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New Approach in Lung Cancer Radiotherapy Offers Better Normal Tissue Sparing

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Abstract

Purpose—Medical images are more than pictures. They contain additional quantitative information which can be interrogated, quantified, and utilized. Besides anatomical information computed tomography (CT) imaging data provides electron density information. Radiotherapy use of this density information is limited to its application only in dose calculations. The direct product of dose, density, and volume forms a quantity called integral dose. The integral dose delivered to a volume of interest is the total energy deposited in that volume. Here it is hypothesized that minimization of the integral dose is advantageous in radiotherapy planning. The purpose of this work is to study the incorporation of quantitative imaging information in radiotherapy inverse optimization through total energy minimization (Energy hereafter).

Design—Twenty lung patient plans were studied. For each patient density was quantified on voxel-by-voxel basis through image gray value-to-density conversion curves. Energy-based objective function was used for inverse radiotherapy plan optimization. The obtained plans were evaluated in the light of current standard of care, based on dose-volume (DVH) optimization approach.

Results—The statistical significance analyses of the results indicated that the doses to normal tissue were between 14% to 45% lower, when Energy-based optimization was used instead of DVH-based optimization.

Conclusion—Incorporation of quantitative imaging information, through CT derived density, in the optimization cost function allows reduction of dose to normal tissue for NSCLC cases. Energy-based radiotherapy plans result in lower normal tissue dose and potentially lower complication rates compared to standard of care.

Keywords

integral dose; mass; IMRT; energy; lung; volume; optimization

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1. Introduction

The prevalent histological types for lung cancer are non-small cell (NSCLC) and small-cell (SCLC) lung carcinomas.[1] In about 80% to 85% of the diagnosed lung cancer cases the histology is NSCLC.[2] Modern radiotherapy of NSCLC employs intensity modulated radiotherapy (IMRT).[3–5] IMRT allows excellent dose conformality, while at the same time sparing the surrounding organs at risk (OARs) and normal tissue. IMRT is achieved through inverse optimization, where computerized software solves series of equations, aiming to satisfy the requirements imposed before the initiation of the optimization. The main goal of the entire optimization process is to shape the radiation intensity in such a way that adequate therapeutic doses are delivered to the tumors, while minimizing the dose to the nearby tissues. In the current IMRT paradigm the objective functions used in the inverse optimization are based on dose-volume concept, i.e. doses to certain volumes of normal tissue or OARs are iteratively adjusted in order to reach an acceptable clinical solution. The dose-volume concept has been around in the last three decades since the introduction of IMRT, with very little attempts for further more meaningful modification. While this might have been an appropriate solution in the past, where dose calculations were performed without density corrections, today all clinically used dose calculation algorithms account for the heterogeneous nature of tissue. The use of more sophisticated objective functions for inverse optimization however has lagged behind. A natural approach for modification of the objective functions is the incorporation of density information which is readily available from the pre-treatment CT data. Almost obvious application of mass in the objective function is to explore the concept of integral dose, where tissue density is explicitly incorporated through voxel (volume element) mass.[6] The concept of integral dose is very popular in radiology, where all modern CT scanners report the integral dose delivered during the CT scan. However, the application of this concept to radiotherapy has been neglected so far. Utilization of integral doses in the inverse objective function is one of the first explicit applications of quantitative imaging information in cancer therapy, which in turn gives a whole new perspective of this completely new approach.

Thoracic cancers are situated in a rather heterogeneous anatomy, where densities can vary from almost air to bone. There are several OARs in the thoracic region, such as spinal cord, heart, esophagus, ribs, and lung, which are sensitive to radiation, and thereby need to be spared as much as possible during treatment plan preparation and treatment delivery. Depending on the tumor location and the relative positions of the anatomical structures, those OARs can affect the achievable treatment plans to different degrees. The thoracic region is very suitable for integral dose-based inverse optimization since the target(s) is embedded within this heterogeneous media where tissue density would affect the optimization convergence,[7] and thereby the use of mass explicitly in the optimization objectives is a logical step toward utilization of this, readily available but unexplored so far, piece of quantitative imaging information.

