Dosimetric validation of two different radiobiological models for parotid gland functionality of tongue cancer

Srimanta Pramanik | Soumen Bera | Sanjoy Roy | Amitabh Ray | Sandip Sarkar | Dipanjan Majumder

Department of Radiation Oncology, Ruby General Hospital, E.M. Bypass, Kasba, Golpark, Kolkata, West Bengal, India

Correspondence
Srimanta Pramanik, Department of Radiation Oncology, Ruby General Hospital, Kolkata, West Bengal, India.
Email: skpramanik20@gmail.com

Abstract

Objective: The aim of this study was to investigate the normal tissue complication probability (NTCP) for parotid gland of ca tongue patients from two different radiobiological models and to establish a dosimetric validity.

Methods: Lyman–Kutcher–Burman (LKB) model and linear quadratic (LQ) model were considered for determination of NTCP and tolerance dose (TD5/5 and TD50/5) for the parotid gland of 67 number of ca tongue patients who were treated with the volumetric arc therapy (VMAT) technique. An in-house developed software on Excel (VBA) was used for this study.

Results: The equivalent uniform dose (EUD) was linearly proportional to the effective volume (veff) for parotid glands and there was a strong correlation between EUD and veff. At EUD = 46 to 47 Gy, the NTCP of parotid was 0.5 for both the models. The tolerance doses, TD5/5 (veff) and TD50/5 (veff) were exponentially reduced with increase of veff for LKB model; whereas these parameters were volume-independent in the LQ model. TD5/5 (veff) and TD50/5 (veff) were 31.98 Gy and 45.98 Gy respectively for all 67 patients in the LQ model. Below TD50/5, NTCP of LKB model was less than the NTCP calculated from LQ model.

Conclusion: One may consider radiobiological LQ model for estimation of clinical tolerance dose for OARs. Due to lack of clinical data, there are inaccuracy in determination of NTCP from LQ model. If sufficient number of tolerance data for partial volumes are available, the prediction of NTCP would be more confident.

KEYWORDS
effective volume, equivalent uniform dose, Lyman–Kutcher–Burman model, normal tissue complication probability, radiobiological model
Three-dimensional radiotherapy plans such as intensity-modulated radiotherapy (IMRT), volumetric arc therapy (VMAT) treatment delivery are highly conformal dose distribution that closely conforms to tumor shape, thus, the surrounding organs at risk (OARs) get the minimum dose. The advent of such sophisticated radiotherapy techniques led to more complex and heterogeneous dose distributions, making implicit evaluation more difficult with dose volume histograms (DVH). In this case, during the evaluation and determination of treatment plans, clinicians may need to rely on relatively vague notions of DVH of different tissues. In the vicinity of a treatment target, the dose distribution around the OARs are often subjected to high-dose partial irradiation, which led to treatment-related complications. Since for the case of head and neck cancer parotid gland is an overlapping structure with the target, the risk of complication is prevalent due to partial volume irradiation with high dose. So a planner should choose a balance between minimizing partial volume irradiation of the parotid and dose uniformity of the target volume without losing the target geometry margin of the high-dose region around a defined target. Therefore, it is important to find out the complication probability of the parotid gland as well as other OARs for each patient when they are treated with IMRT, VMAT, or any other high-modality techniques.

Radiobiological-based evaluation of treatment plans from different radiobiological models can efficiently predict the tumor control probability (TCP) for target and normal tissue complication probability (NTCP) for normal tissues. Though biological based evaluation is still a complex process in the clinic because of the unavailability of sufficient clinical data. However such predictions are still a valuable compliments to clinical experience. In last couple of decades, the quality and quantity of clinical data have begun to improve significantly due to result of increased archiving of 3-D dose distributions and corresponding treatment outcomes. Now a days some commercial treatment planning systems can able to predict radiobiological parameters such as effective uniform dose (EUD), TCP, and NTCP, are available in the market.

By using DVH, Lyman\(^1\) has developed a mathematical model in 1985. With the help of that model the Kutch–Burman (K-B)\(^2\) reduction algorithm was published in 1989 for handling the general case of inhomogeneous organ irradiation. These models are collectively known as the Lyman–Kutch–Burman (LKB) model. Based on the LKB model in 2008 Gary Luxton et al.\(^3\) established a new formula for NTCP as a function of EUD.

