Estimating the Dose-Response Relationship for Ocular Pain after Radiotherapy of Head and Neck Cancers and Skull Base Tumors based on the LKB Radiobiological Model

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ABSTRACT

Background: Radiotherapy is considered a compromise between the amount of killed tumor cells and the damage caused to the healthy tissue. Regarding this, radiobiological modeling is performed to individualize and optimize treatment strategies.

Objective: This study aimed to determine the normal tissue complication probability (NTCP) of acute ocular pain following radiotherapy.

Material and Methods: In this prospective observational study, the clinical data were collected from 45 patients with head and neck cancers and skull-base tumors, and dosimetric data were recorded after contouring the eye globe. Acute ocular pain was prospectively assessed with a three-month follow-up. The Lyman-Kutcher-Berman (LKB) parameters were estimated using the Area Under Curve (AUC) of Receiver Operating Characteristic (ROC) maximization and Maximum Likelihood (MLH) methods, and the NTCP of acute ocular pain was then determined using generalized LKB radiobiological model. The model performance was evaluated with AUC, Brier score, and Hosmer-Lemeshow tests.

Results: Six out of 45 (13.33%) patients developed acute ocular pain (grade 1 or more). LKB model showed a weak dose-volume effect (n=0.09), tolerance dose for a 50% complication (TD_{50}) of 27.54 Gy, and slope parameter (m) of 0.38. The LKB model showed high prediction performance. The LKB model predicted that NTCP would be less than 25% if the generalized equivalent uniform dose (gEUD) was kept below 20 Gy.

Conclusion: The LKB model showed a high performance in determining the NTCP of ocular pain so that the probability of ocular pain will be less than 25% if the eye globe mean dose is kept below 12 Gy.

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Keywords

Normal Tissue Complication Probability; Dose-Response; Radiotherapy; Lyman-Kutcher-Burman; Ocular Pain

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Introduction

After surgery, three-dimensional Conformal Radiation Therapy (3D-CRT) is one of the most important treatments for Head and Neck Cancers (HNC) and brain malignancies. However, advanced radiation therapy is recently developed to increase the delivered

dose to the tumor with the least damage to healthy organs, concerns remain about normal tissue toxicity [1].

Ocular pain is a common side effect among patients with HNC and brain tumors and usually occurs following long-term side effects, such as conjunctiva, lacrimal gland toxicities, cornea toxicities, iris, and lens complications [2, 3]. In the evaluation of the radiological response of Graves' ophthalmopathy patients, who were treated with radiotherapy, the development of ocular pain was observed after the treatment [2]. Continual persistent ocular pain is also reported as a symptom of radiation-induced dry eye syndrome [4].

However, radiotherapy aims to achieve a high Tumor Control Probability (TCP) at a low Normal Tissue Complication Probability (NTCP), the increased dose for a high TCP inevitably leads to increasing the NTCP [5].

Two approaches are considered for further optimization in radiotherapy treatment plans, as follows: 1) Dose-volume Histograms (DVHs) to analyze dosimetric aspects of a plan and 2) biological parameters to estimate TCP and NTCP, resulting from the dose distribution. This estimation is based on clinical responses with respect to target doses and relevant dose-volume limitations. The use of radiobiological models is recently improved and developed due to their advantages [6]. NTCP models cause radiation oncologists and physicists to predict a patient's prognosis for a complication, leading to identifying potential risk groups for better management in clinical decisions [7-9].

Lyman-Kutcher-Burman (LKB) is a well-known NTCP model using the DVH-reduction method to determine the probability of a complication from uniform irradiation of the whole or partial volume of interest. The LKB model assesses the effect of dose and organ volume on the development of complications using three parameters: TD_{50}, which is the radiation dose for a 50% complication probability, and m, which is a free parameter showing the slop of dose-response curve at TD_{50}, and n, which is the volume-dependence parameter [10, 11].

However, radiotherapy-induced ocular complications have been investigated in several studies [2-4], and a few studies have been conducted on NTCP modeling of the eye after radiotherapy [4, 12, 13]. To the best of our knowledge, any study has been conducted on NTCP of ocular pain.

