Iranian Journal of Medical Physics

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Role of Overall Treatment Time When Estimating TCP & NTCP of Head & Neck Radiotherapy Treatment Plans in Altered Fractionation

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ARTICLE INFO

Article type:
Original Paper

Article history:
Received: Sept 26, 2021
Accepted: Jan 31, 2022

Keywords:
Overall Treatment Time
Tumor Control Probability
Normal Tissue
Complication Probability
Accelerated Fractionation
Moderately
Hypofractionation

ABSTRACT

Introduction: The present study demonstrated role of overall treatment time when estimating tumor control probability (TCP) and normal tissue complication probability (NTCP) for moderately hypofractionated and accelerated fractionation schedules in head & neck treatment plans. Repopulation effect in the squamous cell carcinoma is an influencing factor that should be considered when evaluating TCP and NTCP in early responding tissue. This effect can be incorporated by the means of overall treatment time in days.

Material and Methods: The proposed study separated in two parts. In the first case, we assumed four moderately hypofractionated schedules for demonstration, including conventional fractionation schedule (CFS) (70Gy/35 #), fractionation schedule 1 (66Gy/30#), fractionation schedule 2 (60Gy/24#) & fractionation schedule 3 (55Gy/20#). Four independent volumetric modulated arc treatment plans were generated at different fractionation schedules for 15 patient's data set and therefore led to a total of 60 treatment plans. The treatment plan created for CFS is the reference plan for comparison of calculated TCP & NTCP amongst the four plans. The rest three plans for each patient were created simply by changing the dose prescription for FS1, FS2 & FS3, the mean total dose and dose per fraction. In the second scenario, conventional fractionation schedule (66Gy/33# with five fractions per week) compared against accelerated fractionation schedule (66Gy/33# with six fractions per week). The cumulative dose volume histogram for all treatment plans were used for TCP/NTCP estimation by Niemierko EUD, Poisson model and LKB model. The TCP/NTCP calculated in two different way for tumor & oral mucosa of head & neck site. Contrary to the second case, the overall treatment time (OTT) in days not accounted in the first case.

Results: It was statistically significant difference ($p<0.05$) obtained between calculated TCP/NTCP in both moderately hypofractionated and accelerated fractionation schedules.

Conclusion: There is significant impact of OTT and it should be considered when evaluating TCP/NTCP for early responding tissue.

►*Please cite this article as:*
Patel G, Mandal A, Mishra R, Choudhary S, Mishra H. Role of Overall Treatment Time When Estimating TCP & NTCP of Head & Neck Radiotherapy Treatment Plans in Altered Fractionation. Iran J Med Phys 2023; 20: 106-113. 10.22038/IJMP.2022.60625.2020.

Introduction

It is well understood that prolongation of treatment time will reduce overall survival & local control due to the rapid repopulation in early responding tissues (tumor, skin & mucosa). Repopulation decreases radiosensitivity in tumor and normal tissue as the number of surviving target cell increases during treatment period. The onset of repopulation in tumor and normal tissue occurs within the first week after initiation of radiotherapy. The overall treatment time (OTT) is an indirect way to measure repopulation effect. Jose et al explained in his study how prolonging overall treatment time negatively affect local control and the overall survival[1]. The number of clinical trials studies showed that shortening the overall treatment time by means of altered fractionation or accelerated fractionation resulted in improvement of overall survival and loco-regional control in head & neck cancers as well as aggravation of early radiation induced toxicity[2,3]. With modern radiotherapy equipment it is possible to achieve treatment delivery accuracy which boosted confidence among clinicians to practice hypo- fractionated treatment schedules in head & neck cancers. Besides this, moderately hypo-fractionated schedules reduces overall treatment time (OTT). Accelerated fractionation schedules (AFS) is also an available alternative for shortening OTT.

Treatment plans evaluation of fractionation schedules other than conventional fractionation needs to be assessed differently in view of tumour control probability (TCP) and normal tissue complication probability (NTCP). Radiobiological (RB) model based calculation of TCP and NTCP needs attention in altered fractionation schedules. In order to compare

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the expected biological effect of different fractionation schedules biological effective dose (BED) term is introduced which is used in isoeffective dose calculation[4].