The purpose of this work is to investigate the properties of integral dose minimization based inverse optimization (Energy-based hereafter) for NSCLC. This newly proposed inverse optimization paradigm is explored in the light of the current standard of care, realized through dose-volume-histogram (Dvh-based hereafter) optimization.

2. Materials and Methods

2.1. Optimization functions

As the term suggests integral dose is $\int_V D dm$, where D is dose, m is mass, and the integration is over the volume V of interest (VOI). So far integral dose has been used only to explore the properties of treatment plans. [8–10] However, it has been argued recently that integral dose has some far reaching desirable properties, which can be used in radiotherapy inverse plan optimization.[6] The integral dose represents the total energy deposited in a VOI. Therefore, minimizing the integral dose is in essence a minimization of the total deposited energy in that VOI.

The discrete form of the objective function F^j used in this work is presented in

$$F^j = \frac{1}{E_{desired}} \sum_{i \in V} d_i \rho_i v_i = \frac{1}{E_{desired}} \sum_{i \in V} d_i m_i \quad (1)$$

Equation 1, where V denotes the volume of the anatomical structure of interest, d_i is the dose in voxel i , ρ_i is the density of the material in that voxel, m_i is the mass of that material, and v_i is the volume of the voxel.[6] The summation is over all dose voxels contained in the volume of the organ of interest V . The quantity $E_{desired}$ is the desired integral dose which needs to be imparted on the organ of interest. For each anatomical structure considered in the optimization there is only one Energy-based objective function of the type given by Equation 1. Summation overall objective functions F generates a composite objective function outlined in Equation 2. The

$$F = \sum_{j=1}^N F^j \quad (2)$$

normalization to $E_{desired}$ ensures that all objective functions F^j would have comparable magnitudes thereby allowing the generation of the composite objective function. Furthermore, $E_{desired}$ is the only adjustable parameter through which the objective function in Equation 1 can be optimized. Namely, varying this parameter forces the optimizer to change the dose distribution so that a new 3D solution is found.

From the other hand, the most commonly used Dvh-based optimization is realized

$$F^j = \sum_{i \in V} \left(\frac{d_i - d^j}{d^j} \right)^2 \Delta v_i \quad (3)$$

through an objective function denoted by Equation 3. Again, V denotes the volume of the anatomical structure of interest, d_i is the dose in voxel (3D volume element) i of the volume V , $\bar{d}$ is the desired dose in each voxel, and v_i is the normalized voxel volume with respect to the total organ volume V . [6, 11, 12] An optimization function F is created for each optimization objective specified for the organ of interest. In the case of Dvh-based optimization however, more than one objective can be specified for an anatomical structure of interest. As in the case of the Energy-based optimization, the normalization of the voxel volume to the total organ volume is performed such that a composite objective function (cf. Equation 2) can be generated. The adjustable parameter in Equation 3 is the desired dose $\bar{d}$ to the fractional volume of interest.

2.2. Patient Data

The computed tomography (CT) data from twenty NSCLC patients was used in this study. All patients had time-resolved (4D) CT studies, where the 4D data sets were retrospectively reconstructed. The 4D CT scans were performed on a Philips Big Bore Brilliance multi-slice CT scanner (Philips Medical Systems, Cleveland, OH) interfaced with a Varian (Varian Medical Systems, Palo Alto, CA) real-time position management (v. 1.62) respiratory gating system. [13] The range of tumor motion was estimated from the 4D CT data set. In all of the cases used in this study the target range of motion was less than 0.5 cm. According to AAPM TG 76 recommendations no motion management techniques were considered in the process of treatment planning. [14]

The disease stages for the cohort included T2 (7 patients), T3 (10 patients), and T4 (3 patients) with different nodal involvements, ranging from N0 to N3. All patients were treated with conventional RT, while in approximately half of the patients radiation was combined with chemotherapy.

