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SHORT COMMUNICATION

Optimization of radiotherapy fractionation schedules based on radiobiological functions

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Objective: To present a method for optimizing radiotherapy fractionation schedules using radiobiological tools and taking into account the patient´s dose-volume histograms (DVH).
Methods: This method uses a figure of merit based on the uncomplicated tumour control probability (P^+) and the generalized equivalent uniform dose (gEUD). A set of doses per fraction is selected in order to find the dose per fraction and the total dose, thus maximizing the figure of merit and leading to a biologically effective dose that is similar to the prescribed schedule.
Results: As a clinical example, a fractionation schedule for a prostate treatment plan is optimized and presented herein. From a prescription schedule of 70 Gy/35 × 2 Gy, the resulting optimal schema, using a figure of merit which only takes into account P^+, is 54.4 Gy/16 × 3.4 Gy. If the gEUD is included in that figure of merit, the result is 65 Gy/26 × 2.5 Gy. Alternative schedules, which include tumour control probability (TCP) and the normal tissue complication probability (NTCP) values are likewise shown. This allows us to compare different schedules instead of solely finding the optimal value, as other possible clinical factors must be taken into account to make the best decision for treatment.
Conclusion: The treatment schedule can be optimized for each patient through radiobiological analysis. The optimization process shown below offers physicians alternative schedules that meet the objectives of the prescribed radiotherapy.
Advances in knowledge: This article provides a simple, radiobiological-function-based method to take advantage of a patient's dose-volume histograms in order to better select the most suitable treatment schedule.

INTRODUCTION

Radiobiological tools have been used in radiotherapy (RT) clinical decisions since the last century; however, most of the time, they have been used solely for managing treatment interruptions.

Some efforts have been made to extend the use of said radiobiological tools, such as the inclusion of biological evaluation tools in some treatment planning systems.[1] Likewise, there exist other computer applications that can be used to evaluate treatment plans.[2–6] Some authors have proposed spatiotemporal optimization.[7,8] It could be challenging to use these methods in RT departments with high workloads.

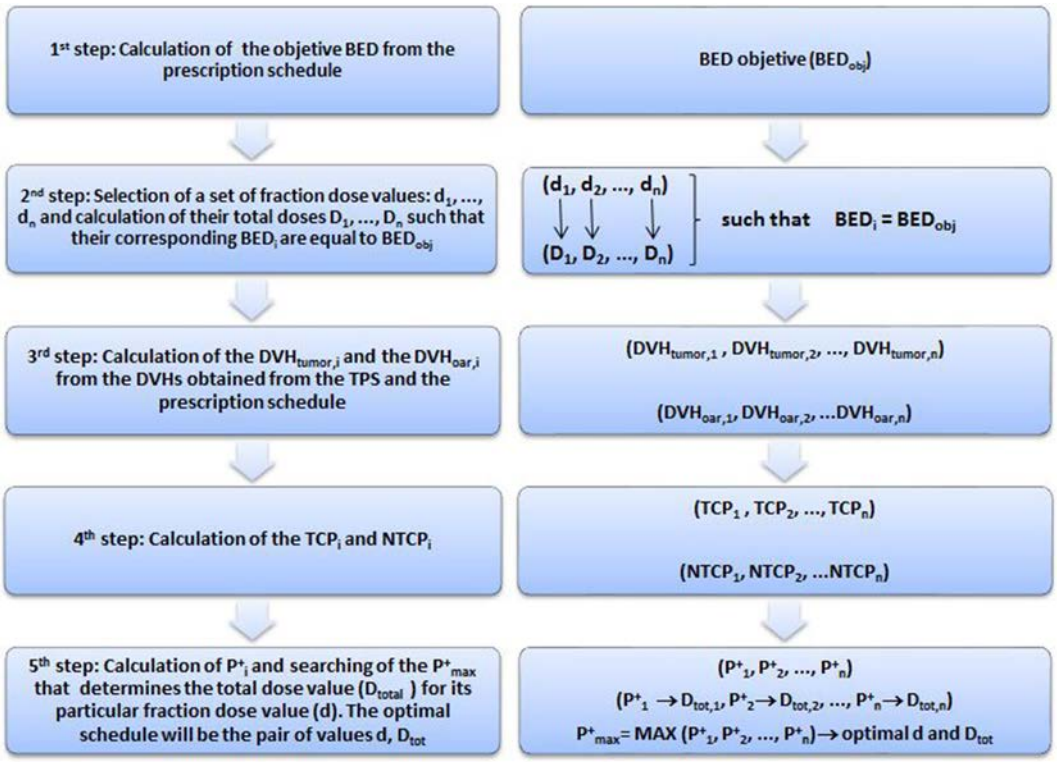
On the other hand, in many cases, new technologies in RT are able to easily meet objectives and handle constraints in terms of the planning target volume (PTV) and the organ at risk (OAR), respectively. This gives rise to the idea that other fractionation schedules are possible in addition to those used for classic conformal RT. If an OAR in two different treatment plans with the same fractionation schedule is irradiated much more in one plan than the other, then it would make sense to think that these two plans should not have the same schedule. Each plan would have its optimal fraction size. Nowadays, there exists a gap between the evolution of technology and the delivery of fractionation schedules.