The repopulation correction factor should be included in case of tissues which are rapidly proliferating, hence BED equation is modified to compensate repopulation factor presented by the equation 2[5]. Therefore, it is better to consider BED equation while estimating TCP/NTCP for early or rapidly proliferating tissue.

There are five fundamental mechanisms of fractionated radiotherapy, redistribution (cell cycle effect), reoxygenation, repair, repopulation and radio sensitivity. Ideally, radiobiological models must incorporate all five mechanisms in their formulation for gaining higher accuracy in determining TCP & NTCP. It can be well appreciated if the existing RB models incorporate all 5Rs of radiotherapy, but there are only few models which considered all five factors for estimating TCP & NTCP. Here in this analytical study we chose Niemierko equivalent uniform dose (EUD) model, Poisson model and Lyman Kutcher Berman (LKB) model, as these models are renowned and simple. Radiosensitivity takes care by all RB models because of α/β ratio which is the ratio of cellular radiosensitivity 'α' to repair capacity 'β'.

Repopulation effect can be considered if equivalent dose (EQD2) calculated using time corrected BED formula where OTT assumed.

Reoxygenation effect takes care by oxygen enhancement ratio (OER) and this parameter is a part of few RB models formulation. Redistribution (cell cycle effect) is very critical to asses and it is not a part of any existing RB models as far as our knowledge permits. The cell repair effect play very interesting role in altered fractionation and it takes care by the parameter of repair half time ($T_{1/2}$) which is incorporated only in some RB models formulation.

Eric J Hall stated that "fraction size is the dominant factor in determining the late effects; whereas the overall treatment time has little influence. By contrast, fraction size and overall treatment time both determine the response of acutely responding tissue". This study aimed to demonstrate how the variation in OTT and fraction size affect the predictions of TCP & NTCP using three radiobiological models for acutely responding tissue in predefined altered fractionation schedules. Late responding tissues are slowly proliferating and assumed to have low α/β ratio, hence no correction for overall treatment time is necessary.[6]

Materials and Methods

We intended to demonstrate variation in outcome of TCP & NTCP in moderately hypo fractionated and accelerated fractionation schedules when overall treatment time in days takes under consideration. This can be achieved when we calculate TCP/NTCP by time corrected BED formula and compared against the calculated TCP/NTCP by simple BED formula which do not consider OTT. The OTT effect exists for early responding tissue therefore TCP/NTCP estimation restricted for tumour and oral mucosa only.

The present study separated in two scenario, in the first scenario, conventional fractionated schedule (CFS) compared against moderately hypo-fractionated schedules, as shown in table (1) & (2). In the second scenario, CFS versus accelerated fractionation schedule (AFS) compared as shown in table (3) & (4) referred from DAHANCA clinical trial.[3]

Table 1. The table presenting BED, time corrected BED, EQD2 and time corrected EQD2 calculated values for tumour in two different fractionation scenario undertaking parameters as (α/β =10, Tk =21 days, Tp= 3, α=0.35)

	Conventional	Moderately schedules	hypo-fractionation	
	70 Gy/35#	66 Gy/30#	60 Gy/24#	55 Gy/20#
Dose/#	2 Gy/#	2.2 Gy/#	2.5 Gy/#	2.75 Gy/#
BED	84	80.52	75	70.1
EQD2	70.0	67.1	62.5	58.4
TCBED	67.5	68.64	68.40	67.46
TCEQD2	56.25	57.2	57.0	56.21
OTT (T)	46	39	31	25

Table 2. The table presenting BED, time corrected BED (TCBED), EQD2 and time corrected EQD2 (TCEQD2) calculated values for oral mucosa in two different fractionation scenario undertaking parameters as (α/β =10, T_k =7 days, Tp= 2.5, α=0.35)

	Conventional	Moderately schedules	hypo-fractionation	
	70 Gy/35#	66 Gy/30#	60 Gy/24#	55 Gy/20#
Dose/#	2 Gy/#	2.2 Gy/#	2.5 Gy/#	2.75 Gy/#
BED	84	80.52	75	70.1
EQD2	70.0	67.1	62.5	58.4
TCBED	53.11	55.18	55.99	55.84
TCEQD2	44.26	45.98	46.66	46.53
OTT	46	39	31	25

