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# Prediction of Pituitary Gland Complications by LKB and Log-Logistic Radiobiological Models in 3D Conformal Radiation Therapy of Head and Neck Tumors

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**ABSTRACT**

***Introduction:*** The pituitary gland is frequently irradiated during radiation therapy of head and neck tumors which can influence the quality of life of the patients after radiation therapy. This study aimed to estimate the normal tissue complication probability (NTCP) for the pituitary gland in head and neck cancers using two radiobiological models.

***Material and Methods:*** *53* patients including *20* cases with nasopharyngeal cancer and *33* cases with brain tumor were studied. The dosimetric properties of each plan including minimum, mean and maximum doses were extracted from the dose-volume histogram curve. For estimation of pituitary gland response for each patient, the BIOPLAN software was used to calculate NTCP by LKB model and Matlab software was applied to calculate NTCP by equivalent uniform dose (EUD) model. Models' parameters including $TD_{50}$, $\gamma_{50}$, and 'a' were extracted from a previous study of radiobiological modeling of pituitary gland response to radiation therapy. For statistical analysis, the T-test was used to compare two models.

***Results:*** The average mean doses of *30.42* and *51.29* (Gy) of the pituitary gland were obtained for nasopharyngeal and brain tumor patients, respectively. The average NTCPs of the pituitary gland for nasopharyngeal patients estimated by LKB and Log-logistic models were *3.84* and *3.91*%, respectively. In brain tumors, the average NTCP was *16.33*% for LKB and *16.41*% for Log-logistic models. The results showed that the log-logistic and LKB models provided comparable results and no statistically significant difference (P-value< *0.05*) was found between two models.

***Conclusion:*** The NTCP results indicated that the average NTCP of the pituitary gland for nasopharyngeal patients was approximately four times lower than that of brain tumors. Finally, implementation of follow up studies and modeling investigations are recommended for accurate estimation of pituitary gland complications following radiation therapy.

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## Introduction

The aim of radiation therapy is to control cancer using radiation while reducing the complication of normal vital organs to the minimum or even zero. However, Radiation therapy, in addition to destroying cancer cells, also damages normal tissues. To achieve this goal, adequate knowledge of tumor and normal tissues received dose will be helpful in treatment planning process. Nowadays, treatment planning of radiation therapy, in addition to dose distributions and dose-volume histogram (DVH) of three-dimensional plans, it relies on the estimation of tumor control probability (TCP) and normal tissue complications probability (NTCP) for plan evaluation [1-4]. Thus, it can be concluded that accurate calculation of NTCP in radiotherapy will help to improve the treatment planning and find the best and most effective treatment plans for treatment.

Radiation therapy plays an important role in the treatment of benign and malignant tumors of the central nervous system [1]. Also, Head and neck cancers are one of the most common cancers in the world and account for 6% of all tumors [5]. Treatment for head and neck cancers varies depending on the location of the tumor and its stage. In head and neck radiotherapy, one of the exposed tissues could be the pituitary gland. Pituitary dysfunction is a disease in which the pituitary gland is not able to produce enough hormones including growth hormone, thyroid stimulating hormone (TSH), adrenocorticotropic [6-8]. In this condition, the secreted hormones from the

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pituitary gland are less or more than normal, normal functioning of the body is affected, and thus the quality of life of the patients is compromised after radiation therapy.

Radiation therapy for brain tumors, nasopharyngeal carcinoma, acute lymphocytic leukemia, or whole body in the preparation for bone marrow transplantation may result in impaired hypopituitarism and secretion of the pituitary gland hormones [9-12]. The first endocrine disorder after radiotherapy is growth hormone deficiency, which is more common in children than in adults [13- 14].

