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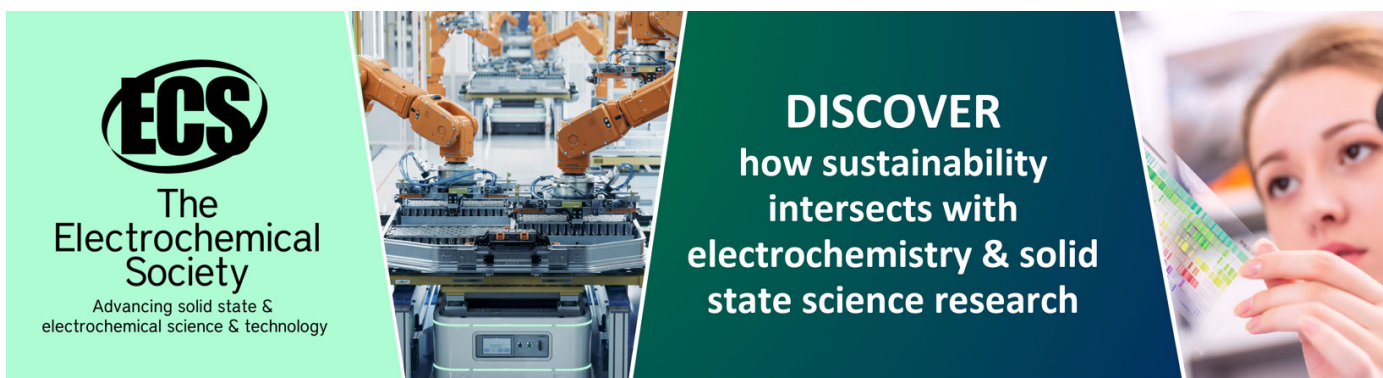
RTtxGap: An android radiobiological tool for compensation of radiotherapy treatment interruption

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RTtxGap: An android radiobiological tool for compensation of radiotherapy treatment interruption

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Abstract. Treatment interruption is not uncommon in radiotherapy. Common reasons for treatment interruption include machine breakdown, holidays and patient severe radiation reactions. Here RTtxGap, an Android application to assist calculations of compensation for treatment gap, is reported. It uses linear quadratic (LQ) model to calculate the biological effective dose (BED) that is used to solve for treatment gap compensations. Solutions are calculated using BED equation, with consideration for tissue proliferation. The accuracy of results has been verified using LQL Equiv software to be accurate within 1%. Five treatment interruption examples were used to illustrate the capability of the software to calculate the treatment compensation schedules. Solving these examples also illustrates the general consensus regarding compensating for unscheduled treatment interruptions, which ultimately involves balancing the BEDs of tumour and organ at risk. In addition to compensation for treatment gap, RTtxGap can also be used to calculate equivalent total dose in 2-Gy fraction (EQD2), to modify treatment schedule and to calculate alternative dose prescriptions having the same isoeffect.

1. Introduction

Treatment interruption is not uncommon in radiotherapy. Common reasons for treatment interruption include machine breakdown, holidays and patient severe radiation reactions. Prolongation of the overall treatment duration due to unscheduled treatment interruption can significantly affect local tumour control. In the case of head and neck tumour, a one day gap can be damaging with a reduction in local tumour control being estimated at 1.4% per day of missed treatment [1]. For recommendations on how to deal with the unscheduled treatment gaps, the reader is referred to The Royal College of Radiologists report [2].

Until sometime in the 90's, the unscheduled treatment interruptions were generally compensated using Orton and Ellis [3] nominal standard dose-time dose factor (NSD-TDF) tables. Following the introduction of the biological effective dose (BED) in 1989, which was originally formulated by Barendsen [4] as extrapolated response dose, the use of NSD-TDF table for treatment compensation has been criticized for being inaccurate. BED, a linear quadratic (LQ)-based formula with the time factor included, is given by

$$BED = nd \left(1 + \frac{d}{\alpha/\beta} \right) - \ln 2 (T - T_k) / \alpha T_p \quad (1)$$



Here, BED is related to n fractions of d Gy given in an overall time of T days in which tumour repopulation does not start until day T_k [5].

