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Knowledge-Driven Robust Framework for Optimizing Institutional Evaluation Limits in Radiation Therapy

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Decision making within institutions benefit from regulations upon individual decision makers. In the context of medical decision making, these regulations are often imposed as evaluation limits. When they are based on knowledge that is extracted from current and past decision data, they inherently include best practices while incorporating institutional restrictions and schools of thought. We study such regulations in the context of modern radiation therapy for cancer patients which relies on inverse optimization of treatment plans. The quality assessment of these plans is computationally prohibitive and is judged subjectively relative to institutional limits. Therefore, the evaluation process cannot be integrated into modeling phase. This disconnect causes trial-and-error adjustments of model parameters and when this fails to produce an acceptable solution, oncologist relax the limits. Current limits are motivated by first principles (radiobiology) and do not warrant high treatment quality. In this work, we develop a framework to directly optimize evaluation limits. The framework extracts knowledge from past treatment data to inform the optimization. To enable decision flexibility, implementation uncertainty is modeled via robust optimization. We apply this framework to head-and-neck cancer radiation therapy. A large set of 100 past treatments were used to optimize new limits. These limits have the advantage that they (a) are more consistent, (b) require less relaxations, (c) enforce higher-quality solutions, and (d) are robust to relaxations. We validate these properties by re-planning additional clinical cases and observe significant improvements compared to the delivered treatments. This framework can be applied to a broad range of real-world decision making problems.

Key words: Institutional regulation, knowledge-driven optimization, robust optimization, evaluation limits, radiation therapy

1. Introduction

When individual decisions are made at an institution, they reflect not only the decision maker's (DM) preference, but also the school of thought of that institution. However, the institution itself

is often times required to ensure certain goals. When these goals are not confined to the preferences of only one individual, Arrow's impossibility theorem instructs the imposition of regulations upon individual DMs to achieve institutional standards (Arrow 1950). Medical decision making in clinical environments is a prominent example, where individual physicians arrive at decisions based on their schools of thought, but no one physician's preference dictates that of the group. To ensure institutional standards, following the impossibility theorem, the medical institution must impose regulations. Moreover, the inborn differences amongst patients directly influence decisions, transforming medical decision making into a unique field and amplifying both the relevance of the impossibility theorem and the necessity for regulations (beyond the economical ramifications).

Regulations traditionally are based on past experience to safeguard against risks. It is possible to leverage past data to take a step toward improving outcomes. In fact, past decisions lend themselves well for this purpose because they contain best judgments and reflect practical constraints that are often not modeled a priori. This creates an impactful opportunity for future DMs to extract knowledge from their own and from their institutions' current and past decisions in order to inform future regulations. Regulations can then become knowledge-based and directly relate to expertise imbedded in past decisions in order to potentially improve the outcome of future decisions. Modern medical decision making can benefit from these regulations as individual DMs seek to personalize decisions for patients while institutions aspire to higher collective standards. In Arrow's terms, the condition on *uniqueness of order* in quantitative diagnostics is inherent, *unrestricted domain* is required for personalized treatments, *weak pareto* is necessary for unanimous physicians to follow their best judgments, *non-dictatorship* is foundational to evidence-based medicine, and *independence of irrelevant alternatives* is given for ranked diagnosis options. Therefore, medical institutions have no choice but to impose regulations for the greater good. When regulations are designed based on the knowledge extracted from past decisions and are optimized to improve outcomes, the goals of both the patients and the clinical institution can be accomplished.

When institutional regulations present themselves as too restrictive in practice, individual DMs may have to deviate from them to accommodate singular circumstances. This challenge is predominant in medical decision making, because the uniqueness of patients often require the DM to deviate from institutional regulations to accomplish a personalized treatment. Therefore, it is imperative for modern institutional regulations to also acquiesce decision flexibility, i.e., decision outcomes maintain quality despite moderately deviating from precise regulations. The integration of these aspects is the focus of this paper, namely to develop a knowledge-driven framework that enables optimized and flexible institutional regulations. We develop this framework in the context of medical decision making and adapt it for cancer radiation therapy as a specific direction, where institutions regulate the limits on radiation dose in treatment planning.

Decision Making in Radiation Therapy. In most developed nations, more than 60% of patients with cancer are treated with Radiation Therapy (RT), and this trend is rising due to recent technological developments, such as stereotactic therapies (American Cancer Society 2015). RT delivers high doses of radiation to control tumorous cancer cells. The main goal in radiation treatment planning is to achieve high radiation dose to tumor while minimizing the dose of surrounding normal tissues. In order to maintain the quality of the treatment, patient independent *evaluation limits* are recommended, e.g., by institutions or by the International Commission for Radiation Units and Measurements (ICRU). When these limits are not followed, the quality of treatment plans degrades (Fairchild et al. 2013).

In RT, a plan is acceptable if the median dose is at 100% of the prescribed dose (ICRU Report-83 2010). Our preliminary results in Figure 1 for head-and-neck cancer show that many planners exceeded this evaluation limit, which also coincides with that of the institution. Similarly, Mohan and Forde (2017) observed the adherence to recommendations to be less 5% for a large set of published plans. Das et al. (2017) highlighted analogous inconsistencies across 10 US academic hospitals. In addition, Das et al. (2008) reported high varbiation in different reported dose limits of RT plans. This variability is attributed to the institutional approaches which often have not adopted

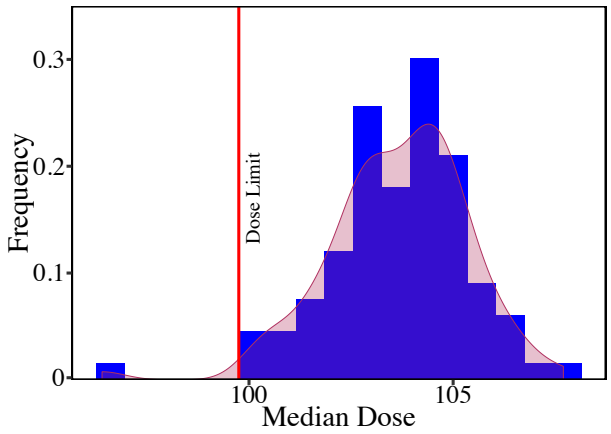

Figure 1 Dose distribution of 100 head-and-neck cancer cases. Many plans exceed the evaluation limit.

the ICRU-83 limits and developed their own set of limits, yet need to deviate from them (Fairchild et al. 2013, Das et al. 2017). Some institutions use limits that were accepted in the past but not currently stated in the ICRU-83 guidelines. The other reason for deviation from dose limits is the challenging and tasking process of treatment planning (Das et al. 2009) which is illustrated in Figure 2. The prevalence of these variations attests to shortcomings in the RT regulations.

From a decision making perspective, planning each patient's treatment can be considered as a new problem. The oncologists use a commercial software that requires clinicians priorities for different anatomical structures and solves a multi-objective optimization model of the spatial dose

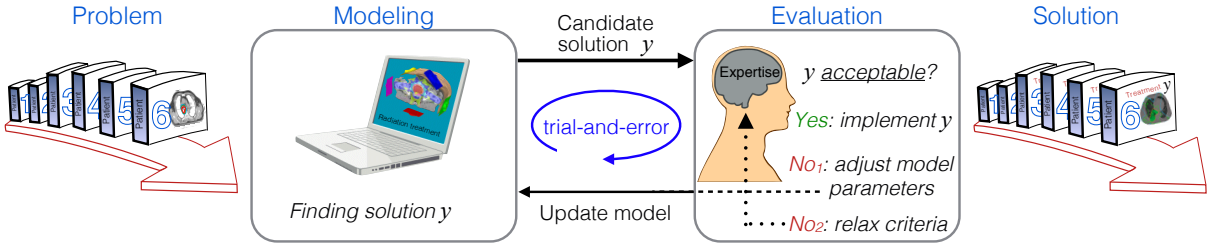

Figure 2 When modeling and assessment are disconnected, a trial-and-error process is often performed.

distribution for the volume of interest (ICRU Report-83 2010). The software generates a candidate solution y (i.e., a treatment plan) which is then evaluated based on different factors such as evaluation limits. If y is considered acceptable, it can serve as the final solution, otherwise the model parameters need to be updated, as illustrated in Figure 2. The modeling and evaluation phases become disconnected because (a) quality measures are computationally prohibitive, (b) the quality cannot be measured quantitatively and requires a medical judgement. This disconnect leads to a trial-and-error process, which is common in many decision making settings involving human judgment. This process illustrated by the loop in Figure 2 and takes a toll on the planner (Das et al. 2009), and continues until either a plan is found that satisfies all evaluation limits (this is rare, see Figure 1), or the oncologist modifies and potentially violates evaluation limits. In fact, the flexibility of post-optimization adjustments to accommodate individual circumstances is necessary in many domains, including medicine. However, since such deviations may render solutions sub-optimal and potentially cause infeasibilities, it is imperative to seek *flexible* solutions that remain feasible in the presence of deviations.

In the planning process, experts' knowledge is embedded in both the modeling and the evaluation phase. In the former, it is explicitly leveraged by the analytical structure of the model. In the latter, however, the knowledge is rather subjective and is instilled in the final solution. Once the final solution is executed, its data is stored and often forgotten.

In this paper, we consider the knowledge stored in past solutions to augment future institutional regulations, as past findings harbor information form the individual decision making process. We develop a framework that robustly optimizes institutional regulations in order to (i) increase decision making efficiency, (ii) directly improve solution quality, and (iii) leverage past decisions. For this, we develop a novel decision optimization framework, which we call Knowledge-Driven Robust (KDR) framework. Radiation therapy in cancer treatment motivates the development of the framework with the goal of optimizing the evaluation limits by not only mitigating treatment risks, but also improving outcomes even under uncertainty (e.g., when clinical discretion and anatomical limitations require the relaxation of evaluation limits).

Lastly, in RT planning, the oncologist demands *flexibility* to adjust the solution to individual circumstances. For example, an oncologist may decide to deviate from recommended lung treatment

limits, because one of the patient's lungs has collapsed. Since evaluation limits are established for most cases and need relaxation for anomalies, optimized limits that offer flexibility can perform well despite deviations.