Radiobiological models are applied to calculate NTCPs and are being developed in different active studies. The available radiobiological models for calculating the likelihood of complications of healthy tissue include Lyman-Kutcher-Burman (LKB), Relative Seriality (RS), Critical Volume (CV), Sigmoidal Dose Response (SDR), and Equivalent Uniform Dose( EUD), etc. [15-19]. Using radiobiological modeling we can predict the rate of changes in the function of the pituitary gland before treatment initiation, and make the necessary steps to minimize it. Different soft wares have been launched to calculate the NTCP so that different NTCP models have been used and are still under optimization. For example, BIOPLAN software was developed to calculate NTCP of various organs by Relative-Seriality and the LKB models [20].

Radiobiological modeling has been applied to different parts of the body such as the thyroid gland [4]. In the study of V. D'Avino, et al., two models of LKB and RS were used to estimate the function of the thyroid gland in 100 patients. No significant differences were found in these models [21]. However, we only found one article addressing the radiobiological modeling of the pituitary gland after external radiation therapy. In this regard, Marzi, et al. used gEUD (generalize equivalent uniform dose) parameter for predicting ear and pituitary gland damage after radiation therapy with proton and photon beam. They proposed two new values for $TD_{50}$ and $\gamma_{50}$ for modeling of pituitary gland complications following radiation therapy [22].

The objective of the current study was to predict the NTCP of the pituitary gland in treatment plans of patients with brain and nasopharyngeal tumors. In the current study, we compared two models and their parameters including LKB and log-logistic models.

## Materials and Methods

### *Patients*

The treatment plans of 53 patients with brain and nasopharyngeal tumors candidate for radiotherapy included in this study. The patients whose pituitary glands were completely or partly exposed to radiation, including brain tumors and nasopharyngeal carcinoma were selected. Table 1 shows the demographic information of the patients. 33 of these patients were men and 20 were women. Of these 33 male patients, 20 were those with brain tumors and 13 with nasopharyngeal carcinoma. There were 13 women with brain tumors and 7 with nasopharyngeal carcinoma. In Figure 1, a 3D-conformal treatment plan for the brain tumor was shown, as it can be seen the pituitary gland is completely located inside the treatment field. Figure 2 is a case of nasopharyngeal carcinoma in which the pituitary gland is completely in the treatment field.

Table 1. Demographic information of patients.

| Gender | Number | Age range (year) | Number of Nasopharynx carcinoma | Number of Brain tumor |
|---|---|---|---|---|
| Male | 33 | 25-75 | 15 | 18 |
| Female | 20 | 20-65 | 10 | 10 |

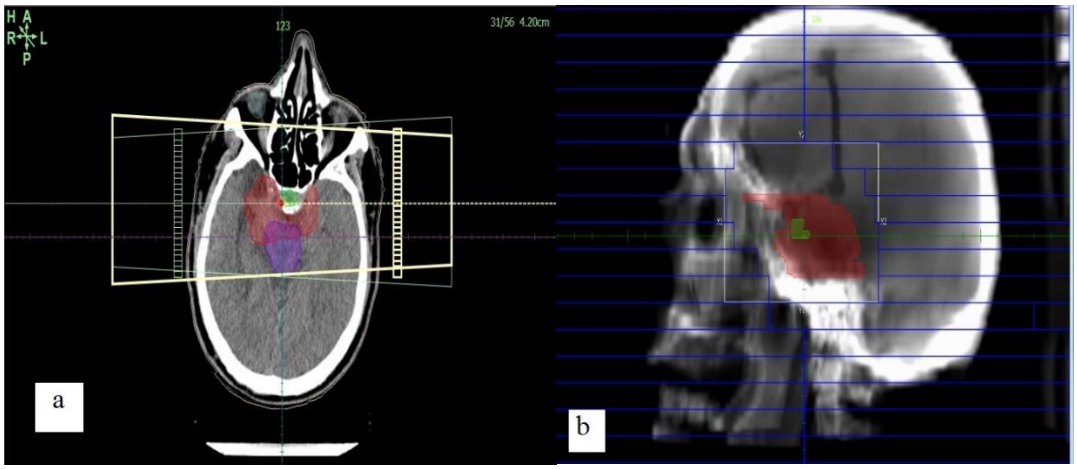


Figure 1. A sample treatment plan for a brain tumor, (a) the axial view and the tumor was depicted in red color, purple for brain stem, and pituitary gland in green. (b) A digitally reconstructed radiograph of the same brain tumor plus multi-leaf collimators depicted with blue color.