Since ocular pain affects the patient's quality of life [4, 14], it seems necessary to prevent this complication after radiotherapy as much as possible. Therefore, we investigated the probability of this complication after 3D-CRT for patients with HNC and skull-base tumors and modeled its NTCP based on LKB radiobiological model.

Material and Methods

Patients' characteristics

This prospective observational study was conducted between 2019 and 2021 at Ramzanzadeh Radiotherapy Oncology Center, Yazd, Iran. A total of 45 patients with HNC and skull base tumors with no history of ocular pain participated, and their demographic characteristics, including gender, age, and history of chemotherapy and radiation therapy, were collected. Different tumor sites of patients, including brain, eye, skin, nasopharynx, and nose were considered to achieve a wide range of dose distribution and therefore the most optimal NTCP modeling [15].

Radiotherapy procedure and Follow-up

Patients were treated by a Siemens linear accelerator (Oncor, Siemens, Germany) at 6 and 18 MV photon energies with a total dose of 45 Gy in 15 daily fractions of 1-3 Gy/fraction. Patients' treatment plans were performed on Computed Tomography (CT) scans (Sumatom, Siemens, Germany) at 5-mm intervals by defining Gross Tumor Volume (GTV), Clinical Target Volume (CTV), and Planning

Target Volume (PTV) on Prowess Panter treatment planning system (Version 2.0, USA).

Both eyes were contoured by a radiation physicist with a 3-mm margin. Differential DVHs and dosimetric parameters were recorded, including D100, D90, D80, V90, minimum, maximum, and mean dose.

An ophthalmologist examined patients before and at a three-month follow-up. The ocular pain was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 [16]. According to CTCAE V4, a sensation of marked discomfort in the eyes is defined as ocular pain and graded as grade 1: mild pain, grade 2: moderate pain, limiting instrumental activities of daily living (ADL), and grade 3: severe pain, limiting self-care ADL. In the present study, a toxicity grade of 1 or more was considered as the endpoint.

LKB parameter estimation

At first, model parameters, including n, m, and TD_{50} were estimated to calculate NTCP based on the LKB model. The parameter n was obtained in such a way, in which the area was maximized under the receiver operating characteristic (ROC) curve [17, 18].

To determine m and TD_{50} parameters, Maximum Likelihood (ML) analysis was employed and the best values of these parameters were obtained by maximizing the Log Likelihood (LLH) function as follows [19, 20]:

$$LLH = \sum_{y(i)=1} \log(NTCP) + \sum_{y(i)=0} \log(1-NTCP) \quad (1)$$

Where if ocular pain occurs, $y(i)$=1, and otherwise, $y(i)$=0. The parameters were estimated by considering the 95% confidence interval [21] by an in-house library for R-studio.

NTCP modeling

After computing the LKB model parameters, NTCP modeling was performed based on the generalized Equivalent Uniform Dose (gEUD) concept [22]. In the first step, the radiation doses in DVHs were converted to an equivalent dose of 2 Gy per fraction (EQD_{2Gy}) to prevent the effect of changes in the dose per fraction on the NTCP calculation, as follows:

$$EQD_{2Gy} = D.\left(\frac{1+d/(\alpha/\beta)}{1+2/(\alpha/\beta)}\right) \quad (2)$$

Where D and d are the prescribed dose and the dose per fraction, respectively. The α/β value was considered equal to 3 Gy [23, 24]. For the next step, the non-uniform radiation dose to the target volume was converted to gEUD using Equation 3:

$$gEUD = (\sum_{i=1}^{N}(EQD_{2Gy})_i^{\frac{1}{n}}\left(\frac{v_i}{v_{tot}}\right))^n \quad (3)$$

Where v_i is the partial irradiated volume of the organ and v_{tot} is the total volume. Finally, NTCP was obtained based on the LKB model as a function of gEUD according to Equation 4:

$$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{\frac{gEUD-D_{50}}{mD_{50}}} \exp\left(-\frac{x^2}{2}\right)dx \quad (4)$$

Statistical analysis and model performance

The Brier's score was used to calculate the difference between actual and predicted results, as the overall performance of the LKB model, which is close to zero for a perfect predictive model [25]. The agreement between the predicted and observed results, as the performance in terms of calibration, was evaluated by the Hosmer-Lemeshow test with a significance level of 0.05. Also, the model's discriminating ability was evaluated by the Area Under Curve (AUC) of ROC [26, 27].