The aim of this study is to present a simple method that uses radiobiological tools to optimize fractionation schedules, which complement the dosimetric improvements brought about by new treatment techniques. The method is based on patients' dose-volume histograms, thus giving rise to individualized optimization.

METHODS AND MATERIALS

The method is based on maximizing the uncomplicated tumour control probability (P^+) function, where $P^+ = TCP \cdot (1 - NTCP)$.[9] This figure gives the optimal total

Figure 1. Steps of optimization process. Optimal dose per fraction (d) and optimal total dose (D_{tot}) are the final result of the process. Biologically effective dose (BED), dose-volume histogram (DVH), tumour control probability (TCP), normal tissue complication probability (NTCP) and uncomplicated tumour control probability (P^+) are involved in different steps of this process.



dose for a fixed fraction size. The approach is based on studying P^+ when the fraction size varies. In this way, a set of solutions for P^+ is obtained, and their maximum will yield the optimal fractionation schedule, that is to say, the optimal total dose for the optimal fraction size.

The schedule prescribed by the oncologist for the tumour is translated into biologically effective dose (BED).[10] This BED is named BED_{obj}. A DVH for the PTV and another for the OAR are obtained from the treatment planning systems at this prescribed schedule. The criterion for choosing the OAR is that its final outcome must be as important as the loss of tumour control.

A summary of the process is shown in Figure 1. A set of doses per fraction must be selected (**di,** where **i** = **1** to **n**) to be used as software input. The programme can manage up to n = 16 doses per fraction every time the application is run. The interval between doses is 0.1 Gy.

For every fraction size ($\mathbf{d_i}$), total dose ($\mathbf{D_i}$) is determined so that the corresponding BED is equal to BED_{obj}. For each $\mathbf{D_i}$, a new $DVH_{tumour,i}$ and a new $DVH_{OAR,i}$ will be obtained from the DVH_{tumour} dose prescription and from DVH_{OAR}, respectively. For example, a DVH obtained for a total dose of 70 Gy can be translated into a DVH with a total dose of 72 Gy if every bin of the 70 Gy DVH is multiplied by the ratio 72/70. DVH only depends on the total dose.

The TCP, NTCP and P^+ curves can be calculated from each of the newly calculated DVHs. There will be as many curves as fraction sizes, which make up the set **n**. The total dose value ($\mathbf{D_{tot,i}}$ - Figure 1) is a value whose P^+ value is at its maximum for each fraction size, **di**. In general, $\mathbf{D_{tot,i}}$ will be different from $\mathbf{D_i}$. Lastly, the maximum value for the set's P^+ will correspond to the optimum fractionation.