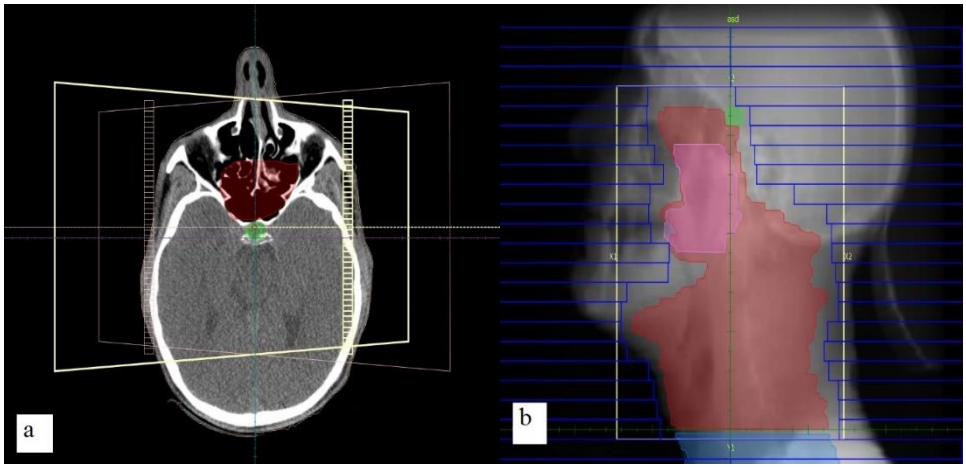


Figure 2. A sample treatment plan for a nasopharynx carcinoma, (a) the axial view and the tumor was depicted in red color, and the pituitary gland was in green. (b) A digitally reconstructed radiograph of the same nasopharyngeal tumor plus multi-leaf collimators depicted in blue color.

Table 2. The parameters for two models of Log-logistic and L-K-B including a, TD50 and $\gamma_{50}$ with 95% confidence interval (CI).

| Organ at risk | Model | a[95%CI] | TD50 [95%CI] (Gy) | $\gamma_{50}$[95%CI] |
|---|---|---|---|---|
| Pituitary gland | Log-logistic | 6.4 [0.9 -8.2] | 60.5 [59.1 -62.0] | 5.2 [3.1 -8.0] |
| | L-K-B | 6.4 [0.9 -8.2] | 60.6 [59.1-62.0] | 4.9 [3.1 -8.0] |

Softwares for treatment planning and NTCP estimation:

In this study, BIOPLAN software (Version, 5.0) was used to calculate NTCP for the LKB model. BIOPLAN is a software that evaluates a treatment plan for the biological response of irradiated tissues [20].

Also, the Matlab software (R2015a) was used to calculate the Log-logistic model. For NTCP calculation by BIOPLAN, cumulative DVH of each patient was extracted as a text file from TiGRT (Linatech, Sunnyvale, CA, USA) treatment planning system and convert to differential DVH. Then, the DVH was normalized to 2 Gy dose per session by the formula of linear quadratic ($EQD2_i$) and using the parameters of $TD_{50}$ and $\gamma_{50}$, NTCP for the pituitary gland for each patient was calculated.