Statistical analysis was performed by SPSS version 24, and the obtained values were shown as mean and standard deviation (mean±standard deviation). Qualitative variables were compared using Pearson's $\chi 2$ test or Fisher's exact test. An independent t-test was used to compare quantitative variables. A P-value of less than 0.05 was considered a statistically significant difference.

Results

Patients' characteristics and toxicity

The patients' characteristics and dosimetric data are shown in Table 1. The mean age of the patients, including 20 females and 28 males was, 50.04 years. A total of 84.44% of patients had a brain tumor, and 6 patients (13.33%) were diagnosed with ocular pain (grade 1+) during three months of follow-up. The mean eye dose for patients with and without ocular pain was 4.33 and 4.03 Gy, respectively (*P*-value=0.89), and the maximum eye dose was 14.16 and 10.86 Gy, respectively (*P*-value=0.52). Other variables, such as age, gender, concurrent chemotherapy, and history of radiotherapy did not show any significant effect on the incidence of ocular pain (*P*-value>0.05).

Estimated parameters for the LKB model

TD_{50} and m were obtained as 27.54 Gy (95% CI: 18.7-40 Gy) and 0.38 (95% CI: 0.31-0.48), respectively, by using the maximum likelihood estimation method. The n parameter was also obtained at 0.09 from the AUC maximization method (Table 2). Figure 1 shows the profile likelihood of TD_{50} and m.

NTCP of ocular pain

The parameters m and TD_{50} were used to obtain NTCP of ocular pain as a function of gEUD and mean dose based on the LKB model. The NTCP curve of ocular pain is shown in Figure 2, in which the 50% probability of the complication occurring at about 28 Gy is almost in line with the maximum likelihood estimation (27.54 Gy).

LKB model performance

The prediction performance of the LKB model in terms of overall, discrimination, and calibration is listed in Table 3. The ROC curve of the LKB model related to the sensitivity in

Table 1: Characteristics and dosimetric data of radiotherapy patients with head and neck cancers and skull-base tumors

Variable	Values	[c]*P*-value
Gender		
Female	19 (42.2%)	0.19
Male	26 (57.8%)	
Mean Age (years)	50	-
Tumor site		
Brain	38 (84.44%)	-
Nasopharyngeal	4 (8.88%)	-
Nose	1 (2.22%)	-
Skin	2 (4.44%)	-
Eye	19 (42.2%)	-
Eyes mean dose (Gy)		
0-10	28 (58.33%)	-
10-20	7 (14.6%)	-
20-30	11 (22.91%)	-
30-40	2 (4.16%)	-
[a]Ocular pain		
Yes	6 (13.33%)	-
No	39 (86.66%)	-
History of radiotherapy	7 (15.55%)	0.19
Concurrent chemotherapy	12 (26.7%)	0.55
[b]gEUD (Gy)		
With ocular pain	15.34	0.20
Without ocular pain	9.71	
[b]Mean Dose (Gy)		
With ocular pain	4.33	0.89
Without ocular pain	4.03	
[b]Maximum dose (Gy)		
With ocular pain	14.16	0.52
Without ocular pain	10.86	

[a] Ocular pain with grade 1+ was considered.

[b] Mean dose, generalized equivalent uniform dose (gEUD) and maximum dose of contoured eyes

[c] The significant levels of the variables are related to the complication

Table 2: Lyman-Kutcher-Burman (LKB) parameters of acute ocular pain

Parameter	Estimation
n	0.09
m	0.38 (0.31-0.48)
[a]TD_{50} (Gy)	27.54 (18.7-40 Gy)

[a] Tolerance dose for a 50% complication

terms of 1-specificity is shown in Figure 3. The AUC of the ROC curve showed the discriminative ability of the LKB model equal to 0.88. The Hosmer-Lemeshow test showed a proper calibration performance with a value of 1.7 (*P*-value>0.05). The performance was also obtained with a Brier score of 0.09.

