting of thoracic functional radiotherapy. KBP models were originally designed with standard PTV and OAR spatial distributions in mind. The relationship between a ventilation contour and the target can be different than a standard OAR/PTV relationship due to the spatial heterogeneity of the ventilation image itself. The KBP functional model generated in this study, on average, outperformed the human planner for six out of 13 dose metrics considered. Among the 5 differences that were statistically significant, all were in favor of the KBP generated plans. These data demonstrate that the KBP model can, on average, produce plans at least as good as plans generated by an experienced planner.

Dosimetric improvements using our KBP model were modest in comparison to a previously published lung model[31] by Fogliata et al. Fogliata et al. generated a KBP model for locally advanced (stage IIIA and B) lung cancers and validated with a closed loop (validation plans were a part of the model) and open loop (validation plans were not a part of the model) approach. For example, in the model published by Fogliata et al. dosimetric improvements in the near-maximum esophageal dose (D_{1cc}) were 3.9 Gy. Our model demonstrated a modest improvement in the maximum esophagus dose (0.74 Gy). Our improvements to mean lung dose were 0.66 Gy compared to improvements of 1.2 Gy and 0.8 Gy in the ipsilateral and contralateral lungs, respectively, from the Fogliata study. Furthermore, improvements we observed were significant in five of 13 dose metrics, V20Gy and mean dose to functional lung, V20Gy and mean dose to lung minus GTV, and mean esophageal dose, compared to the majority of dose metrics showing significance by Fogliata. While it is possible that dosimetric savings in our study were constrained by the addition of an additional, functional lung structure, and the associated set of dose constraints used in optimization, a previous study[9] demonstrated that functional sparing could be achieved with minimal impact to other critical structures.

To the best of our knowledge, the current work is one of the first implemented knowledge-based planning in the realm of functional-guided thoracic radiotherapy. Previous work[28] published by Li et al. examined knowledge-based planning for pelvic bone marrow sparing in gynecological patients. The Li study demonstrated automated planning routines that were capable of producing consistently high quality plans with respect to a validation set. An emphasis in the study was placed on the applicability to clinical trials with defined dosimetric objectives and how plan quality can be improved through the use of a knowledge-based model.

Our translation of knowledge-based planning to ventilation avoidance planning techniques in thoracic radiotherapy is a valuable contribution to the area of functional- guided planning for two reasons. First, the distribution of functionality throughout the lung can be highly variable and patient-specific. The non-intuitive distributions of the ventilation contour and relative lack of experience for planners can make it challenging to achieve optimal sparing of functional lung during the optimization process. Presented as a visual example, Figure 2 shows the ventilation contour displayed in an axial, coronal, and sagittal CT slice. Through the use of DVH estimations and auto-generated plan objectives, KBP is positioned well to

bridge the gap in experience between traditional planning techniques and functional-guided planning.

The second benefit to implementing KBP in functional-guided radiotherapy is the potential to improve plan quality consistency. Studies have shown that KBP can improve the consistency of plan quality[28, 32]. Although most current trials are single-institution, several on-going thoracic functional radiotherapy trials are multi-centers efforts. Furthermore, if the results of the initial early phase trials are successful, the next logical step will be expanded, national, multi-center efforts. As with any novel planning techniques (and especially given the difficult planning scenarios with functional avoidance) plan consistency and quality across multiple centers will be a challenge. KBP has the potential to aide with plan quality in large, multi-center efforts in functional avoidance radiotherapy.

There are a few limitations to our study that should be addressed. First, functional-guided planning using 4DCT ventilation imaging is a new treatment technique that is being investigated in several, ongoing clinical trials. As such, the approach to planning and implementation of the treatment technique is being refined based on clinical data from the trials. We developed the knowledge-based planning model based on our own trial experience and published retrospective studies[3, 8]. This means that as functional-guided radiotherapy matures, knowledge-based planning models must adapt to changes in strategy. Most importantly, this includes changes in which dose-function metrics are emphasized in optimization and inclusion criteria determining which patients stand to benefit most from functional-guided radiotherapy. Model refinement based on changing priorities within the treatment strategies is an important task. This can be achieved by modifying the training set to be reflective of current priorities or by refining the older plans in an effort to build a larger training set indicative of up-to-date treatment strategies[33]. The commercial implementation of knowledge-based planning presented in our study allows for these changes by selectively editing data sets and auto-generated optimization parameters according to user preferences.