***Radiobiological models***

The concept of equivalent uniform dose (EUD) was described by Niemierko as an absorbed dose for a non-uniform distribution of doses in the tumor volume [18]. The concept of EUD was used for the tumors, but later it was employed for both the tumor and normal tissue which is called gEUD [23-25]. Two radiobiological models including LKB and log-logistic were used to calculate NTCP for the pituitary dysfunction before radiotherapy [22]. The complication endpoint for the pituitary gland was considered as outside of normal reference range for hyperprolactinemia, delayed thyroid-stimulating hormone response to the thyroid-releasing hormone, panhypopituitarism. Thus model parameters were derived from the study of Marzi, et al. which proposed these parameters based on their clinical follow-up [22]. The parameters were shown in table 2.

Both models can be explained mathematically by the following equations:

For gEUD or EUD:

$$gEUD = (\sum_i V_i D_i^a)^{\frac{1}{a}} \quad (1)$$

$V_i$ is the volume fraction of the organ which receives a dose of $D_i$. The parameter "a" indicates the dose-response behavior of the pituitary gland in the current study.

For both groups, a = 6.4 was considered.

For LKB model:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{\frac{-x^2}{2}} dx \quad (2)$$

$$t = \frac{gEUD - TD50}{m \times TD50} \quad (3)$$

$$m = \frac{\pi}{8\gamma 50} \quad (4)$$

Log-logistic model:

$$NTCP = \frac{1}{1+\left(\frac{TD50}{gEUD}\right)^{4\gamma 50}} \quad (5)$$

$TD_{50}$ is a tolerance uniform dose delivered to the whole organ that results in a *50%* complication rate. $\gamma_{50}$ denotes the slope of the dose-response curve at $TD_{50}$. m is the inverse of the slope of the curve.

## Results

For 20 patients with nasopharyngeal carcinoma an average mean dose of 30.42 Gy, and 33 patients with brain tumors an average mean dose of 51.29 Gy were

obtained. Calculation of the NTCP for pituitary was performed using two radiobiological models of LKB and log-logistic. The average of the minimum dose, the maximum dose, and the mean dose was 27.44 (Gy), 43.13 (Gy), 36.19 (Gy), respectively for nasopharyngeal patients. Table 3 shows the dose received by each nasopharyngeal patient with the predicted NTCP by both radiobiological models. Due to NTCP dependence on the absorbed dose, decreasing patient dose reduces the NTCP. The mean NTCPs calculated for nasopharyngeal patients in LKB and Log-logistic models were 3.84 and 3.91%, respectively. In brain tumors, this value was 16.33% for LKB and 16.41% for Log-logistic.

For brain tumor patients the average of the minimum dose, the maximum dose, and the mean dose was 47.87(Gy), 54.31(Gy), 51.32 (Gy) respectively. Table 4 shows the planned doses and the NTCP level for each brain tumor patient. Compared to nasopharyngeal patients, the normal tissue complication probability in patients with brain tumors was higher because the pituitary gland is almost completely in the main field and received higher doses.

In Figure 3, cumulative DVH of the pituitary gland for patients with nasopharyngeal cancer were depicted. As can be seen, there is a wide range of DVHs for nasopharyngeal cancers. Because in some patients the field was big enough to include the pituitary gland while in some cases field was so that the partial volume of pituitary gland was irradiated.

Figure 4, shows the cumulative DVH of the pituitary gland for brain tumors. Unlike nasopharyngeal cancers, in most cases, the pituitary gland was completely inside the radiation field for brain tumors which led to higher doses to the pituitary gland.

Figures 5 and 6 show the NTCP in terms of EUD, estimated by both LKB and Log-logistic models for brain tumors and nasopharynx. According to this chart, these two models have very close results. Both models estimate the likelihood of normal tissue complications closely and with very little difference. The statistical test (T-Test) was performed between two models and no statistically significant (P-value<0.05) was seen between the estimated NTCPs for two patient groups.