2.3. Treatment Planning

For the purposes of realistic estimation of lung doses without motion management, a mid-ventilation phase, representing an average phase over the entire breathing cycle, was selected for treatment planning purposes. [15] In the estimation of this mid-ventilation phase, an analytic sinusoidal function was used as a clinical approximation of respiratory motion to calculate the probability density function of the motion. [16, 17] Based on that probability density function, the phase used for inverse optimization and dose calculation corresponds to 25%. [18] Another alternative would be to use an average density projection or a free-breathing CT scan for the purposes of density and mass calculations, since the Energy-based optimization might be affected by the volume averaging of the CT raw data. This effect would be investigated in a follow-up study.

In addition to mid-ventilation, a maximum intensity projection CT data set was generated for contouring purposes. [19] The gross tumor volume (GTV) was derived from the maximum intensity projection data, combined with all other available diagnostic imaging studies (i.e., CT, MRI, or PET-CT). A clinical target volume was derived from the GTV by a uniform expansion of approximately 0.5 cm, while a planning target volume (PTV) was obtained from the CTV by an additional uniform expansion of 0.5 cm. In addition, heart, spinal cord,

esophagus, and healthy lung were contoured. The lungs were contoured with the help of a Pinnacle3 (Philips Medical Systems, Fitchburg, WI) treatment planning system automatic contouring tool, where default (lower and upper limits set to 800 and 4096 HUs respectively) CT threshold values were used. The lung contours were then visually inspected and verified on each CT slice.

For each patient, two deliverable IMRT plans were created.[7, 20, 21] In each of those plans dose-based objective functions were used for the PTV. Those functions included minimum, maximum, and uniform dose for the target volume. The objective functions for the OARs however differed. In the first plan they were dose-volume based (DVH plan)[11, 12, 22] according to the current clinical standard of care. In the second plan, the optimization objectives utilized the density derived imaging information, and were based on energy minimization (Energy plan).[6] In all other aspects, namely dose grid resolution, number of beams (seven co-planar 6 MV), beam directions, number of segments in the step-and-shoot IMRT, segment area, and minimum monitor units per segment, the plan set-ups were identical. The dose calculations were performed with Pinnacle TPS collapsed cone convolution dose calculation algorithm, which is suitable for dose calculations in heterogeneous media.[23–25] In both the DVH and the Energy plan the minimum, the maximum and the uniform dose objectives for the PTV were set to the same values. The prescription doses to the PTVs ranged from 6600 to 7600 cGy, prescribed in 200 cGy daily fractions. The individual patient prescriptions were based on the constraints that dose to 2% of spinal cord should be less than 4500 cGy, doses to 20% and 30% of lung volumes are less than 3000 and 2000 cGy respectively, one third of the heart and 50% of the esophagus receive less than 3000 cGy. IMRT optimization was carried over with successive reduction of doses to OARs according to the DVH- and Energy-based optimization objectives, until standard deviation of dose across the PTV became 4%.[26]

2.4. Analyses

As it was mentioned above DVH-optimization is for a large part the modern standard of care in modern radiation therapy. Therefore, the doses derived from the DVH optimization were used as a reference standard to which the Energy-based doses were compared in the analyses. The performance of each optimization scheme was assessed on the basis of commonly used dose-volume indices (DIs), [7, 27, 28] since DVH metric is the tool of choice in the clinical decision making. The tallied DIs included dose to 95% of the PTV volume, doses to 2% of the cord, 33% of the heart, doses to 15%, 30%, and 50% of the esophagus, as well as doses to 20% and 30% of total lung volume. Furthermore, volumes encompassed by 2000 cGy and 3000 cGy isodose lines were cross-compared.

Another surrogate for dose-volume metric, rather commonly used for plan comparisons, is based on generalized equivalent uniform doses (gEUDs).[29, 30] This metric conveys the biological significance of the radiation dose, and its effects on tissue. There are different normal tissue complication probability (NTCP) models, derived on the basis of this metric, with the most commonly used being the Lyman-Kutcher-Burman (LKB) model.[31, 32] Therefore, in addition to DIs, gEUDs were also tallied for evaluation of the treatment plans.

