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Scientific Article

Multiobjective, Multidelivery Optimization for Radiation Therapy Treatment Planning

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Abstract

Purpose: To introduce multiobjective, multidelivery optimization (MODO), which generates alternative patient-specific plans emphasizing dosimetric trade-offs and conformance to quasi-constrained (QC) conditions for multiple delivery techniques.

Methods and Materials: For M delivery techniques and N organs at risk (OARs), MODO generates M $(N + 1)$ alternative treatment plans per patient. For 30 locally advanced lung cancer cases, the algorithm was investigated based on dosimetric trade-offs to 4 OARs: each lung, heart, and esophagus (N = 4) and 4 delivery techniques (4-field coplanar intensity modulated radiation therapy [IMRT], 9-field coplanar IMRT, 27-field noncoplanar IMRT, and noncoplanar arc IMRT) and conformance to QC conditions, including dose to 95% (D95) of the planning target volume (PTV), maximum dose (Dmax) to PTV (PTV-Dmax), and spinal cord Dmax. The MODO plan set was evaluated for conformance to QC conditions while simultaneously revealing dosimetric trade-offs. Statistically significant dosimetric trade-offs were defined such that the coefficient of determination was >0.8 with dosimetric indices that varied by at least 5 Gy.

Results: Plans varied mean dose by >5 Gy to ipsilateral lung for 24 of 30 patients, contralateral lung for 29 of 30 patients, esophagus for 29 of 30 patients, and heart for 19 of 30 patients. In the 600 plans, average PTV-D95 = 67.6 ± 2.1 Gy, PTV-Dmax = 79.8 ± 5.2 Gy, and spinal cord Dmax among all plans was 51.4 Gy. Statistically significant dosimetric trade-offs reducing OAR mean dose by >5 Gy were evident in 19 of 30 patients, including multiple OAR trade-offs of at least 5 Gy in 7 of 30 cases. The most common statistically significant trade-off was increasing PTV-Dmax to reduce dose to OARs (15 of 30). The average 4-field plan reduced total lung V20 by 10.4% ± 8.3% compared with 9-field plans, 7.7% ± 7.9% compared with 27-field noncoplanar plans, and 11.7% ± 10.3% compared with 2-arc noncoplanar plans, with corresponding increases in PTV-Dmax of 5.3 ± 5.9 Gy, 4.6 ± 5.6 Gy, and 9.3 ± 7.3 Gy.

Conclusions: The proposed optimization method produces clinically relevant treatment plans that meet QC conditions and demonstrate variations in OAR doses.

Introduction

Modern radiation therapy relies on physician experience, knowledge of clinical trials, and established national guidelines to guide treatment decisions. Patient-specific variations, including age, comorbidities, and performance status, are routinely considered in radiation oncology plan design; however, this is within the

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confines of physician-specific prior experience, training, and guidelines. Treatment care plans are designed based on demonstrated benefit for a majority of patients, implying there exists a minority of patients who did not benefit from a given treatment care plan. The patient-specific dose trade-offs as functions of preferential sparing of an organ at risk (OAR), treatment objectives, and treatment technique are not routinely considered. This work presents a radiation therapy multiobjective, multidelivery optimization (MODO) to explore patient-specific dose trade-offs while conforming to clinical, quasi constrained (QC) conditions. We introduce the concept of QC conditions, as opposed to true constraints, because strict conformance to conflicting constraints is not possible.

Current treatment decisions are initially conveyed to the care team in prescribing radiation therapy by specificying variables including treatment machine, beam-delivery techniques, normal tissue dosimetric objectives, and desired target dosimetry. We claim that these specifications should be made based on knowledge of the patient-specific achievable dosimetry. Meyer et al[1] make a similar argument in describing a multiplan framework, claiming that multiple plans should be generated before selecting a patient-specific optimal radiation therapy. The major obstacle to implementation of this paradigm shift is the existence of powerful and robust optimization method that can conform to clinical constraints and demonstrate trade-offs in patient-specific achievable dosimetry. Automated optimization algorithms are being explored with increasing frequency[2-6]; however, existing approaches are based on a single, prescriptive model of preference, which is predefined by physician- and site-specific goals. With significant human effort, conventional systems allow for a set of solutions to be computed and compared (eg, comparing 3-dimensional conformal radiation therapy vs intensity modulated radiation therapy [IMRT]), and the Raysearch system (Raysearch Laboratories, Stockholm, Sweden) performs multicriteria optimization based on human-input objective functions.[7-9] Other developments, including auto-planning,[2,10] pareto navigation,[7-9] and knowledge-based treatment planning,[11,12] all require significant human interaction in objective function design and do not consider variations in treatment delivery strategies. Unlike existing methods, we propose an algorithm that encompasses multiple planning techniques (eg, beam and couch arrangements) and does not rely on human input of population or historical dose-volume objectives to explore dosimetric trade-offs.

The clinical constraints of radiation therapy are likely patient, and not population, specific. Therefore, development of a multiplan algorithm should explore target and OAR dosimetry in terms of trade-offs, not in terms of strictly constrained solutions. A clinically acceptable treatment plan is a subjective concept, which is likely patient, institution, dosimetrist, physicist, and physician dependent. The trade-off space we propose characterizes the range of achievable dosimetry encompassing patient-specific geometric variations and multiple delivery variations. To reduce the dimension of this complex problem, we adopt the method of Craft et al,[7] where the trade-off space is reduced to the list of target and OAR doses. Other researchers sought to create a concise decision space for radiation therapy planning after computation of a basis-set of plans, including Spalke et al,[13] who reduced the decision space via principal component analysis of beamlet fluence. Stabenau et al[14] reduced the number of basis plans generated using principal component analysis of the fluence vectors. Both of these studies considered variation in the beamlet space to determine an efficient representation of the achievable dosimetry space, but in clinical implementation a more direct communication of achievable dose and trade-offs is desirable. The space that characterizes the gain and loss in target and OAR dosimetry is the simplest multi-objective framework we can imagine.