Table 3. Data of nasopharyngeal patients, including the minimum, maximum, mean doses and NTCP calculated using the two radiological models (LKB and Log-logistic).

| Patient number | Min dose(Gy) | Max dose(Gy) | Average dose(Gy) | EUD (Gy) | NTCP (L-K-B)% | NTCP (log-logistic)% |
|---|---|---|---|---|---|---|
| 1 | 11.07 | 40.84 | 29.12 | 32.12 | 0.00 | 0.00 |
| 2 | 7.55 | 41.24 | 30.51 | 32.77 | 0.00 | 0.00 |
| 3 | 2.03 | 5.57 | 3.17 | 2.78 | 0.00 | 0.00 |
| 4 | 11.85 | 26.69 | 15.95 | 17.47 | 0.00 | 0.00 |
| 5 | 5.17 | 32.39 | 14.49 | 25.24 | 0.00 | 0.00 |
| 6 | 33.00 | 43.90 | 40.46 | 39.78 | 0.02 | 0.01 |
| 7 | 25.13 | 52.51 | 41.45 | 46.16 | 0.20 | 0.30 |
| 8 | 10.73 | 56.78 | 38.24 | 40.50 | 0.60 | 0.20 |
| 9 | 26.50 | 40.05 | 31.92 | 32.69 | 0.00 | 0.00 |
| 10 | 58.57 | 59.68 | 59.19 | 63.66 | 63.30 | 74.62 |
| 11 | 40.25 | 46.19 | 42.69 | 39.47 | 0.00 | 0.01 |
| 12 | 44.20 | 45.12 | 44.82 | 44.47 | 0.00 | 0.16 |
| 13 | 31.72 | 43.49 | 38.59 | 38.22 | 0.00 | 0.00 |
| 14 | 4.44 | 32.88 | 17.04 | 22.65 | 0.00 | 0.00 |
| 15 | 40.65 | 41.61 | 41.16 | 39.85 | 0.00 | 0.01 |
| 16 | 37.84 | 53.14 | 46.44 | 46.20 | 0.00 | 0.10 |
| 17 | 29.92 | 52.29 | 46.72 | 46.40 | 0.14 | 0.11 |
| 18 | 42.58 | 44.70 | 43.71 | 43.88 | 0.00 | 0.12 |
| 19 | 46.90 | 49.82 | 49.06 | 48.85 | 0.80 | 1.33 |
| 20 | 38.66 | 53.73 | 49.07 | 48.97 | 0.90 | 1.33 |

Table 4. Data of patients with brain tumors, including the minimum, maximum, mean doses and NTCP calculated using the two radiological models (LKB and Log-logistic).