Research Questions. Given that Arrow's impossibility theorem suggests institutional regulations and given that in RT (*i*) necessary modifications routinely violate institutional evaluation limits (i.e., regulations), (*ii*) a limit does not enforce treatment optimality, and (*iii*) DMs' discretions affect outcomes, our research questions are:

Q1) Knowledge Extraction: how can knowledge from past plans facilitate limit improvement?

Q2) Performance Optimization: how can evaluation limits be optimized to improve performance?

Q3) Flexibility: how can optimized limits allow for individualized accommodations?

Q1 seeks a systematic way to leverage past decisions to improve institutional evaluation limits. *Q2* motivates an optimization framework to narrow the leeway a evaluation limit may allow for suboptimal solutions, while *Q3* pursues limits that are insensitive to uncertainties, e.g., from an individual patient's health circumstances.

In this paper, we address these questions in RT planning setting in which the modeling and evaluation process are disconnected and require experts' intervention. To the best of our knowledge, this is the first systematic optimization framework for institutional regulations and evaluation limits that leverages existing knowledge and allows decision flexibility.

Main Contributions. The main contributions of this paper are

- *Developing a data-driven framework to robustly optimize institutional regulations.* We use the current limits and extract knowledge from past data to reflect the practical relation amongst the limit components. We then develop robust counterparts for ellipsoidal uncertainty sets and provide an algorithm to systematically mitigate potential infeasibilities when uncertainties arise. The optimized evaluation limits curb the trial-and-error process and allow for reproducible, speedy, and, more importantly, high-quality treatments. This framework can be implemented in any institution in order to find improved evaluation limits.
- *Developing a new quality metric for radiation plans.* In RT, the plan quality is inspected visually, rendering the judgement to become subjective. We develop a quantitative metric that provides a unique quality score based on different point-wise measures. The deviation of a plan from the ideal is measured directly at the control points. We discuss the reliability of this metric along with statistical justification.
- *Providing new evaluation limits for head-and neck cancer treatment.* We study the case of a large set of clinical head-and-neck RT plans. We compare the proposed and the standard limits for a variety of uncertainty sizes and show that our results provide higher quality plans and prevent over-relaxation of thresholds.

- *Improving clinically RT treatment planning.* We used the optimized evaluation limits to devise new radiation therapy plans for head-and-neck cancer patients at the department of Radiation Oncology at NYU Langone Health. The resulting plans are compared to the delivered plans of these patients in order to access practicability, robustness, and the quality of treatment plans. We report a sizable improvement in all three aspects, when the optimized evaluation limits are used. In addition, our clinically validated limits shorten the RT planning process time.

In the following, we first provide the relevant background on RT evaluation limits, robust optimization, and chance constrained optimization. We then introduce the KDR framework in Section 3 and present our clinical implementation in Section 4 along with the clinical validation in Section 5.

Notation. Lowercase italic is used to denote scalars; bold lowercase and uppercase is used to denote vectors and matrices. The i-th component of vectors is represented by $[\cdot]_i$. In the general or RT specific context, we use "regulations" or "evaluation limits" interchangeably. All proofs are relegated to the electronic companion.

2. Background

We divide the discussion into four sections of control limit improvement methods, current RT evaluation techniques, and overview on robust optimization and chance constrained programming.

2.1. On Control Limit Improvement Methods

Clinical control limits maintain a baseline of quality in patient care and mitigate risks. They are imposed either institutionally or by review boards. Threshold improvement methods are either qualitative (Shiffman and Greenes 1994, Clubb and Dahm 2011) or quantitative (Guiraud et al. 2010, Meyer et al. 2012). Both directions result in a trial-and-error procedure.

In RT, control limits are recommended by review boards (ICRU Report-83 2010). The limits are driven by biological thresholds for the irradiated planning target volumes (PTV) and toxicity levels for the organs at risk (OAR), both of which are obtained from clinical trials and consensus of thought leaders. Despite all advancements, a methodological framework for control limit optimization in the medical community, to the best of our knowledge, is lacking. We seek a first step towards this direction.

2.2. On Radiation Therapy Plan Evaluation

For specific cancer sites, ICRU Report-83 recommends planning aims on dose control points, i.e., dose received by a fraction of the volume. These planning aims are denoted as D_2, D_{50}, and D_{95} for specific cancer sites, where D_z refers to the amount of dose that was received by $z\%$ of the tumor volume. D_2 often represents the *maximum dose*, i.e., less than 2% of the tumor volume receives

more dose than D_2. Similarly, D_{50} reflects the *median dose*, i.e., half of the volume elements receive at least this amount of dose. Since most plans violate D_{50}, it is also possible to employ V_{100} as an auxiliary evaluation limit for *prescribed volume*, where V_z is the fractional volume that receives at least $z\%$ of the prescription dose. And lastly, D_{95} is often used as the most important limit and reflects the minimum dose that the entire (95%) tumor volume should receive.

When evaluating treatment plans, these control points are compared to the recommended aims. Often, the recommendations of ICRU Report-83 on these points are either adapted or modified by specific institutions and serve to guide the decisions of individual planners. The overall dose distribution is then visualized by a dose-volume histogram (DVH), displaying the fraction of volume that receives at least a certain amount of dose (inverse histogram) (Drzymala et al. 1991).

To improve the efficiency of the evaluation process, one approach compares the current plan to a set of previous patients' plans, requiring a data base of past plans (Moore et al. 2011, Wu et al. 2009). The other approach compares alternative plans of the same patient, such as data envelopment analysis (DEA). It determines whether the current plan can be improved relative to its peers (Lin et al. 2013). The power of DEA, hinges on the quality, availability, and the number of past plans. The second class of methods use multi-objective optimization (Romeijn et al. 2004). The common vein is to offer a variety of Pareto optimal plans of the same patient (Holdsworth et al. 2010). Prioritized goal programming techniques yield comparable plans (Wilkens et al. 2007). The main shortcoming of these methods is the computational burden of generating a sizable number of alternative plans.

Both methods are limited to a pre-specified set of control limits and pursue different paths to select the best. Both may also result in unacceptable plans when uncertainties occur. A methodological approach to control limit adjustment is lacking, to the best of our knowledge. This paper seeks to optimize control limits based on plan quality by reducing the leeway for suboptimality while adhering to current planning aims and enabling the necessary flexibility for clinicians.

2.3. On Robust Optimization

Robust optimization (RO) has become an attractive method in recent years to address uncertainties (Ben-Tal et al. 2009, Bertsimas et al. 2011). The set-based description of uncertainty allows to maintain the problem complexity for a variety of set geometries, making RO computationally tractable for realistic-sized problems. We focus on decision uncertainty in the context of implementation errors. A decision vector $\mathbf{x} \in \mathbb{R}^n$ can sustain errors and realize as $\mathbf{x} + \mathbf{\Delta x}$, where $\mathbf{\Delta x}$ resides in an uncertainty set $\mathcal{U}$. The robust optimization problem becomes

$$\min_{\mathbf{x}} \max_{\mathbf{\Delta x} \in \mathcal{U}} \{ f(\mathbf{x} + \mathbf{\Delta x}) \,:\, g(\mathbf{x} + \mathbf{\Delta x}) \leq \mathbf{b} \}. \tag{1}$$

If the structures of f and g are not known, we provide a nonconvex method (Bertsimas et al. 2010b). When their structures and the geometry of $\mathcal{U}$ can be leveraged, then (1) can be reformulated tractably. More recently, robust counterparts for implementation errors were derived under specific assumptions (Ben-Tal et al. 2015).

Different sources of uncertainty in RT optimization have been addressed via RO, e.g., respiratory motion (Chu et al. 2005, Nohadani et al. 2010), simulation errors (Nohadani et al. 2009), or setup errors (Bertsimas et al. 2010a). What unites these current approaches is that they addressed technological aspects of RT and not its control limits, which is the focus of this paper.

2.4. On Chance Constrained Programming

To mitigate conservatism, chance constrained optimization was proposed for probabilistic errors. The paradigm of RO can then be extended to warrant a probability P of constraint satisfaction (Erdoğan and Iyengar 2006, Calafiore and El Ghaoui 2006). The chance constrained RO problem for implementation uncertainties becomes

$$\min_{\mathbf{x}} \max_{\mathbf{\Delta x}\in\mathcal{U}} \{f(\mathbf{x}+\mathbf{\Delta x}) \,:\, P\left(\{g(\mathbf{x}+\mathbf{\Delta x})\leq \mathbf{b}\}\right)\geq \alpha\}\,, \tag{2}$$

where $0\leq\alpha\leq 1$. Notice the difference to standard RO that guarantees constraint satisfaction for all realizations in $\mathcal{U}$, including the worst-case. For brevity, we focus on parameter uncertainty.

Chance constrained RO methods have also been developed for RT application. A conditional value at risk approach was used to optimize RT plans (Ahmed et al. 2010) and recently extended to proton therapy (An et al. 2017). These studies were focused on delivery constraints to anatomical volumes and not on control limit violations. This work seeks to provide a systematic approach to address the latter.

3. Knowledge-Driven Robust Framework

We now develop the KDR framework that robustly optimizes institutional control limits and provides a range of model parameters that lead to acceptable solutions with high quality and in short time. The overall problem that this project aims to solve is the one in Figure 2, more formally shown in Figure 3. It illustrates the trail-and-error that a decision maker is using between the two phases of Modeling (i.e., optimization) and Evaluation. The general optimization problem has decision variables $\mathbf{y}$, with the multi-objective function weighted by $\boldsymbol{\lambda}=(\lambda_1,\lambda_2,\ldots,\lambda_\ell)$. In RT, when optimizing a treatment plan $\mathbf{y}$ via $\min\sum_j \lambda_j g_j(\mathbf{y})$, the goal is to distribute the prescribed dose to the tumor (g_1) while reducing the exposure of healthy tissue ($g_2, g_3, \ldots, g_\ell$), resulting in a

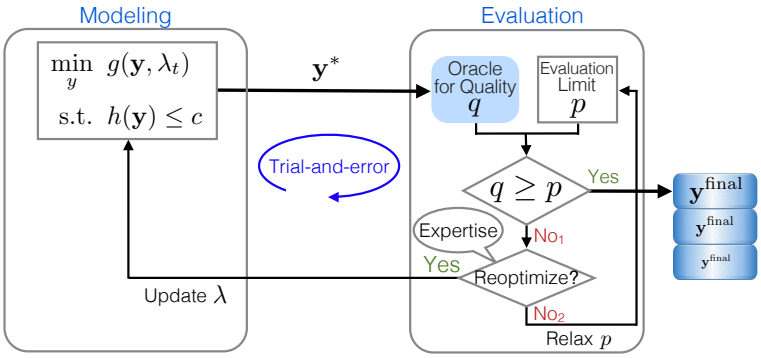

Figure 3 Two phases of decision making. For a candidate solution $\mathbf{y}^*$, each criterion q_i is compared against the control limit p_i, resulting in either adjusting $\boldsymbol{\lambda}$ or relaxing p_i. Solutions $\mathbf{y}^{\text{final}}$ are typically stored.

multi-objective problem with different weights λ_j. In some cases, dose homogeneity and biological aspects are also considered.