MODO generates alternative treatment plans without human interaction or supervision. This work demonstrates the conformance to QC conditions and extraction of dosimetric trade-offs to OARs for advanced lung cancer.

Methods and Materials

MODO algorithm

The MODO objective function separates QC dose-volume conditions from other objectives. We define w_{qc} as the weighting of the QC objective O_{qc}, and for all other regions of interest (ROIs) w_{roi} is the importance weighting of the objective O_{roi}. The ROIs include OARs (with generic dose-volume objectives) and virtual structures, including rings about the target volume and other virtual structures. The objective function is defined such that

$$f = \sum_{\text{constraints}} \mathrm{w_{qc}O_{qc}} + \sum_{roi} \mathrm{w_{roi}O_{roi}} \quad (1)$$

The algorithm varies w_{qc} and w_{roi} in multiple iterations. The minimization of f and generation of deliverable treatment plans are the inner-most iterations of the qcMCO algorithm. Minimization used the ORBIT direct machine parameter optimizer (DMPO, Raysearch Laboratories) and the Smartarc extension of the DMPO optimizer[15] in the Pinnacle research treatment planning system version 9.710 (Philips Healthcare, Fitchburg, WI)

as appropriate for the treatment technique. This optimizer uses quasi-Newton descent[16] similar to the Broyden-Fletcher-Goldfarb-Shanno method[17] and includes an iterative update of the inverse Hessian.[18] This optimizer will not find global minima of the defined objective function, but it will search the local minima and settle on a solution when a fixed number of iterations are completed.[19] Wu and Mohan[19] detail the many local minima presented by objective functions such as Equation 1 and state that "their presence and consequences are not considered impediments in finding satisfactory solutions in routine optimization of IMRT plans using gradient method." This point is especially relevant when the true objective function is uncertain, which is certainly the case in patient-specific IMRT optimization.

The MODO algorithm as tested in this work performs the following sequential optimization:

$$\begin{aligned}&\text{for m}\in \text{M Machine delivery techniques}\\&\quad\text{for n}\in(0,\text{N})\ \text{OARs to tradeoff dose}\\&\qquad(1)\ f_{mn}=\text{DMPO}(f)\\&\qquad\text{s.t. } \text{w}_{\text{qc}}=100,\ \text{w}_{\text{n}}=\text{K},\ \text{w}_{\text{roi}}=1\ \forall\,\text{rois}\neq\text{n}\\&\qquad(2)\ f'_{mn}=\text{DMPO}(f_{mn})\\&\qquad\text{s.t. } \text{w}_{\text{qc}}=100,\ \text{w}_{\text{roi}}=\text{K}\cdot\text{w}_{\text{roi}}\ \forall\,\text{rois}\\&\qquad(3)\ \text{save plan}\ f'_{mn}\end{aligned}$$

The objective weight for ROI n is w_n. The knockdown factor, K, was set to 10^{-6}, but it could be varied to create different solutions. This factor was experimentally determined to sufficiently knockdown the importance of the n^{th} OAR objective to see gains (or trade-offs) to others in step 1. In step 2, K served to alter the objective function to conform to QC conditions. When $n = 0$, all $w_{roi} = 1$, and this solution serves as a basis for comparison. For the varying OARs, if no trade-off exists between the n^{th} OAR and other objectives, the solution of step 2 remains approximately equivalent to the $n = 0$ case, with the value of the objective function differing by a constant factor. If a trade-off exists, step 2 will reveal different solutions.

Dosimetric trade-offs were explored through generation of a covariance matrix with columns defined by lists of QC conditions, target dose indices, and OAR dose indices. From this covariance matrix we find correlations between increasing or decreasing dose to structures and describe the patient-specific decision space.

Algorithm evaluation

We evaluated the algorithm for conventional radiation therapy fractionation (2 Gy per fraction) for the treatment of locally advanced lung cancer. We tested whether the MODO algorithm reveals dosimetric trade-offs to OARs while simultaneously conforming to QC objectives for 30 patients with locally advanced lung cancer. The patient images and contours were collected on an institutional review board–approved study. For each patient, 4 delivery techniques and 4 OARs resulted in $M * (N + 1) = 20$ plans per patient.

The QC conditions included dose to 95% (D95) of the planning target volume (PTV) = 70 Gy, PTV maximum dose (Dmax) ≤77 Gy, and spinal cord Dmax <45 Gy. These QC conditions were based on clinical criteria; in the clinical plans for these patients the Dmax to the spinal cord was 47.4 Gy, with 3 of 30 of patients over 45 Gy. PTV-D95 ranged from 74.2% to 101.4% of prescription isodose, and PTV-Dmax ranged from 103.4% to 119.8% of prescription isodose. To achieve these conditions, the dose-volume objectives input into the optimizer were varied for a subset of patients. We used V10 <10% and Dmax <35 Gy for all OARs. Two rings were included in optimization, a 2-cm ring about the PTV with objective Dmax <63 Gy and V20 <10%, and a 1-cm ring 2-cm away from the PTV with objective Dmax <12 Gy. We report on the algorithm's conformance to these conditions for all patients and as a function of delivery technique for a fixed set of input dose-volume objectives implemented in the DMPO optimizer. We also report on dose homogeneity index (DHI), defined as PTV-D95/PTV-D5, and conformity index (CI), defined as the 70 Gy volume per PTV.