| Patient number | Min dose(Gy) | Max dose(Gy) | Average dose (Gy) | EUD (Gy) | NTCP (L-K-B)% | NTCP (log-logistic)% |
|---|---|---|---|---|---|---|
| 1 | 49.82 | 50.22 | 50.06 | 50.29 | 2.52 | 2.20 |
| 2 | 45.98 | 57.29 | 54.00 | 52.98 | 6.70 | 6.15 |
| 3 | 58.73 | 60.33 | 59.56 | 59.75 | 43.14 | 45.00 |
| 4 | 48.04 | 54.25 | 50.72 | 48.29 | 1.15 | 0.91 |
| 5 | 36.84 | 42.22 | 41.15 | 40.20 | 0.03 | 0.02 |
| 6 | 40.54 | 41.35 | 40.84 | 46.80 | 0.63 | 0.48 |
| 7 | 50.62 | 52.00 | 51.46 | 52.11 | 4.95 | 4.30 |
| 8 | 37.24 | 64.40 | 44.22 | 42.99 | 0.11 | 0.09 |
| 9 | 44.82 | 46.07 | 45.62 | 46.00 | 0.45 | 0.36 |
| 10 | 48.18 | 49.48 | 48.74 | 48.25 | 1.14 | 0.90 |
| 11 | 37.35 | 46.29 | 43.19 | 42.00 | 0.07 | 0.05 |
| 12 | 56.58 | 61.19 | 59.35 | 59.25 | 39.18 | 40.00 |
| 13 | 48.24 | 51.25 | 50.13 | 50.49 | 2.70 | 2.27 |
| 14 | 50.39 | 54.90 | 52.58 | 52.74 | 6.10 | 5.40 |
| 15 | 43.32 | 58.46 | 54.29 | 53.25 | 7.30 | 6.58 |
| 16 | 40.25 | 54.15 | 49.64 | 47.83 | 0.97 | 0.76 |
| 17 | 45.55 | 56.34 | 51.99 | 50.82 | 3.10 | 3.00 |
| 18 | 48.94 | 49.54 | 49.34 | 53.97 | 9.35 | 8.50 |
| 19 | 6.03 | 41.23 | 20.60 | 23.00 | 0.00 | 0.00 |
| 20 | 28.97 | 51.24 | 43.43 | 42.97 | 0.11 | 0.08 |
| 21 | 53.03 | 57.60 | 55.99 | 54.53 | 11.20 | 10.32 |
| 22 | 60.65 | 61.10 | 60.91 | 61.43 | 56.63 | 57.87 |
| 23 | 49.78 | 50.96 | 50.32 | 50.72 | 2.97 | 2.50 |
| 24 | 50.01 | 50.80 | 50.57 | 51.01 | 3.31 | 2.80 |
| 25 | 60.43 | 64.28 | 60.03 | 64.55 | 77.54 | 79.40 |
| 26 | 59.19 | 60.06 | 59.70 | 59.81 | 43.61 | 44.06 |
| 27 | 52.61 | 53.03 | 52.91 | 54.46 | 10.97 | 10.08 |
| 28 | 53.93 | 54.34 | 54.16 | 54.39 | 10.75 | 9.86 |
| 29 | 57.12 | 57.75 | 57.43 | 59.31 | 39.65 | 39.85 |
| 30 | 52.45 | 59.59 | 57.45 | 56.70 | 21.36 | 22.70 |
| 31 | 56.89 | 61.70 | 58.72 | 58.64 | 34.47 | 35.00 |
| 32 | 47.09 | 57.04 | 53.13 | 58.48 | 33.24 | 35.00 |
| 33 | 60.29 | 61.93 | 61.45 | 62.34 | 63.53 | 65.30 |

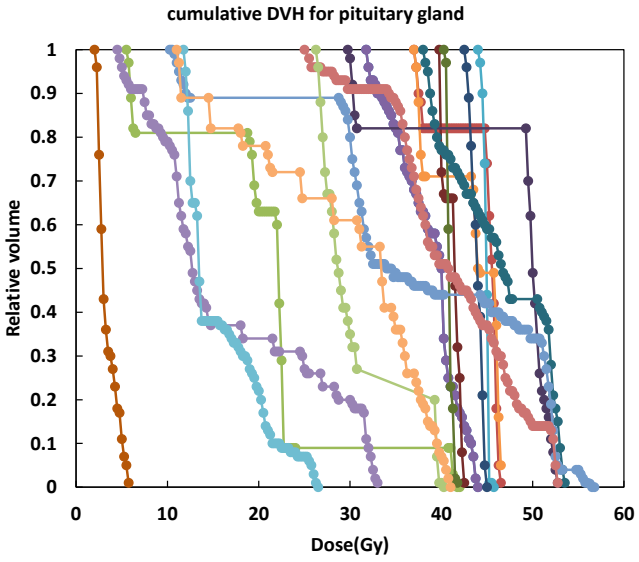


Figure 3. Dose-volume histograms of pituitary gland for all patients with nasopharyngeal carcinoma

