Efficient Outcomes-Driven IMRT Treatment Planning Using Commercial Treatment Planning Systems: CMS-Elekta Monaco

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The lecture is structured in four points:

1. Prioritization of planning objectives
2. The application of biological models in a typical scenario of normal tissue limited target dose
3. Biological models for normal tissues and the target
4. Sensitivity analysis in the context of multi-criteria optimization

Commonly, radiotherapy planning requires that a multitude of treatment goals are formulated which have varying levels of importance. Some examples:
1. The goal "spare as much as possible" implies that the severity and/or the frequency of the normal tissue dose response do not justify the slightest reduction in target dose.
2. The goal "observe limit x if possible but never violate limit y" implies that the dose response is severe enough that a compromise between this goal and the target goal has to be found.
3. The goal "do not exceed some limit z" implies that the dose response of the normal tissue complication does justify a target dose reduction and becomes dose limiting.

Regardless of whether the goals are expressed by biological or physical models, the TPS has to provide means to organize them according to their priority. Here, it is helpful to distinguish between *objectives* and *constraints*. If a goal is treated as a constraint, the TPS should guarantee that this goal is always met. In contrast, treating a goal as an objective may lead to a situation where it is not met because other goals compete with it. If competing goals are handled as constraints, this can result in a situation where the constraints cannot be fulfilled at the same time, thus causing an ill-posed and infeasible prescription.

In the above examples, goal 1 is a typical objective, while goal 3 is a typical constraint. Goal 2 requires user interaction because a trade-off with the target has to be found if either both or none of the limits x or y can be achieved. It can be treated as a constraint which is modified by the user in an attempt to find the best compromise. In this case, the TPS should provide tools that allow the exploration of the possible consequences on the target dose (also known as sensitivity analysis).

The TPS Monaco provides 4 levels of goal prioritization:

1st order constraints: goal will always be met.
2nd order constraints: goal will be met unless a 1st order constraint competes *(to avoid infeasible prescriptions).*
1st order objectives: goal will be met or even exceeded if constraints do not prevent this
2nd order objectives: goal will be met or even exceeded if constraints do not prevent this and 1st order objectives are all met.

In a scenario where normal tissues are dose limiting, a typical assignment of priorities to treatment goals reads like this:

1st order constraints:	dose limiting normal tissues, severe complications
2nd order constraints:	minimum dose constraints, minimum dose-volume constraints for targets. Notice: dose increasing goals and dose decreasing goals cannot be 1st order constraints at the same time!
1st order objectives:	maximize target equivalent uniform dose (EUD). Try to find the best target dose possible under the normal tissue constraints given. Notice, 2nd order constraints as above are not essential, it is sufficient to define a target objective
2nd order objectives:	increase dose conformity, minimize normal tissue integral dose, etc.

Different scenarios exists where normal tissues are not explicitly dose limiting, e.g. stereotactics. Here, biological models for normal tissues are naturally not as important and maximum physical dose conformity acts as a substitute criterion for biological endpoints.

Biological models are most advantageous for severe side-effects in the dose limiting scenario for the following reasons:

1. They consider the entire range of the organ dose and hence provide a build-in balance between high, intermediate and low doses. They can be modeled to express the dose-response specific volume effect. Hence, in above example 2, the model may favor either limit x or limit y depending on the case in question, or even provide a continuous range of compromises between those alternatives, with equal risk of toxicity.
2. It is helpful to think of a biological model as of an infinite set of *linked* dose-volume objectives. In effect, each dose bin in the DVH is given a specific weight, and the weighted volumes of all bins are added together. Hence, biological models can control multiple aspects of a dose distribution in parallel and can replace multiple dose-volume constraints.
3. They allow for a simplified sensitivity analysis because each organ-associated dose-response is expressed as a single goal, not a multitude of e.g. dose-volume constraints for one organ. Hence, a trade-off between the target volume goals and the organ sparing goals can be found more easily.
4. The absolute value of the goal constraint can be standardized for a patient population and even linked to outcome predictions in some cases. By using standardized normal tissue constraints, the more difficult cases in a population automatically receive more sophisticated dose distributions whereby all possible degrees of freedom are explored, while the simple cases can be treated with more resource-friendly treatment plans.

The models of choice for normal tissues in the TPS Monaco are two variants of the equivalent uniform dose formalism. One is suited for organs with a serial dose-response mechanism and a small volume effect, like rectum, bladder, bones, heart or nervous tissue. It has one parameter, k = 1/n, which is the organ specific volume effect parameter and the desired goal is specified in terms of the organ EUD. The greater k, the steeper the dose response curve and the smaller the volume effect.

$$F = 1/N \sum_{i=1}^{N} D_i^k \qquad EUD = F^{1/k}$$

The other one is suited for organs with a parallel dose-response mechanism and a large volume effect, like lung, liver, kidneys and parotids. It has two parameters, the critical dose (similar to a dose-volume constraint) D_0 and the volume effect parameter k. The desired goal is specified in terms of the integral organ damage in per cent.