Discussion

Advances in head and neck radiotherapy

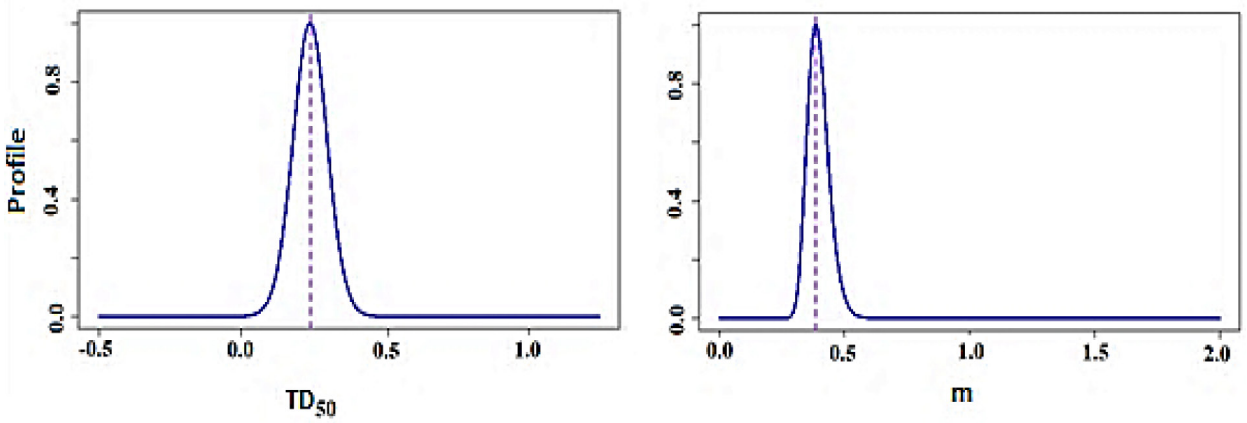

Figure 1: Likelihood estimation profile of parameters m and tolerance dose for a 50% complication (TD_{50}) of eye globe for a fixed value of n=0.09

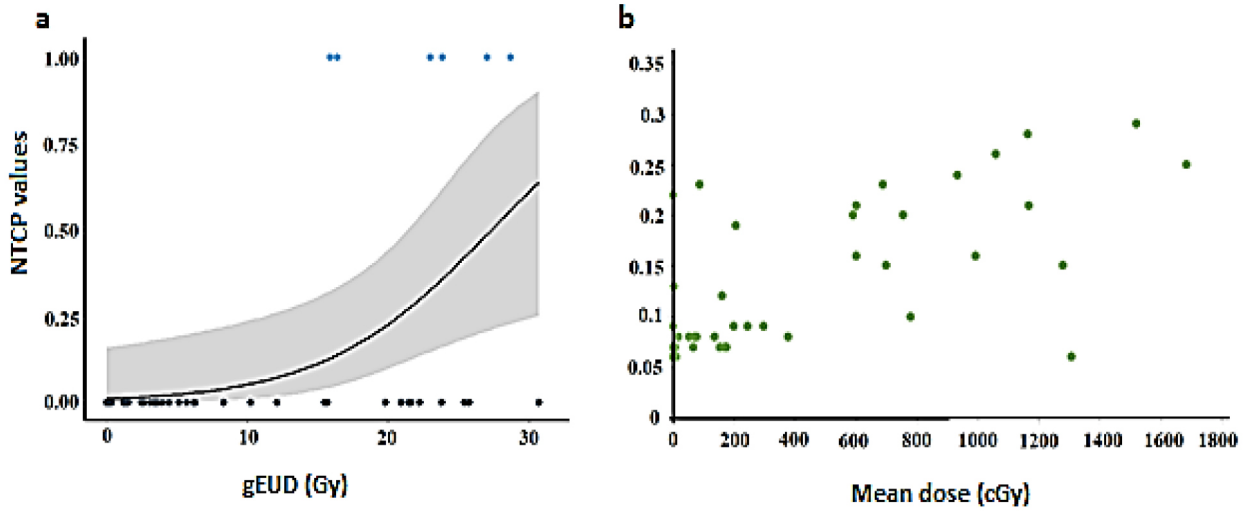

Figure 2: Normal tissue complication probability (NTCP) of ocular pain (grade 1+) based on Lyman-Kutcher-Burman model as a function of a) generalized uniform dose (gEUD) and b) mean dose.

