Volume 21, No 1 | International Journal of Radiation Research, January 2023

Predicting radiation therapy outcome of pituitary gland in head and neck cancer using Artificial Neural Network (ANN) and radiobiological models

S. Shahbazi[1,2], R. Ferdosi[3], R. Malekzadeh[2], R. Egdam Zamiri[4], A. Mesbahi[1,2,4*]

[1]Molecular Medicine Research Center, Institute of Biomedicine, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Medical Physics, School of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Department of Health Information Technology, Faculty of Management and Medical Informatics, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Radiation Oncology Department, Shahid Madani Hospital, Medical School, Tabriz University of Medical Sciences, Tabriz, Iran

▶ ***Original article***

***Corresponding author:**
Asghar Mesbahi, Ph.D.,
E-mail:
amesbahi2010@gmail.com

Received: December 2021
Final revised: August 2022
Accepted: September 2022

Int. J. Radiat. Res., January 2023; 21(1): 53-59

DOI: 10.52547/ijrr.21.1.7

Keywords: *NTCP, radiobiological model, ANN, pituitary gland, radiotherapy.*

ABSTRACT

***Background*:** Pituitary dysfunction is one of the complications associated with head and neck radiation therapy. Here, radiobiological and artificial neural network (ANN) models were used to estimate the normal tissue complication probability (NTCP) of the pituitary gland. ***Materials and Methods*:** Fifty-one adult patients with nasopharyngeal carcinoma and brain tumor were studied. Two radiobiological models of Lyman Kutcher Burman (LKB), log-logistic, and ANN were employed to calculate the NTCP of the pituitary gland for all patients. BIOPLAN and MATLAB softwares were used for all calculations. The necessary parameters for each radiobiological model were calculated using Bayesian methods. R^2 (coefficient of determination) and root-mean-square error (RMSE) parameters were used for the ANN method to get the best estimate. The area under the receiver operating characteristic (ROC) curve (AUC) and Akaike information criterion (AIC) were used to compare the models. ***Results*:** The respective mean NTCPs for nasopharyngeal patients with LKB and log-logistic models were 54.53% and 50.83%. For brain tumors, these values were 62.23% for LKB and 53.55% for log-logistic. Furthermore, AIC and AUC values for LKB were 77.1 and 0.826 and for log-logistic were 71.9 and 0.902, respectively. AUC value for ANN was 0.92. ***Conclusions*:** It can be deduced that LKB and log-logistic methods make reliable estimations for NTCP of the pituitary gland after radiotherapy. Moreover, the ANN approach as a novel method for NTCP calculations performed better than the two conventional analytical models as its estimations were much closer to the clinical data.

INTRODUCTION

Today, radiation therapy (RT) is a key approach utilized extensively to treat solid tumors independently or in conjunction with surgery and chemotherapy in advanced stages [(1)]. Unfortunately, in addition to destroying cancerous cells, radiation therapy damages surrounding normal tissue and causes early or late complications that impact the patient's quality of life [(2)]. An initial and important step for patients receiving radiotherapy is treatment planning. Evaluating treatment plans can ensure the proper amount of radiation to tumoral volume is delivered while preserving the surrounding vital healthy tissue [(3)]. Dose distribution and dose-volume histogram (DVH) are two important and standard indicators in ranking and selecting an appropriate treatment plan for each patient. Recently, radiobiological modeling and estimating the extent of normal tissue complication probability (NTCP) as well as tumor control probability (TCP) have been proposed as the best technique to facilitate the treatment process [(4, 5)], as the main goal of radiobiological modeling is to determine the best treatment plan for each patient to ensure that the highest dose reaches the tumor with the least damage occurring to the surrounding normal tissue. Therefore, radiobiological modeling to provide a reliable estimate of NTCP and TCP in radiation therapy is currently under further evaluation [(6-8)]. The highest TCP and lowest NTCP in some treatment planning systems are the main criteria for accepting a treatment plan. Radiobiological modeling has been used to estimate the NTCP of different healthy organs and tissues [(9, 10)]. For example, Marzi *et al.* used two models, Lyman Kutcher Burman (LKB) and log-logistic, to predict the complications of the pituitary gland. They found no significant differences between the two methods, and both predicted the complications of the pituitary gland at a reliable level [(11)]. The LKB model is one of the oldest and most well-known models for predicting the effects of

[DOI: 10.52547/ijrr.21.1.7]

healthy tissue. Lee et al. also showed that the LKB model can be used to estimate the rate of xerostomia in head and neck radiotherapy [12]. In a study on hypothyroidism, 174 patients with nasopharyngeal carcinoma were studied using logistic regression to predict thyroid complications. These patients were followed for 24 months, and the maximum dose received by the pituitary gland was found to be the most effective factor in hypothyroidism [13].