Additionally, the presented results comparing knowledge-based planning metrics with traditional planning could be skewed by not running additional optimizations beyond the first pass through with the knowledge-based planning approach. We took this approach in order to objectively present the differences between methods. In reality, multiple optimizations are typically performed, and we don't envision that changing with knowledge-based planning. What KBP does provide is a high-quality initial plan upon which small changes may result in further dosimetric improvements of the plan all while helping to maintain a consistent level of plan quality.

Conclusion

Functional-guided radiotherapy is an exciting new treatment strategy that has the potential to reduce toxicity events associated with lung cancer radiotherapy. The novelty of the treatment technique and lack of experience associated with it present problems in its implementation. The use of a knowledge-based planning (KBP) model helps to address these shortcomings by estimating achievable dose reductions to critical structures and areas of functional lung

while also providing an optimization template to improve plan quality and consistency. The current work successfully implemented a KBP model for functional-guided radiotherapy. The plans generated with KBP outperformed user-generated plans for six out of 13 dose metrics evaluated. Among the five dose metrics that were significantly different between KBP and user-generated plans, all were in favor of the KBP model. The consistent improvement among the significant differences points towards a feasible approach towards improving plan quality in functional-guided radiotherapy.

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References

1. Seppenwoolde Y, De Jaeger K, Boersma LJ, Belderbos JSA, Lebesque JV. Regional differences in lung radiosensitivity after radiotherapy for non-small-cell lung cancer. *International Journal of Radiation Oncology Biology Physics*. 2004; 60:748–58.
2. Vinogradskiy Y, Castillo R, Castillo E, Tucker SL, Liao Z, Guerrero T, et al. Use of 4-Dimensional Computed Tomography-Based Ventilation Imaging to Correlate Lung Dose and Function With Clinical Outcomes. *International Journal of Radiation Oncology Biology Physics*. 2013; 86:366–71.
3. Faught AM, Yamamoto T, Castillo R, Castillo E, Zhang J, Miften M, et al. Evaluating which dose-function metrics are most critical for functional-guided radiotherapy with CT ventilation imaging. *International Journal of Radiation Oncology* Biology* Physics*. 2017
4. Lan F, Jeudy J, Senan S, van Sornsens de Koste JR, D'Souza W, Tseng H-H, et al. Should regional ventilation function be considered during radiation treatment planning to prevent radiation-induced complications? *Medical Physics*. 2016; 43:5072. [PubMed: 27587037]
5. Yaremko BP, Guerrero TM, Noyola-Martinez J, Guerra R, Lege DG, Nguyen LT, et al. Reduction of normal lung irradiation in locally advanced non-small-cell lung cancer patients, using ventilation images for functional avoidance. *International Journal of Radiation Oncology Biology Physics*. 2007; 68:562–71.
6. Lavrenkov K, Christian JA, Partridge M, Niotsikou E, Cook G, Parker M, et al. A potential to reduce pulmonary toxicity: the use of perfusion SPECT with IMRT for functional lung avoidance in radiotherapy of non-small cell lung cancer. *Radiother Oncol*. 2007; 83:156–62. [PubMed: 17493699]
7. Bates EL, Bragg CM, Wild JM, Hatton MQ, Ireland RH. Functional image-based radiotherapy planning for non-small cell lung cancer: A simulation study. *Radiother Oncol*. 2009; 93:32–6. [PubMed: 19552978]
8. Waxweiler T, Schubert L, Diot Q, Faught A, Stuhr K, Castillo R, et al. A complete 4DCT-ventilation functional avoidance virtual trial: Developing strategies for prospective clinical trials. *Journal of Applied Clinical Medical Physics*. n/a-n/a.
9. Faught AM, Miyasaka Y, Kadoya N, Castillo R, Castillo E, Vinogradskiy Y, et al. Evaluating the Toxicity Reduction with CT-Ventilation Functional Avoidance Radiotherapy. *International Journal of Radiation Oncology* Biology* Physics*.
10. Kabus S, von Berg J, Yamamoto T, Opfer R, Keall PJ. Lung ventilation estimation based on 4D-CT imaging. :73–83.
11. Guerrero T, Sanders K, Castillo E, Zhang Y, Bidaut L, Pan T, et al. Dynamic ventilation imaging from four-dimensional computed tomography. *Phys Med Biol*. 2006; 51:777–91. [PubMed: 16467578]
12. Reinhardt JM, Ding K, Cao K, Christensen GE, Hoffman EA, Bodas SV. Registration-based estimates of local lung tissue expansion compared to xenon CT measures of specific ventilation. *Medical Image Analysis*. 2008; 12:752–63. [PubMed: 18501665]

