Role of LQ Model to Address Effect of Missed Treatment Days in External-Beam Radiotherapy

During external-beam radiotherapy (EBRT), radical treatment plans get affected due to machine failures and interruptions in delivery due to patients' absence due to clinical or personal reasons compromising treatment outcomes. Radiobiology of EBRT indicates that prolongation of overall treatment time (OTT) adversely affects local control of tumors. In most populated countries like India, many radiation therapy centers in the periphery have only one external-beam RT machine, either linear accelerator (LA) or tele-isotope cobalt machine. With no other alternate options, treatment completion of remaining fractions poses problems. Therefore, when the gap period prolongs beyond a week, the patients face an unfortunate situation, affecting therapy outcomes. Linear quadratic method with "biologically effective dose (BED)" is recommended by the Royal College of Radiologists (RCR)[1,2] to correct for treatment breaks. It is realized that if an interruption occurs toward the end of the treatment, more will be the total dose (D) compared to interruptions in the initial part. Another older method based on time–dose–fractionation (TDF) factor concepts[3] is also practiced in many clinics though mostly it is an obsolete method.

The BED for acute and late effects of connective tissues ($BED_{10,Acute}$, $BED_{3,Late}$) and BED local tumor control ($BED_{10,Tumor}$)[2] assume 28 days OTT as the limit for accelerated growth for head-and-neck malignancies, as given by equations 1–3.

$$BED_{10,Tumor} = N.\ d.\ (1 + d/10) - K\ (T-T_k) \quad (1)$$

$$BED_{10,Acute} = N.\ d.\ (1 + d/10) - 0.25(T) \quad (2)$$

$$BED_{3,\ Late} = N.\ d.\ (1 + d/3) \quad (3)$$

For tumor and acute effects, the generally accepted values of $\alpha/\beta = 10$, and for late effects of normal tissues, ($BED_{3\ Late}$) $\alpha/\beta = 3$ are in use. An empirical parameter $K = 0.9$ in Equation (1) is the BED required to offset repopulation, suggested in this LQ model. Citing a multicenter meta-analysis for larynx RT[2], it had been brought out a mean value for $K = 1.2$ (with range 0.8–2.2). Therefore, for general treatment interruptions, the RCR recommendations used $K = 0.9$ in all their examples. BED_{decay} per day amounts to $0.9/(1 + 2/10) = 0.75$ Gy/day. The daily physical dose to offset repopulation after time T_k ($T_k = 28$ days for head-and-neck malignancies) is therefore 0.75 Gy per day due to regrowth. For 2 Gy/fraction, this implies that $0.75/2 \times 100\% = 38\%$ dose is wasted to combat repopulation[2] effect after $T_k = 28$ days. Equation 2 shows that for normal tissues, for early effects (acute), there is some amount of repair effect along with $\alpha/\beta = 10$ for normal tissues. For BED for late effects $\alpha/\beta = 3$ in Equation (3), it is assumed that there is no repair built in as far as late effects are considered. This implies that, as per L, Q formulation (Equation 2), the $BED_{10,Acute}$ does not increase if fraction size remains the same.

A recent microdosimetric kinetic model[4] brought out the effect of interruption in radiation dose delivery. The authors assessed the lineal energy distribution for human salivary gland tumor and highlighted the need for a dose compensating factor for decay of biological effectiveness if there is interruption even during the delivery of dose in a single fraction itself. A dose compensating factor (at 1 Gy/min), when an interruption occurred at half the irradiation duration, was about 3% for 2 Gy if $\tau = 20$ min and for 5 Gy and 8 Gy if $\tau = 10$ min where τ is the interruption between two segments in total dose delivery, during one fraction. Therefore, radiotherapy clinics shall apply necessary correction in physical dose if there is an elongation of OTT to correct for the aggressiveness of involved tumor re-growth before the end of the course. Furthermore, calculation of loss of BED has to be done with reliable knowledge of biokinetic parameters such as Tk, Tp, and α value for the tumor. This may vary from tumor to tumor. When additional fractions had to be used to compensate for the loss of BED, the important limitation is the increased BED to the late responding normal tissues. This may result in an unacceptable level of late normal tissue morbidity.