Table 3. The table presenting BED, time corrected BED, EQD2 and time corrected EQD2 calculated values for conventional and accelerated fractionation schedule of tumor undertaking parameters as (α/β =10, Tk =21 days, Tp= 3, α=0.35)

	Conventional	Accelerated
	66 Gy/33# (5#/wk)	6#/wk
Dose/#	2 Gy/#	2 Gy/#
BED	79.2	79.2
EQD2	66	66
TCBED	64.02	68.64
TCEQD2	53.35	57.2
OTT	44	37

Table 4. The table presenting BED, time corrected BED, EQD2 and time corrected EQD2 calculated values for conventional and accelerated fractionation schedule of oral mucosa undertaking parameters as (α/β =10, Tk =7 days, Tp= 2.5, α=0.35)

	Conventional	Accelerated
	66 Gy/33# (5#/wk)	6#/wk
Dose/#	2 Gy/#	2 Gy/#
BED	79.2	79.2
EQD2	66	66
TCBED	49.89	55.44
TCEQD2	41.58	46.2
OTT	44	37

The linear-quadratic (LQ) is the fundamental model applied for isoeffective dose calculation and its validity is considered up to 6 Gy per fraction. Beyond this range the dose-response curve keep on bending presenting inconsistency with *in vitro* survival curves.[7] Therefore, LQ model is good for low dose approximation and useful for comparing different fractionation schedules. Hence, biological effective dose (BED) term is introduced as shown below.

$$BED = nd\,(1+d/(\alpha/\beta)) \quad (1)$$

Where, n,d and α/β are the number of fractions, dose per fraction of fractionation schedule and a ratio of linear to quadratic component, respectively.

The time corrected BED (TC BED) formula which is a modified form of BED formula with an overall treatment time factor included is given by;

$$BED = nd\left(1+\frac{d}{\alpha/\beta}\right)-\frac{log_e 2}{\alpha Tp}(T-Tk) \quad (2)$$

Where, T is the overall treatment time in days (with first day = Day 0, not Day 1) Tk is the onset of kick-off time of repopulation in the tissue of interest α is a radiosensitivity coefficient of non-repairable damage

Tp is a doubling time of head and neck cancer repopulating cells after Tk

The equivalent dose (EQD_2) at 2 Gy/fraction is the dose conversion formula when fractionation schedule varies from the conventional fractionation schedule. It can be defined by two different formulas as mentioned below;

$$EQD2 = Di\left(\frac{\frac{\alpha}{\beta}+di}{\frac{\alpha}{\beta}+2}\right) \quad (3)$$

$$EQD2 = \frac{BED}{\left(1+\frac{2}{\alpha/\beta}\right)} \quad (4)$$

Where, Di is the total dose and di is the dose per fraction of the reference fractionation schedule.

Radiobiological models

In-house developed program named RBMODELV1 build in MATLAB 2016b version software opted following biological models.

EUD based TCP and NTCP models

Equivalent uniform dose (EUD) represents that, if the dose is distributed uniformly throughout the organ or tissue can produce the same biological effect as of the dose distributed non-uniformly in the same organ or tissue.

$$\mathrm{EUD} = \left\{\sum_{i=1}(v_i D_i^a)\right\}^{\frac{1}{a}}$$

Where, a is a tissue specific parameter and different for normal tissue and tumor tissue, and V_i is the volume representing the i^{th} fractional volume receiving dose Di.

Normal tissue complication probability can be calculated by the below formula.

$$\mathrm{NTCP} = \frac{1}{\left[1-\left(\frac{TD_{50}}{EUD}\right)^{4\Upsilon 50}\right]}$$

Where, TD_{50} is the dose representing 50% complication risk if uniformly distributed throughout the organ volume. Υ_{50} is a parameter represents the slope of the dose-response sigmoid curve and it has no unit.

Similarly, tumor control probability (TCP) can be calculated by the below formula.

$$\mathrm{TCP} = \frac{1}{\left[1-\left(\frac{TCD_{50}}{EUD}\right)^{4\Upsilon 50}\right]}$$

Where, TCD_{50} is the dose required to control 50% of the tumors when delivered homogeneously throughout the tumor of interest.