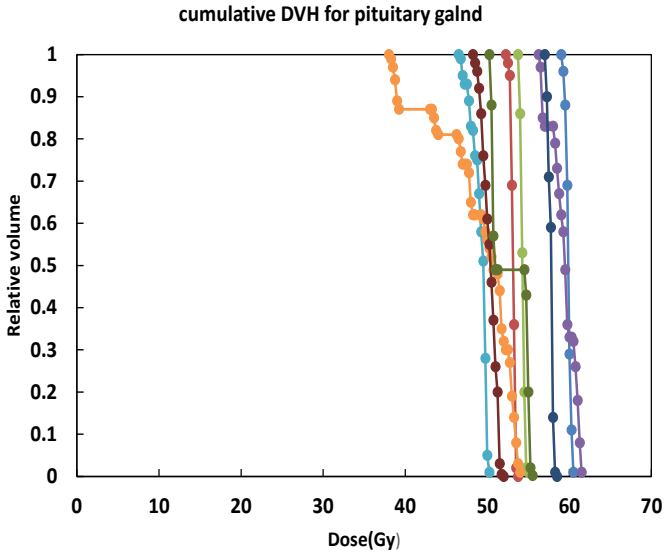


Figure 4. Dose-volume histograms of pituitary gland for all patients with brain tumors.

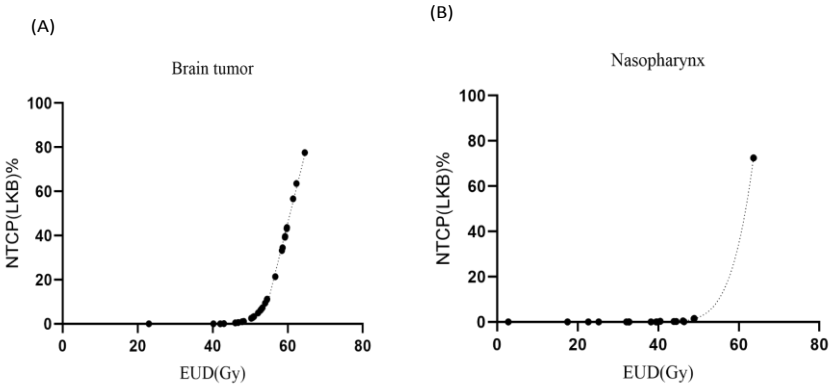


Figure 5. Estimated dose-response curve for pituitary dysfunction using LKB Model for brain tumors (A) and nasopharyngeal tumors (B).

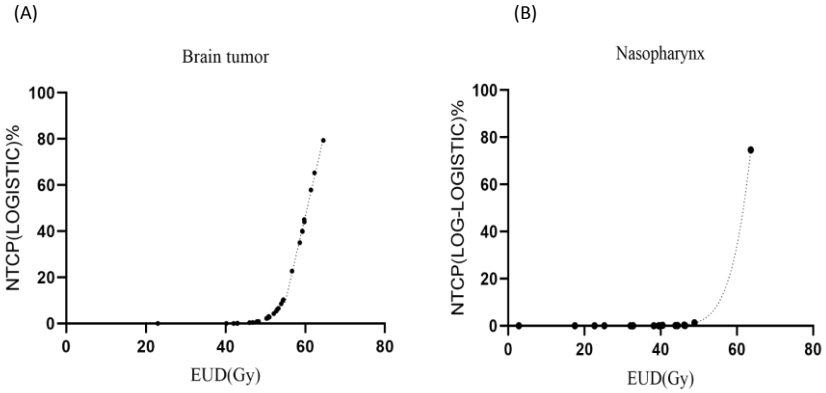


Figure 6. Estimated dose-response curve for pituitary dysfunction using Log-Logistic Model for brain tumors (A) and nasopharyngeal tumors.