In the case where unscheduled treatment interruptions occur, equation (1) is used in current practice to calculate the required remaining schedule. However, calculating treatment compensation when many patients are involved can be a very taxing job. Here, RTtxGap, an Android application developed to assist these calculations based on Equation 1, is reported.

2. Methodology

RTtxGap was developed using JavaScript scripting language. It was compiled for Android devices using Intel® XDK. It uses LQ-model to calculate the BED, equivalent total dose in 2-Gy fraction (EQD2), treatment gap correction and alternative fractionation schedules. Solutions are calculated using Equation 1. To offer more flexibility, solutions are searched using iterative method instead of direct mathematical solving of the BED equation.

As stated by [6], the main difficulty in practical applications of the LQ-model is knowing what parameter values to use in individual calculations. However, more data has been available since that statement made in 2001. Many of this data are found compiled within the LQL Equiv software [7], a software developed collaboratively by the CHD Castelluccio radiotherapy unit in Ajaccio and the University of Corsica. It is a free software released under the GNU license. It was decided that this data is used as it is in RTtxGap and the LQL Equiv software is used to verify results from RTtxGap.

Table 1. Verifications of BED and EQD2 calculation results from RTtxGap using LQL Equiv software. Notice that results calculated by RTtxGap are within 1% for BED values and are within 2% for EQD2. The higher EQD2 errors are due to the coarse iterative steps used in the RTtxGap program to arrive at the EQD2 solutions.

Target/OAR	Prescription	Tumour BED			Tumour EQD2		
		TtxGap	LQL-Equiv	% diff	RTtxGap	LQL-Equiv	% diff
Breast/lung	50Gy/25\#	80.52	80.5	0.02	50.0	50.0	0.00
	42.4Gy/16\#	81.11	81.0	0.14	50.0	50.3	-0.60
Prostate/rectum	70Gy/35\#	113.84	113.8	0.04	70.0	70.0	0.00
	60Gy/20\#	117.73	117.7	0.03	72.0	72.4	-0.55
NPC/std acute	60Gy/30\#	57.00	57.0	0.00	60.0	60.0	0.00
	57.2Gy/26\#	57.56	57.4	0.28	60.0	60.5	-0.83

Target/OAR	Prescription	OAR BED			OAR EQD2		
		TtxGap	LQL-Equiv	% diff	RTtxGap	LQL-Equiv	% diff
Breast/lung	50Gy/25\#	63.36	63.4	-0.06	50.0	50.0	0.00
	2.4Gy/16\#	66.77	66.5	0.41	52.0	52.5	-0.95
Prostate/rectum	70Gy/35\#	91.20	91.2	0.00	70.0	70.0	0.00
	60Gy/20\#	97.75	97.8	-0.05	74.0	75.0	-1.33
NPC/std acute	60Gy/30\#	72.00	72.0	0.00	60.0	60.0	0.00
	7.2Gy/26\#	69.78	69.8	-0.03	58.0	58.2	-0.34

Due to the small telephone screen, separate mini task is performed on separate tabs in RTtxGap. To use the software to calculate possible treatment compensation for unscheduled treatment gap, a user will first enter the tumour type and organ at risk (OAR) so that the LQ parameters, α and β values, for both tumour and OAR can be determined from lists of parameters stored in the program. Then, the original treatment dose prescription is entered. In the next tab, the user enters details for treatments that have already been delivered, including the number of days treatment has been missed. The number of days, instead of the number of fractions, missed should include weekends. This is to allow for greater flexibility of the software to calculate for cases with large treatment gaps. Although large treatment gaps are not generally advised in practice, it can be useful for academic purposes. In the final tab, the

maximum number of fractions, the number of fractions per day, the allowed minimum and maximum dose per fraction, and treatment aim are entered. Four options for treatment aims are defined, namely conservative, aggressive, set maximum physical dose, set maximum OAR BED and set minimum tumour BED. For conservative aim, OAR BED is retained in the new compensated schedule, whereas tumour BED is retained in aggressive mode. If one wants to make sure that tumour BED does not fall below a certain percentage of the original planned value, set the minimum tumour BED option has to be used. One might evaluate this if upon choosing the conservative mode, the resultant tumour BED is found to be unacceptably low. By the same token, one can limit how high the OAR BED can be, in percentage of planned value, by using the last option in the aim.