We considered 4 delivery strategies ($M = 4$): a 4-beam coplanar arrangement, a 9-beam coplanar arrangement, a 27-beam noncoplanar arrangement, and noncoplanar 2-arc deliveries on a Varian TrueBeam linear accelerator. The 27-beam plans included couch angles up to 30°, and the arc plans included 15-degree couch angles. These couch angles were not deliverable at fixed source to axis distance for all patients, including those with an isocenter >5 cm lateral from the image isocenter, or patients with large pitch due to an inability to lay flat.

Plans were optimized with up to 500 control points per plan; arcs were optimized at 2-degree spacing. These large variations in technique contrast varying historical and modern approaches and serve to demonstrate the robustness of the MODO algorithm to beam arrangements. All plans were designed with 6 MV photons; only 4-field plans were varied for left- and right-sided patients. Dosimetric trade-off exploration was carried out for ipsilateral lung, contralateral lung, heart, and esophagus (N = 4). We report on the algorithm's ability to uncover dosimetric trade-offs between OARs and between QC conditions as a function of patient-specific factors and as a function of delivery technique. The covariance matrix for trade-off evaluation included the QC conditions: PTV-D95, PTV-Dmax, Cord-Dmax, and mean dose to OARs including ipsilateral lung (MLD_{ips}), contralateral lung (MLD_{con}), heart, and esophagus (MED). Statistically significant dosimetric trade-offs were defined such that the coefficient of determination between dosimetric indices that varied by ≥5 Gy between different plans was >0.8 (strong correlation).

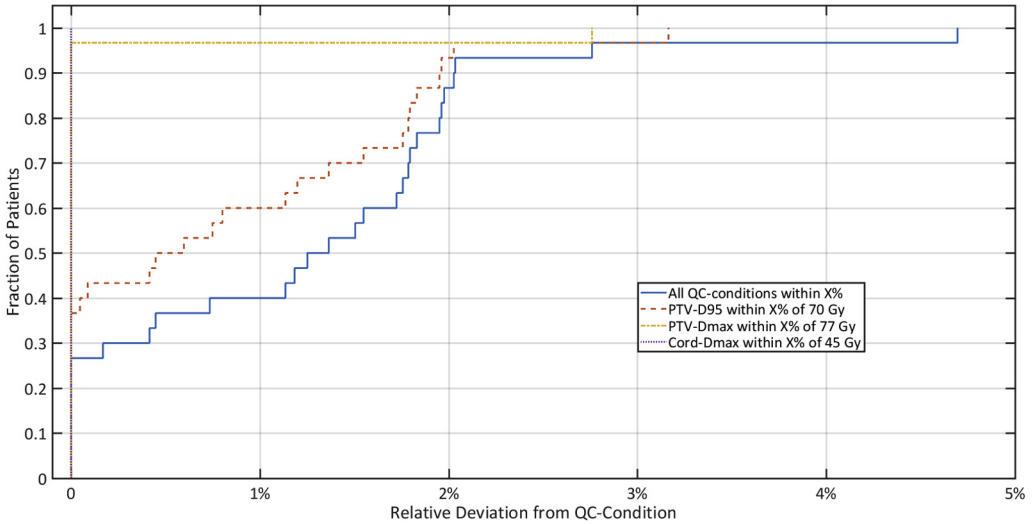

Figure 1 The fraction of patients for whom the optimization reveals at least 1 plan that achieves the 3 quasi-constrained (QC) conditions to within X% is shown. The figure shows all patients have at least 1 plan that simultaneously meets all QC conditions to within 5%.

Results

Conformance to QC conditions

In the 600 plans computed without human interaction, average PTV-D95 = 67.6 ± 2.1 Gy, PTV-Dmax = 80 ± 5Gy, and spinal cord Dmax among all 600 plans was 51.4 Gy. Cord Dmax was >45 Gy in 141 plans and >50 Gy in 13 of 600 plans. The dose volume objectives (O_{qc}) that achieved these criteria were PTV-Dmin >69 Gy, PTV-D98 >70 Gy, PTV-Dmax <73 Gy, and spinal cord Dmax <45 Gy. DHI and CI were 0.90 ± 0.05 and 1.12 ± 0.42, respectively. In 4-field plans, DHI and CI were 1.24 ± 0.48 and 0.87 ± 0.05 and had on average 9.4 ± 4.0 control points per beam. In 9-field and 27-field plans, DHI was equal at 0.90 ± 0.04; CI was 0.98 ± 0.10 in 9-field plans and 0.95 ± 0.14 in 27-field plans. The 9-field plans had on average 14.5 ± 14.3 control points per beam; 27-field plans had 6.7 ± 6.7 control points per beam. In arc plans, CI was 0.88 ± 0.17 and DHI was 0.93 ± 0.04.

Assuming the 3 QC conditions must strictly be met, MODO succeeded for 8 of 30 patients. For at least 1 plan for all 30 patients considered, our algorithm found a solution that met the QC condition to within 5%, and for 26 of 30 patients at least 1 plan presented a solution that met all QC conditions to within 2%. Figure 1 shows the cumulative distribution functions of achieved conditions for the 30 patients.