The gEUD parameters a for the different organs were obtained from the literature.[33–37] The specific values are listed in Table 1.

A statistical equivalence tests were used to determine the minimum doses, as well as the isodose volumes, such that the reference and the compared quantities were deemed statistically equivalent. In essence, the statistical analysis estimates what increase in dose or volume is needed from the results of the Energy-based optimization so that it can be considered statistically equivalent to the results of the DVH-based optimization. The test was performed for each tallied index using two one-tailed paired t -tests for p -values of less than 0.05.[7, 18]

3. Results

Figure 1 exemplifies the DVH and the isodose comparisons for one case from the patient cohort. On the left hand side the DVHs are presented, while on the right hand side the isodoses for three views, axial (top), sagittal (middle), and coronal (bottom) are presented. The column with isodose plots to the farthest right outlines the Energy-based plan, while the other outlines the isodose distributions obtained from the DVH-based optimization. The figure provides an indication that for this particular case the Energy-optimized plan is capable of reducing the dose to the contralateral lung and the low and intermediate dose to the heart, esophagus and spinal cord.

3.1. Comparison of dose indices

In comparison and presentation of the DIs, isodoses, and isovolumes normalization was utilized. For each patient the Energy-derived DIs, isovolumes, and gEUDs were normalized to their counterparts derived from the DVH plan. This normalization is arbitrary, but in this case DVH-derived quantities were used as reference, since DVH optimization is the current standard of care. The employed normalization sets a common scale on which the paired quantities can be presented on a common plot.[7, 27, 38] Since PTV doses were normalized such that for each case 95% of the PTV received the same dose with DVH and Energy optimization (cf. the PTV DVHs on Figure 1) target DIs would not be presented in graphical format. The use of identical target objective function for optimization and the use of identical prescription dose on case-by-case basis would warrant equivalent therapeutic effect with both optimization approaches.

Figure 2 presents the normalized DIs and isovolumes for all OARs. The top panel contains spinal cord, heart, and esophagus data, while the bottom panel contains the lung data. The legends in the two panels outline the meaning of the symbols on these scatter plots. In addition, a dotted line, representing the value of one, is plotted in each panel. The purpose of this line is to aid the comprehension of the results. By the virtue of the performed normalization if a plotted number is greater than unity it means that the corresponding tallied quantity derived from the Energy-based plan is larger than their counterpart from the DVH-based plan, and vice versa. The top panel of the figure shows that for 87 out of 100 indices for heart, spinal cord, and esophagus the Energy-based plans result in lower doses. The differences range from +7% ($DI_{2\%}^{cord}$ for patient 14) where DVH-derived dose is lower, to about -60% ($DI_{2\%}^{cord}$ for patient 5) where the Energy-derived cord dose is lower.

The results for the lung DIs and isovolumes in the bottom panel are qualitatively very similar to the results for the OARs from the top panel. Again, in 74 out of the 80 tallied DIs and isovolumes the Energy-based plans are delivering lower doses to the lungs as compared to DVH-based plans. The differences are with a somewhat smaller magnitude ranging from +10% to -40%.

3.2. Comparison of gEUDs

The normalized gEUDs are presented on Figure 3. The normalization is performed similarly to the normalization for Figure 2. From the 80 gEUDs for the spinal cord, the heart, the esophagus, and the lungs only in 3 instances are the normalized gEUDs greater than unity, i.e. in those 3 cases the DVH-derived gEUDs are lower than the Energy-derived gEUDs. The magnitude is similar to the one observed in the top panel of Figure 2 – ranging from +10% (spinal cord gEUD for patient 16) to more than -60% (spinal cord gEUD for patient 18).