The LKB model

According to Lyman-Kutcher-Burman model, normal tissue complication probability can be calculated by the following mathematical formula;

$$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t}\exp\left(-\frac{t^2}{2}\right)\cdot dt$$

$$\text{where } t = \frac{\left[D - TD_{50/5}(v)\right]}{m\cdot TD_{50/5}(v)}$$

The model parameters are n, m, and TD_{50}; Where, n determines the magnitude of the volume effect and accounts for differences in tissue architecture; m measures the slope of the sigmoid curve represented by the integral of the normal distribution; and TD50 representing the uniform dose throughout the volume of organ that results in 50% complication risk.

The linear quadratic Poisson TCP model

The radiobiological model that most extensively used for describing dose response relation for tumor tissue is based on Poisson statistics. The tumor control probability expressed as;

$$\mathrm{TCP} = \exp(-N\,p\,(D)) \quad (5)$$

Where, N is the number of clonogens or cells present initially before irradiation, and p(D) is the probability of cell survival fraction after receiving the dose D.

$p(D) = \exp(-\alpha D)$,

The equation (5) can be reformulate by including two parameters Υ_{50} and D_{50} describing normalized slope and dose at the point of 50% probability of control.

$$TCP = \left(\frac{1}{2}\right)^{Exp\left[2\gamma_{50}\left(1-\frac{D}{TCD_{50}}\right)/\ln 2\right]}$$

In present study, 15 patients of head & neck site cancer selected for treatment planning and data acquisition. The present study assumed four fractionation schedules for demonstration purpose, including conventional fractionation schedule (70Gy/35 #), fractionation schedule 1 (66 Gy/30#), fractionation schedule 2 (60Gy/24#) & fractionation schedule 3 (55Gy/20#). These fractionation schedules are commonly practiced and referred in various studies.[8][9,10] Four independent volumetric modulated arc (VMAT) treatment plans were generated for four different fractionation schedules for each patient, therefore results in a total of 60 treatment plans. The Eclipse treatment planning system (Version 11.3, Varian Medical Systems, Palo Alto) used for planning and dose calculations of all treatment plans. The treatment plan created for CFS is the reference plan for TCP & NTCP comparison amongst the four plans. The rest three plans for each patient were created simply by changing the dose prescription for FS1, FS2 & FS3, mean total dose and dose per fraction. No plan optimization and dose calculation have been performed for the rest three plans for each patient. In second scenario, conventional fractionation schedule (66Gy/33# with five fractions per week) compared against accelerated fractionation schedule (66Gy/33# with six fractions per week).

For each patient, there are four dose volume histograms (DVH) which is exported in the form of cumulative DVH text file to the in-house developed program in MATLAB (Version 2016b) to calculate Equivalent Uniform Dose (EUD), Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP).

The program used some coding from Niemierko et al research article.[11] This program used to calculate EUD, TCP and NTCP for four different plans of 15 patients by three different radiobiological models Niemierko EUD, Poisson model and Lyman-Kutcher-Burmen (LKB) model in two cases. In the first case EQD_2 is calculated by simple BED formula and in the second case EQD_2 is calculated by the time corrected BED. TCP is calculated for tumour and NTCP calculated for oral mucosa of 15 patients. We selected very basic models commonly used by researchers. LKB is most commonly used model and QUANTEC dose constraints have been validated in the various clinical studies.[12,13]

Statistical analysis

Statistical analysis was carried out using IBM SPSS for windows, version 20.0. A paired sample t-test applied to asses' statistical significance between calculated TCP & NTCP for two different fractionation schedules. *P-value* ≤ 0.05 was considered significant for statistical interference.

Results

Figure 1 represents the mean values of calculated TCP by EUD model for conventional fractionation schedule (CFS), fractionation schedule 1, fractionation schedule 2, and fractionation schedule 3 which is 93, 91, 85.3 & 76.2%, respectively. It shows decreasing trend as dose per fraction increases when simple BED formula incorporated for EQD2 calculation.

Figure 2 represents the mean values of calculated TCP by EUD model for conventional fractionation schedule (CFS), fractionation schedule 1, fractionation schedule 2, and fractionation schedule 3 which is 70.4, 73.4, 72.4 & 69.8% respectively, when time corrected BED formula incorporated for EQD2 calculation.