Figure 2 shows the maximum deviation from all QC conditions as a function of delivery technique for all plans; 78% of the 2-arc plans meet all QC conditions to within 5%, whereas just 30% of 4-field plans meet QC conditions to within 5%.

Failure to meet QC conditions was due to both patient-specific geometry and plan delivery strategies. Examples of patient-specific variations include 10 of 30 patients with no spinal cord Dmax >45 Gy owing to the spinal cord geometry with respect to the target; 6 of 30 patients had >10 plans each with spinal cord Dmax >45 Gy owing to proximity to the target. For PTV-Dmax, the dominant factor in meeting or violating the 110% objective was planning technique, with statistically significant differences in PTV-Dmax distributions among 4-field coplanar (84.6 ± 5.7 Gy), 9-field coplanar (79.3 ± 3.1 Gy), and 27-field noncoplanar (80.0 ± 3.5 Gy), and noncoplanar arc (75.3 ± 3.5 Gy). Only 9-field coplanar and 27-field noncoplanar PTV-Dmax distributions were not significantly different ($p = .07$).

Revealing statistically significant trade-offs

The MODO plans demonstrate the ability to vary mean dose by >5 Gy to contralateral lung for 29 of 30 patients, esophagus for 29 of 30 patients, and heart for 18 of 30 patients, thus demonstrating that for most lung patients, radiation oncologists can significantly vary dose to these critical OARs and still achieve reasonable (QC) target dosimetry. The ability to spare these critical, often uninvolved OARs was due to statistically significant dosimetric trade-offs (ie, reducing an OAR dose required increasing dose to another structure).

For 27 of 30 patients, a statistically significant dosimetric trade-off of at least 2 Gy was found, including multiple trade-offs of at least 5 Gy between multiple OARs in 7 of 30 cases. Figure 3 shows a dose-volume histogram (DVH) for the 20 plans for 1 patient. In this

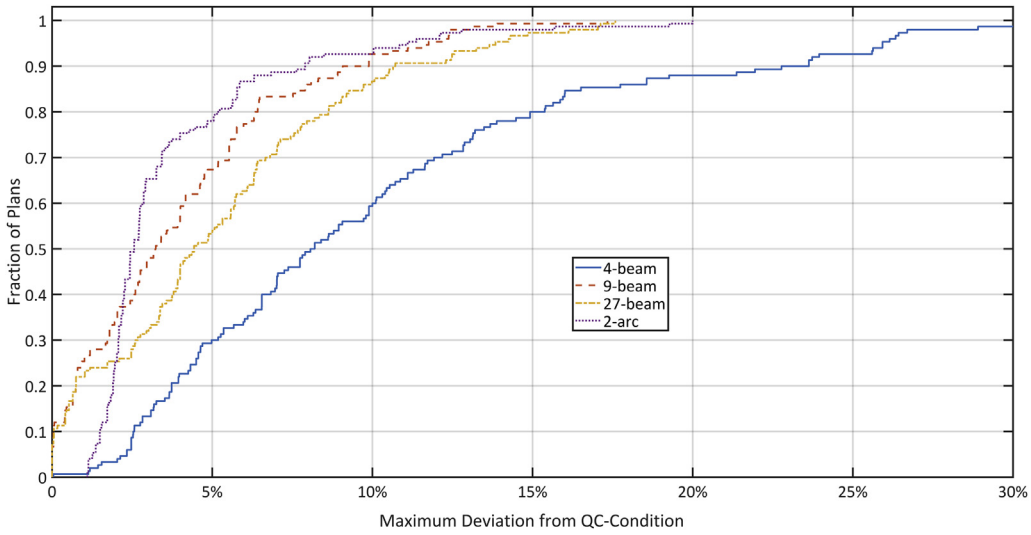

Figure 2 Fraction of all plans that meet all quasi-constrained conditions to within X% as a function of delivery technique.

case, variations in PTV dose, total lung dose, and esophagus dose >5 Gy were revealed. Plans that increase PTV-Dmax (shown in markers) also showed low esophagus and lung DVH values.

The most common statistically significant trade-off was increased PTV-Dmax to reduce OAR dose (15 of 30 patients). The coefficient of variation for these 15 patients indicates a strong correlation ($r^2 > 0.8$) in the relationship between increasing PTV-Dmax and corresponding reductions in mean OAR dose. Mean OAR dose as a function of increasing Dmax in the PTV is shown graphically in Figure 4 for esophagus and heart. For 7 patients, increasing PTV-Dmax led to at least 5 Gy reductions in MED. For 3 patients, mean heart dose could be reduced by >5 Gy by increasing PTV-Dmax. Historically, the radiation oncologist may only be shown plans that achieve PTV-Dmax <110% of prescription dose and therefore may not be aware of the additional sparing of these often uninvolved OARs by sacrificing target dose homogeneity. Although PTV-Dmax = 150% of prescription isodose is not likely to be accepted clinically, extending the QC condition of PTV-Dmax <77 Gy shows tremendous potential in reduced OAR dose.

In the lung, statistically significant trade-offs to spare contralateral lung (reducing mean dose by >5 Gy) were evident in 12 of 30 patients. In 4-field plans, which conformally avoid the contralateral lung, the ability to reduce dose by increasing maximum dose is intuitive. The average 4-field plan reduced total lung V20 by 10.4% ± 8.3% compared to 9-field plans, 7.7% ± 7.9% compared to 27-field noncoplanar plans, and 11.7% ± 10.3% compared to 2-arc noncoplanar plans. These lung dose reductions corresponded to increases in PTV-Dmax of 5.3 ± 5.9 Gy, 4.6 ± 5.6 Gy, and 9.3 ± 7.3 Gy compared to 9-field, 27-field, and arc plans, respectively. Figure 5 shows the relationship between MLD for each lung and increasing PTV-Dmax.