The use of other methods, such as artificial intelligence, for predicting NTCP in radiation therapy planning have also been studied recently [14, 15]. ANN is an ideal method for processing information that is inspired by the biological nervous system and processes information like the brain. It consists of the components of layers and weights. Network behavior also depends on communication between members. ANN has also been used to estimate the response of different organs to radiotherapy [16, 17]. In a study conducted by Gulliford *et al.*, ANNs were able to predict the side effects of prostate radiotherapy [18]. Ochi et al. used an ANN model to predict survival in patients with uterine cervical cancer, and according to their results, the neural network was able to predict the survival of patients after radiotherapy [19]. Mahdavi *et al.* used an ANN to predict dose before administration in patients with prostate and nasopharynx using the IMRT technique; according to their results, ANN has the ability to predict dose before treatment [20].

Hypopituitarism is a complication of head and neck radiotherapy [21, 22]. Short-term follow-up studies have shown that in patients with brain tumors treated with radiotherapy, a 25% reduction in the secretion of pituitary hormones is observed [23]. In a long-term follow-up study (8 years), 88.8% of patients had pituitary dysfunction growth hormone (GH) deficiency as the most common pituitary dysfunction, followed by gonadotropin, adrenocorticotropic hormone (ACTH), and thyroid-stimulating hormone (TSH) deficiency, in percentages of 86.9%, 34.6%, 23.4%, and 11.2%, respectively [24]. Pituitary gland hormone disorders were studied in a meta-analysis by Appelman-Dijkstra *et al.*, who reported GH deficiency (45%), gonadotropin deficiency (30%), TSH deficiency (25%), and ACTH deficiency (22%), respectively. According to these studies, the dysfunction of the pituitary gland affects the quality of life of patients for a long time [25].

The aim of this study was to evaluate and rank the predictive power of three methods in estimating pituitary gland complications after radiation therapy for first time. For this purpose, radiobiological models of LKB and log-logistic and ANN-based model were used to calculate NTCP. The performance of the models was assessed and then compared to find and recommend the best model.

METHODS AND MATERIALS

Patient selection and follow up

The inclusion criterion for this study was normal pituitary gland function, so an initial blood test was performed to determine the growth hormone levels in the study group. Fifty-one patients with head and neck cancers treated by radiotherapy were selected from among the patients in whom part or all of the pituitary gland was located in the main field of treatment. This study was conducted after the review and approval of the ethics committee (approving body: Tabriz University of Medical Sciences, Tabriz, Iran; registration number: IR.TBZMED.VCR.REC.1397.126. and date of registration: 15th of March 2018).

Twenty–five patients (fifteen males and ten females) were selected from nasopharyngeal patients and twenty-six patients from brain tumor patients (sixteen males and ten females). The average age of the men and women was 50 and 42.5 years, respectively. Demographic, clinical, and treatment characteristics of patients and therapeutic information of the pituitary glands were presented in table 1. It should be noted here that several hormones are impacted by radiation therapy of the pituitary glands, including ACTH, TSH, and GH. However, based on previous studies, GH was considered in the current study as an indicator of early complications of the pituitary gland after radiotherapy [26, 27]. Before starting the treatment, the patients were subjected to hormonal tests to check the normal activity of the pituitary gland. The patients were followed for twelve months after the end of treatment, and GH hormone tests were performed on them every three months. NTCP for the participants was calculated with two radiobiological models, LKB and log-logistic, and an ANN-based model.

Table 1. Demographic, clinic and therapeutic information of the patients.

Characteristic	Number of patients
Sex	
Male	31
Female	20
Mean age (y)	
Male	50±25
Female	42.5±14.5
Cancer site	
Nasopharynx	25
Brain tumor	26
Mean dose of pituitary gland (Brain tumor) (Gy)	
Minimum	47.77
Maximum	54.21
Mean	51.22±7.9
Mean dose of pituitary gland (nasopharynx) (Gy)	
Minimum	27.34
Maximum	43.03
Mean	36.09±12
Volume of pituitary gland (mL), mean±SD	0.76±0.3

[DOI: 10.52547/ijrr.21.1.7]

Radiobiological modeling

LKB (Lyman-Kutcher-Burman) model

The LKB model was first proposed by Lyman-Kutcher-Burman, and NTCP was calculated by equation (1) [28].