In the second phase, an oracle (e.g., a DVH in radiation plans) quantifies the quality of $\mathbf{y}^*$ as $\mathbf{q} = (q_1, q_2, \ldots, q_r)$, which is then evaluated against control limits $\mathbf{p} = (p_1, p_2, \ldots, p_r)$, say by comparing each $q_i \ge p_i$. If all conditions are satisfied, then $\mathbf{y}^*$ is accepted as the final solution $\mathbf{y}^{\text{final}}$. However, if some of $q_i < p_i$, then the decision maker has two options to obtain an acceptable solution: (i) Changing some weights λ_j and re-optimize the model, or (ii) relaxing some control limits p_i. This is exactly what occurs in the evaluation phase of RT planning. The oncologist uses an oracle to translate the optimized plan $\mathbf{y}^*$ into dosimetric quality $\mathbf{q}$ (e.g., DVH), where evaluating $\mathbf{q}$ is a qualitative process and requires oncologists' knowledge that is not incorporated in the modeling phase. The oncologist then compares $\mathbf{q}$ to the institutional control limits $\mathbf{p}$ (e.g., dose limits D_z). If $\mathbf{q}$ satisfies all control limit $\mathbf{p}$, the plan $\mathbf{y}^*$ is acceptable and is ready to guide the radiation beam during delivery. However, if some q_i violate their recommended control limits p_i, then the oncologist returns to the optimization phase, resets some parameters λ_j to obtain a new solution. This trial-and-error process continues until the oncologists decides that plan is acceptable, resulting in $\mathbf{y}^{\text{final}}$. Note the tradeoffs involved in each phase of this decision making: in the modeling phase, the tradeoff is among the multiple objectives (g_j) of the optimization, and in the evaluation phase, the tradeoff is among different control limit components p_i for the quality metric q_i. The human decision maker (oncologists in RT) judges on these tradeoffs chiefly guided by *experience* and *expertise*, which are subjective and can vary based on schools of thought. As a result, many acceptable plans $\mathbf{y}^{\text{final}}$ violate some of the recommended limits, as evidenced in our analysis of Figure 1.

Once decisions are finalized and implemented, they are stored in databases. However, since the trace of this subjectivity is ingrained in $\mathbf{y}^{\text{final}}$, past collections of data $\{\mathbf{y}^{\text{final}}\}$ can serve to extract decision tendencies by retrospectively computing their quality $\mathbf{q}$. Therefore, we can extract past evaluation limit decisions as following:

Evaluation limit Decision $\mathbf{x}$***:*** The knowledge from a past solution $\mathbf{y}^{\text{final}}$ can be extracted as $\mathbf{x} = \mathbf{q}(\mathbf{y}^{\text{final}})$.

When arriving at a (past) final plan for a patient, the oncologists must have assessed its quality $q(\mathbf{y}^{\text{final}})$ as acceptable. Therefore, it is justified to consider this $\mathbf{q}$ as their decision on the appropriate dose limit $\mathbf{x}$ for that patient. We denote these decisions with vector $\mathbf{x} = [x_1, \ldots, x_n]$. The KDR framework considers a set of past $\mathbf{x}$ and recommended limits $\mathbf{p}$ as the input and seeks to optimize new evaluation limits that inherently improve plan quality while allowing flexibility. The overall

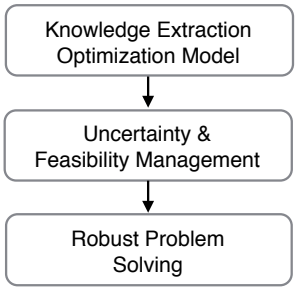

Figure 4 Framework: steps 1&2 build the model, 3&4 manage uncertainty, and 5&6 optimize evaluation limits.

KDR framework has six main sequential steps, summarized in Figure 4:

Step 1. Extracting knowledge from past decisions as input.

Step 2. Constructing constraints, objective function, and uncertainty set.

Step 3. Applying uncertainty to the objective function and the constraints.

Step 4. Managing infeasibility and potentially relaxing constraints.

Step 5. Constructing the robust optimization model.

Step 6. Providing new optimized robust evaluation limits.

In what follows in this section, we will discuss each step in details. The two main threads of each step are based on their role in the optimization problem, namely establishing the constraints and developing the objective. The final output of KDR framework is the optimized evaluation limits which have higher quality, are less likely to be relaxed by oncologists, and allow decision flexibility.

3.1. Step 1—Input and Knowledge

We divide the inputs based on whether they inform the constraints or the objective. We now discuss both aspects of the optimization.

Step 1—Constraints: In this step, there are three main elements.

Current Limits p: The information of the current evaluation limits $\mathbf{p}$ is already available and can be directly employed (see Figure 3, evaluation phase). These are the recommended upper bounds on dose to specific organs as well as lower limits on the prescribed dose to the tumor (see e.g. ICRU Report-83 2010).

Decision Correlations: As described in Figure 2, the decision making is needed for a sequence of problem settings, e.g. different cancer patients require radiation treatment. As a result, the modeling and evaluation phase are repeated, resulting in a collection of solution $\{\mathbf{y}^{\text{final}}\}$ and subsequently a collection of their evaluation limit decisions $\{\mathbf{x}\}$. Since each of the problems (patients) have their unique settings and because the decision making process includes subjective discretion, there are sizable variations within $\{\mathbf{x}\}$ observables. Therefore, decision correlations can be extracted from the collection $\{\mathbf{x}\}$, as illustrated in Figure 5.

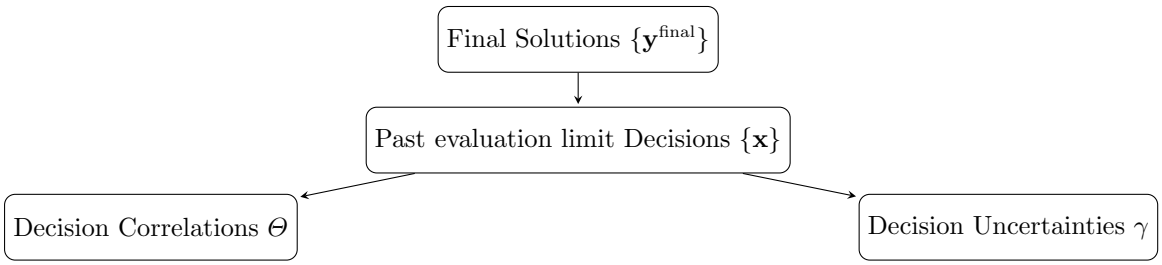

Figure 5 Solutions $\{\mathbf{y}^{\text{final}}\}$ harbor knowledge on limit decisions, correlations, and uncertainties (see Figure 3).

> ***Decision Correlation:*** Past decisions $\{\mathbf{x}\}$ can be leveraged for statistical estimators Θ, such as the mean $\boldsymbol{\mu}$ and the covariance matrix $\boldsymbol{\Sigma}$, which allow to establish correlations amongst the decision components x_i.

In clinical settings, it has been shown that some of the limits are correlated to each other. For example, Roy et al. (2016) revealed that when clinicians meet the limits on the median dose to the tumor, the probability of violating the minimum dose increases, constituting a negative correlations. Similarly, they identified a positive correlation between satisfying the maximum dose and the median dose criteria. Taking these correlations into account ensures clinical applicability of the results of the KDR framework.

To achieve this, we consider the sample mean and correlation coefficients on the dose limits. Depending on the application, other statistical or machine learning methods can be employed to extract the necessary knowledge.

Decision Uncertainties: As with decision correlations, we can also extract the level of practically occurring uncertainty in each decision x_i from the collection of past decisions $\{\mathbf{x}\}$. The assessment of the level of uncertainty is necessary for allowing future and optimized evaluation limits to permit this level of uncertainty while maintaining the quality. In other words, taking these uncertainties into account during the optimization of future regulations enables flexibility for the DM to potentially deviate from the limits in order to accommodate patient specific treatments without jeopardizing the quality.

Decision Uncertainty: The variations amongst the decisions x_i are used to determine the geometry and the size of the uncertainty set, which we symbolically denote with γ.

In other words, we capture the variability (e.g., probability distribution of) each control limit decision. For example, if the distribution of all decisions on x_i has a high variability, this implies that a future control limit on x_i requires larger flexibility. Large spread on some x_i indicates a low priority of clinicians on this attribute, whereas a low spread on other decisions x_j indicates a high priority and the need for close adherence to control limits. When analyzing correlations, Roy et al. (2016) also reported Sizable uncertainties in the dose limits from the past data were reported by Roy et al. (2016), which revealed ellipsoidal contours. We therefore consider ellipsoidal uncertainty to account for error correlation.