Figure 6 shows boxplots of DVH metrics for total lung, heart, and esophagus revealed by the MODO algorithm. The difference between boxplots for different patients shows a fundamental flaw in assuming that a globally defined Pareto-efficient frontier exists for a given patient population (eg, using population-based planning strategies). Consider patient 1 and patient 2, for example: The range of achievable V20 differs by 20% and does not overlap, with V20 ranging from 0.15 to 0.35 for patient 1 and from 0.35 to 0.55 for patient 2. For other patients, there is negligible variation between the multiple plans, indicating a limitation of the patient-specific problem. Understanding this achievable dose for each patient ideally will enable the radiation oncologist to select patient-specific optimal plans.

Discussion

The ability to visualize and compare multiple delivery strategies, each with multiple dosimetric trade-offs for individual patients, is the focus of our future work in transitioning this algorithm into clinical implementation. Although the algorithm opens up the possibility of patient-specific optimal planning, it also may confine solutions to those for which a priori information is defined. In these cases, manual definition of many QC conditions may be necessary. Breedveld et al[20] have developed such a system, where a large number of objectives and constraints are included in a beam-angle and multicriteria optimization.

The MODO algorithm is based on multiple objective inputs to a gradient-descent, nonglobal optimizer. In

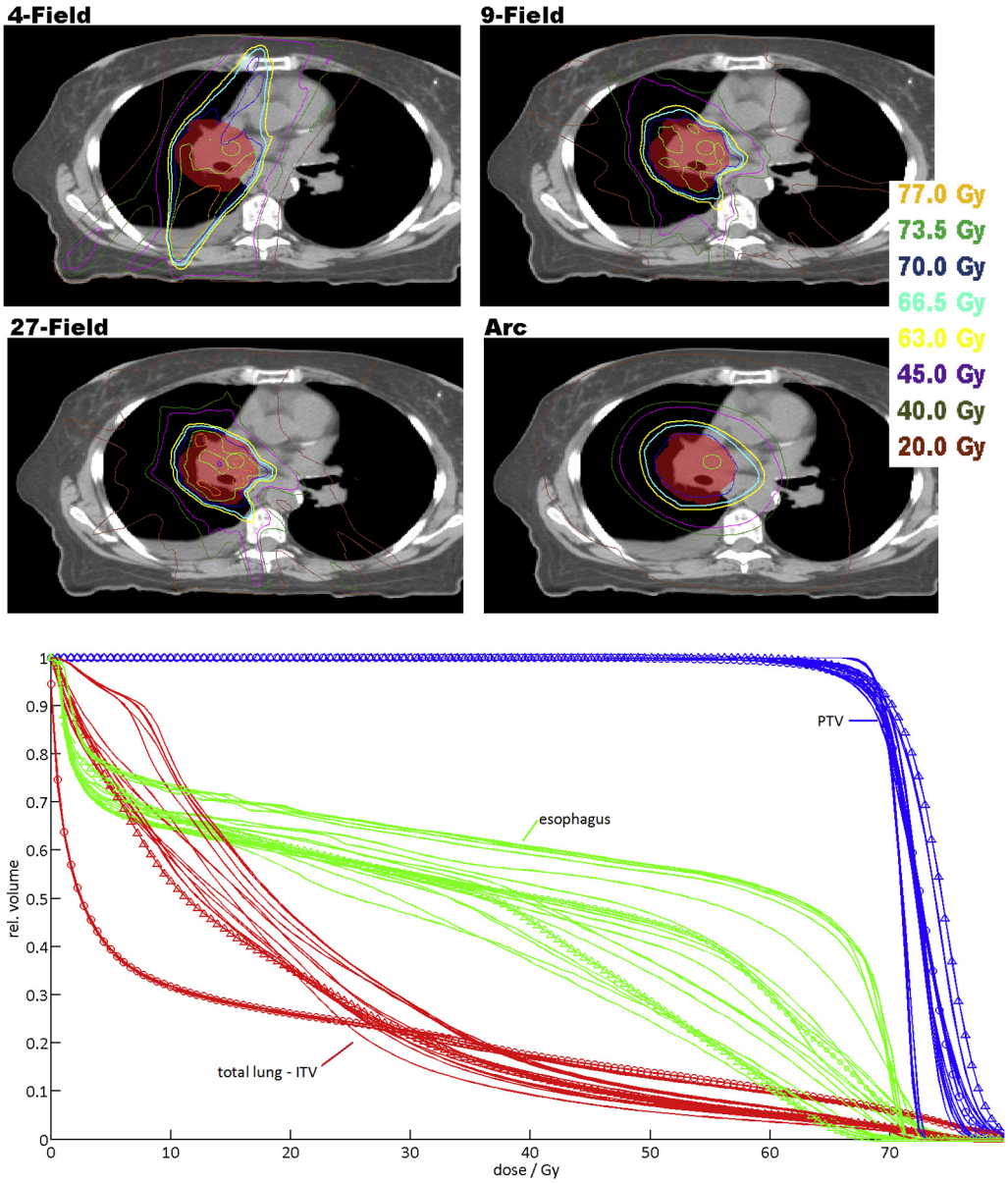

Figure 3 Isodoses are shown for 4-representative plans for 1 patient. For the same patient, the 20 DVHs are shown including trade-offs in total lung, esophagus, and PTV. DVHs with markers correspond to 2 different plans. The radiation oncologist has the ability to choose to significantly vary lung, esophagus, and PTV dose. *Abbreviations:* DVH = dose-volume histogram; PTV = planning target volume.