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

$$t = \frac{D_{eff}-TD_{50}}{mTD_{50}} \quad (1)$$

$$D_{eff} = \left(\sum_i v_i D_i^{\frac{1}{n}}\right)^n$$

where D_{eff} was the dose that was an equivalent uniform dose (EUD), TD_{50} was the dose whose complication risk was 50%, m was the slope of the sigmoid curve, and n was the volume effect parameter. The v_i was the fraction of the volume of the limb that received the dose D_i.

Log-logistic model

The EUD model was first proposed by Niemierko for non-uniform dose distribution in tumors [29]. To use the concept of EUD in normal tissue, Niemierko proposed equation (2) called gEUD [30].

$$gEUD = \sum_i (V_i D_i^a)^{1/a} \quad (2)$$

Here a was the volume effect parameter. To calculate the NTCP for the log-logistic model, equation (3) was used.

$$NTCP = \frac{1}{1+\left(\frac{TD50}{gEUD}\right)^{4\gamma 50}} \quad (3)$$

The γ_{50} was the slope of the dose-response curve in TD_{50}. There were different types of software for calculating NTCP.

In this study, BIOPLAN software was used for LKB model and MATLAB software was used for log-logistic model [31]. The parameters used in these models were calculated by Bayesian method and the fitting of the models was performed using Stan software package and in R 3.3.2 software [32].

ANN (Artificial neural network) based model

The techniques of current study had focused on multilayer perceptron (MLP) [33]. Many of the same units were called nodes, which were similar to the processing units in brain neurons. These nodes were made up of a number of layers (input, hidden, and output layers) (figure 1) that were connected by weights, representing the interstitial synapses in the brain [34]. In the present study, six nodes in the input layers included the minimum, maximum, mean, total prescribed dose, and pituitary gland volume. 80% of the input nodes was given to the network for training and 20% was intended for the test part. MATLAB software was used for this purpose. The hidden layer nodes were changed and finally, the output layer was NTCP, calculated by the network. For ANN model, the statistical indices of RMSE and the R^2 were used to evaluate the proposed models. RMSE showed the difference between the value predicted by the model and the actual value. R^2 indicated the probability of correlation between the data predicted by the model and the actual data.

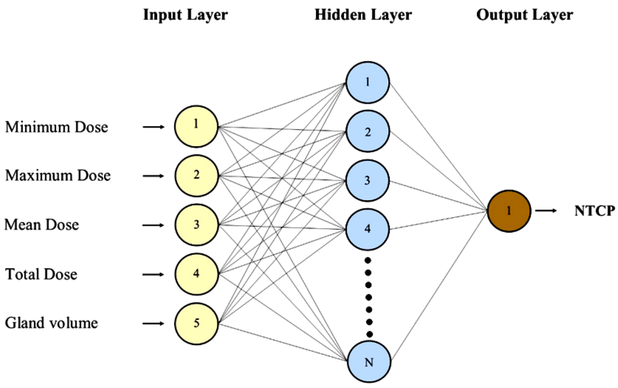

Figure 1. Multilayer artificial neural network (ANN) model in current study.

Performance evaluation of models

Finally, the area under the ROC curve (AUC) and Akaike Information Criterion (AIC) were used to evaluating the performance of the investigated models in this study. AIC was used to rank the radiobiological models. The AIC evaluation criterion indicated the amount of information lost by the model, and therefore the smaller the AIC evaluation criterion, the better and more appropriate the model was compared to the other models.

RESULTS

The mean doses received by the pituitary glands in patients with brain tumors and nasopharyngeal cancers were 51.22 and 36.09 (Gy), respectively. Average pituitary gland volume in patients was 0.76 (mL).

Table 2 showed the parameters of the models with 95 %CI. As shown in this table 2, the TD_{50} values for the LKB model and the log-logistic model were 31.33 and 25.56 (Gy), respectively. Based on these parameters, NTCP was calculated for each of the models. The mean NTCP calculated for brain tumor patients with LKB and log-logistic models was 62.23% and 53.55%, respectively. For nasopharyngeal patients, the mean NTCP calculated with LKB and log-logistic models is 54.53% and 50.83%, respectively, which is shown in table 3 and figure 2 showed the dose-response curve for the pituitary gland using the LKB model in the two patient groups. According to the figure 2, the probability of complications increases with increases to mean dose. Figure 3 displayed the dose-response curve for the pituitary gland in the two patient groups using the log-logistic model. The ROC curve shown in figure 4a illustrations that the log-logistic model was more consistent with clinical data,

[DOI: 10.52547/ijrr.21.1.7]

because AUC was larger with it than with the LKB model. The AIC criterion for ranking models was also used. As shown in table 4, the AIC of the log-logistic model was 71.9 and for the LKB model was 77.1, which again indicates that the log-logistic model was more consistent with the clinical data.