## Discussion

The purpose of this study was to predict the complications of the pituitary gland after radiotherapy with two radiobiological models (LKB and Log-logistic). 53 patients with brain tumors and nasopharyngeal carcinoma were studied. A comparison of these two methods revealed no significant differences in NTCP estimations for each patient (Tables 3 and 4). Additionally, patients with brain tumors showed a significantly higher probability of pituitary gland dysfunction compared to nasopharynx patients. This difference originates basically from the average higher doses of the pituitary gland received by the brain tumor

group (Figure 3 and 4). For nasopharynx and brain tumors patients, the pituitary gland received an average EUDs of 37.6 (Gy) and 51.83 (Gy) respectively. Considering the NTCP dependence on the dose, its level was lower for nasopharyngeal patients than brain tumors. Therefore, according to the predictions of NTCP, it was expected that the probability of complications of the pituitary gland in patients with brain tumors would be higher than those of the nasopharynx patients. Our findings were in accordance with the recent data provided for dose constraints of pituitary gland [26; 27]. On the other hand, there are several suggested dose constraints for pituitary gland in the literature. In a recent article by Silvia, et al., the proposed dose constraints for the pituitary gland as an organ at risk were the maximum dose less than 50 Gy while less than 25 or 30 Gy in children [26]. However, in another study, the mean dose of 45 Gy or less was suggested as a dose constraint of pituitary gland to prevent panhypopituitarism. While, the dose constraint of 20 Gy or less was proposed to avoid growth hormone deficiency in the patients with head and neck tumors [27]. In a study by Emami, et al., they reported the maximum dose of 45 Gy for incidence of panhypopituitarism [1]. As it can be seen in figure 4, in most of the patients with brain tumors, the pituitary gland received a dose higher than 45 Gy which resulted in higher NTCP for this group of patients. While for nasopharynx patients (figure 3), the average EUD of 37.6 was lower than the proposed dose constraint and lead to lower NTCPs for pituitary gland.

In an only modeling study by Marzy, et al., of the 103 patients, 45 cases had late complications and in 58 cases no complications were observed [22]. They used different endpoints for staging the pituitary gland dysfunction following radiation therapy. However, considering all types of dysfunctions including reduction of growth hormone, Panhypopituitarism, Hyperprolactinemia, Hypothyroidism, the parameters of 'a', $TD_{50}$, and $\gamma_{50}$were proposed by fitting the calculated NTCPs to the follow-up data. There was not considerable difference between two models of LKB and Log-logistic in estimation of NTCPs using log-likelihood (LL), Akaike Information Criterion (AIC) methods. Also, in their study, an important risk factor for pituitary dysfunction with an average gEUD greater than 65 Gy was reported. Our results for NTCP calculations were in close agreement with their data.

In cancers of the head and neck where the pituitary gland is exposed to radiation, the risk of pituitary gland complication is between 8 and 50% which mainly results in growth hormone deficiency after radiation therapy [13; 14]. Many studies have been performed on the radiation response of the pituitary gland, but little is available in the field of modeling and predicting the possibility of its complications. For instance, in a study by Darzy, et al., the main causes of impaired pituitary gland have been reported in terms of the dose of the pituitary gland, the patient's age during treatment, sex, and the number of treatments [28]. In another study by Pai, et al., the minimum and maximum doses of the pituitary received 50 and 70 (Gy), respectively, and the lowest dose of 18 Gy for the incidence of disorders in the pituitary gland has been reported [11].

By calculating NTCP using two models of LKB and Log-logistic and comparing them by the statistical paired t-test, it was found that there were no significant differences between them and almost the performance of the two models was very similar in the estimation of NTCP for the pituitary gland following radiation therapy. Finally, it should be mentioned that due to the lack of follow-up data, it was not possible to determine which model works better than the other, so further clinical studies are recommended to confirm the studied radiobiological models.

## Conclusion

In the current study, the results of two LKB and Log-logistic radiobiological models were very close in estimating pituitary gland complications for both groups of patients. However, according to studied models, the radiotherapy of brain tumors revealed a considerably higher probability of complication of pituitary gland compared to patients with nasopharyngeal cancer. It is evident that the pituitary complications affect the quality of life and health of patients after radiation therapy. Therefore, it is essential to estimate NTCP of the pituitary gland in treatment planning for all patients receiving radiotherapy of the head-and-neck region. It should be emphasized here that for more accurate NTCP calculations using DVH data of patients, more follow-up studies and modeling investigations are required.

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