RCR guidelines recommend (1) retaining the same OTT and change dose/fraction but add dose at 2 fractions/day at optimal Dose/fraction, (2) the use of adding extra fractions without altering fraction size, (3) retaining the same OTT, by increasing the size of dose fractions, and/or (4) alter the conventional 5 fractions/week and adding Saturdays' and Sundays' treatments. In the case of more than one fraction/day, it becomes essential that a minimum gap of 6h between successive fractions in a single day. It is to be restricted, to have 1.5-1.7 Gy/fr to protect normal tissue morbidity. In the above background, we bring out our experience in applying LQ corrections applied during the year 2019, when a cobalt treatment machine (Theratron 780E) was down resulting in a break of 11 days in OTT. Thirty-six of 40 patients (90%) were head-and-neck radical treatments. They had treatment breaks in the early, middle, and late part of 7 weeks' regimen. The same 2 Gy/Fr size was maintained increasing the number of total fractions, the treatments planned in weekends also, thereby increasing the total physical dose for the proposed new resultant OTT. The same 2 Gy/fraction was retained because most of our patients did not have a good physique and are nutrition deprived.[5] Most of them are treated using custom-built aluminum tissue compensators applying lateral opposing fields.[6] As 2 fractions in a daily regimen will likely to double the number of patients on each day in this single machine, and restriction in human resources, we resorted to retain daily single fractions only. We checked the conventional method of TDF factor method also, for comparison.

It can be seen in Tables 1 and 2, the modified OTT increase from 0 to 25 days depends on the occurrence of break-in treatments. The median number of patients had extra fractions 2–5. An increase in physical dose went even up to 8 fractions, which implies that for a planned radical dose of 70 Gy, biological equivalent correction for dose was significantly large in number. The compliance to the planned compensated regimen in all the patients is highlighted in Table 3. Our calculations showed that the TDF method (at cumulated TDF from 20 till 100), in spite of, whether treatment interruption occurred earlier or later, gave correction of only 1 extra fraction. Corrections on the accumulated TDF were from 0.820 to 0.975 which is clinically an insignificant correction on the total treatments, which appeared non-realistic.

In 6Fr/wk protocol patients, the extra dose required were 8 and 10 Gy for the needed BED_{10}, which resulted in an increase of 15.7% for BED_3 late effects. Conventional dose category of 27 patients had extra dose due to increase in the number of up to 7 fractions, with physical dose up to 84 Gy. In the second group with varied total added fractions, an increase of the weighted value of BED_3 of 8.5% was observed. One patient with a 66 Gy prescription did not require an extra fraction as this patient could get compensated by extra weekend fractions, within the same OTT. Another 60 Gy prescription group had extra 2–7 fractions, with an increased weighted BED_3 of 13.3%. The last group of 50 Gy prescription patients had 2–3 extra fractions resulting in the weighted increase of BED_3 as 10.1%.

In terms of acceptance of the dose correction strategy, all the patients could complete the altered total dose to compensate for the breaks. The skin reactions and mucositis grades at the time of completion RT were within the acceptable limits. There were lung complications which be seen in the last column in

Table 1: Details of planned excess overall treatment time with and added 2 (Gy) fractions

Regimen number	Increase in OTT (days)					Number of added 2 (Gy) fractions					+Dose (Gy)
	0-5	5-10	10-15	15-20	20-25	0-1	2-3	4-5	6-7	8	
1	-	-	2	-	-	-	-	2	-	-	8-10
2	11	7	6	3	1	5	11	8	3	1	2-16
3	1	-	-	-	-	1	-	-	-	-	-
4	-	2	4	-	1	-	3	3	1	-	4-12
5	-	2	-	-	-	-	2	-	-	-	4-6

OTT: Overall treatment time

Table 2: Linear-quadratic model suggested extra fractions and added total dose

Break after "*n*" fractions	RT plan					
	Correction for RT interruptions 70 (Gy)		Correction for RT interruptions 60 (Gy)		Correction for RT interruptions 50 (Gy)	
	Extra fractions	Extra dose (Gy)	Extra fractions	Extra dose (Gy)	Extra fractions	Extra dose (Gy)
3-10	0	0	-	-	-	-
12-16	2	4.0	3	6.0	2-3	4-6.0
17-28	4	8.0	4-5	8-10.0		
29-32	6-7	12-14				

RT: Radiotherapy

Table 3: Compliance of increased overall treatment time and summary at completion of corrected regimen