Also, as shown in table 5, for the neural network to reach the best data estimates, the nodes needed to be changed. As can be seen, by changing the nodes and calculating the RMSE and R^2 for the network training and test parts, the best case was observed in node 3. The lower the RMSE was and the closer R^2 is to one, the better estimate will be, and the closer the neural network predictions will be to the clinical data. Figure 4b and table 5 showed the ROC curve and the AUC, respectively, for each of the nodes. According to the results, the best area under the curve was for node 3.

Table 2. The parameters for two models of Lyman Kutcher Burman (LKB), and log-logistic including a, TD_{50}, m, n and γ_{50} with 95% confidence interval (CI).

Models	Parameter	Value	95% CI
LKB	n	0.0254	0.0064-0.0676
	TD_{50} (Gy)	31.33	23.83-39.17
	m	2.24	1.22-3.47
log-logistic	a	2.5	0.013-1.6
	TD_{50} (Gy)	25.56	15.96-35.61
	γ_{50}	0.0523	0.0018-0.2

Table 3. Average normal tissue complication probability (NTCP, %) using the two radiological models (Lyman Kutcher Burman (LKB), and log-logistic).

Models	NTCP (%) (Nasopharynx)	NTCP (%) (Brain tumor)%
LKB	54.535±6.88	62.23±4.51
log-logistic	50.83±3.84	53.55±1.22

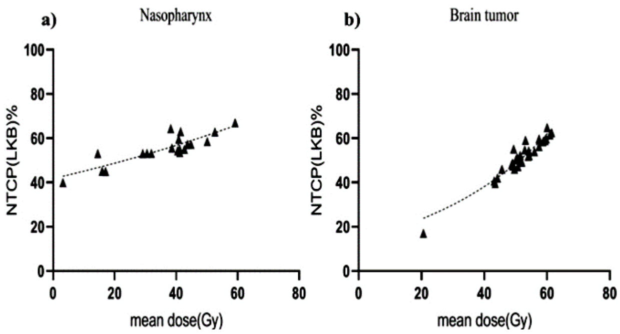

Figure 2. Dose-response curve for pituitary gland disorder using LKB model: **a)** for nasopharynx patient, **b)** for brain tumor patient.

Table 4. Model ranking based on widely Akaike's information criterion (WAIC). LKB: Lyman Kutcher Burman. AIC: Akaike Information Criterion. AUC: Area under the ROC Curve.

Model	AIC	AUC
LKB	77.1	0.826
log-logistic	71.9	0.902

Table 5. AUC for each of the hidden layers nodes. AUC: Area under the ROC Curve.

Nodes	AUC
2	0.909
3	0.92
4	0.908
5	0.748

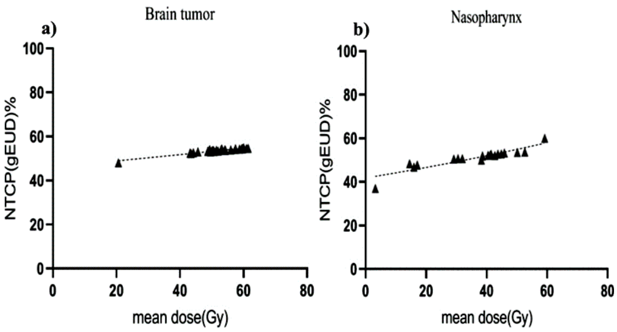

Figure 3. Dose-response curve for pituitary gland disorder using log-logistic model: **a)** brain tumor patients, **b)** nasopharynx patients.