As stated above, prescribed histograms are transformed to adapt each bin of the DVH for the total dose, which is changing. After that, the DVHs are transformed into their isoeffective doses in 2 Gy fractions, using the linear-quadratic (LQ) formalism to take into account the changes in the doses per fraction. Also, within the process, a Monte Carlo method is used to describe inter-patient variability in sensitivity through α and β, the radiobiological parameters of the LQ model. Specific α and β values are derived using pseudo-random numbers and the Weibull cumulative probability. The method requires knowing the mean α and β values, and their respective deviations, but these values are difficult to obtain, even *in vitro*, and caution must be used in the selection of said values. The process takes on the radiobiological parameter uncertainties which are used to calculate TCP and NTCP indices.

Ebert conducted a study in which TCP and equivalent uniform dose (EUD) were analysed, concluding that EUD could be a more robust index for optimizing a treatment plan in which radiobiological parameters are not well known.[11] He

recommended that EUD and TCP indices are to be considered together as a more complete tool for evaluating dose. In order to follow this recommendation, a figure of merit, based on gEUD, was introduced.[12,13] This figure of merit was defined as follows:

$$f = f_{tumor} \times f_{oar} \quad (1)$$

Where,

$$f_{tumor} = \frac{1}{1 + gEUD_o/gEUD} \quad (2)$$

And

$$f_{oar} = \frac{1}{1 + gEUD/gEUD_0} \quad (3)$$

where $gEUD_0$ represents the value which corresponds to the prescribed dose for the tumour and the dose for 50% complication probability (TD50) for the OAR.[14]

The total figure of merit that combines the notions of gEUD and P^+ (whose value must be the maximum value) is calculated as:

$$f_{total} = P_i^+ \times f_i \quad (4)$$

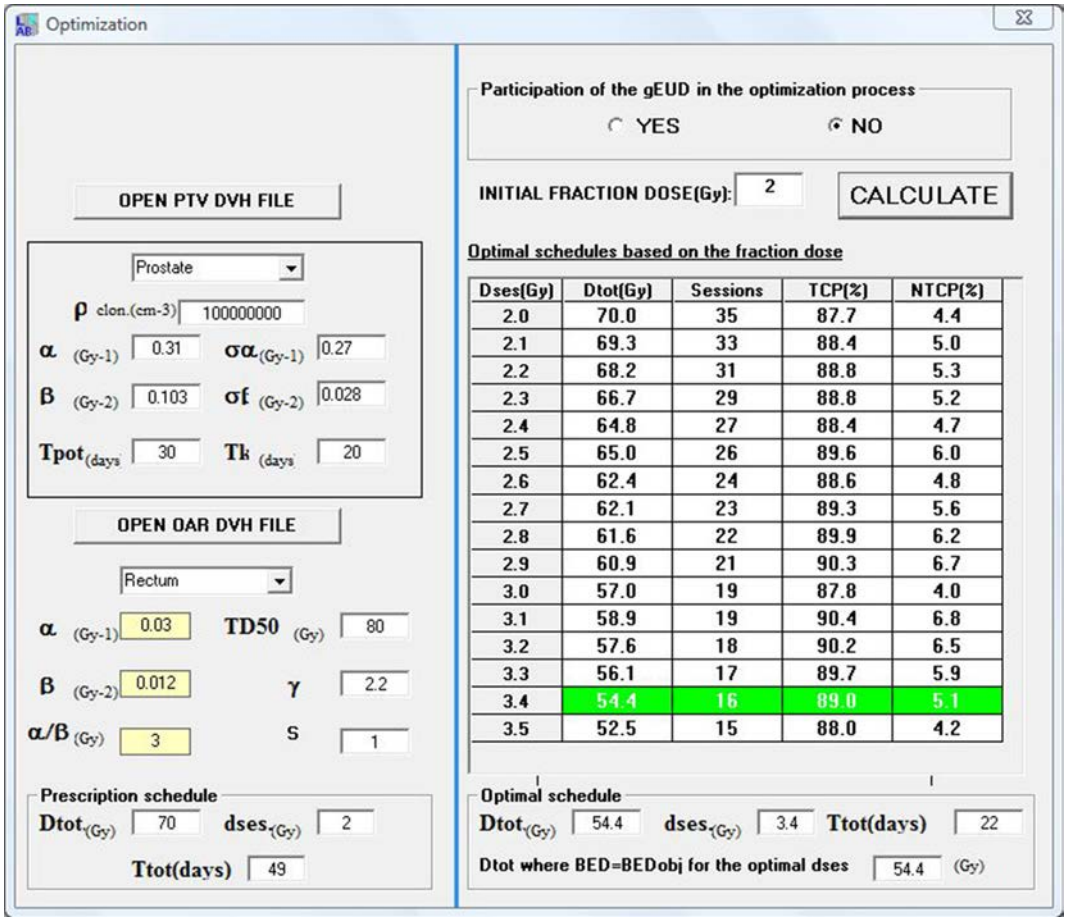
where i (1, *n*).