$$F = 1/N \sum_{i=1}^{N} \frac{1}{1+(D_0/D_i)^k} \qquad Damage = 100\% \times F$$

Although both models are derived from established normal-tissue-complication probability (NTCP) models, the goals are not quantified as complication probabilities. EUD and integral damage on the one hand and NTCP on the other are linked by a one-to-one relationship, so controlling (as a constraint) or minimizing (as an objective) one always controls or minimizes the other. One great advantage of EUD/mean damage is that safe values for goals can be found simply by retrospectively analyzing a set of acceptable dose distributions, even on an institution-by-institution basis. Outcome scoring is not required in order to relate past practice with future optimization goals, and thereby preserve valuable experience. Notice further, that complication scoring is notoriously imprecise if complications are a rare event, thus making especially such values as D_5 (dose causing 5% complication risk) unreliable. Therefore, dose optimization becomes more consistent if raw EUD values are used.

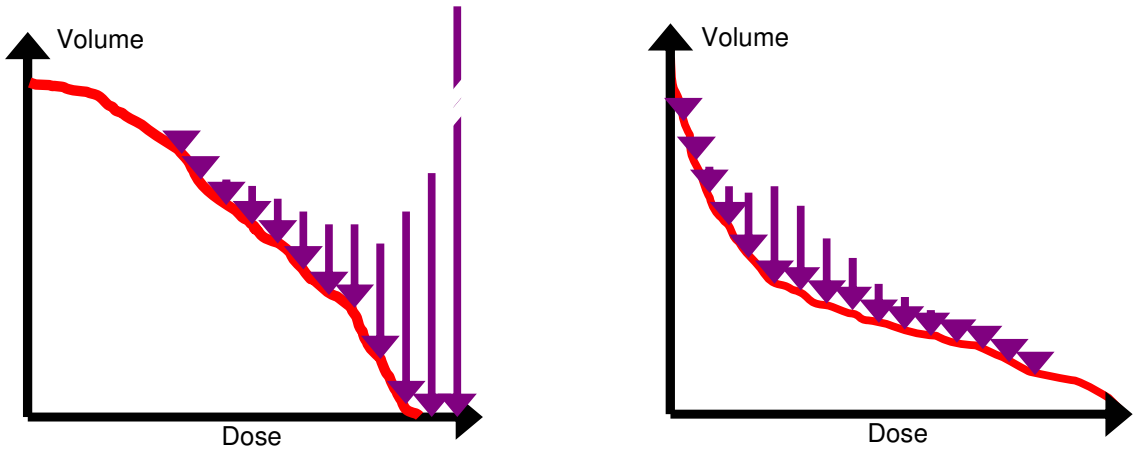

Fig 1: Interpretation of biological cost functions as a set of linked dose-volume-constraints. The length of the arrow corresponds to the weight of the dose bin in the optimization. Left, generalized EUD for organs with a small volume effect, high penalty for high doses. Right, integral damage model for organs with a large volume effect, high penalty for intermediate doses, low penalty for low and high doses.

For target volumes, the same arguments can be made in favor of EUD over TCP. In particular, notice that TCP cannot be computed meaningfully for a planning target volume PTV, which contains the actual tumour tissue plus a substantial margin of normal tissue. EUD, on the other hand, can be computed for any volume by:

$$F = 1/N \sum_{i=1}^{N} \exp(-\alpha D_i) \qquad EUD = -1/\alpha \log(F)$$

Notice that target EUD expresses only the goal to achieve a sufficient dose, but does not limit the dose maximum in the target volume, which is a separate goal.

In a scenario where normal tissues are dose limiting, the target EUD may not be achievable with the goal constraints initially chosen. In this case, it is important to identify those constraints which have the greatest influence on the target. The TPS Monaco provides four tools to do that.

1. Before convergence, status indicators show qualitatively which goals have the greatest influence on target EUD. Thus, it is possible to quickly identify prescriptions which can cause trouble.
2. After convergence, it is possible to identify the causes for each cold spot in the target, and give a specific break-down of the contributions of each normal tissue goal to this particular cold spot.
3. Also after convergence, the bulk influence of a normal tissue goal on the target EUD can be computed, thus giving an indication about how much a constraint may be relaxed or tightened to improve the planning result.
4. The change in dose distribution can be predicted that results from the adjustment of a single goal constraint. Thus, time-consuming trial-and-error can be reduced to a minimum.

Concluding, biological optimization cannot solve the fundamental problem of radiotherapy, that a desirable dose distribution may not be physically feasible. Also, if physically optimized plans and biologically optimized plans are compared, it is natural that the biological plans are better by biological metrics and vice versa. It is impossible to rank these methods on a comparison basis. The strong points of biological optimization are the following:

1. A number of dose-volume constraints can be replaced by a single biological model, thus making the plan optimization simpler.
2. It is straightforward to extrapolate past experience to modern techniques because the models and goals can be calibrated against previously applied dose distributions.
3. In very complex cases, biological models can use more degrees of freedom and do this more safely than isolated dose-volume constraints.