technology led to acceptable dose distribution in tumors and normal tissues. However, there is still a risk of severe side effects for healthy organs and tissues such as eyes, cornea, and lenses [28].

Ocular pain in patients with HNC and brain tumors, who underwent radiotherapy, is often reported along with other eye complications, affecting the patient's quality of life [3, 4, 29]. The present study investigates the incidence and NTCP of ocular pain following 3D-CRT.

A total of 45 patients, who underwent standard radiotherapy with a mean prescribed dose of 45 Gy in 1.8-3 Gy/fraction, were included in the study. After a three-month follow-up, 6 patients (13.33%) showed acute ocular pain with grade 1 or more.

Few studies have been conducted on ocular complications, and most studies have reported ocular pain as a result of other complications. Claus et al. reported ocular pain over one month as a symptom of dry eye in patients undergoing Intensity Modulated Radiation Therapy (IMRT) [29]. Also, in Bhandare et al. study, 18 patients who experienced dry eye reported continual ocular pain after treatment [4].

The maximum radiation dose to patients' eyes with and without ocular pain was 14.16 Gy and 10.86, respectively, showing no significant difference (*P*-value=0.52). Also, the difference in the mean eye dose in patients with and without eye pain was not signifi-

Table 3: Performance of the Lyman-Kutcher-Burman model (LKB) for estimating normal tissue complication probability (NTCP) of ocular pain

Performance quantity	LKB model
Overall	
Brier	0.09
Discrimination	
Area under curve (AUC)	0.88
Calibration	
Hosmer-Lemeshow test	1.7 (*P*-value=0.98)