Specialized in-house software, LQlab, has been developed to perform these calculations—while likewise having the ability to perform other radiobiological calculations of interest.[15]

RESULTS

To serve as a clinical example, a fractionation schedule for a prostate treatment plan was optimized. This kind of tumour was chosen because of its low α/β ratio and the positive effect of hypofractionated schedules. The rectum was selected because of its peculiarity of being the most critical OAR meeting the restrictions. The prescription schedule was 70 Gy/35 × 2 Gy. Figure 2 shows the LQlab optimization interface. The radiobiological parameters of the tumour (prostate) and the OAR's complication (necrosis/stenosis) can be selected from a dropdown. The values included in the programme were taken from references.[16,17] In any event, the application allows the user to change these parameters. The prescription dose,

Figure 2. Optimization example using the dose-volumen histograms (DVH) of a planning target volume (PTV) and an organ at risk (OAR) which correspond to a prostate and rectum, respectively. The option of gEUD's participation is set to NO. The optimal schedule and total dose, whose BED = BED_{obj} for the optimal dose per fraction, are shown at the bottom right of the figure. gEUD, generalized equivalent uniform dose.



the gEUD's participation in optimization and the initial fraction dose ($\mathbf{d_1}$) had to be specified as well.

The output is shown in table format. All the tested fraction dose values (**Dses**) are shown in the first column. For each of these fraction sizes, the optimization results are shown in rows as total dose (**Dtot**), **sessions**, **TCP(%)** and **NTCP(%)**. LQlab highlights the optimal result from all those available. This optimal schedule is 54.4 Gy/16 × 3.4 Gy. Figure 3 shows the maximum value for this set's P^+ at 3.4 Gy per fraction. Incidentally, the BED value is equal to BED_{obj}:

$$BED_{obj} = BED\ (70\ Gy/35\ \times\ 2\ Gy)$$
$$= BED\ (54.4\ Gy/16\ \times\ 3.4Gy)$$

The TCP and NTCP values for this optimal schedule are 89 and 5.1%, respectively (Figure 2). These values are very close to the 87.7 and 4.5% values obtained from the prescription schedule. In this case, the difference arises in terms of total treatment time - the patient would finish treatment 27 days earlier with the optimal schedule.

In order to make use of the gEUD's contribution, the "**Participation of the gEUD in the optimization process**" option must be set to **YES**.

In this case, the resulting optimal schedule is 65 Gy/26 × 2.5 Gy, and once again:

$$BED_{obj} = BED\ (70\ Gy/35\ \times\ 2\ Gy)$$
$$= BED\ (65\ Gy/26\ \times\ 2.5\ Gy)$$

This last option, when selected, chooses schedules with lower fraction sizes, since the gEUD function does not negatively affect treatment time prolongation.