Step 1—Objective:

DVH is an important tool to evaluate complex three-dimensional dose distributions (ICRU Report-83 2010). The quality of treatment plans is routinely inspected visually based on the cumulative dose volume histogram, as displayed in Figure 6. The ideal dose distribution (i.e., $\text{DVH}_{\text{ideal}}$)

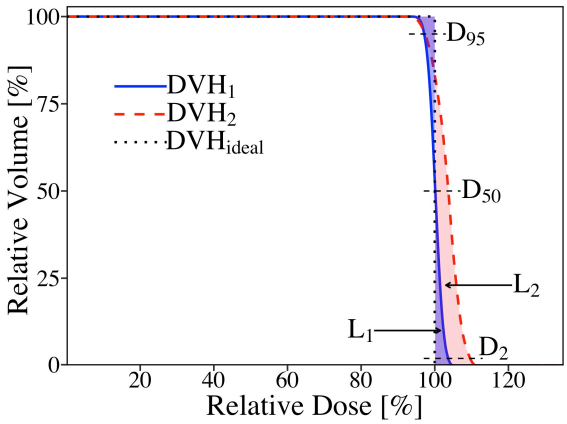

Figure 6 Two clinically acceptable target dose distributions DVH_1 and DVH_2. The shaded areas highlight deviations L from the ideal plan and the dashed lines the clinical criteria (intersections with DVH).

exhibits perfect tumor conformality and dose uniformity, i.e., 100% of the tumor volume receives 100% of prescribed dose, as displayed by the dotted line in Figure 6. However, realistic plans typically deviate from $\text{DVH}_{\text{ideal}}$. To quantitatively measure this deviation and use it as the optimization objective, we now introduce a deviation metric as a corresponding performance measure.

3.2. Step 2—Constructing Constraints and Objectives

We now construct the objectives and constraints of the optimization problem, which provides new evaluation limits that improve the treatment quality. The functional structure of this optimization problem determines its computational efficiency, which is of paramount importance to real-world

applicability. This step incorporates the extracted knowledge of the previous step with the goal of maintaining tractability of the optimization problem.

Step 2—Constraints: Two sets of constraints are necessary. First, we impose *Protocolar Constraints* (PC) to ensure acceptability of final solutions with regard to already established limits $\mathbf{p}$. The set of PC is typically based on bounds and can be straightforwardly modeled as

$$\text{PC:} \qquad \mathbf{A}\mathbf{x} \leq \mathbf{p}, \tag{3}$$

where $\mathbf{A} \in \mathbb{R}^{m \times n}$ for the m evaluation limits that are imposed on decisions $\mathbf{x} \in \mathbb{R}^n$ with the evaluation limits $\mathbf{p} \in \mathbb{R}^m$. In RT, $\mathbf{p}$ corresponds to upper and lower bounds on the dose limits as well as inequalities amongst them. Therefore the elements in A can take values of 0 or ± 1 (see Figure 3).

In addition, we impose *Relational Constraints* (RC) to account for real-life limitations and experts' knowledge in order for the solution to be practical. The set of RC describes the correlations amongst the elements of past decision $\{\mathbf{x}\}$, using statistical estimators. In RT, such correlations are observed amongst the dose limits for each patient and a multivariate normal distribution approximates the data well (Roy et al. 2016). Therefore, a mean $\boldsymbol{\mu}$ and covariance matrix $\boldsymbol{\Sigma}$ can be extracted to define the set of RC as

$$\text{RC:} \qquad (\mathbf{x} - \boldsymbol{\mu})^\top \boldsymbol{\Sigma}^{-1} (\mathbf{x} - \boldsymbol{\mu}) \leq h. \tag{4}$$

The upper bound h can be estimated from the χ^2 statistics for an α confidence probability as $h = \chi^2_m(\alpha)$. For example, if the goal is to include 95% of past treatment plans with regard to four dose limit decisions, h has to equate $\chi^2_4(0.95)$. The mean $\boldsymbol{\mu}$ of each decision component reflects clinicians' tendencies, e.g., $\boldsymbol{\mu}$ can reveal a preference to overdose in order to limit the risk of cancer recurrence. On the other hand, the correlations expose planners' tradeoffs, e.g., $\boldsymbol{\Sigma}$ can represent the preference of one dose limit over another. In general, the set of RC may also include potential evaluation limit violations. That means, the intersection of PC and RC may not bo nonempty. We will discuss this issue in Step 4.

Beyond the current evaluation limits and past decisions, the set of all constraints have to account for implementation uncertainties as well. This is captured in the construction of the uncertainty set whose structure and size depend on the underlying application.

Definition 1 *For a full rank matrix* $\mathbf{Q}$ *and parameter* $\gamma \geq 0$*, the set* $\mathcal{U} = \{\boldsymbol{\Delta}\mathbf{x} \mid \|\mathbf{Q}\boldsymbol{\Delta}\mathbf{x}\|_2 \leq \gamma\}$ *is an ellipsoidal uncertainty set.*

Errors with known correlations can be modeled with ellipsoidal sets. In what follows, we will employ $\mathcal{U}$ for PC and RC to capture implementation uncertainties. Furthermore, since decisions $\mathbf{x}$ and uncertainties $\boldsymbol{\Delta}\mathbf{x}$ are assumed to follow the same distribution with different means, we will use $\boldsymbol{\Sigma}$ to describe the correlations amongst the components of $\boldsymbol{\Delta}\mathbf{x}$ as well. In RT, such ellipsoidal sets

reflect the confidence interval of future decisions, i.e., the probabilistic aspect of a future plan to adhere to the current evaluation limits and match past plans. In particular, $\mathcal{U}$ allows to naturally model the fact that uncertainties in one of the limit components directly affect the amount of uncertainty that other components may experience.

Step 2—Objective: As discussed in Step 1, we consider the deviation from ideal plan $\text{DVH}_{\text{ideal}}$ as the overall measure for treatment quality. A negative deviation from $\text{DVH}_{\text{ideal}}$ (i.e., dose $< 100\%$) displays an underdose to the tumor, while a positive deviation (dose $> 100\%$) exhibits an overdose. In clinical practice, underdose is avoided as far as possible in order to prevent disease progression. This typically comes at the risk of overdosing. This tradeoff is observed in our analysis of Figure 1, namely that the median dose D_{50} consistently exceeds its recommended criterion. Loveless et al. (2013) quantified this deviation by measuring the area between the realized and $\text{DVH}_{\text{ideal}}$ (shaded sections in Figure 6) using the discretized dose d_i and volume v_i points

$$\tilde{L} = \sum_{d_i \leq 100} (d_i - d_{i-1})\,(100 - v_i) + \sum_{d_i \geq 100} (d_i - d_{i-1}) v_i. \tag{5}$$

Note that the typical inspection of the DVH is visual and not all dose and volume points are regulated by dose limits. In fact, clinical recommendations are imposed only on a small subset of the DVH points. In this study, this subset consists of D_2, D_{50}, D_{95}, and V_{100}, which constitute the elements of the decision $\mathbf{x}$. Since past decisions are available on only these components, we approximate the summation in $\tilde{L}$ by the left and right Riemann sum over the components of $\mathbf{x}$ as

$$\begin{aligned} L_{\text{right}} &= (100 - V_{100})(100 - D_{95}) + V_{100}(D_{50} - 100) + 50(D_2 - D_{50}), \\ L_{\text{left}} &= 0 + 5(100 - D_{95}) + 50(D_{50} - 100) + 2(D_2 - D_{50}), \\ L &\approx \frac{1}{2}(L_{\text{right}} + L_{\text{left}}). \end{aligned} \tag{6}$$

We validate the quality of this approximation in Section 4 based on clinical treatment data. For brevity, we refer to L as $f(\mathbf{x})$ in the objective function of our framework. That means, $f(\mathbf{x})$ is the function that maps decisions ($\mathbf{x}$) to the *treatment quality* measure L.

3.3. Step 3—Applying Uncertainty

Often, the oncologist requires post-optimization adjustments to meet individual circumstances. This flexibility is imperative in many domains of medicine and beyond. However, an otherwise optimal decision becomes suboptimal or, in some cases, infeasible, when in their implementation deviations occur. In order to ensure that decisions are flexible and remain feasible at the same time, the KDR framework models flexibility as *implementation errors*. Specifically, for decision to become

feasible, the constraints have to hold for any implementations that lies within the uncertainty set. Correspondingly, the objective should be optimized for possible deviations as well. This poses an infinite dimensional problem. Following the paradigm of RO as in Problem (1), both of these statements have to also hold for extreme uncertainties. This consideration allows to reduce the problem to a tractable reformulation. For the constraint extremes, we discuss both the worst-case that ensures all constraints to be satisfied, and the chance constrained case, because we seek for the framework to be generally applicable. For the objective extremes, we consider the worst-case approach to warrant a lower bound on the performance. We now discuss each component.

Step 3—Constraints - worst-case: IF constraints hold for the worst-case $\mathbf{\Delta x} \in \mathcal{U}$, then they also hold for any $\mathbf{\Delta x}$. For the set of PC in (3) and the set of RC in (4), the worst-case are

$$\text{worst-case } PC: \qquad \max_{\mathbf{\Delta x}\in\mathcal{U}} \mathbf{A}(\mathbf{x}+\mathbf{\Delta x}) \leq \mathbf{p} \tag{7}$$

$$\text{worst-case } RC: \qquad \max_{\mathbf{\Delta x}\in\mathcal{U}} (\mathbf{x}+\mathbf{\Delta x}-\boldsymbol{\mu})^\top \mathbf{\Sigma}^{-1}(\mathbf{x}+\mathbf{\Delta x}-\boldsymbol{\mu}) \leq h. \tag{8}$$

Each row i in (7) constitutes a different protocolar constraint. Therefore, constraint (7) is separable and can be reformulated for each i. This means in the RT case that each evaluation limit will find its own maximizer within the uncertainty set and can be computed separately. Constraints (8) can be reformulated for $\mathcal{U}$, using the concept of simultaneously diagonalizable (SD) matrices.

Definition 2 *Two symmetric matrices* $\mathbf{A}$*, and* $\mathbf{B}$ *are called simultaneously diagonalizable, if there exists a non-singular matrix* $\mathbf{S}$ *such that both* $\mathbf{S}^\top\mathbf{AS}$ *and* $\mathbf{S}^\top\mathbf{BS}$ *are diagonal.*

In Definition 2, if one of the matrices is positive definite, then both matrices are SD. Golub and Van Loan (2012) discuss different methods to obtain S. The following theorem provides a reformulation for Constraints (7) and (8).