The radiobiological bearings of the empirical model based on the linear quadratic (LQ) model, proposed by Kallman et al.\(^4\) and modified by Zaider and Amols\(^5\) has been published in 1999. Based on these articles, Kehwar TS et al.\(^6\) studied the NTCP using the best fit of normal tissue tolerance dose into the NTCP equation of the linear quadratic model.

In this study, two radiobiological models (LKB and LQ) are used to estimate the radiobiological parameters for the parotid gland functionality, considering the end-point result of xerostomia, and to validate these parameters for clinical use.

Aim of the study was to estimate radiobiological parameters from two different radiobiological models and investigate the NTCP for the parotid gland of ca tongue cases treated with VMAT treatment plans.

2 METHODS & MATERIALS

The CT simulation for all patients were done in the supine position on all-in-one (AIO) base plate, and patients were immobilized with five clamp thermoplastic cast. The neck nodal clinical target volumes were delineated referring to consensus guidelines by Vincent Gregoire et al.\(^7\) For all patients, cervical neck nodal level I–V were delineated. So bilateral submandibular glands and sublingual glands were included inside the treatment volume. The parotid glands were contoured separately as OARs as per the guidelines by Charlotte Brouwer et al.\(^8\) A 0.5-cm margin was added to clinical target volume (CTV) for obtaining the planning target volume (PTV) according to our departmental protocol\(^9\) for the head and neck cancers. A typical illustration of clinical target volume to planning target volume margin and dose distribution around the target has been given in Figure 8.

In this study, we considered two radiobiological models: one was LKB model and another was linear quadratic (LQ) model for the investigation of NTCP, TD\(_{5/5}\) and TD\(_{50/5}\) for the parotid gland of 67 number of ca tongue patients, treated with VMAT techniques in Eclipse treatment planning systems (Varian Medical Systems, Palo Alto, CA, USA). The cumulative DVH was extracted from treatment planning systems and analyzed by an in-house developed software with Visual Basic for Applications (VBA) in excel developer mode of Microsoft Office 2013 (Microsoft, Redmond, WA, USA) for the investigation of radiobiological parameters.

A short discussion on abovesaid two models are given below. These models are discussed in details in different literatures.\(^3,5,6,10-12\)

The LKB model is a method for calculating the single effective fractional volume corresponding to irradiation to a particular reference dose, and thereby determining the NTCP for a partial volume irradiation.

2.1 Lyman model

The expression of the NTCP in the Lyman model (Lyman 1985)\(^1\) for uniform irradiation of an organ to dose D is given by

\[
\text{NTCP} = c(u) = 1/\sqrt{(2\pi)} \cdot \int_{-\infty}^{\infty} e^{-t^2/2} dt
\]

where

\[
u = (D - TD_{50}) / (m \cdot TD_{50})
\]

TD\(_{50}\) is the whole organ dose for which NTCP is 50%, and m is a dimensionless parameter.
For the case of uniformly irradiation of a volume (v) to dose (D), the NTCP using the formula with $TD_{50}$ replaced by a partial volume-dependent parameter $TD_{50}(v)$ is given by

$$TD_{50}(v) = TD_{50}(1) \cdot v^{-n}$$  \hspace{1cm} (3)

Where, the exponent, $n > 0$, is the parameter that determines the volume dependence, and $TD_{50}(1) = TD_{50}$, is the value for uniform organ irradiation. The fractional volume is expressed as $v = V / V_{ref}$, where $V_{ref}$ is the reference volume for the OAR, usually taken to refer to the entire volume of the OAR.

### 2.2 | Lyman-Kutcher-Burman (LKB) model

With the help of the Lyman model, Kutcher and Burman (1989)$^2$ developed a volume reduction algorithm for an inhomogeneously irradiated OAR and the resulting model is referred to as the LKB model. In the LKB model, the partial effective volume $v_{eff}$ is expressed as

$$v_{eff} = v_i \left( \frac{d_i}{d_{ref}} \right)^{\frac{1}{2}}$$  \hspace{1cm} (4)

where $v_i$ is each irradiated fractional subvolume ($i = 1, \ldots, k$, $\sum v_i = 1$) irradiated with dose $d_i$ and the reference dose $d_{ref}$.