LKB: Lyman-Kutcher-Burman

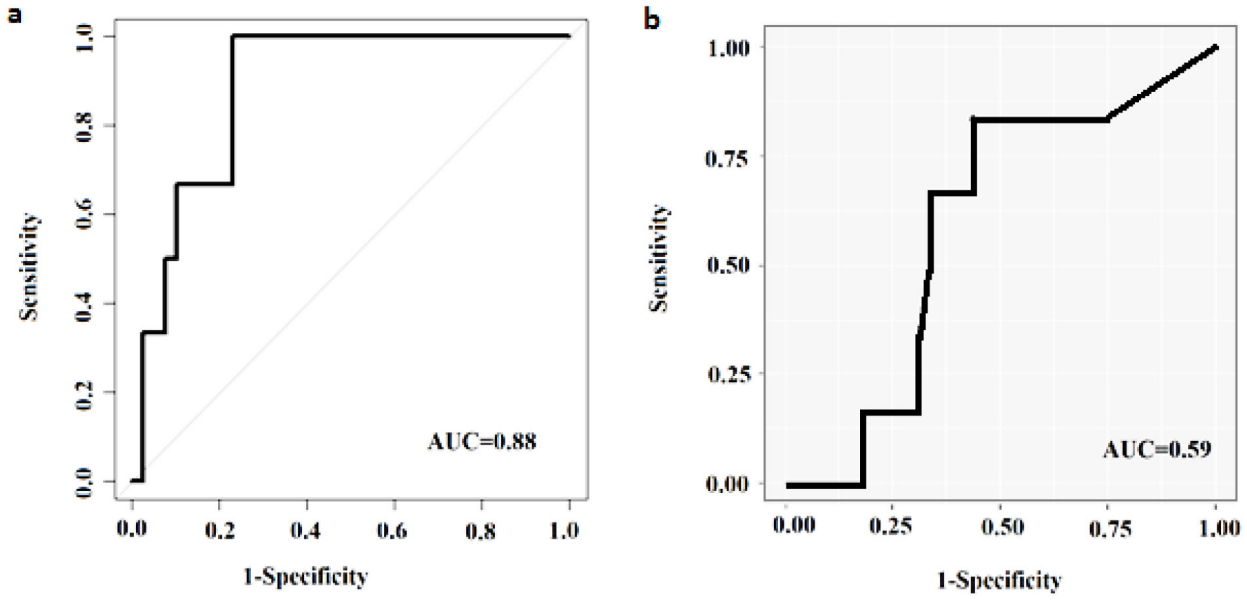

Figure 3: Receiver operating curve for a) Normal tissue complication probability based on Lyman-Kutcher-Burman model; b) Eye globe maximum dose. (AUC: Area Under Curve)

cant (*P*-value=0.89). The results of our study showed that the eye globe's maximum dose is not a predictor of ocular pain, and this can be inferred from the ROC curve of the maximum dose with its low AUC in Figure 3b (AUC=0.59). However, this AUC value is not reliable, the maximum dose thresholds for ocular pain and dry eye were 6.78 Gy and 30 Gy, respectively, in the Claus study [29]. Therefore, ocular pain can occur independently of complications such as dry eyes.

The TD_{50} of ocular pain was also equal to 27.54 Gy, which is less than the TD_{50} reported for complications, such as dry eyes and optic neuropathy (28.4 Gy and 70.12 Gy, respectively) [30, 31], showing greater radiation sensitivity of the eye in case of pain.

The parameter n is related to the volume effect, and its values are between 0 and 1 for serial and parallel structures, respectively [32]. The value of n for different parts of the eye, including the optic nerve and retina, has been reported in the range of 0.20-0.25 [33-35]. In the current study, the value of parameter n for the whole eye was obtained as 0.09, which can be considered a serial structure for whole eye to its proximity to zero

Figure 3a shows that the NTCP of ocular pain has a sigmoid shape, and less than 25% of its values are obtained for a gEUD of less than 20 Gy, which is equivalent to a mean eye globe dose of 12 Gy (Figure 3b). The performance of the LKB model in determining NTCP of ocular pain was evaluated in three areas of overall, discrimination, and calibration performance. The difference between the actual and predicted results determines the overall performance of the model. We obtained a Brier score of 0.09, which is very close to zero, indicating the good overall performance of the model. Also, the AUC value was estimated at 0.88, showing the very good discrimination ability of the LKB model. The accordance between the predicted and observed outcomes led to the acceptable calibration performance of the model. Using the "goodness of fit" test of Hosmer-Lemshew, the calibration coefficient was 1.7, which did not cause to rejection model (*P*-value>0.05).

In the current study, the limitations are as follows: 1) the analysis is conducted on the data of only one radiotherapy department, which can result in less validated results [36], 2) the LKB model uses only dosimetric data in modeling. Considering clinical factors along with dosimetric factors using logistic regression analysis can increase NTCP models performance, and 3) The present study considers two eyes as one organ, while some studies consider paired organs as separate and model each one separately, and perhaps this issue has a positive result on the performance of modeling [37, 38].

Conclusion

In the present study, the LKB radiobiological model was well performed in determining NTCP of grade 1+ ocular pain as an endpoint following radiation therapy of head and neck cancer and skull base tumors. NTCP data showed that the probability of ocular pain can be reduced below 25% by delivering a mean dose of less than 12 Gy to the eye globe in the treatment planning.

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Authors' Contribution

N. Momeni collected the data, and drafted and wrote the manuscript. Z. Roozmand and MA. Broomand helped in writing the manuscript and collecting patient data. N. Hamzian was responsible for designing the study, performing data analysis, and supervising all the work steps. All authors contributed to the interpretation of the findings and read and approved the final manuscript.

Ethical Approval

This prospective study was approved by the National Ethics committee at Shahid Sadoughi University of Medical Science, Yazd (IR.SSU.MEDICIN.REC.1399.206).

Informed consent

All patients filled the informed consent form before entering the study.

Conflict of Interest

None

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