Figure 3 represents the mean values of calculated NTCP for oral mucosa by EUD model for conventional fractionation schedule (CFS), fractionation schedule 1, fractionation schedule 2, and fractionation schedule 3 which is 46.4, 42.2, 35.5 & 29.6% respectively showing decreasing trend as dose per fraction increases when simple BED formula incorporated for EQD2 calculation. Similarly mean values of NTCP calculated for oral mucosa by LKB model for CFS, FS1, FS2 & FS3 are 50.25, 48, 45.8 & 42.6% respectively, indicating decreasing trend as shown in Figure 4.

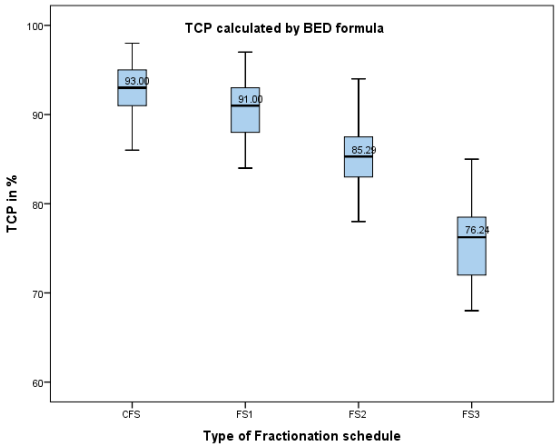

Figure 1. Box plot represents the TCP calculated by EUD model (Niemierko) employed with BED formula for four different fractionation schedules. The box represents interquartile range (IQR), the black line in mid of box shows median value of data. The whiskers represents maximum and minimum calculated value whereas upper, middle and lower border of box represents the first, median and third quartile respectively.

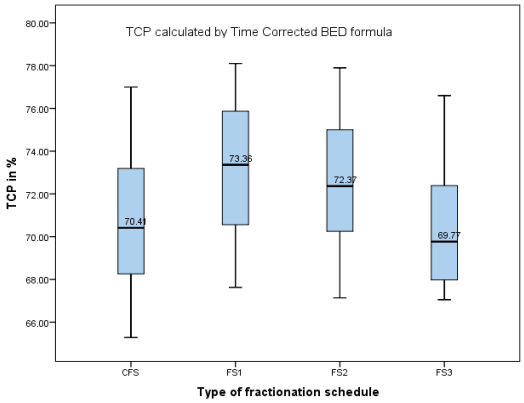

Figure 2. Box plot represents the TCP calculated by EUD model (Niemierko) employed with time corrected BED formula for four different fractionation schedules. The box represents interquartile range (IQR), the black line in mid of box shows median value of data. The whiskers represents maximum and minimum calculated value whereas upper, middle and lower border of box represents the first, median and third quartile respectively.

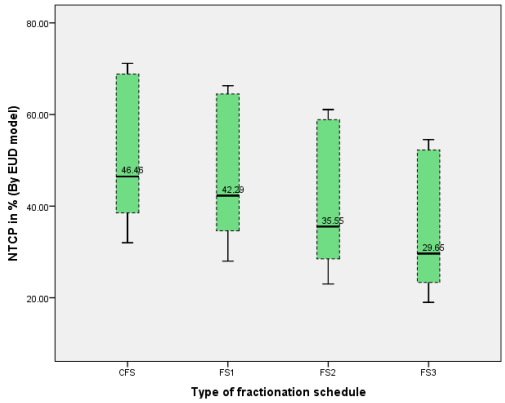

Figure 3. Box plot represents the NTCP calculated for oral cavity by EUD model (Niemierko) employed with BED formula for four different fractionation schedules. The box represents interquartile range (IQR), the black line in mid of box shows median value of data. The whiskers represents maximum and minimum calculated value whereas upper, middle and lower border of box represents the first, median and third quartile respectively.

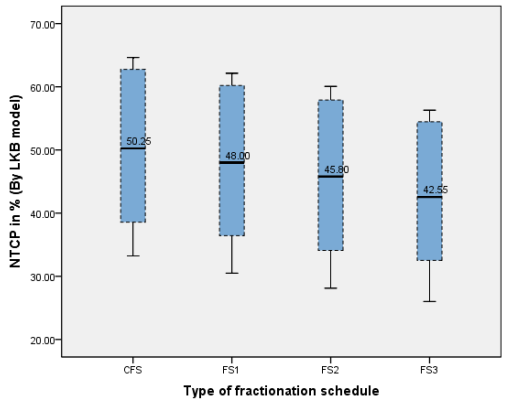

Figure 4. Box plot represents the NTCP calculated for oral cavity by LKB model employed with BED formula at four different fractionation schedules. The box represents interquartile range (IQR), the black line in mid of box shows median value of data. The whiskers represents maximum and minimum calculated value whereas upper, middle and lower border of box represents the first, median and third quartile respectively.