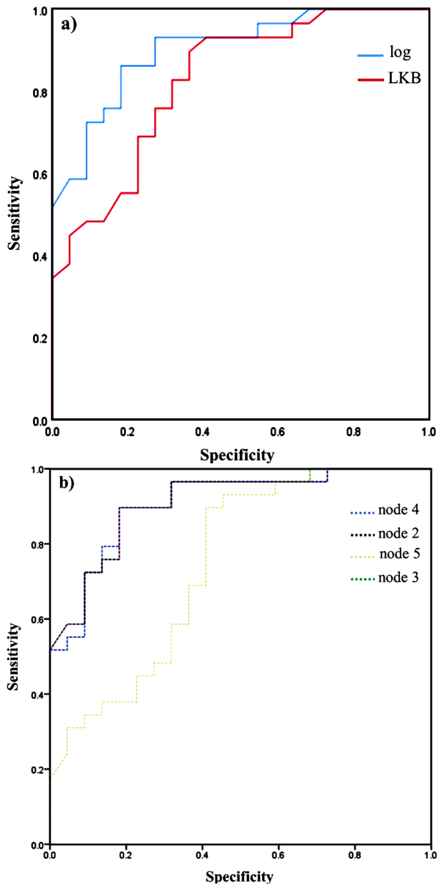

Figure 4. ROC (Receiver Operating Characteristic) curves for: **a)** Lyman Kutcher Burman (LKB) and log-logistic models, **b)** artificial neural network (ANN) for each of the hidden layer node.

DISCUSSION

According to table 1, the average dose received by the pituitary gland of brain tumor patients was higher than that received by nasopharyngeal patients. Therefore, it was expected that the probability of complications would be higher in patients with brain tumors than in patients with nasopharyngeal cancer. The mean NTCP (%) was predicted more accurately by both models in brain tumor patients than in patients with nasopharyngeal cancer. According to these results, the LKB model predicts the probability of complications more accurately than the log-logistic model. Also, it can be seen that predictions by the log-logistic model were closer to the clinical data (table 4). In the study of Marzi *et al.*, which is similar

[DOI: 10.52547/ijrr.21.1.7]

to the current study, the LKB and log-logistic models had very close results with only a slight difference in AIC. The AIC of their LKB model was 92.3 and of the log-logistic model was 92.4 [11]. Similar to current study, the AIC values herein were 77.1 for the LKB model and 71.9 for the log-logistic model (table 4). In another comparison with the ROC curve, the AUC was larger in the log-logistic model than in the LKB model, indicating that the log-logistic model predicted more closely to the clinical data. The results of Marzi *et al.* [11], however, indicated that the AUC was larger with the LKB model than with the log-logistic model.

Many studies have used ANNs to predict the effects of various organs on the body after radiotherapy. For the first time, the current study used a neural network to predict the complications of the pituitary gland after head and neck radiotherapy. As shown in table 5, the neural network was performed with different hidden layers nodes to achieve the best prediction. One hidden layer with 3 nodes was the best estimate. Thomas et al. used ANN and logistic regression (LR) to predict the survival of radiotherapy-treated head and neck patients. According to their results, ANN predicted more accurately than LR (35).

In head and neck cancers treated with radiotherapy, when part or all of the pituitary gland is exposed to radiation, the probability of pituitary gland disorders developing is 8% to 50%, the primary one of which is growth hormone deficiency [36]. Many studies have recommended a prescribed dose for the pituitary gland. For example, Silvia *et al.* recommended a dose of less than 50 Gy for adults and less than 25 or 30 Gy for children [37]. Pai *et al.* reported a dose of 50-70 Gy for the pituitary gland [38]. In the study by Emami *et al.*, maximum doses greater than 45 Gy caused panhypopituitarism [39]. As can be seen in figures 2 and 3, in most brain tumor patients, the pituitary gland received a dose between 40-60 Gy, which resulted in higher NTCP for these patients. For patients with nasopharyngeal carcinoma (figures 2 and 3), however, the mean dose of 36.09 Gy was lower than the suggested dose constraint and caused lower NTCPs for the pituitary gland.

Oinam *et al.* compared two radiobiological models, LKB and Niemierko. According to their findings, the LKB model estimated the same effects when using healthy tissue standards to calculate the NTCP, but the Niemierko model could not reproduce the same effects. When these two models were examined for clinical data, however, the LKB model had a different response than the Niemierko model. Compared to the current study, the Niemierko model was closer to the clinical data.

In another study performed on the prostate, the effects of healthy tissue on the rectum were calculated using the LKB model and compared with the multivariate logistic model. The findings and the AUC comparison for both models indicated that the logistic model could estimates more closely to clinical data. AUC for LKB and logistic models in said study was 0.6 and 0.75, respectively; in the current study, they were 0.826 and 0.902, respectively [40].