3.3. Statistical analyses

Statistical analyses tests were performed in order to categorize the spread of the DIs, isovolumes, and gEUDs, observed on Figures 2 and 3. Table 2 contains the data for the DIs and the isovolumes. In the first column the interrogated quantity is given, in the second column the average value of the index is presented (either in cGy or cm³), the third column outlines the interval required for statistical equivalence in absolute units, and the last column is the percent change required for a statistical equivalence between the two optimization schemes. Note, that the average tallied indices presented in the second column are derived from the DVH-optimized plans. The last column of the table indicates that the achievable sparing of the OARs by Energy-based inverse optimization ranges from 12% to more than 45%. Table 2 is similar to Table 2, but the presented data is for the statistical equivalence of the gEUDs and the average doses to lungs and heart. The differences are quantitatively very similar to the differences observed for the DIs and the isovolumes.

4. Discussion

A close inspection of Equations 1 and 3 demonstrates the clear difference between the forms of the Energy- and Dvh-based optimization functions. While Dvh-based optimization function is purely dose-volume based, where all voxels are treated equally, the Energy-based optimization function from the other hand contains physical density explicitly. From physics stand point it may seem counterintuitive that this dependence on density will significantly affect the convergence of the optimization solution. However, it has been shown that even differences in dose calculation algorithm can result in different optimization solutions.[7] In that work it was found that the effects of density on the dose calculations do not affect the target coverage, while substantial differences in the OAR doses were observed. Therefore, it should not be unexpected that the incorporation of the density into the optimization function would have much more pronounced effect on the obtained solution. It has been shown recently that even almost undistinguishable features, such as tumor textures can have dramatically different impact on the therapy outcomes.[39–41] Thereby, incorporation of density information into the radiotherapy inverse optimization function is a natural evolution of the field of radiation therapy.

It should be noted however that Energy-based optimization did not outperform Dvh-based optimization for all investigated DIs and gEUDs. It is difficult to pinpoint a single factor that contributes most significantly to the observed differences. Inverse optimization is a complex process, where tens of thousands parameters are varied simultaneously by the optimization algorithm so that the solution converges. Furthermore, different patients have different anatomies (relative organ positions and organ sizes), different physiologies (different density distributions), and different tumor locations. All of those factors, combined with certain planning set-ups (beam number, beam directions, allowed number of segments, etc.), probably contribute to the performance of each specific optimization approach on an individual patient basis.

To put in a perspective the implications of the use of Energy-based inverse optimization a NTCP model is used for illustrative purposes. This utilized model is based on the original work by Kutcher *et al.*, and is presented on Figure 4.[32] The population derived changes in the gEUDs can range from 13% to 45% as can be concluded from Table 3. On an individual basis however, they can be even larger. Depending on the absolute value of the gEUD those differences may make an appreciable difference. If average lung dose is of the order of 1400 cGy, a change of 13% in gEUD would result in a modest 3% decrease of NTCP. In case that the average lung dose is of the order of 2500 cGy however, a gEUD difference of 13% would result in NTCP change of approximately 10%, which becomes non-negligible. The situation with the heart NTCP is rather similar. If the heart dose results in a low gEUD, i.e. toward the low dose part of the NTCP curve a large change of the gEUD would have little effect on the probability change. However, if the gEUD is above 1500 cGy, then a change of ~45% in the heart gEUD can result in about ~9–10% difference in the NTCP. Likewise, if esophageal gEUD changes from 1500 cGy to 2000 cGy (35% increase based on Table 3 data) the NTCP change would be about 4%. If the esophageal dose in a particular case is approximately 3000 cGy then a change of 35% would result in gEUD of 4050 cGy which would translate into NTCP change of almost 20%.