13. Christensen GE, Song JH, Lu W, El Naqa I, Low DA. Tracking lung tissue motion and expansion/compression with inverse consistent image registration and spirometry. *Medical physics*. 2007; 34:2155–63. [PubMed: 17654918]
14. Castillo R, Castillo E, Martinez J, Guerrero T. Ventilation from four-dimensional computed tomography: density versus Jacobian methods. *Physics in Medicine and Biology*. 2010; 55:4661–85. [PubMed: 20671351]
15. Du KF, Bayouth JE, Cao KL, Christensen GE, Ding K, Reinhardt JM. Reproducibility of registration- based measures of lung tissue expansion. *Medical Physics*. 2012; 39:1595–608. [PubMed: 22380392]
16. Yamamoto T, Kabus S, Lorenz C, Mittra E, Hong JC, Chung M, et al. Pulmonary Ventilation Imaging Based on 4-Dimensional Computed Tomography: Comparison With Pulmonary Function Tests and SPECT Ventilation Images. *International Journal of Radiation Oncology* Biology* Physics*. 2014
17. Brennan D, Schubert L, Diot Q, Castillo R, Castillo E, Guerrero T, et al. Clinical Validation of 4-Dimensional Computed Tomography Ventilation With Pulmonary Function Test Data. *International Journal of Radiation Oncology Biology Physics*. 2015; 92:423–9.
18. Fuld MK, Easley RB, Saba OI, Chon D, Reinhardt JM, Hoffman EA, et al. CT-measured regional specific volume change reflects regional ventilation in supine sheep. *Journal of Applied Physiology*. 2008; 104:1177–84. [PubMed: 18258804]
19. Mathew L, Wheatley A, Castillo R, Castillo E, Rodrigues G, Guerrero T, et al. Hyperpolarized He-3 Magnetic Resonance Imaging: Comparison with Four-dimensional X-ray Computed Tomography Imaging in Lung Cancer. *Academic Radiology*. 2012; 19:1546–53. [PubMed: 22999648]
20. Vinogradskiy Y, Koo PJ, Castillo R, Castillo E, Guerrero T, Gaspar LE, et al. Comparison of 4-Dimensional Computed Tomography Ventilation With Nuclear Medicine Ventilation-Perfusion Imaging: A Clinical Validation Study. *International Journal of Radiation Oncology Biology Physics*. 2014; 89:199–205.
21. Kipritidis J, Siva S, Hofman MS, Callahan J, Hicks RJ, Keall PJ. Validating and improving CT ventilation imaging by correlating with ventilation 4D-PET/CT using 68Ga-labeled nanoparticles. *Medical physics*. 2014; 41:011910. [PubMed: 24387518]
22. Yamamoto T, Kabus S, von Berg J, Lorenz C, Keall PJ. Impact of Four-Dimensional Computed Tomography Pulmonary Ventilation Imaging-Based Functional Avoidance for Lung Cancer Radiotherapy. *International Journal of Radiation Oncology Biology Physics*. 2011; 79:279–88.
23. Yamamoto T, Kabus S, Klinder T, Lorenz C, von Berg J, Blaffert T, et al. Investigation of four-dimensional computed tomography-based pulmonary ventilation imaging in patients with emphysematous lung regions. *Physics in Medicine and Biology*. 2011; 56:2279–98. [PubMed: 21411868]
24. Bayouth J, Du K, Christensen G, Smith B, Buatti J, Reinhardt J. Establishing a relationship between radiosensitivity of lung tissue and ventilation. *International Journal of Radiation Oncology* Biology* Physics*. 2012; 84:S31–S2.
25. Moore KL, Appenzoller LM, Tan J, Michalski JM, Thorstad WL, Mutic S. Clinical implementation of dose-volume histogram predictions for organs-at-risk in IMRT planning. 1. IOP Publishing; 012055
26. Appenzoller LM, Michalski JM, Thorstad WL, Mutic S, Moore KL. Predicting dose-volume histograms for organs-at-risk in IMRT planning. *Medical physics*. 2012; 39:7446–61. [PubMed: 23231294]
27. Yuan L, Ge Y, Lee WR, Yin FF, Kirkpatrick JP, Wu QJ. Quantitative analysis of the factors which affect the interpatient organ-at-risk dose sparing variation in IMRT plans. *Medical physics*. 2012; 39:6868–78. [PubMed: 23127079]
28. Li N, Carmona R, Sirak I, Kasaova L, Followill D, Michalski J, et al. Highly Efficient Training, Refinement, and Validation of a Knowledge-based Planning Quality-Control System for Radiation Therapy Clinical Trials. *International Journal of Radiation Oncology* Biology* Physics*. 2017; 97:164–72.