Tomatis *et al.* used an ANN to predict rectal complications in prostate patients, and the results were compared by the logistic regression method. In their study, 718 patients with a prescribed dose of 70-80 Gy were followed for at least 36 months. According to their results, AUC for the independent test set was 0.704 for ANN and 0.655 for LR; for cross-validation evaluation, it was 0.714 and 0.636 for ANN and LR, respectively. These results indicate that the ANN can predict rectal complications more accurately than LR [41].

Pudasaini *et al.* also used ANN to predict radiobiological markers in lung cancer. NTCP and TCP as ANN output, and planning target volume (PTV), treatment method, tumor site, prescribed dose, fraction number, maximum dose for tumor, and mean dose for organs at risk were selected as the ANN input. Moreover, 70% and 30% of the data were used for training and testing, respectively. The overall regression for predicting NTCP and TCP in ANN was 0.94. RMSE was 0.007 for training and 0.024 for testing. The results indicated that ANN can be planned to anticipate radiobiological parameters at a 5% error rate, which is showed by the regression value [42]. DD Cho *et al.* also used an ANN to predict complications in patients with head and neck cancer after external radiotherapy. In their study, 73 patients with advanced head and neck diseases were studied. Eleven input nodes and 22 hidden nodes were given to the neural network according to the available data. Fifty-one, 11, and 11 patients were used for training, validation, and testing, respectively. According to the results obtained in this study, ANN is an effective method for predicting complications after radiation therapy such as distant metastasis and other complications [43]. These results fit in perfectly with the current study.

Similarly, Bryce *et al.* investigated patient survival in head and neck squamous cell carcinoma (SCCHN) using ANN and LR models. According to their results, ANN more accurately predicted survival than LR [44]. In another study, ANN and SVM (support vector machines) were used to predict bladder and rectal complications in 321 patients with prostate cancer; the AUC was 0.7. According to the results, ANN showed greater sensitivity to SVM [45].

By calculating NTCP using two radiobiological models (LKB and log-logistic) and ANN and comparing the results with AUC, it was found that the ANN predictions were more accurate than those of two other radiobiological models and closer to the follow-up data.

To sum up, because NTCP is dependent on the dose received by the pituitary gland, in the current study, patients with brain tumors were more likely to

[DOI: 10.52547/ijrr.21.1.7]

have complications than patients in the nasopharyngeal carcinoma group. Considering the AIC test results, the log-logistic model estimated more closely to the follow-up data in both groups of patients. Predictive results with the ANN method developed in this study used error measurement criteria; however, based on the AUC results, the ANN produced closer predictions to the follow-up data compared to the LKB and log-logistic models. In association with other radiobiological models and higher patient populations, application of the ANN method is recommended.

ACKNOWLEDGMENTS

This study was financially supported by the Molecular Medicine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

Ethical approval: The study was approved and performed in accordance with the Tabriz University of Medical Sciences Ethics Committee (approval no: IR.TBZMED.VCR.REC.1397.126).

Conflict of interest: The authors declare that they have no competing interests.

Funding: This study was supported by the by the Molecular Medicine Research Center (grant no: 59621), Tabriz University of Medical Sciences, Tabriz, Iran.

Author contribution: SS: Performed the models and the simulations, drafted the manuscript; RF: Performed the data analysis; RM: Drafted the manuscript and designed the figures; REZ: Provided the experimental data; AM: Supervised the research, conceived the study and were in charge of overall direction and planning work**.** All authors read and approved the final manuscript.