problems for which the objectives and objective functions are unknown and uncertain, use of a nonglobal optimizer to rapidly find varying representative solutions is a reasonable approach. This method is distinct from methods that explore the Pareto-efficient frontier; if objectives are unknown and uncertain, then Pareto navigation is not feasible.[21] However, Alber et al[22] point out the degeneracy of the IMRT problem, where multiple solutions achieve clinically equivalent results according to large, flat regions of the Pareto-efficient front. Llacer et al[23] describe the phenomena of the existence of multiple local minima and the lack of clinical effect in generating clinical treatment plans by comparing nonglobal optimization to simulated annealing (which can find global minima). These results suggest Pareto navigation and the proposed approach of MODO may result in similar solutions.

To further improve the algorithm, dynamic input of QC dose-volume conditions via regression analysis of previously treated patients, or knowledge-based input to MODO, is under investigation. The analysis of previous radiation data to derive new treatments is a standard

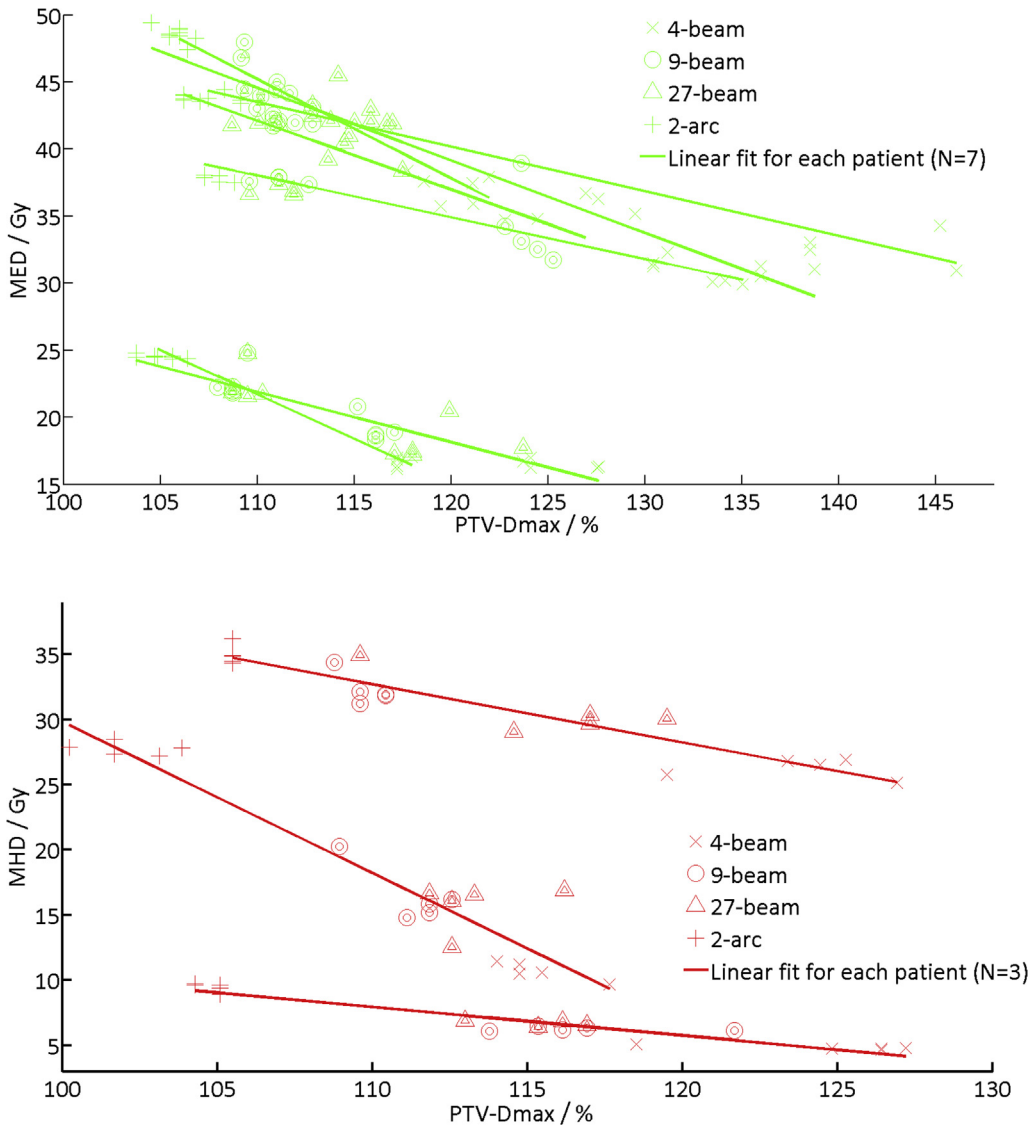

Figure 4 Mean esophagus dose (MED, top) and mean heart dose (MHD, bottom) as a function of increasing planning target volume maximum dose (PTV-Dmax). Each marker is a multiobjective, multidelivery optimization plan, and each line is a patient-specific linear fit of the trade-off between mean organ at risk (OAR) dose and PTV-Dmax for patients with at least 5 Gy variations in mean OAR dose.

approach in knowledge-based planning.[3,11,19] Several efforts have focused on automated treatment planning using previously treatment patients to find or perform quality assurance of appropriate treatment plans.[3,4,11,21,22,24,25]

Olsen et al[4] describe a template-based approach to an automated treatment plan workflow using historical data. Moore et al[3] have evaluated automated planning based on a database of patients with pancreatic cancer. McIntosh and Purdie[26] describe the ability to accurately predict dose values prior to treatment plan optimization. The MODO algorithm incorporates elements of knowledge-based planning by establishing QC conditions based on previously accepted clinical treatment plans. Additional data-driven methods will enhance the algorithm by refining the acceptable deviations in QC dose-volume parameters.