When all needed information is entered, the calculate button at the bottom right of the screen will be enabled. Upon hitting the calculate button, the new remaining treatment schedule will be reported together with the total physical dose, the percent tumour BED and the percent OAR BED, both are with respect to the planned values, and their respective EQD2 values. The new schedule can be recalculated after changing any of the mentioned parameters. This can be used for fine tuning of the results. Results were verified using LQL Equiv software. Note that LQL Equiv calculates BED and EQD2 values for particular given schedules but it does not automatically find solutions for treatment interruptions. To illustrate the usage of RTtxGap in calculating compensations for unscheduled treatment interruptions, examples presented in reference [8] are reworked.

3. Results and discussion

The prescribed BED and EQD2 values for both tumours and organ at risk in three treatment cases, namely breast carcinoma, prostate carcinoma and nasopharyngeal carcinoma, are summarized in table 1. Results calculated by RTtxGap are within 1% for BED values and are within 2% for EQD2. The higher EQD2 errors are due to the coarse iterative steps used in the RTtxGap program to arrive at the EQD2 solutions.

Since table 1 data does not evaluate the capability of RTtxGap in finding solutions for treatment interruptions, results of calculations for the same tumour targets and organ at risks were evaluated. For these cases, seven days of unscheduled treatment gaps, i.e. 5 missed fractions, were introduced after the first ten fractions. The lost five fractions were compensated by having two fractions per day treatment for the first ten fractions following the gaps. Then RTtxGap were used to calculate the remaining fractions. The results of this are summarized in table 2. Again, results calculated by RTtxGap are within 1% for BED values and are within 2% for EQD2.

Table 2. Worked examples for cases where the treatments were missed for the whole third week. Compensations include 10 two-fraction per day treatments followed by regular treatment for the rest of the fractions. The resultant BEDs and EQD2 were confirmed using LQL Equiv software.

Target/OAR	Prescription	Tumour BED			Tumour EQD2		
		RTtxGap	LQL-Equiv	% diff	RTtxGap	LQL-Equiv	% diff
Breast/lung	50Gy/25\#	81.39	81.4	-0.01	50.0	50.6	-1.19
Prostate/rectum	70Gy/35\#	114.65	114.7	-0.05	70.0	70.5	-0.71
NPC/std acute	60Gy/30\#	57.15	57.2	-0.08	60.0	60.2	-0.33

Target/OAR	Prescription	OAR BED			OAR EQD2		
		RTtxGap	LQL-Equiv	% diff	RTtxGap	LQL-Equiv	% diff
Breast/lung	50Gy/25\#	63.43	63.5	-0.11	50.0	50.1	-0.20
Prostate/rectum	70Gy/35\#	95.67	95.7	-0.03	73.0	73.4	-0.54
NPC/std acute	60Gy/30\#	72.25	72.3	-0.07	60.0	60.2	-0.33

Dale *et al.* [8] has worked out five examples to illustrate usage of BED equation to solve for problems with unscheduled treatment gaps in nasopharyngeal carcinoma cases whose original prescriptions are 70 Gy/35 fractions. The first example deals with situation where unscheduled gap occurs for the whole

third week into treatment. The second example deals with the lost of the whole sixth week of treatment whereas the third example deals with the lost of what was supposed to be the final week of treatment. The fourth example deals with lost of the last two treatment weeks. The last examples deal with lost of the final thirteen fractions. The OAR chosen for this case is the standard acute effect, i.e. linear quadratic model without consideration for tissue repopulation. This represents the worst case scenario for acute adverse effect of treatment that might disrupt treatment. The results are summarized in table 3.