REFERENCES

1. Alterio D, Marvaso G, Ferrari A, *et al.* (2019) Modern radiotherapy for head and neck cancer. *In Seminars in Oncology, **46**(3): 233-245*.
2. Ferlay J, Soerjomataram I, Dikshit R, *et al.*(2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer, **136**(5): E359-E86*.
3. Niemierko A and Goitein M (1991) Calculation of normal tissue complication probability and dose-volume histogram reduction schemes for tissues with a critical element architecture. *Radiat Oncol J, **20**(3): 166-76*.
4. Warkentin B, Stavrev P, Stavreva N, *et al.* (2004) A TCP-NTCP estimation module using DVHs and known radiobiological models and parameter sets. *J Appl Clin Med Phys, **5**(1): 50-63*.
5. Niemierko A and Goitein M (1993) Modeling of normal tissue response to radiation: the critical volume model. *Int J Radiat Oncol Biol Phys, **25**(1): 135-45*.
6. Mesbahi A, Rasouli N, Mohammadzadeh M, *et al.* (2019) Comparison of radiobiological models for radiation therapy plans of prostate cancer: Three-dimensional Conformal versus Intensity Modulated Radiation Therapy. *J Biomed Phys Eng, **9**(3): 267*.
7. Hamming-Vrieze O, Depauw N, Craft D, *et al.* (2019) Impact of setup and range uncertainties on TCP and NTCP following VMAT or IMPT of oropharyngeal cancer patients. *Phys Med Biol, **64**(9): 095001*.
8. Frometa-Castillo T, Pyakuryal A, Wals-Zurita A, *et al.* (2020) Proposals of models for new formulations of the current complication-free cure (P+) and uncomplicated tumor control probability (UTCP) concepts, and total normal tissue complication probability of late complications. *Int J Radiat Biol, **96**(7): 847-850*.
9. Ghasemi Jangjoo A, Nasiri B, Jafari-Koshki T, *et al.* (2020) Radiobiological modeling of acute esophagitis following radiotherapy of thorax and head-neck tumors: A comparison of lyman kutcher burman with equivalent uniform dose-based models. *Iranian J Med Phys, **17**(4): 225-34*.
10. Namdar AM, Mohammadzadeh M, Okutan M, *et al.* (2018) A review on the dosimetrical and radiobiological prediction of radiation-induced hypothyroidism in radiation therapy of head-and-neck cancer, breast cancer, and Hodgkin's lymphoma survivors. *Pol J Med Phys Eng, **24**(4): 137-48*.
11. De Marzi L, Feuvret L, Boulé T, *et al.* (2015) Use of gEUD for predicting ear and pituitary gland damage following proton and photon radiation therapy. *Br J Radiol, **88**(1048): 20140413*.
12. Lee T-F, Chao P-J, Wang H-Y, *et al.* (2012) Normal tissue complication probability model parameter estimation for xerostomia in head and neck cancer patients based on scintigraphy and quality of life assessments. *BMC cancer, **12**(1): 567*.
13. Luo R, Wu VW, He B, *et al.* (2018) Development of a normal tissue complication probability (NTCP) model for radiation-induced hypothyroidism in nasopharyngeal carcinoma patients. *BMC cancer, **18**(1): 1-8*.
14. Boon IS, Au Yong T, Boon CS (2018) Assessing the role of artificial intelligence (AI) in clinical oncology: utility of machine learning in radiotherapy target volume delineation. *Medicines, **5**(4): 131*.
15. Tu JV (1996) Advantages and disadvantages of using artificial neural networks versus logistic regression for predicting medical outcomes. *J Clin Epidemiol, **49**(11): 1225-31*.
16. Hosseini-Ashrafi M, Bagherebadian H, Yahaqi E (1999) Pre-optimization of radiotherapy treatment planning: an artificial neural network classification aided technique. *Phys Med Biol, **44**(6): 1513*.
17. Isaksson M, Jalden J, Murphy MJ (2005) On using an adaptive neural network to predict lung tumor motion during respiration for radiotherapy applications. *Med phys, **32**(12): 3801-9*.
18. Gulliford SL, Webb S, Rowbottom CG, *et al.* (2004) Use of artificial neural networks to predict biological outcomes for patients receiving radical radiotherapy of the prostate. *Radiat Oncol J, **71**(1): 3-12*.
19. Ochi T, Murase K, Fujii T, *et al.* (2002) Survival prediction using artificial neural networks in patients with uterine cervical cancer treated by radiation therapy alone. *Int J Clin Oncol, **7**(5): 0294-300*.
20. Mahdavi SR, Tavakol A, Sanei M, *et al.* (2019) Use of artificial neural network for pretreatment verification of intensity modulation radiation therapy fields. *The British Journal of Radiology, **92**(1102): 0190355*.
21. Pekic S, Miljic D, Popovic V (2018) Hypopituitarism following cranial radiotherapy. Endotext [Internet]: MDText. com, Inc.
22. Lamba N, Bussiere MR, Niemierko A, *et al.* (2019) Hypopituitarism After Cranial Irradiation for Meningiomas: A Single-Institution Experience. *Pract Radiat Oncol, **9**(3): e266-e73*.
23. Gebauer J, Mehta P, Fahlbusch FB, *et al.* (2020) Hypothalamic-Pituitary Axis Dysfunction after Whole Brain Radiotherapy–A Cohort Study. *Anticancer Res, **40**(10): 5787-92*.
24. Kyriakakis N, Lynch J, Orme SM, *et al.* (2016) Pituitary dysfunction following cranial radiotherapy for adult-onset nonpituitary brain tumours. *Clin Endocrinol, **84**(3): 372-9*.
25. Appelman-Dijkstra NM, Kokshoorn NE, Dekkers OM, *et al.* (2011) Pituitary dysfunction in adult patients after cranial radiotherapy: systematic review and meta-analysis. *Int J Clin Endocrinol Metab, **96**(8): 2330-40*.
26. Merchant TE, Rose SR, Bosley C, *et al.* (2011) Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. *J Med Oncol, **29**(36): 4776*.
27. Vatner RE, Niemierko A, Misra M, *et al.* (2018) Endocrine deficiency as a function of radiation dose to the hypothalamus and pituitary in pediatric and young adult patients with brain tumors. *J Med Oncol, **36**(28): 2854*.
28. Mohan R, Mageras G, Baldwin B, *et al.* (1992) Clinically relevant optimization of 3-D conformal treatments. *Med phys, **19**(4): 933-44*.
29. Niemierko A (1997) Reporting and analyzing dose distributions: a concept of equivalent uniform dose. *Med phys, **24**(1): 103-10*.
30. Niemierko A (1999) A generalized concept of equivalent uniform dose (EUD). *Med Phys, **26**(6): 1100*.
31. Sanchez-Nieto B and Nahum A (2000) BIOPLAN: software for the biological evaluation of radiotherapy treatment plans. Med Dosim;25(2):71-6.