Winkel et al[5] describe a method similar to a single iteration of the MODO algorithm for prostate cancer; their proposed method performs a sequential optimization using the Monaco treatment planning system (Elekta AB, Stockholm, Sweden). Unlike their algorithm, MODO also reveals trade-offs, which is a goal of the Pareto-navigation features of the RaySearch-MCO algorithm. The Pareto-efficient frontier is determined by the user-defined optimization objectives. To the contrary, we argue the true objectives are unknown and should be determined on a patient-specific basis according to achievable dosimetry.

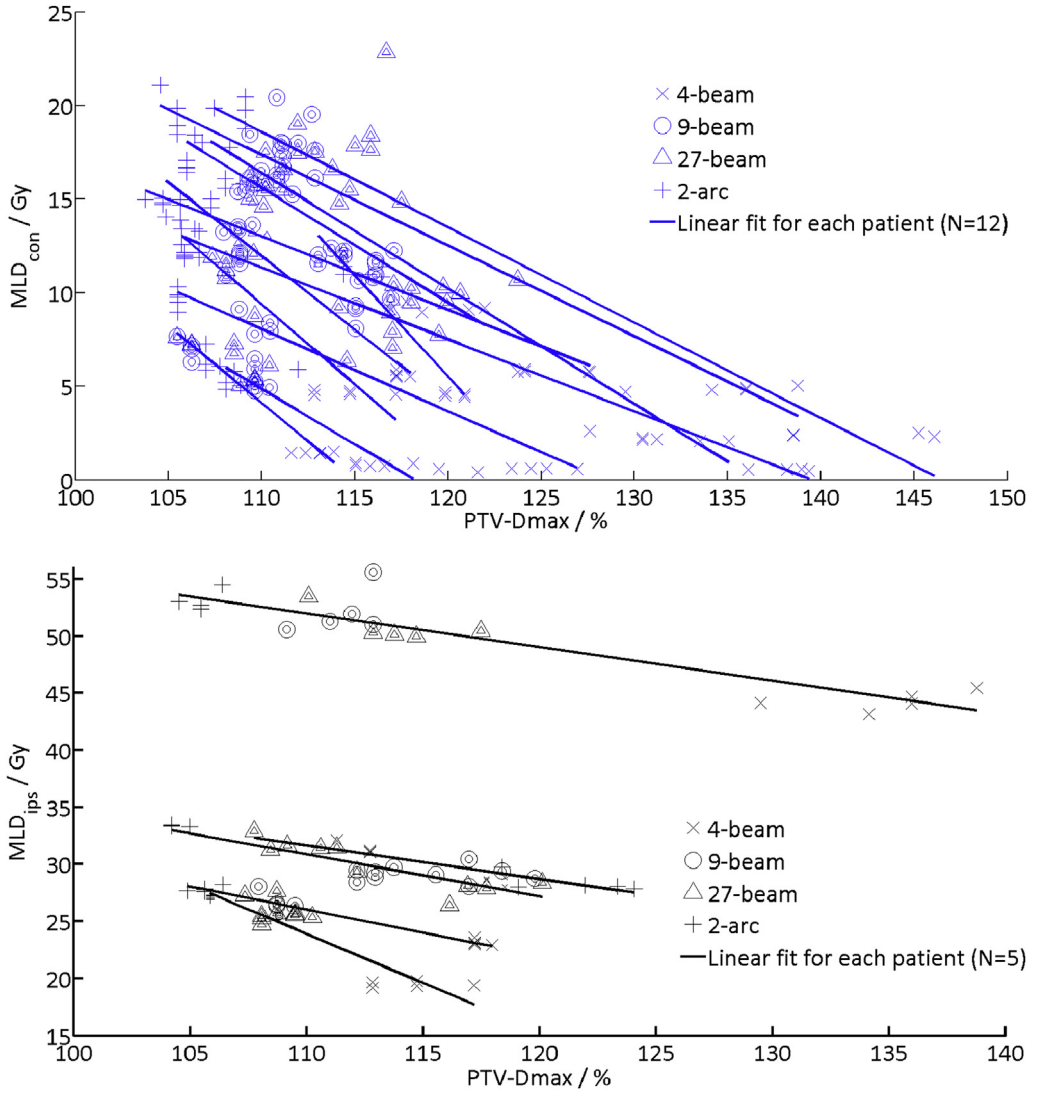

Figure 5 Mean lung dose for contralateral lung (MLD_{con}, top) and mean lung dose for ipsilateral lung (MLD_{ips}, bottom) as a function of increasing planning target volume maximum dose (PTV-Dmax). Each marker is a multiobjective, multidelivery optimization plan, and each line is a patient-specific linear fit of the trade-off between mean organ at risk dose and PTV-Dmax.