DISCUSSION

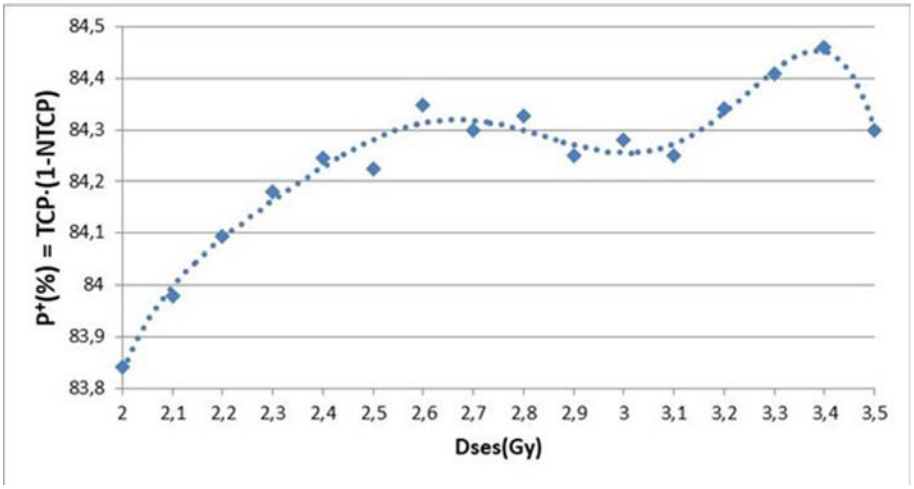
The absolute values of the TCP and NTCP depend on the uncertainty of the radiobiological parameter values used in the TCP and NTCP models. Nevertheless, these optimization process results are independent from those absolute values, as the relevance of these calculations stems from the relative differences among the values obtained from the different fraction sizes. What matters is for users to be able to compare different schedules—not just select the optimal one. After all, dose response is accepted as being a complex issue that involves several factors, with RT being just one of those factors. The resulting optimal schedule may not be the best from a clinical point of view. This is the reason why it can be of interest to offer the physician several alternative schedules which would align with the prescription. Having alternatives of this type at one's disposal is what could be most clinically applicable. Although P^+ could lead low total doses, the user can always compare the biological effect of the prescription dose for the tumour to the calculated optimal schedule at the bottom right of Figure 2. In cases where BED < BED_{obj}, the users can add sessions to the optimal schedule or choose another schedule with a TCP which is equal to, or greater than, the medical prescription.

As a result, the trend in the future could be to prescribe in BED units instead of prescribing based on the total dose/dose per fraction pair, as said doses could be obtained after an optimization process. The dose prescription would, thus, be specific to each patient, as the patients' DVHs have to be used in the process. That is to say, optimization brings about an individualized dose prescription.

The clinical history of the patient and other concomitant or adjuvant treatments will have to be taken into account in order for optimal schedules with high doses per fraction to be acceptable. Likewise, a trustworthy immobilization system combined with image guidance would be necessary to deliver these high fraction sizes with an acceptable uncertainty level.

The results from different trials comparing radiation toxicity in hypo-fractionation versus conventional RT should likewise be taken into account.[18] More specifically, in the case of the prostate cancer, some recent reviews highlight the precautions to be considered in the case of moderate hypo-fractionation (2.4–3.4 Gy);

Figure 3. Calculated P^+ values obtained through the TCP and NTCP values of the Figure 2 versus doses per fraction. The maximum value is located at 3.4 Gy per fraction whose optimal schedule is 54.4 Gy/16 × 3.4 Gy. NTCP, normal tissue complication probability; TCP, tumour control probability.



extreme hypo-fractionation regimes (>4 Gy) should be restricted to prospective clinical trials.[19]

CONCLUSIONS

RT treatment schedules can be optimized on a patient-by-patient basis through radiobiological analysis. The optimization process discussed herein can provide physicians with alternative schedules which meet the objectives and constraints of the RT prescription. The patient history and the available technical resources for delivering treatments must be taken into account in order to accept the results yielded from the process in the event that the fraction dose increases.

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