In the LKB model, the total effective fractional volume irradiated to dose $d_{ref}$ that would give the same NTCP as the inhomogeneously irradiated OAR is given as the sum of all the effective sub-volumes in the DVH:

$$v_{eff} = \sum_{k=1}^{k} v_{eff}$$  \hspace{1cm} (5)

Explicitly, the LKB model gives the NTCP by Equation (1) with the variable $u$, given by

$$u = \frac{(d_{ref} - TD_{50}(v_{eff}))}{(m \cdot TD_{50}(v_{eff}))}$$  \hspace{1cm} (6)

In Kutcher-Burman (Kutcher and Burman 1989;$^2$ Kutcher et al. 1991$^{12}$), $d_{ref}$ was taken as the maximum dose to the DVH, which ensured that $v_{eff} < 1$. This choice is arbitrary; however, it was observed that the NTCP is same for any choice of $d_{ref}$ in the LKB model.

### 2.3 | Relationship between LKB variables and EUD

By generalized Niemierko$^{10,12}$ formula EUD of an OAR is defined as an equivalent uniform dose which, if applied to the entire volume of the OAR, would result in the same NTCP as the effective volume Kutcher–Burman DVH reduction algorithm, calculated for any reference dose.

$$EUD = d_{ref} \times v_{eff}$$  \hspace{1cm} (7)

### 2.4 | Linear quadratic (LQ) model

The equation of the NTCP model, which has radiobiological bearings, can be written as:

$$NTCP(D, v) = \exp \left[ -N_0v^{-k}\exp(-\alpha D \times RE) \right]$$  \hspace{1cm} (8)

Equation (8) is similar to the equation proposed by Zaider and Amols$^3$, which is based on the Poisson cell kill model, where $N_0$ is considered to be the clonogenic cell density of the tumor, $k$ is a positive parameter, and $v$ is the uniformly irradiated partial volume of the tissue/organ (i.e. $v = V / V_{ref}$, where $V$ is the uniformly irradiated volume of the normal tissue/organ). The $\Gamma = [1 + d/(\alpha / \beta)]$, is the coefficient of lethal damage, and $\alpha / \beta$ is the ratio of the coefficients of lethal and sublethal damage. $D$ is the normal tissue dose in terms of $TD_{5/5}$ or $TD_{50/5}$ delivered with $d$ dose per fraction. The expression in the exponent exp($-\alpha D$T) is a part of the LQ model for cellular survival.

If $RE = R$, the relative effectiveness (RE) per unit dose, then the Equation 8, the expression of NTCP can be written as:

$$NTCP(D, v) = \exp \left[ -N_0v^{-k}\exp(-\alpha D \times RE) \right]$$  \hspace{1cm} (9)

where BED = $D \times RE$. If the exponent of the partial volume $v$ is taken as $k = -1$, then the product of $N_0v$ represents the total number of clonogenic cells in the tumor volume, and the expression will be of the tumour control probability (TCP) model. However, in Equation 8, $N_0$ and $k$ are assumed to be non-negative adjustable parameters, and are allowed to vary depending on the type of tissue/organ.

In the present study, the NTCP values of the parotid were compared for the LKB and LQ models using the cumulative DVH generated in the treatment planning systems (Eclipse version 13.6; Varian Medical System) for the tongue cancer patients. An in-house mathematical algorithm with Visual Basic for Applications was developed in Microsoft Excel 2013 for the analysis of NTCP, EUD, $v_{eff}$, $TD_{50}$ (1), $TD_{5/5}$ (1), $TD_{50/5}$($v_{eff}$), and $TD_{5/5}$ ($v_{eff}$) from both models. Using cumulative DVH data, the algorithm generated the desired radiobiological parameters, and compared the given results. The 67 number of patients with tongue cancer treated with VMAT techniques were included in this study. The dose prescription was 60-66 Gy in 30-33 fractions for all cases. All treatment plans were generated in Eclipse treatment planning systems, optimized with a photon optimizer (PO version 13.6.23) and calculated with the anisotropic analytical algorithm (AAA version 13.6.23) with calculation grid size 2.5mm. The occurrence of xerostomia was used as the end-point result to calculate NTCP for the parotid.

### 3 | RESULTS

The primary effective volume ($v_{eff}$) and EUD values for all patients were calculated. The behavior of EUD with $v_{eff}$ is plotted in Figure 1.

There is a linear relationship between EUD and $v_{eff}$, with a strong positive correlation coefficient ($r$) of 0.882 and 0.875 for the right and
left parotid respectively. Thus, EUD increases with an increase of effective volume (veff).