[DOI: 10.52547/ijrr.21.1.7]

32. Vance A (2009) Data analysts captivated by R's power. New York Times, **6**(2009).
33. Abraham TH (2002) (Physio) logical circuits: The intellectual origins of the McCulloch–Pitts neural networks. *J Hist Behav Sci, **38** (1): 3-25*.
34. Kucuk N, Manohara S, Hanagodimath S, *et al.* (2013) Modeling of gamma ray energy-absorption buildup factors for thermoluminescent dosimetric materials using multilayer perceptron neural network: A comparative study. *Radiat Phys Chem, **86**: 10-22*.
35. Bryce TJ, Dewhirst MW, Floyd Jr CE, *et al.* (1998) Artificial neural network model of survival in patients treated with irradiation with and without concurrent chemotherapy for advanced carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys, **41**(2): 339-45*.
36.Darzy KH (2009) Radiation-induced hypopituitarism after cancer therapy: who, how and when to test. *Nat Clin Pract Endocrinol Metab, **5**(2): 88-99*.
37. Scoccianti S, Detti B, Gadda D, *et al.* (2015) Organs at risk in the brain and their dose-constraints in adults and in children: a radiation oncologist's guide for delineation in everyday practice. *Radiat Oncol J, **114**(2): 230-8*.
38. Pai HH, Thornton A, Katznelson L, *et al.* (2001) Hypothalamic/ pituitary function following high-dose conformal radiotherapy to the base of skull: demonstration of a dose–effect relationship using dose–volume histogram analysis. *Int J Radiat Oncol Biol Phys, **49**(4): 1079-92*.
39. Emami B, Lyman J, Brown A, *et al.* (1991) Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys, **21**(1): 109-22*.
40. D'Avino V, Palma G, Liuzzi R, *et al.* (2015) Prediction of gastrointestinal toxicity after external beam radiotherapy for localized prostate cancer. *Radiat Oncol J, **10**(1): 1-9*.
41. Tomatis S, Rancati T, Fiorino C, *et al.* (2012) Late rectal bleeding after 3D-CRT for prostate cancer: development of a neural-network-based predictive model. *Phys Med Biol, **57**(5): 1399*.
42. Pudasaini M, Leventouri T, Pella S, *et al.* (2021) Estimation of radiobiological indices in radiotherapy of lung cancer using an artificial neural network. Bulletin of the American Physical Society.
43. Cho DD, Wernicke AG, Nori D, *et al.* (2014) Predicting radiation therapy outcome for head and neck cancer patients using artificial neural network (ANN). *Int J Radiat Oncol Biol Phys, **90**(1): S852*.
44. Bryce TJ, Dewhirst MW, Floyd Jr CE, *et al.*(1998) Artificial neural network model of survival in patients treated with irradiation with and without concurrent chemotherapy for advanced carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys, **41**(2): 339-45*.
45. Pella A, Cambria R, Riboldi M, *et al.* (2011) Use of machine learning methods for prediction of acute toxicity in organs at risk following prostate radiotherapy. *Med phys, **38**(6Part1): 2859-67*.

[DOI: 10.52547/ijrr.21.1.7]