Figure 5 represents the mean values of calculated NTCP for oral mucosa by EUD model for conventional fractionation schedule (CFS), fractionation schedule 1, fractionation schedule 2, and fractionation schedule 3 which is 11.4, 13.4, 15.3 & 15.8% respectively, showing increasing trend as dose per fraction increases when time corrected BED formula incorporated for EQD2 calculation. Similarly mean values of NTCP calculated for oral mucosa by LKB model for CFS, FS1, FS2 & FS3 are 25.3, 27.9, 29.5 & 30% respectively indicating increasing trend as shown in figure 6.

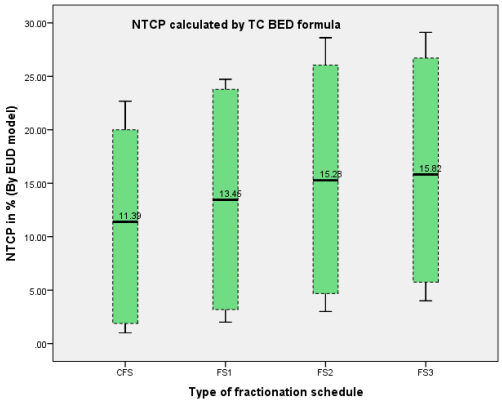

Figure 5. Box plot represents the NTCP calculated for oral cavity by EUD model (Niemierko) employed with time corrected BED (TC-BED) formula at four different fractionation schedules. The box represents interquartile range (IQR), the black line in mid of box shows median value of data. The whiskers represents maximum and minimum calculated value whereas upper, middle and lower border of box represents the first, median and third quartile respectively.

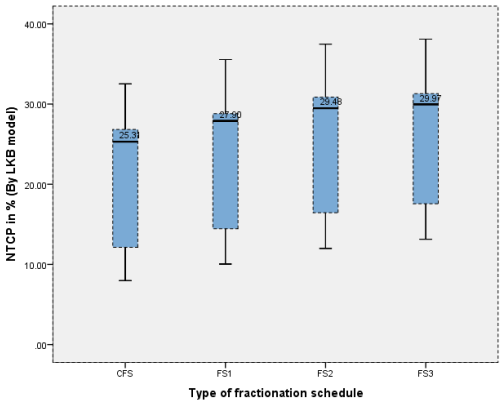

Fig 6. Box plot represents the NTCP calculated for oral cavity by LKB model employed with time corrected BED (TC-BED) formula for four different fractionation schedules. The box represents interquartile range (IQR), the black line in mid of box shows median value of data. The whiskers represents maximum and minimum calculated value whereas upper, middle and lower border of box represents the first, median and third quartile respectively.

The present study compared calculated TCP for tumors by Niemierko EUD model & Poisson model in conventional fractionation schedule (66 Gy in 33 fraction with 5 fraction per week) versus accelerated fractionation schedule (66 Gy in 33 fraction with 6 fraction per week) and observed statistical significant difference ($p<0.05$) as shown in figure 7 & 8. The figure 7 & 8 represents that

calculated TCP by EUD model & Poisson's model for AFS (mean values 72.9 &73.2) is higher than CFS (mean values 59.6 & 59.3) when time corrected BED formula employed.

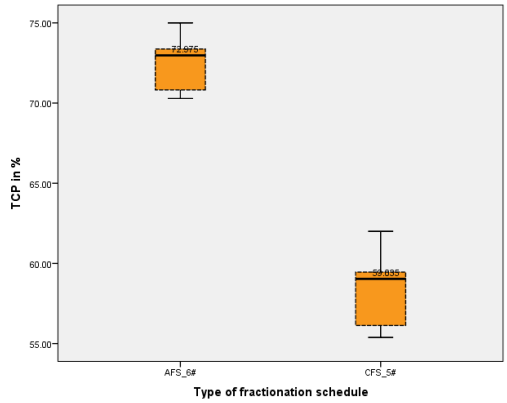

Figure 7. Box plot represents the TCP calculated by EUD model (Niemierko) employed with time corrected BED formula for accelerated and conventional fractionation schedules. The box represents interquartile range (IQR), the black line in mid of box shows median value of data. The whiskers represents maximum and minimum calculated value whereas upper, middle and lower border of box represents the first, median and third quartile respectively.