Figure 2 illustrates that EUD is directly proportional to the mean dose (Dmean) of parotid gland. The correlation coefficient (r) values are 0.995 and 0.993 for the right and left parotid respectively and this indicates a strong positive correlation between EUD and Dmean.

Figure 3 represents the NTCP for both models (the LKB and LQ), and is compared as a function of EUD. Initially, the gradient of NTCP is less steeper up to EUD value of 32–33 Gy, and it has increased rapidly with an increase of EUD. The value of NTCP is 0.5 at EUD value 46–47 Gy. The NTCP for the LQ model is higher than that of the LKB model till 46 Gy and after 46 Gy NTCP for the LKB model is more than the LQ model.

The variation of 50% tolerance dose (TD50/5) with respect to effective volume (veff) for the right and left parotid has been evaluated in the LKB model and it is shown in Figure 4. The TD50/5 exponentially decreases with an increase of veff.

Figure 5 shows that the 5% tolerance dose [TD5/5(veff)] is exponentially decreasing with an increase of the effective volume (veff).

The value of TD5/5 is 29.6% lower than TD50/5 (veff) for both parotids. For the LKB model, our result shows that the mean tolerance doses of TD50/5 (veff) for the right and left parotid were 81.764 Gy and 80.877 Gy, respectively. The mean tolerance doses of TD5/5 (veff) for the right and left parotid were 57.555 Gy and 56.931 Gy, respectively, for the LKB model.

When the parotid gland is considered as a normal tissue, the LQ model shows that the NTCP is independent of its volume. The 50% tolerance dose TD50/5 (V = 1) for the whole parotid and TD50/5 (veff) for effective volume of parotid remained same which is 45.98 Gy for both the parotid glands. The 5% tolerance doses, TD5/5 (V = 1) for the whole parotid and TD5/5 (veff) for the effective volume of parotid were unchanged for every case, the value of TD5/5 is 31.98 Gy for both the parotids. Therefore, the tolerance dose is independent of the effective volume (veff) of the parotid in the LQ model.

Figure 6 represents a comparison of the NTCP between the LKB and LQ models for the right and left parotids. From patient number 1–63 for the right parotid, and 1–62 for the left parotid in the LQ model, the NTCP values were higher compared to the LKB model, and from patient numbers 64–67 for the right parotid, and 63–67 for the left
FIGURE 3  Variation of normal tissue complication probability (NTCP) with respect to effective uniform dose (EUD) for the right (Rt) and left (Lt) parotids

FIGURE 4  Tolerance dose (TD)$_{5/5}$ decreases exponentially as a function of effective volume ($v_{eff}$) in the Lyman–Kutcher–Burman (LKB) model for the (a) right and (b) left parotids

The parotid, the NTCP value is higher in the LKB model. The average NTCP values for the left and right parotid for the LKB model were 0.168 and 0.151 respectively. On the other hand the average NTCP values of the LQ model for the left and right parotid were 0.1873 and 0.168 respectively.

4  DISCUSSION

The phenomenological Lyman model gives the NTCP for an organ as a sigmoid function of the dose to which it is uniformly irradiated. We have seen that the LKB algorithm gives the same NTCP as uniform
FIGURE 6 Variation of normal tissue complication probability (NTCP) of the right and left parotids for 67 patients

FIGURE 7 For linear quadratic (LQ) and Lyman–Kutcher–Burman (LKB) models, normal tissue complication probability varies with dose for the whole organ in the figure on the left, and in the figure on the right, normal tissue complication probability varies with dose at different effective volumes \( (v_{\text{eff}}) \) of the parotid.

organ irradiation to dose \( E \), where \( E \) is the equivalent uniform dose (EUD) of Niemierko\(^1\) (1999). Expressing NTCP in terms of EUD represents a step toward simplifying the conceptual framework for modeling the probability of expected complications using DVH from the proposed treatment plan.