Theorem 1 *For the ellipsoidal uncertainty set* $\mathcal{U}$*,* $\mathbf{S}^\top\mathbf{\Sigma}^{-1}\mathbf{S} = diag(\delta_1,\ldots,\delta_n)$*, and* $\mathbf{S}^\top\mathbf{Q}^\top\mathbf{QS} = diag(\alpha_1,\ldots,\alpha_n)$*, the robust counterpart of both Constraints* (7) *and* (8) *is given by*

$$\begin{aligned}
&\mathbf{A}_k^\top\mathbf{x} + \gamma \parallel \mathbf{A}_k^\top\mathbf{Q}^{-1} \parallel_2 \leq b && \forall k = 1,\ldots,m\\
&\sum_{i=1}^{n} w_i + \gamma^2 v + (\mathbf{x}-\boldsymbol{\mu})^\top\mathbf{\Sigma}^{-1}(\mathbf{x}-\boldsymbol{\mu}) \leq h\\
&[\mathbf{S}^\top(\mathbf{\Sigma}^{-1}(\mathbf{x}-\boldsymbol{\mu}))]_i^2 + (w_i - v\alpha_i + \delta_i)^2 \leq (w_i + v\alpha_i - \delta_i)^2 && \forall i = 1,\ldots,n\\
&\delta_i(v-1) \leq 0 && \forall i = 1,\ldots,n\\
&v \geq 0.
\end{aligned}$$

Theorem 1 reformulates the infinite-dimensional Constraints (7) and (8) into a finite number of robust constraints, making the optimization problem solvable efficiently for a realistic size setting.

Step 3—Objective: In the presence of uncertainties, the objective of the optimization problem becomes a minimization of the worst-case via

$$\min_{\mathbf{x}} \max_{\mathbf{\Delta x}\in\mathcal{U}} f(\mathbf{x}+\mathbf{\Delta x}).$$

Since an optimized evaluation limit $\mathbf{x}$ has to remain valid and robustly optimal for all possible uncertainties $\mathbf{\Delta x}\in\mathcal{U}$, we only consider the worst-case setting. This is important in the context of RT, as an optimal set of evaluation limits has to yield plans that remain acceptable even in the worst case, i.e., the largest level of clinicians' flexibility. Note that the probabilistic version follows similar steps, hence we forgo detailed discussion.

3.4. Step 4—Managing Infeasibility

The feasible set defined by the constraints may become empty, when uncertainties are encountered. This occurs when at least one of the following sets is empty:

$$\text{Worst-case Protocolar Set (WPS):} \quad \{\mathbf{x} \mid \max_{\mathbf{\Delta x}\in\mathcal{U}} \mathbf{A}(\mathbf{x}+\mathbf{\Delta x}) \le \mathbf{p}, \mathbf{x}\ge 0\} \tag{9}$$

$$\text{Worst-case Relational Set (WRS):} \quad \{\mathbf{x} \mid \max_{\mathbf{\Delta x}\in\mathcal{U}} (\mathbf{x}+\mathbf{\Delta x}-\boldsymbol{\mu})^\top \mathbf{\Sigma}^{-1}(\mathbf{x}+\mathbf{\Delta x}-\boldsymbol{\mu}) \le h, \mathbf{x}\ge 0\} \tag{10}$$

$$\text{Constraint set:} \quad \text{WPS}\cap\text{WRS}. \tag{11}$$

We now discuss how to manage potential infeasibilities, namely by first inspecting them and, if they occur, by subsequently finding the optimal relaxation of the constraints to achieve feasibility.

Feasibility Check: To probe the feasibility of the set (11), we cast an *auxiliary problem* that follows the robust counterpart from Theorem 1 as

$$\begin{aligned}
Z^* = \min \sum_{j=1}^{m+2n+1} & z_j \\
\text{s.t. } & \mathbf{A}_k^\top \mathbf{x} + \gamma \parallel \mathbf{A}_k^\top \mathbf{Q}^{-1} \parallel_2 + s_j = b + z_j && \forall j, k = 1,\dots,m \\
& \sum_{i=1}^{n} w_i + \gamma^2 v + (\mathbf{x}-\boldsymbol{\mu})^\top \mathbf{\Sigma}^{-1}(\mathbf{x}-\boldsymbol{\mu}) + s_{m+1} = h + z_{m+1} \\
& [\mathbf{S}^\top(\mathbf{\Sigma}^{-1}(\mathbf{x}-\boldsymbol{\mu}))]_i^2 (w_i - v\alpha_i + \delta_i)^2 + s_j = (w_i + v\alpha_i - \delta_i)^2 + z_j \\
& && \forall i, \forall j = m+2,\dots,m+n+1 \\
& v\alpha_i - \delta_i - s_j + z_j = 0 && \forall i, \forall j = m+n+2,\dots,m+2n+1 \\
& s_j, z_j, v \ge 0, && \forall j
\end{aligned} \tag{12}$$

where $\mathbf{s}$ denotes a vector of slack variables, indexed for clarity. In this auxiliary problem (12), $Z^* = 0$, if the intersection in (11) is nonempty and $Z^* > 0$ otherwise. In other words, when using past data to construct the constraints, a nonzero Z^* indicates that the DM violated evaluation limits. It also means that in order to obtain solutions to the overall limit optimization problem, one or more constraints need to be relaxed.

Relaxing Constraints: Figure 7 provides a procedure that systematically relaxes constraints in order to attain a nonempty feasibility set. This procedure has two main steps. First, the size

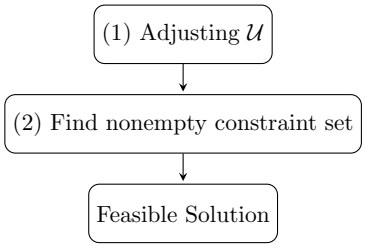

Figure 7 Procedure to relax robust protocolar and relational constraints to achieve a nonempty constraint set.

of the uncertainty set may be adjusted in order to obtain a nonempty WRS. In the second step, *RC*s remain fixed to maintain the integrity of data, and *PC*s are relaxed to in order to obtain a non-empty WPC. The details of these two steps are as following.

1) Adjusting $\mathcal{U}$: For a nonempty WRS, the size of uncertainty set $\mathcal{U}$ is modified. The following theorem determines the optimal bound on the set size γ.

Theorem 2 *For $h \geq 0$, a full rank matrix $\mathbf{Q}$, and a positive definite matrix $\mathbf{\Sigma}$ with decompositions $\mathbf{S}^\top \mathbf{\Sigma}^{-1} \mathbf{S} = diag(\delta_1, \ldots, \delta_n)$ and $\mathbf{S}^\top \mathbf{Q}^\top \mathbf{Q} \mathbf{S} = diag(\alpha_1, \ldots, \alpha_n)$, the WRC is a non-empty set, if*

$$\gamma^2 \leq h \cdot \min_i \frac{\alpha_i}{\delta_i}.$$

The result of Theorem 2 means that if $\gamma^2 > h \cdot \min_i \frac{\alpha_i}{\delta_i}$, then the size of the uncertainty set has to be reduced to $\gamma^2 = h \cdot \min_i \frac{\alpha_i}{\delta_i}$ in order to attain a nonempty WRC set. In the context of an ellipsoidal set, consider the neighborhood $\mathcal{N} = \{\mathbf{x} \mid \|\mathbf{Q}(\mathbf{x} - \tilde{\mathbf{x}})\| \leq \gamma\}$ around a decision $\tilde{\mathbf{x}}$ for a full rank $\mathbf{Q}$ and positive definite $\mathbf{\Sigma}$. Then $\mathcal{N}$ and RC cast two ellipsoids with sizes γ and h, respectively. If there exists a neighborhood $\mathcal{N}$ with $\mathcal{N} \subseteq RC$, then the WRC is nonempty. Using Theorem 2 and SD, we can define two new ellipsoids $\widehat{\mathcal{N}}$ and $\widehat{RC}$ with a common axes. By comparing the length of $\widehat{\mathcal{N}}$ and $\widehat{RC}$ on each axis, the largest set size can be found. Since $\gamma^2 \leq h \cdot \min_i \frac{\alpha_i}{\delta_i}$, WRC in (10) is non-empty. We now discuss how to obtain non-empty robust protocolar constraint sets.

2) Nonempty Constraint Sets: Here, we relax PC, while the uncertainty set and RC keeping fixed. For this, an auxiliary problem similar to (12) is solved

$$
\begin{aligned}
Z^{**} = \min \sum_{j=1}^{m} \|z_j\|_0 & \\
\text{s.t. } \mathbf{A}_k^\top \mathbf{x} + \gamma \|\mathbf{A}_k^\top \mathbf{Q}^{-1}\|_2 + s_j &= b + z_j && \forall j,k = 1,\dots,m \\
\sum_{i=1}^{n} w_i + \gamma^2 v + (\mathbf{x}-\boldsymbol{\mu})^\top \boldsymbol{\Sigma}^{-1}(\mathbf{x}-\boldsymbol{\mu}) &\le h \\
[\mathbf{S}^\top(\boldsymbol{\Sigma}^{-1}(\mathbf{x}-\boldsymbol{\mu}))]_i^2 + (w_i - v\alpha_i + \delta_i)^2 &\le (w_i + v\alpha_i - \delta_i)^2 && \forall i = 1,\dots,n \\
v\alpha_i - \delta_i &\ge 0 && \forall i = 1,\dots,n \\
v, s_j, z_j &\ge 0, && \forall j = 1,\dots,m
\end{aligned}
$$

with $z_j = 0\ \forall j = m+1,\dots,m+2n+1$. This problem finds the smallest number of relaxation for WPS in (9) that is necessary to attain feasibility. If $Z^{**} = 0$, then the intersection in (11) is nonempty and, hence constraint relaxation is not required. On the other hand, if $Z^{**} > 0$, the nonzero optimal solution z_j^* determines the constraints that need relaxation. For this, we solve another auxiliary problem that is similar in structure to (12) but with an objective function that minimizes the total amount of necessary constraint relaxations, using a sufficiently large M as

$$
\begin{aligned}
\min \sum_{j=1}^{m} y_j & \\
\text{s.t. } \mathbf{A}_k^\top \mathbf{x} + \gamma \|\mathbf{A}_k^\top \mathbf{Q}^{-1}\|_2 + s_j &= b + y_j && \forall j,k = 1,\dots,m \\
\sum_{i=1}^{n} w_i + \gamma^2 v + (\mathbf{x}-\boldsymbol{\mu})^\top \boldsymbol{\Sigma}^{-1}(\mathbf{x}-\boldsymbol{\mu}) &\le h \\
[\mathbf{S}^\top(\boldsymbol{\Sigma}^{-1}(\mathbf{x}-\boldsymbol{\mu}))]_i^2 + (w_i - v\alpha_i + \delta_i)^2 &\le (w_i + v\alpha_i - \delta_i)^2 && \forall i = 1,\dots,n \\
v\alpha_i - \delta_i &\ge 0 && \forall i = 1,\dots,n \\
y_j &\le M\|z_j^*\|_0 && \forall j = 1,\dots,m \\
v, s_j, y_j &\ge 0. && \forall j = 1,\dots,m
\end{aligned}
$$

Note that in this step of the KDR framework, updated PCs are determined without conflicting with input decision data, because the set of RC is kept fixed. Therefore, the final set of constraints after managing infeasibility can be employed in the robust problem. Furthermore, the ensured feasibility of this step also allows for all criteria x_i to be optimized simultaneously, which is an impactful advantage of this approach. In RT planning, this property allows to reduce time and ambiguity in the trial-and-error decision making process.