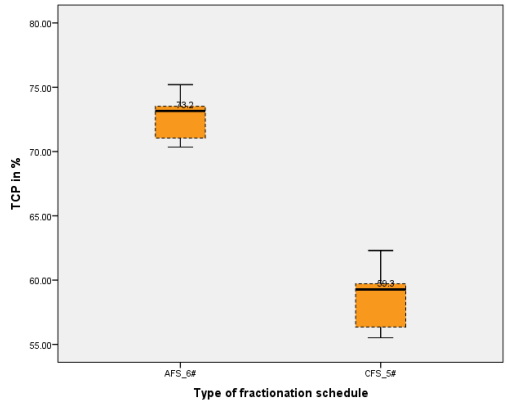

Figure 8. Box plot represents the TCP calculated by Poisson's model employed with time corrected BED formula for accelerated and conventional fractionation schedules. The box represents interquartile range (IQR), the black line in mid of box shows median value of data. The whiskers represents maximum and minimum calculated value whereas upper, middle and lower border of box represents the first, median and third quartile respectively.

Similarly, there is statistically significant difference between ($p<0.05$) calculated NTCP for oral mucosa by EUD model & LKB model in conventional fractionation schedule (66 Gy in 33 fraction with 5 fraction per week) versus accelerated fractionation schedule (66 Gy in 33 fraction with 6 fraction per week). The Figure 9 represents that calculated NTCP by EUD model & LKB model for AFS (mean values 18 & 25) is higher than CFS (mean values 11 & 20) when time corrected BED formula incorporated. The above results indicate that TCP & NTCP calculation based on time corrected BED formula can only able to differentiate between CFS & AFS as it consider the effect of overall treatment time and keeping the same dose per fraction for both the schedule.

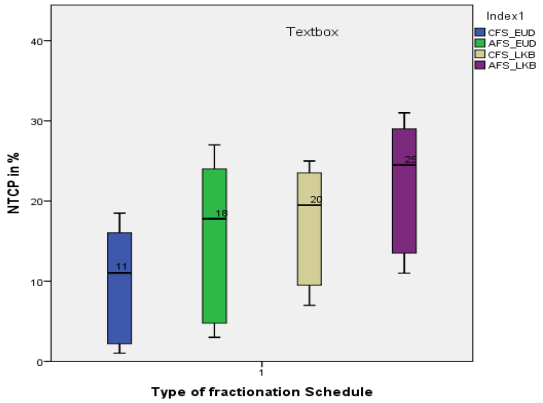

Figure 9. Box plot represents the NTCP calculated for oral cavity by EUD model & LKB model employed with time corrected BED formula for accelerated (AFS) and conventional fractionation schedules (CFS). The box represents interquartile range (IQR), the black line in mid of box shows median value of data. The whiskers represents maximum and minimum calculated value whereas upper, middle and lower border of box represents the first, median and third quartile respectively. The blue box indicates NTCP for CFS whereas green box shows NTCP for AFS calculated by EUD model. The grey box indicates NTCP for CFS whereas violet box shows NTCP for AFS calculated by LKB model.

Discussion

The present study is concentrated to understand the observed differences when OTT consider for estimation of TCP and NTCP for early responding tissue (tumor and oral mucosa). In this study four fractionation schedules as shown in table(1), designed such that though their dose per fraction and physical doses are different, the biological effective doses are approximately equal (maximum difference of 1 Gy) when OTT is considered. These fractionation schedules (FS1, FS2 & FS3) are commonly practices, and it provides a trend which helps in comparison. The trend is like that dose per fraction increases and OTT decreases.

It is clinically observed that for high dose per fractionation schedules, the relative toxicity for oral mucosa is also more. The calculated NTCP by simple BED formula does not follow and showed reverse trend as shown in Fig (3), since the effect of repopulation in tissue is ignored in calculation hence presenting wrong scenario.