5. Conclusion

In this work a new inverse optimization paradigm was applied to radiotherapy treatment planning for NSCLC. In this new paradigm the objective cost function used in the IMRT optimization is represented by an integral of dose over mass. Thereby, the solution of the IMRT problem is converted into minimization of the total deposited energy for the healthy anatomical structures in proximity to the irradiated tumors. The results obtained from the Energy-based IMRT optimization for the patient cohort were reviewed in the light of most commonly used dose-volume optimization results. It was found that for majority of the patient cases the direct incorporation of quantitative imaging information in the objective optimization function results in lower doses to the surrounding healthy tissue for equivalent therapeutic effect. With more and more patients being cancer survivors, lower normal tissue doses would translate to decreased side effects as well as reduction of radiation induced cancers.

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Figure 1.

Dose-volume histograms and isodose plots for an arbitrary case. In the panel on the left the solid lines represent the DVHs derived from the DVH-based optimization, while the dashed lines correspond to the DVHs derived from the Energy-based optimization. The two panels on the right represent isodose plots in three different orientations, where the farthest right column represents the isodoses from the Energy-based plan. The isodose of the absolute dose levels are color coded in the figure legend.

Figure 2.

Normalized DIs and isovolumes for all organs at risk, used as dose limiting structures in radiotherapy plan optimization. The top panel presents the DIs for spinal cord, and esophagus, while the bottom panel outlines the data for lung.

Figure 3.

The same as Figure 2, but the plotted quantities are normalized gEUDs.

Figure 4.

Example normal tissue complication model based on LKB formalism. NTCP curves for the anatomical structures of concern in the thoracic region are presented. The curve designation is explained in the figure legend.

Table 1

Values of parameter a , used in gEUD calculations. The table outlines the anatomical site, the value of the quantity, the treatment site which was used for parameter estimation, and the source from where the value was obtained.

Organ	Value of parameter a	Treatment site	Reference
Spinal cord	7.4	Head-and-neck	[36]
heart	6.0	Hodgkin lymphoma survivors	[34]
esophagus	1.5	Lung	[33]
lungs	1.0	Lung	[35, 37]

Table 2

Results from the statistical equivalence tests, indicating the differences between the two optimization schemes ($p < 0.05$). The analyses indicate what the necessary increases in doses or volumes are for the Energy-based plans, so that they are statistically equivalent to the DIs and isovolumes obtained from the DVH-based plans.

Dose Volume Index	Average Reference Value of Tallied Index derived from DVH- based plans (range)	Statistical Equivalence Interval	Percent change for equivalency (% Sparing)
cord DI _{2%}	1465 cGy (125 cGy – 3896 cGy)	562 cGy	38
heart DI _{33%}	854 cGy (23 cGy – 2503 cGy)	391 cGy	46
esophagus DI _{30%}	1614 cGy (147 cGy – 5088 cGy)	578 cGy	36
esophagus DI _{50%}	1538 cGy (129 cGy – 2996 cGy)	665 cGy	43
esophagus DI _{15%}	2900 cGy (228 cGy – 5049 cGy)	589 cGy	20
lungs DI _{20%}	2476 cGy (180 cGy – 2992 cGy)	307 cGy	12
lungs DI _{30%}	1682 cGy (77 cGy – 1996 cGy)	327 cGy	19
Isovolum 2000 cGy	836 cm ³ (175 cm ³ – 1664 cm ³)	120 cm ³	14
Isovolum 3000 cGy	527 cm ³ (127 cm ³ – 1083 cm ³)	77 cm ³	15

Table 3

The same as Table 2 but for generalized equivalent uniform doses.

gEUD	Average Value of Reference Tallied Index (range)	Statistical Equivalence Interval	Percent change for equivalency (% Sparing) [%]
cord ($a = 7.4$)	1085 cGy (97 cGy – 2896 Cgy)	488 cGy	45
heart ($a = 6.0$)	450 cGy (40 cGy – 5014 cGy)	194 cGy	43
heart ($a = 1.0$)	962 cGy (24 cGy – 2196 cGy)	296 cGy	31
esophagus ($a = 1.5$)	1460 cGy (134 cGy – 3300 cGy)	283 cGy	19
lungs ($a = 1.0$)	1384 cGy (318 cGy – 2272 cGy)	175 cGy	13