29. Waxweiler TV, Schubert LK, Diot Q, Castillo R, Castillo E, Guerrero TM, et al. Towards a 4DCT-Ventilation Functional Avoidance Clinical Trial: Determining Patient Eligibility. *International Journal of Radiation Oncology• Biology• Physics*. 2015; 93:E416–E7.
30. Castillo E, Castillo R, Martinez J, Shenoy M, Guerrero T. Four-dimensional deformable image registration using trajectory modeling. *Physics in Medicine and Biology*. 2010; 55:305–27. [PubMed: 20009196]
31. Fogliata A, Belosi F, Clivio A, Navarria P, Nicolini G, Scorsetti M, et al. On the pre-clinical validation of a commercial model-based optimisation engine: Application to volumetric modulated arc therapy for patients with lung or prostate cancer. *Radiotherapy and Oncology*. 2014; 113:385–91. [PubMed: 25465726]
32. Shiraishi S, Tan J, Olsen LA, Moore KL. Knowledge-based prediction of plan quality metrics in intracranial stereotactic radiosurgery. *Medical physics*. 2015; 42:908–17. [PubMed: 25652503]
33. Chatterjee A, Serban M, Abdulkarim B, Panet-Raymond V, Souhami L, Shenouda G, et al. Performance of Knowledge-Based Radiation Therapy Planning for the Glioblastoma Disease Site. *International Journal of Radiation Oncology• Biology• Physics*. 2017; 99:1021–8.

Figure 1.

A regression plot of the geometric distribution principal component score is presented for the functional contour. The plot can be used to assess the consistency of the plans included in the KBP model.

Figure 2.

An example of a typical ventilation contour is presented in axial (left), coronal (center), and sagittal (right) planes. The distribution of the contour is unique to each patient and can appear diffuse and speculated in some patients and more evenly distributed in others.

Table 1

Knowledge-based planning generated optimization objectives for the functional-guided radiotherapy model are presented.

Structure	Volume (%)	Objective Dose (cGy)	Priority
PTV	0	110% of Rx	230
	100	100% of Rx	200
Ventilation - PTV	*	1000	70
	*	2000	80
	*	3000	70
	*	4000	70
	Line	*	80
Esophagus	0	*	50
	Line	*	50
Heart	Line	*	50
Lungs -PTV	*	2000	60
	Line	*	60
Spinal Cord	0	*	50
	0	4500	130

* Asterisks are used to denote fields in which the model auto-generated the objective value.

Table 2

Model training results were assessed by examining coefficient of determination values (R^2) average coefficient of variation (X^2) for each of the trained structures.

Structure	R^2	X^2
Esophagus	0.79	1.09
Heart	0.79	1.13
L. Lung	0.92	1.11
R. Lung	0.98	1.22
Lungs	0.94	1.24
Lungs -PTV	0.93	1.24
Cord	0.67	1.20
Ventilation	0.90	1.15
Ventilation -PTV	0.81	1.00

Table 3

A comparison of the average dose metrics from the 20 patient validation set. ‘KBP’ denotes plans generated using knowledge-based planning while ‘Non-KBP’ were user generated plans. PTV doses are reported as a percentage of the prescription dose. Significance was tested using a Wilcoxon Signed Rank test.

Structure	Objective	Average Value		p-Value
		Non-KBP	KBP	
PTV	V100%	94.9%	94.2%	0.27
	D95%	99.8%	99.6%	0.56
	Max Dose	115.6%	116.1%	0.70
Functional Lung	V20 _{Gy}	20.5%	18.7%	0.005
	Mean Dose	1299 cGy	1204 cGy	0.001
Lung - GTV	V20 _{Gy}	25.1%	23.5%	0.01
	Mean Dose	1385 cGy	1319 cGy	0.002
Heart	V30 _{Gy}	6.1%	6.5%	0.90
	V40 _{Gy}	3.0%	3.2%	0.92
	Mean Dose	855 cGy	829 cGy	0.20
Cord	Max Dose	3189 cGy	3371 cGy	0.10
Esophagus	Mean Dose	2617 cGy	2477 cGy	0.005
	Max Dose	5258 cGy	5344 cGy	0.25