Considering the values \( n = 0.7 \), \( m = 0.18 \), and \( T_{D50} (1) = 46 \) taken from the study of Gary Luxton et al.\(^3\) for xerostomia as end-point result of the parotid in Equations (1), (2), and (3) (methods and materials section-2), the NTCP was calculated from the Lyman model. Using cumulative DVH data, the effective volume \( (v_{\text{eff}}) \) was calculated from Equation 4, given in the methods and material section. Since there is a certain positive value of \( n \) in the LKB model, the tolerance dose in Equation 3 is a function of \( v_{\text{eff}} \). In the Results section 3, the Figures 4 and 5 represented the nature of the tolerance doses of \( T_{D50} (v_{\text{eff}}) \), \( T_{D5/5} (v_{\text{eff}}) \), which is exponentially decreasing as \( v_{\text{eff}} \) increases.

The Kallman\(^4\) Poisson cell kill model, modified by Zaider and Amols\(^5\), has a radiobiological base and it is a linear quadratic model. The value of \( k \) in equation 10 in Section 2 indicates that the organs
that have a higher value of $k$, have higher volume dependency than that of a lower value of $k$. No volume dependency could be estimated for the parotid, where only two-point data, the tolerance doses, TD$_{5/5}$ and TD$_{50/5}$, were given only for a single volume in the study by Kehwar TS et al. Hence, the parameters $\alpha$, $k$, and $N_0$ cannot be computed, as that would require more than two points of data. Therefore, the value of parameter $k$, for the parotid is adjusted to zero. The organs that have more point tolerance doses are provided in the literature the calculated values of the parameters have better confidence. In the case where the tolerance doses are provided for the NTCPs at 5% and 50% only for a single partial volume, the computation of the $k$ value is not possible, hence there will be much less confidence in the result.

Figure 7 was a graphical representation of the NTCP for the LKB and LQ models. Figure 7 shows the variation of NTCP with respect to the dose for whole organ (parotid) volume ($v = 1$) for both models. Initially, the NTCP increases with the increase of dose at the same rate for both models. When the NTCP crossed the value 0.5, the LKB model was more steeper than the LQ model. These differences of the curves were due to the nature of the mathematical approach for the calculation of NTCP.

Figure 7 shows the variation in the NTCP with dose for the effective volume ($v_{\text{eff}}$). As the LKB model is based on the normal distribution of the tolerance data, and does not have any correction with radiobiological processes and findings, it cannot be accounted for varying tissue-specific radiobiological parameters. In this scenario, the NTCP for the LKB model is volume dependent; hence, the tolerance doses, TD$_{50/5}$ and TD$_{5/5}$, are different for each patient with variation in $v_{\text{eff}}$. For example, TD$_{50/5}$ values are 52.5 Gy, 70.4 Gy, and 73.3 Gy, and TD$_{5/5}$ values are 36.9 Gy, 49.5 Gy, and 51.6 Gy for $v_{\text{eff}}$ values 0.828, 0.545, and 0.514, respectively. In contrast, the two-point tolerance data for the parotid are reported only for one partial volume ($v = 1$, whole organ volume). Hence, the curve between NTCP and dose is a single line, and does not show volume dependency in the LQ model.

In the LQ model, the factor $\alpha\Gamma$ has two tissue-specific radiobiological coefficients, $\alpha$ and $\beta$, which account for $\alpha$-cell kill (lethal damage) and $\beta$-cell kill (sublethal damage), respectively. Therefore, these NTCP findings are more relevant than the LKB model. However, the main limitation of using the LQ model is that there is no definite value of $\alpha/\beta$ reported in the literature. It is possible to find a range of $\alpha/\beta$ values reported in different studies. It is possible to find out the volume effect of the parotid from the LQ model if sufficient clinical data are available. So in this kind of study one can find out the patient-specific tolerance dose and epidemiological tolerance dose for the parotid gland and other organs.
5 | CONCLUSION

The LKB model shows that the NTCP of each OAR has volume dependency. Clinically, it is very true that the NTCP of parallel-like structures, such as the parotid, larynx, rectum, and bladder etc. are volume-dependent. Since the LKB model does not have any correction for the radiobiological process, clinical verification of NTCP calculated from the LKB model is very much required. Whereas the LQ model considers radiobiological correction. However, due to a lack of thorough investigation of clinical findings of end-point results of some OARs, such as the parotid, larynx, and thyroid there are inaccuracy in determining of the parameters $\alpha$ and $\beta$ and $N_0$ from Equation B. If sufficient clinical data are available, using the LQ model it is possible to determine the patient-specific tolerance dose, as well as the epidemiological tolerance dose, for parotid and other organs with high accuracy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Srimanta Pramanik https://orcid.org/0000-0001-7366-0788

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