In contrast, when repopulation effect takes into account and NTCP calculated based on time corrected BED, the result is in accordance with clinical observation. It is worth to be noted that there is significant drop in NTCP values based on simple BED formula versus time corrected BED formula calculated by both Niemierko & LKB models as shown in figure 3,4,5&6. These observations required clinical evidence and author would like to recommend that the individuals must perform clinical validation of radiobiological models, when NTCP estimated based on time corrected BED formula.

From the proposed study, it has been found that the accuracy in TCP/NTCP estimation is supposed to be compromised when dose per fraction increases against conventional dose per fraction. This may be because the predicted TCP/NTCP based on biological parameters

derived from conventional dose per fraction and cannot be assumed that it will represent same underlying biology for higher dose per fraction.

There are some studies which derived biological parameters specific to altered fractionation schedules and expecting more studies in order to build reliable data for the application of radiobiological models in various altered fractionation schedules.

Radiation induced oral mucositis can cause treatment interruption for several days which directly impact local tumour control rates due to the repopulation of tumor clonogenic cells. Moderately hypofractionated treatments schedules improves efficacy outcome of head and neck cancer with a higher incidence of acute effect such as ulcerative mucositis which ultimately result in treatment interruptions.[14–16] Therefore, the NTCP estimation of oral mucosa has required special attention in the case of altered fractionation schedules. In the case of moderately hypo-accelerated fractionation schedules, the implementation of radiobiological models for TCP/NTCP estimation should be avoided or done very cautiously.

There could be major difference between the predictive probabilities and observed outcome which is possible because of the biological parameters used in the calculation of radiobiological models are based on the conventional dose per fraction regimen and the reliability is under the shadow of doubt.

In the accelerated fractionation schedules, TCP/NTCP prediction will be incorrect without considering OTT in days. From the table (3) & (4), it is noted that physical doses for CFS & AFS is equal and the difference appears only when time corrected BED incorporated for TCP and NTCP calculation for tumour & oral mucosa.

We excluded TCP and NTCP estimation for hyper fractionation schedules because the biological parameters used in the calculations derived with the assumption of one fraction per day and five fractions per week. For considering two fractions per day, the concept of repair half time needs to be addressed carefully.

The author is not confident that implementation of radiobiological models are suitable for hyper-fractionation schedules and it can be limitation in the authors view. The concept of repair half time play major role in hyper-fractionation and it is quite complex besides this derived biological input parameters available in literature based on single fraction per day.[17] Hyper-fractionation schedules proved their excellence in terms of clinical outcome against conventional and hypo-fractionation schedules in squamous cell carcinoma of head & neck cancer, therefore theimplementation of radiobiological models needs to be explore for various altered hyper-fractionation schedules.

The inclusion of time corrected BED in TCP/NTCP estimation is important because during radiotherapy, treatment interruptions are common and there are several reasons machine breakdown, holydays etc. The tumour biological effective dose (BED) reduces by a factor of 0.7 Gy/day after 21 days and in case of acute mucosa it is 0.8 Gy/day after 7 days, including weekends for repopulation.[15,18] Hence, in such cases the predicted TCP and NTCP gets corrected automatically because the OTT in days is a part of calculation which is not possible with simple BED formula.

Until recently, biological based treatment planning system provided by the manufacturer bring the capability of the biological optimization and evaluation feature, but it should be cautiously use with the knowledge of that the TCP/NTCP calculation based on time corrected BED or simple BED formula can significantly affect the outcome.[19]

There are some limitations of the study such as the use of few radiobiological models. As shown in the literature, there is differences in the accuracy of TCP/NTCP outcome at various radiobiological models. There are several challenges associated with applied radiobiological models, including missing data, prediction of multiple complication grades at different times, over fitting and non-linear dose relationship which limits the prediction power of the models.[20]

Conclusion

Here we demonstrated that the uncertainty and inaccuracy in TCP/NTCP estimation increases as move away from conventional dose fractionation schedules. The biological input parameters derived from conventional dose fractionation schedules should be cautiously used while calculating NTCP for moderately hypo-fractionation and accelerated fractionation schedules in head & neck cancer. There is significant impact of OTT and it should be considered when evaluating the TCP/NTCP for early responding tissues.

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