Similar to Dale *et al.* [8] findings, the results indicate that for cases where the overall treatment duration can be maintained, it should be done so. Maintaining the total treatment duration make it possible to maintain both tumour and OAR BEDs without even having to actually calculate them. In our case, this is achieved through delivery of two fractions per day. It is also possible to use treatments over the weekend to maintain the total treatment duration, though this is not considered by RTtxGap. When it is no longer possible to maintain the total treatment duration, treatment compensations to maintain tumour BEDs inevitably translate into higher OAR BEDs. The effect can be minimized by minimizing the resulting extra treatment durations, again through multiple treatment fractions per day and/or treatment during weekends. If this is not possible, i.e. treatment can only be continued with single fraction per day as usual, fractionation schedule that results in lower OAR BED can be considered. This can be easily done in RTtxGap by choosing the third treatment aim, and set the maximum allowable values for the OAR BED. This, however, translates into a lower value for tumour BED that can compromise the efficacy of the treatment. A user can try different combinations of requirements to arrive at an optimum solution. A user, for example, can try setting the minimum required tumour BED to numbers slightly below 100% of the prescribed tumour BED and evaluate whether a better OAR BED can be achieved.

Table 3. Worked examples from Dale *et al.* [8] for the case of nasopharyngeal carcinoma. Descriptions of the examples can be found in the text. Here, RTtxGap aims are mostly selected to maintain tumour BED (aggressive aim) and whenever BED3 is mentioned, the aim is to not let OAR BED go beyond the values in the bracket.

Example	RTtxGap aim	Compensation	Tumour		OAR	
			%BED	EQD2	%BED	EQD2
Example 1	aggr(2#/day)	10+10(2#/day)+15	100.24	70.0	100.36	70.0
Example 2	aggr(2#/day)	25+10(2#/day)	100.24	70.0	100.36	70.0
Example 3	aggr(2#/day)	30+5(2#/day)	99.78	68.0	101.87	71.0
	aggr(1#/day)	30+7	100.00	70.0	105.71	74.0
Example 4	aggr(2#/day)	25+10(2.25 Gy/# in 2#/day)	99.79	71.0	102.43	71.0
	aggr(1#/day)	25+14	100.00	70.0	111.43	78.0
	BED3 (106%)	25+11(2.15 Gy/#)	95.10	65.0	105.64	73.0
Example 5	aggr(2#/day)	22+13(2.2 Gy/# in 2#/day)	100.04	70.0	104.86	73.0
	aggr(1#/day)	22+16(2.15 Gy/#)	99.65	68.0	112.61	78.0
	BED3 (107%)	22+13(2.3 Gy/#)	96.06	65.0	106.64	74.0

One has to be careful when high dose per fraction is used in treatment compensations. The higher sensitivity of the late-responding normal tissue to changes in dose per fractions, due to lower α - β ratio, means more biological dose proportion to normal tissues are given for higher dose per fraction is used [8].

The results of any BED calculations for radiotherapy treatment gaps should not be taken as an absolute indicator in clinical decision making. Instead, it should be used as a guide to be considered among other factors such as patient's response. One has to be aware that LQ-model, which these calculations are based on, is considered an oversimplification of the biological systems [8]. Moreover the data for variables in Equation 1 are scarce and are currently drawn from only limited number of publications [9]. As such, it is not 100% robust.

4. Conclusion

The values for planned tumour BED and OAR BED reported by RTtxGap are verified to be exactly the same as those obtained from LQL Equiv software. The BED values for the calculated new schedules are within 1% of the values calculated using LQL Equiv. It should be noted that LQL Equiv does not calculate a new schedule. Instead, new schedule is guessed by the user, from which BED values for both tumour target and OAR are calculated. For verification in this work, the guessing job is replaced by new schedule results from RTtxGap.

Worked out examples from nasopharyngeal carcinoma cases illustrates the general consensus regarding compensations for treatment such as the effect of overall time extensions, of the dose per fraction and the needs to balance tumour and OAR BEDs when treatment period has to be prolonged.

In addition to calculating for treatment gap compensation, RTtxGap can also be used for three other purposes, i. e. to calculate EQD2 for a prescribed dose, to modify treatment schedule for reasons such as finishing treatment before a holiday and to prescribe dose fractionation using alternative schedules, example of which includes calculating the hypofractionation dose for treatment of breast carcinoma.

It is important to note that because RTtxGap uses LQ-model for all its calculations, it should not be used when the dose per fraction is large, generally more than 5 Gy per fraction (5 Gy/#). Users should also take extra care when a long treatment gap is involved. Furthermore, it is assumed that complete repairs have taken place between fractions, which means that if two fractions per day is chosen, the fractions have to be separated by at least 6 hours.

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