Regimen	Number patients	BED_{10} plan	Total dose (Gy)		Planned BED_3	BED_3 (weighted)	> BED_3 (%)	Skin reaction		Mucositis		Others (pneumonia)
			Plan	Actual				Grade	*n*	Grade	*n*	
6 Fr/wk	2	74.1	70	78-80	116.7	135.0	15.7	II	2	II	2	-
5 Fr/wk	27	67.8	70	70-84	116.7	126.6	8.5	I	3	I	2	5
								II	20	II	19	
								III	1	III	1	
								IV	1	-	-	
5 Fr/wk	1	64.8	66	66	110	110	-	IV	1	IV	1	
5 Fr/wk	7	62.1	60	64-74	100	113.3	13.3	I	2	I	1	
								II	4	II	3	
5 Fr/wk	2	58.0	50	54-56	83.3	91.7	10.1	-	-	-		

BED: Biologically effective dose

Table 3. As the RT fields were localized with lower border of the treatment fields not extending beyond the suprasternal notch level, lung complications could not be correlated to the excess physical dose.

In the interest of proper patient care, especially in a rural setup with single RT machine (either LA or isotope machine), it is strongly recommended that strategies be planned for proper management of radiation therapy without breaks. These clinics cannot effectively apply multifraction per day regime to correct for treatment breaks when a large patient number involved. What method described in this script was one of the solutions because of a large number of patients needing BED correction. The presented data also validates that radical cobalt treatments are possible in head-and-neck radiotherapy, without increased morbidity supporting the continuation of telecobalt machines to take care of large radiotherapy patient loads.[7] This report highlights that when the existing machines are beyond 7 years, there will be increased breakdowns expected, and administration shall take appropriate steps to make the second radiotherapy machine available, in the interest of un-interrupted RT patient care. If there is a break in RT, radiotherapy technologists may bring to the notice for gap corrections so that radical treatments are correctly executed. What was followed in our work is one particular solution. A general method shall be tried to maintain OTT with re-planning to 2 fractions/day, not exceeding 1.6 Gy/fraction, and minimum 6 h interfraction interval.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Ramamoorthy Ravichandran, Tarani Mondal, Bandana Barman, Gopal Datta, Ravi Kannan[1]

Departments of Radiation Oncology and [1]Surgical Oncology, Cachar Cancer Hospital and Research Centre, Meherpur, Silchar, Assam, India

Address for correspondence: Dr. Ramamoorthy Ravichandran, Department of Radiation Oncology, Medical Physics Unit, Cachar Cancer Hospital and Research Centre, Meherpur, Silchar - 788 015, Assam, India.
E-mail: ravichandranrama@rediffmail.com

Received on: 03-02-2021 Review completed on: 07-02-2021
Accepted on: 08-02-2021 Published on: 05-05-2021

References

1. The Timely Delivery of Radical Radiotherapy: Guidelines for the Management of Unscheduled Treatment Interruptions. 4th ed. London. The Royal College of Radiologists; 2019. Available from: http//www.rcr.ac.uk. [Last accessed on 2019 Oct 08].
2. Dale RG, Hendry JH, Jones B, Robertson AG, Deehan C, Sinclair JA. Practical methods for compensating for missed treatment days in radiotherapy, with particular reference to head and neck schedules. Clin Oncol (R Coll Radiol) 2002;14:382-93.
3. Orton CG, Ellis F. A simplification in the use of the NSD concept in practical radiotherapy. Br J Radiol 1973;46:529-37.
4. Kawahara D, Nakano H, Saito A, Ozawa S, Nagata Y. Dose compensation based on biological effectiveness due to interruption time for photon radiation therapy. Br J Radiol 2020;93:20200125.
5. Sharma D, Kannan R, Tapkire R, Nath S. Evaluation of Nutritional Status of Cancer Patients during Treatment by Patient-Generated Subjective Global Assessment: A Hospital-Based Study. Asian Pac J Cancer Prev 2015;16:8173-6.
6. Ravichandran R, Barman B, Datta G, Kannan R. External Beam Radiotherapy with Telecobalt Machine: Tissue Deficiency Compensation in Head-and-Neck Region and Effect on Skin Reactions. J Med Phys 2019;44:135-8.
7. Ravichandran R. Has the time come for doing away with Cobalt-60 teletherapy for cancer treatments. J Med Phys 2009;34:63-5.

Access this article online	
Quick Response Code:	Website: www.jmp.org.in
	DOI: 10.4103/jmp.JMP_24_21

How to cite this article: Ravichandran R, Mondal T, Barman B, Datta G, Kannan R. Role of LQ model to address effect of missed treatment days in external-beam radiotherapy. J Med Phys 2021;46:52-4.