As decision making in radiation therapy becomes more complex with the introduction of new technology and new clinical trial results, the set of patient-specific objectives becomes increasingly difficult to estimate for each patient. By incorporating an increasing number of decision variables in the automated planning process, we move away from the treatment planning system paradigm and into a treatment decision paradigm where many alternative treatment plans are presented to the physician for informed decision making and definition of patient-specific objectives. For example, MODO demonstrates that that increasing PTV-Dmax can significantly reduce OAR dose, and demonstrating this fact to physicians may change the definition of clinically acceptable plans.

Conclusions

We have developed an automated radiation therapy optimization algorithm that shows potential to conform to clinical constraints and reveal dosimetric trade-offs. The proposed algorithm has the potential to work with existing radiation therapy hardware and software (eg, with a commercial solver) and has the potential to transform radiation oncologist decision making into alternative-based, patient-specific plan selection. In considering alternative delivery techniques, the algorithm found that the ideal delivery technique to best spare a given OAR was patient dependent. Dosimetric trade-offs of 5 Gy or more were evident in 19 of 30 patients, and trade-offs of

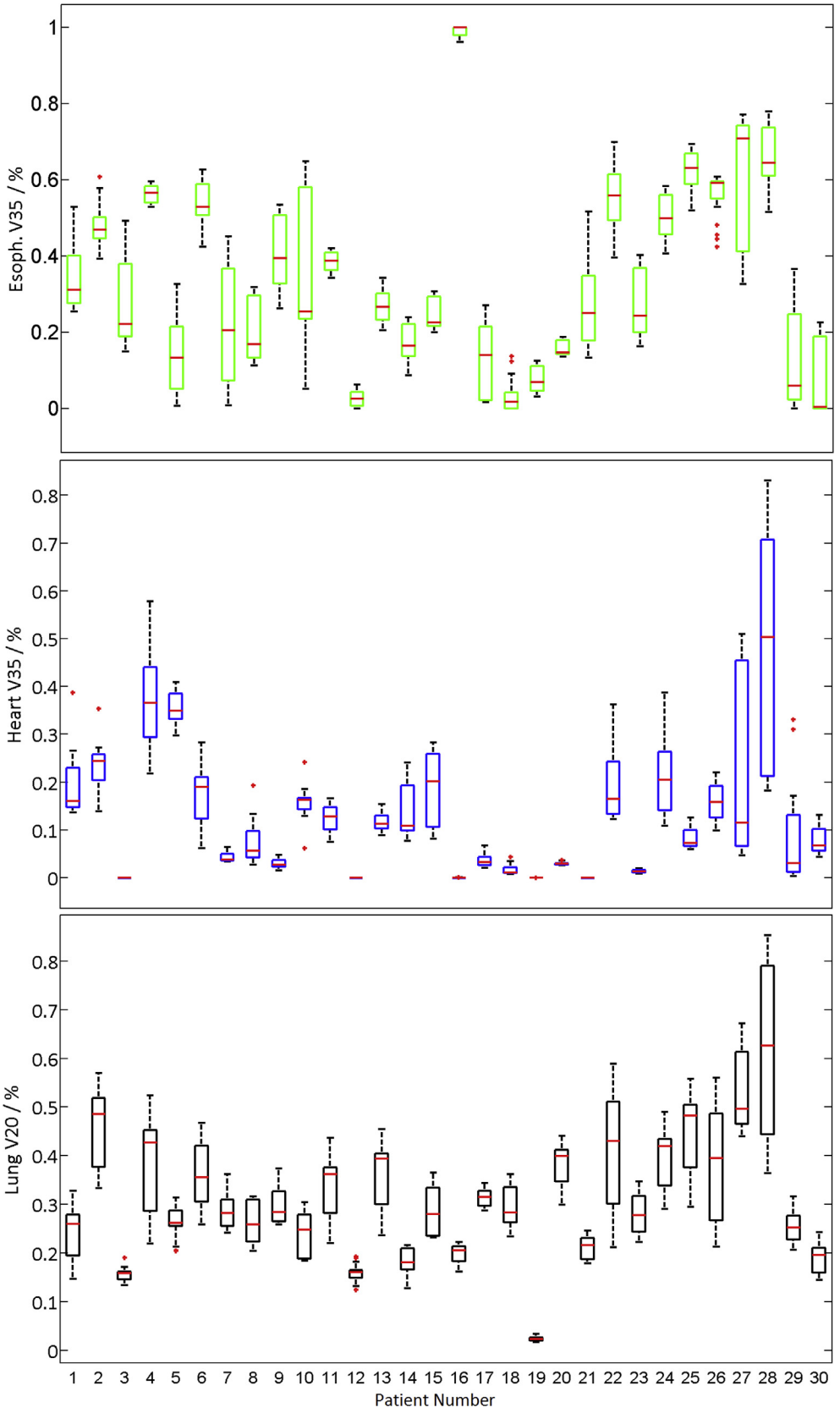

Figure 6 Boxplots show the 25th and 75th percentile of dose-volume parameters, with whiskers covering 99.7% of the range of achieved values for each patient including esophagus V35, heart V35, and total lung V20. The differences in achievable dose-volume metrics for each patient demonstrate the importance of defining patient-specific optimal solutions.

≥5 Gy for multiple OARs was found for 7 of 30 patients primarily through increasing PTV-Dmax. The MODO algorithm has the potential to demonstrate ranges of patient-specific achievable dosimetry based on an array of factors.

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