3.5. Step 5—Constructing The Robust Model

With the robust objective and constraints from Step 3, we can assemble the robust model. When using the worst-case approach, the structure of the problem can be exploited to maintain the complexity of the robust problem. Note that Theorem 1 also holds for non-convex objectives. We next discuss the probabilistic approach as it pertains RT.

Step 5—Constraints - chance constrained evaluation limits: In many settings, if sufficiently many constraints are satisfied, the solution is regarded as protected against uncertainties. When constraints represent evaluation limits, this approach gains practical importance because, at times, realistic solutions may require violation of some of the limits.

To this end, it is natural to consider the uncertainties $\mathbf{\Delta x}$ to follow some distribution. Since relational constraints reflect past decisions and are not subject to optimization, we discuss chance constrained solutions only with regard to *PC*s, which can be expressed as

$$\text{Chance constrained } PC: \quad \mathbb{P}(\mathbf{A}_i(\mathbf{x}+\mathbf{\Delta x}) \leq b_i) \geq \eta_i. \tag{13}$$

Note that η_i controls the level of conservatism. Moreover, the result directly offers a probability interpretation that is often desired in practice. The following lemma reformulates Constraint (13).

Lemma 1 *If $\mathbf{\Delta x}$ follows a normal distribution $\mathcal{N}(0, \mathbf{\Sigma})$ with the cumulative density ϕ, the chance constrained PC in* (13) *is equivalent to $b_i - \mathbf{A}_i^\top \mathbf{x} \geq \phi^{-1}(\eta_i)\sqrt{(\mathbf{A}_i^\top \mathbf{\Sigma} \mathbf{A}_i)}$.*

Lemma 1 displays a similar structure as exhibited in the robust counterpart of Theorem 1, enabling a probabilistic interpretation of the corresponding robust problem. Furthermore, when using real-world data, $\boldsymbol{\eta}$ can be directly related to the quantile of $\mathbf{A}^\top \mathbf{x}$. In RT, the matrix $\mathbf{A}$ is extracted from past treatment plans.With the structure and the interpretation of the robust problem, we now briefly discuss the computational effort of solving the robust optimization problem.

3.6. Step 6—Solving The Robust Model

The structure of the objective function, constraints, and the geometry of the uncertainty set determines the computational effort to solve this problem. For m initial evaluation limits and n decisions, the number of decision variables in the robust problem is $2n+1$. Nonconvex objective functions require differing initial points for the optimization to ensure optimality within the range. The RT study presents such a case, where we ensure optimality by a large number of initial $\mathbf{x}$, which will be discussed in Section 4.

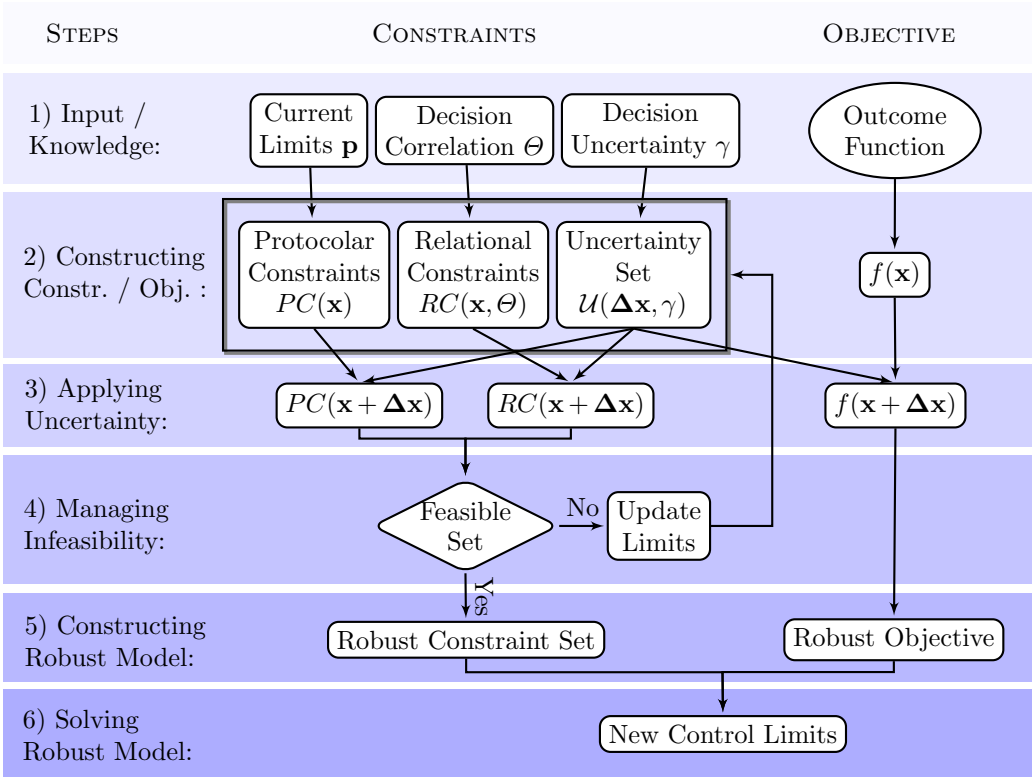

Figure 8 KDR framework: knowledge from past solutions serves to robustly optimize future evaluation limits $\mathbf{x}$.

Summary

To reconcile individual preferences of DMs within an institution and safeguard standards, regulations are needed, following the impossibility theorem (Arrow 1950). The KDR framework offers a systematic way to incorporate past decisions $\mathbf{x}$ to construct and solve an optimization problem for future regulations. The framework has six steps in order to convert past decisions to knowledge (Step 1), build the optimization model (Step 2), incorporate uncertainty (Step 3), manage infeasibilities (Step 4), construct, and solve the optimization problem (Step 5 and 6). Figure 8 provides the outline of KDR framework.

In the next two sections, we implement and validate the KDR framework in a clinical setting to obtain radiation therapy plans for head-and-neck cancer patients. To this end, we first employ a large dataset of past treatments (*training cases*) to extract knowledge and generate optimal evaluation limits, before probing these limits on a new set of patients (*testing cases*). The anatomical characteristics and clinical aims for both sets are comparable. This setting ensures independence of knowledge extraction and testing environment. The following section discusses the implementation and Section 5 presents the validation study.

4. RT Study: KDR Framework Implementation

In this section, we demonstrate our results of optimizing the RT evaluation limits (planning aims) by employing a large set of historic treatment plans. For this, we follow the steps of the KDR framework and specify the RT related details whenever necessary.

For knowledge extraction, comparable past delivered treatment plans of a hundred Head-and-Neck cancer patients have been selected and serve as training data. Although the planners were different, they all used the same treatment planning system (Eclipse, Varian Medical System, Palo Alto, CA) and followed the same institutional planning aims of

$$D_2 \leq 107\%, \quad D_{50} = 100\%, \quad \text{and} \quad D_{95} \geq 95\%$$

of the prescribed dose. Since we seek to improve upon these dose limits, we define the decision variable as $\mathbf{x} = [D_2, D_{50}, D_{95}, V_{100}]$. Note that V_{100} is included since many of the plans fail to satisfy D_{50} and this additional component allows a higher degree of freedom when optimizing. This definition of $\mathbf{x}$ also directly applies to the quality measure in (6). We now discuss the steps of the KDR framework in relation to RT planning.

Step 1—Input and Knowledge: The decision vector $\mathbf{x}$ of past plans serve as input data $\{\mathbf{x}\}$. For example, a past treatment plan with a given spatial dose distribution can be used to extract its corresponding decision vector $\mathbf{x}$ from the dose-volume points D_2, D_{50}, D_{95}, and V_{100}. Therefore, from collection of past plans, we obtain 100 such decision vectors $\mathbf{x}$. Following the discussion of Section 3.1, the statistical estimators of mean and covariance from the collection of past decisions $\{\mathbf{x}\}$ are computed as

$$\hat{\boldsymbol{\mu}} = \begin{bmatrix} \overline{D}_2 \\ \overline{D}_{50} \\ \overline{D}_{95} \\ \overline{V}_{100} \end{bmatrix} = \begin{bmatrix} 108.4 \\ 103.9 \\ 98.5 \\ 88.49 \end{bmatrix} \quad \text{and} \quad \hat{\boldsymbol{\Sigma}} = \begin{bmatrix} 5.1 & 2.6 & -0.5 & 4.6 \\ 2.6 & 2.3 & 1.1 & 9.5 \\ -0.5 & 1.1 & 4.0 & 14.7 \\ 4.6 & 9.5 & 14.7 & 90.3 \end{bmatrix}. \tag{14}$$

Constraints: To construct PC, we leverage the protocols stated above, leading to

$$D_2 \leq 107, \qquad D_{50} = 100, \qquad D_{95} \geq 95. \tag{15}$$

Here, V_{100} is the fractional volume receiving the full prescribed dose and coincides with D_{50} in the ideal setting, i.e., $V_{100} = 50\%$. Since there are no clinical aims on V_{100}, we refrain from constructing a PC for V_{100}.

Objective: For the objective function, we use the quality metric L of a treatment plan as in (6). To validate that L is a dependable approximation of the true metric $\tilde{L}$ in (5), we computed both measures for the 100 *training* patient plans. We observed that 92% of the plans exhibit an approximation error of less than 10%, which is within clinical variations and hence tolerable. Therefore, we will employ L as the objective function in the following.

Step 2—Constructing Constraints and Objective: Based on the extracted $\hat{\boldsymbol{\mu}}$ and $\hat{\boldsymbol{\Sigma}}$, we can now construct the relational and protocolar constraints.

Constraints: For PC, we directly use the relationship in (15). The corresponding coefficients are

$$\mathbf{p} = \begin{bmatrix} 107 \\ 100 \\ -95 \\ 0 \end{bmatrix}, \quad \text{and} \quad \mathbf{A} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}. \tag{16}$$

The RCs enforce practical considerations and imbed clinicians' expertise. This is reflected in the correlations amongst decisions, which can be detected in $\hat{\boldsymbol{\Sigma}}$ and motivates ellipsoidal constraints as in (4). Therefore, the coefficient of RC are given by $\hat{\boldsymbol{\mu}}$ and $\hat{\boldsymbol{\Sigma}}$.

Objective: For the objective function, we employ the plan quality metric L from (6), which can be written as $L(\mathbf{x}) = \mathbf{x}^\top \mathbf{D}\mathbf{x} + 2\mathbf{g}^\top \mathbf{x} + c$. For the past data, we determine the corresponding objective coefficients to be

$$\mathbf{g} = \begin{bmatrix} 13 \\ -0.5 \\ -26.25 \\ -50 \end{bmatrix}, \quad \mathbf{D} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0.25 \\ 0 & 0 & 0 & 0.25 \\ 0 & 0.25 & 0.25 & 0 \end{bmatrix}, \quad \text{and} \quad c = 2750.$$

With this setting, the *nominal optimization problem* is then given by

$$\begin{aligned} \min_{\mathbf{x}} \quad & \mathbf{x}^\top \mathbf{D}\mathbf{x} + 2\mathbf{g}^\top \mathbf{x} + c \\ \text{s.t.} \quad & \mathbf{A}\mathbf{x} \leq \mathbf{p} \\ & (\mathbf{x} - \hat{\boldsymbol{\mu}})^\top \hat{\boldsymbol{\Sigma}}^{-1} (\mathbf{x} - \hat{\boldsymbol{\mu}}) \leq h. \end{aligned} \tag{17}$$

Note that while the objective function is non-convex, the quadratic constraint is convex, resulting in a convex feasibility set.

Step 3—Applying Uncertainty: Given an oncologist's discretion in relaxing constraints during treatment planning in order to suffice clinical and anatomical considerations, our goal is

to provide a new set of evaluation limits that yield high quality outcomes despite deviation. In order for the plans to withstand such uncertainty, we postulate that they have to also hold for the worst-case errors within a set that bounds all uncertainties. Following this RO paradigm, we establish this set based on the extracted knowledge and relate $\mathbf{Q}$ and the size γ^2 to the above estimators. Note that $\hat{\mathbf{\Sigma}}$ is positive definite in this study.

Constraints: Since the constraints have to also hold for the worst case, we replace them by their robust counterparts from Theorem 1.

Objective: The robust counterpart of the objective in Problem (17) can be expressed as

$$\begin{aligned} \min_{\mathbf{x},z} \quad & z \\ \text{s.t.} \quad & z \geq \max_{\mathbf{\Delta x}} (\mathbf{x}+\mathbf{\Delta x})^\top \mathbf{D}(\mathbf{x}+\mathbf{\Delta x}) + 2\mathbf{g}^\top(\mathbf{x}+\mathbf{\Delta x}) + c \\ & \mathbf{\Delta x}^\top \mathbf{\Sigma}^{-1} \mathbf{\Delta x} \leq \gamma^2. \end{aligned} \tag{18}$$

Here, we approximate $\mathbf{\Sigma}$ with the extracted $\hat{\mathbf{\Sigma}}$, and define $\hat{\mathbf{\Sigma}^{-1}} = \mathbf{Q}^\top \mathbf{Q}$. For this setting, Theorem 1 provides a tractable reformulation to be used in the overall robust problem.

Step 4—Managing infeasibility: Since the *PC* and *RC* sets are constructed independently, the union of their robust counterparts may result in an empty set, i.e., the robust problem may render infeasible. In RT, each types of constraints is independently feasible, but it is their combination that leads to infeasibilities. The procedure to establish feasibility is illustrated in Figure 7.

Step 5—Constructing and Solving the Robust Model: The RO problem with a non-convex objective can be efficiently solved with standard solvers. To reduce the likelihood of local optimality, we randomly sampled the initial $\mathbf{x}$. Table 1 presents the robust optimal evaluation limits $\mathbf{x}^*$ for varying sizes of the uncertainty set γ^2. Depending on the level of flexibility γ^2 a clinician may require, $\mathbf{x}^*$ can serve as new and optimized evaluation limits. The last row of Table 1 also exhibits the evaluation limits that are currently used in the institution. We observe that all $\mathbf{x}^*$ are within the current limits and only D_{50}^* marginally deviate, which is supported by the clinical observation that all D_{50} limits were exceeded. Having optimized the limits $\mathbf{x}^*$, we now embark on validating them in a clinical setting for real-world benchmarking. In the next section, we describe this validation process.

5. RT Study: Clinical Validation

The results from Table 1 served as dose limits to conduct re-plan a new set of head-and-neck patients. To achieve statistical significance, while maintaining the overhead on the clinical staff, 12 past patients were selected that were not included in the previous 100-plan set and resembled the

Uncertainty size	Robust optimized limits $\mathbf{x}^*$		
γ^2 [Gy^2]	D_2^*[%]	D_{50}^*[%]	D_{95}^*[%]
1	102.2	100.1	98.1
2	103.5	100.8	98
3	104.4	101.5	98.5
Institutional limits $\mathbf{p}$	≤ 107	$= 100$	≥ 95

Table 1 Optimized robust evaluation limits for different uncertainty sizes.

cohort anatomically and in their planning aims. Only one oncologist conducted replanning to ensure homogeneity in decision making and experience. Furthermore, to increase out validation sample size, each case was re-planned four times from the the same initial settings (without learning).

We label the original clinical plans which were planned based on $\mathbf{p}$ and delivered to the patients as "delivered plans," and their corresponding re-designed treatments which were planned based the optimized evaluation limits $\mathbf{x}^*$ as "KDR-optimized plans." While each case included 20 to 40 different dosimetric structures, in the following, we focus on the tumor and report only its spatial dose distribution. For consistency, $\mathbf{x}^*$ at $\gamma^2 = 2$ from Table 1 was used for replanning. When evaluating the resulting dose points D_z to the underlying limits $\mathbf{x}^*$, we aim to answer the following four clinical questions.

CQ1. (Implementability) How do current and robust optimized limits differ?

CQ2. (Adherence) Can oncologists satisfy the robust optimized limits?

CQ3. (Plan quality) Do the robust optimized limits improve plan quality?

CQ4. (Plan robustness) How do deviation from both limits affect plan quality?

For validation, *CQ1* probes whether the robust optimized limits $\mathbf{x}^*$ can be used for treatment planning or whether they exhibit obstacles that are not present when using $\mathbf{p}$. Clinical question *CQ2* examines whether planning with $\mathbf{x}^*$ requires violating them and if so, how does it differ from planning using $\mathbf{p}$. *CQ3* studies potential changes to plan quality, and lastly *CQ4* evaluates the effect of possible violation of either of the evaluation limits on plan quality.

5.1. Implementability

In the general medical context, Shiffman et al. (2005) have shown that when guidelines are designed to be easily implementable, they will be followed and actually implemented in practice. Since institutional limits $\mathbf{p}$ are already used in clinical practice, they can be considered as implementable. For our optimized limits $\mathbf{x}^*$ to be implementable, they have to be within the interval of the institutional limits. Table 1 suggests this to be the case. In fact, we observe that our D_2^* and D_{95}^* are within the current evaluation limits. Furthermore, D_{50}^* is close to the current criteria of 100, which practically mimics the idealized dose distribution. The real test, however, is to actually

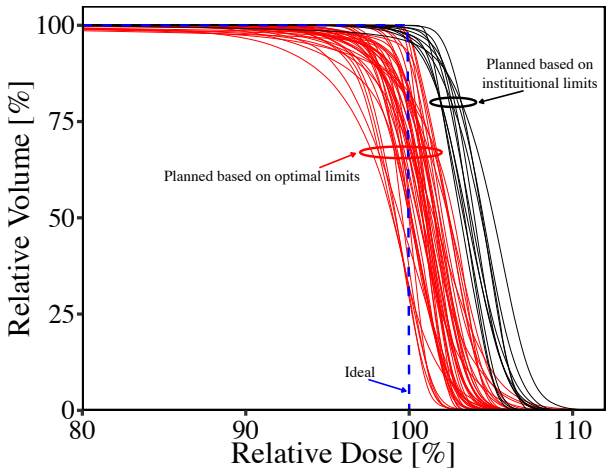

Figure 9 Target DVH of the clinical cases planned based on institutional and optimized limits.

plan new treatments using the optimized $\mathbf{x}^*$. For 12 head-and-neck patients, this was conducted multiple times independently, and Figure 9 displays the tumor DVH of this clinical experiments. The physicians did not resist to employ $\mathbf{x}^*$ for their planning purposes. Furthermore, the treatment planning software did not need any adjustment and could be used as in its customary setting. In fact, the optimization did not produce any infeasible plans, even on the first run and no further trial-and-error adjustments were necessary. These aspects clearly attest to the implementability of the optimized evaluation limits.

Observation 1 *The proposed optimized evaluation limits are implementable in practical setting.*

This indicates that future treatments can be planned following new limits from a corresponding KDR framework without additional modification to the modification to clinical practice of the planning software. Furthermore, since $\mathbf{x}^*$ is optimized under uncertainties ranging up to $\gamma^2 \geq 2$, they also offer increased flexibility as will be discussed in the following.

5.2. Adherence

To maintain a high treatment quality, it is imperative to adhere to evaluation limits. The second question *CQ2* probes potential of limit violation as they become necessary in practice. In other words, it explores Step 4 of the KDR framework by applying it to dose limit relaxation and the interaction with flexibility.

In this experiment, we measure the fraction of treatments that satisfy the limits based on which they were planned. We extract the dose points D_z from the spatial dose distribution of both the KDR-optimized plans and the delivered plans, and compare them to the limits which served to design the plans, namely to $\mathbf{x}^*$ and $\mathbf{p}$, respectively. For the former, we have to take the allowed flexibility into account, since the KDR-optimized plans maintain their quality within $\mathbf{x}^* \pm \gamma \|\mathbf{A}^\top \mathbf{Q}^{-1}\|_2$,

where $\mathbf{Q}^\top\mathbf{Q} = \hat{\mathbf{\Sigma}}^{-1}$ and $\hat{\mathbf{\Sigma}}$ is given by (14) and A by (16), stemming from the training dataset. For the latter, we replace the equality limit for D_{50} to be within $\pm 0.5\%$, i.e., when the dose point is $99.5 \leq D_{50} \leq 100.5$, the treatment is considered satisfying the limit (see Roy et al. 2016). The limit adherence to each limit component is reported in Table 2. It shows that the KDR-optimized

		Satisfying plans			
Treatment plans	Reference dose limits	D_2	D_{50}	D_{95}	All
KDR-optimized plans	Optimized limits $\mathbf{x}^*$	95%	100%	91%	87%
Delivered plans	Institutional limits $\mathbf{p}$	42%	17%	100%	0%

Table 2 Fraction of the clinical plan satisfying dose limits.

plans all satisfy the key dose limit of D_{50} and most of them also the lower and upper limits. This indicates that an oncologist needs to violate $\mathbf{x}^*$ only in at most 9% of the cases. When comparing the dose points of the delivered plans with their respective limits $\mathbf{p}$, D_{95} was always satisfied. This confirms the fact that D_{95} was the clinical aim that clinicians always ensured, when planning these treatments. However, the clinically most critical limit of D_{50} required deviations in most cases (83%). Such a level of violation was also observed in the training cases (99%) data, as discussed earlier. In Section 5.4, we will discuss the impact of such limit violations on the quality of treatments.

Observation 2 *The robust optimized decisions proposed by our KDR framework require less limit relaxations in practical settings.*

When the collection of all evaluation limit components are compared, 87% of the KDR-optimized plans satisfy all three optimized limits, whereas none of the delivered plans adhere all limit components concurrently, as shown in the right column of Table 2.

Note that the size of the uncertainty set γ^2, which reflects the amount of decision flexibility, can be adjusted to achieve a certain level of constraint satisfaction. As γ^2 grows, the fraction of satisfaction for all criteria will increase. The tested $\gamma^2 = 2$ can be considered fairly moderate, and yet it is remarkable that using our $\mathbf{x}^*(\gamma^2 = 2)$, the number of satisfying plans jumps to 87 while improving the quality. In other words, this experiment demonstrates improved evaluation limit adherence while improving plan quality.

Furthermore, since RT treatment planning is a multi-objective process with potentially competing objectives, as visualized in Figure 2, Observation 2 also implies that using $\mathbf{x}^*$ will also curb the trial-and-error attempts, because less limit violations occur. This suggests that the KDR framework is capable of simultaneously optimizing multiple and potentially competing decision components, since the KDR framework warrants a mutually feasible set. Both aspects can improve

the efficiency of the overall planning process. Next we will compare the quality of treatments when planned based on institutional or based on optimized limits.

5.3. Plan Quality

From the dose distributions in Figure 9, we observe that the delivered plans tend to overdose, which was also observed from the 100 training cases. More interestingly, we observe that *all* dose distributions of the KDR-optimized plans are separated from delivered plans. In fact, the plans based on our proposed $\mathbf{x}^*$ are sizably closer to $\text{DVH}_{\text{ideal}}$ (see dotted line in Figure 6).

To quantitatively compare the plan quality, we compute the area between the realized dose distribution and the corresponding $\text{DVH}_{\text{ideal}}$. Since the entire spatial dose distribution is known, we used the exact metric of $\tilde{L}$ in (5) to compute the quality of both the delivered plans and the KDR-optimized plans. The mean $\tilde{L}$ of the delivered plans is 388, resembling the analysis of the training cases. However, the mean $\tilde{L}$ of the KDR-optimized plans is 143, sizably improved over treatments planned based on institutional limits. In fact, a paired t-test on $\text{mean}(\tilde{L}^{\text{delivered plans}}) - \text{mean}(\tilde{L}^{\text{KDR-optimized plans}}) \geq 140$ resulted a p-value of $p = 10^{-4}$, revealing a clear separation between the two sets of plans and an improved quality of the KDR-optimized plans by at least 140, which is quite remarkable. Further statistical analysis follows Figure 10 in Section 5.4.

Observation 3 *The robust optimized limits proposed by our KDR framework improves the plan quality significantly.*

This observation provides the answer to CQ3. It also highlights the improvements that are possible when future treatments are planned based on evaluation limits proposed by our KDR framework. Since deviations from limits are inherent to treatment planning and necessary to meet clinical goals, we next probe the optimized limits under implementation uncertainty.

5.4. Plan Robustness

In clinical practice, oncologists often need to relax evaluation limits to meet anatomical or dosimetric objectives. For example, when a tumor is in close proximity to some OAR such as the spinal cord, planners tend to reduce the maximum dose to tumor. As discussed, we model this required flexibility by the notion of uncertainty. To address the clinical question *CQ4*, we first quantify quality degradation in order to then compare the delivered plans and KDR-optimized plans under limit uncertainty. While the Table 2 reports on the number of plans that violate limits, here we aim to quantify the amount of violation. For this, we define a measure v^i that calculates the amount of limit violation for each plan i as

$$v^i(\mathbf{x}) = \left((D_2^i - x_1)_+^2 + (D_{50}^i - x_2)^2 + (D_{95}^i - x_3)_-^2\right)^{\frac{1}{2}},$$

where $v^i(\mathbf{p})$ (or $v^i(\mathbf{x}^*)$) is the limit violation of plan i from the current evaluation limits $\mathbf{p}$ (or optimized limits $\mathbf{x}^*$), and $(\cdot)_\pm$ the positive or negative part of the argument. Note that this metric measures the Euclidean norm of the deviation and coincides with the size of the uncertainty set γ for spherical sets.

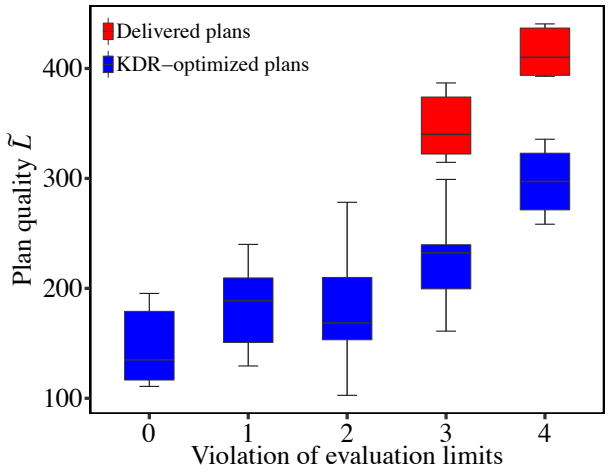

Figure 10 Box plot of quality measure $\tilde{L}$ for different deviations from evaluation limits v^i: red (higher boxes) for delivered plans; and blue (lower) for KDR-optimized plans.

Figure 10 shows a box plot for both the delivered plans and the KDR-optimized plans. The violations $v^i(\mathbf{x})$ are binned for 1Gy of violation for clarity of exposition. We observe that delivered plans exhibit violations that are $\geq$ 3Gy (box plots start at 3Gy). This means that it was not possible for the actually delivered plans to be within $\leq$ 2Gy of $\mathbf{p}$. Furthermore, their quality measure $\tilde{L}$ is significantly higher and increases faster with v than the KDR-optimized plans. When comparing the maximums of the boxes for the worst-case $\tilde{L}$ in Figure 10, we observe that those of the KDR-optimized plans grow moderately, attesting the robustness of the optimized evaluation limits $\mathbf{x}^*$.

Observation 4 *For a given level of limit violation, KDR-optimized plans have a better quality than delivered plans, even in the worst case.*

Summary of Observations

Observations 4 allows to conclude that the optimized evaluation limits ensure higher quality. Observation 2 attests to the flexibility of the optimized limits. Furthermore, the combination of Observation 1 and the fact that the optimized limits were successfully validated in the clinical setting strongly suggests that the KDR framework and the resulting optimized evaluation limits can be implemented and their advantages can be leveraged in clinical practice without changing policies, software, or devices.

6. Conclusion

To safeguard institutional standards, Arrow's impossibility theorem instructs regulations on individual decision makers. To construct optimal institutional regulations, we developed a framework which extracts knowledge from past decision data to account for individual schools of thought and practical constraints that are not modeled. To accommodate singular circumstances such as patient's anatomy, the regulations and their evaluation limits are designed to be flexible within a range. The robust optimization component of our framework ensures possible deviations to perform acceptably, enabling flexibility in decision making while maintaining quality. This framework is general and can be leveraged in many real-world applications.

To demonstrate the performance, we motivate the development with the problem of treatment planning in cancer radiation therapy. We extracted knowledge from a large collection of past treatment data to inform the model. In fact, we developed a new quantitative metric for treatment assessment to overcome the current clinical limitation of visual inspections. We computed new optimized evaluation limits and validated clinically on a new set of patients. The proposed dose limits reveal themselves as implementable without further adjustments to clinical practice. We observed that these optimized limits lead to higher quality treatments than when current thresholds are used. We also report the treatment quality to be preserved despite limit deviations, attesting robustness and decision flexibility. Therefore, the proposed regulations can be directly used in clinical practice, improve outcomes and enable decision flexibility. Because the structure of the proposed framework is general, it is directly applicable to a broad range of group decision making settings that seek to leverage system inherent knowledge for optimal institutional regulations.

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