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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

Mostafa Alizade-Harakiyan[1,6], Amir Ghasemi Jangjoo[2,*], Behnam Nesiri Motlagh[2,3], Tohid Jafari-Koshki[4], Murat Okutan[5], Asghar Mesbahi[1,6,7]

1. Molecular Medicine Research Center, Institute of Biomedicine, Tabriz University of Medical Sciences, Tabriz, Iran
2. Department of Radiology and Radiotherapy, School of Medicine, Tabriz University of Medical Science, Tabriz, Iran
3. Department of Radiation Oncology, Tabriz Vali-Asr Hospital, Tabriz, Iran
4. Department of Statistics and Epidemiology, Faculty of Health, Tabriz University of Medical Sciences, Tabriz, Iran
5. Department of Medical Physics, Radiation Oncology Institute, Istanbul University, Istanbul, Turkey
6. Department of Medical Physics, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
7. Medical Radiation Sciences Research Team, Tabriz University of Medical Sciences, Tabriz, Iran

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ABSTRACT

Introduction: The current study aimed to compare the performance of radiobiological models in predicting acute esophagitis (AE) complications after three-dimensional conformal radiation therapy (3D-CRT).

Material and Methods: Out of a total of 100 patients, 50 patients with concurrent chemotherapy and 50 patients without such therapy were treated with different total doses and a daily dose range of 1.8-2.4 Gy on the basis of 5 days a week for 3 months. Predictions of AE were based on Lyman–Kutcher–Burman (LKB) and equivalent uniform dose (EUD)-based radiobiological models. Consequently, 3 months of follow-up were performed to monitor the complication incidence among the studied patients. Receiver operating characteristic (ROC) and univariable logistic regression analyses were carried out to determine the effect of mean dose, volume percentage, and weight loss percentage on the probability of AE grade ≥ 2.

Results: The EUD-based model showed a better concordance with the clinical data for all patients (area under the curve [AUC]=0.919) and the concurrent chemoradiotherapy (CCRT) group (AUC=0.986). For the radiation therapy group, the LKB model had a better performance than the EUD-based model (AUC=0.921). Grade ≥ 2 esophagitis occurred 37.94±4.0 and 68.39±7.1 days after the initiation of radiation therapy in the chemoradiation and radiation therapy groups, respectively.

Conclusion: The EUD-based model showed a higher agreement with the follow-up data. The incidence time of grade ≥ 2 AE in the CCRT was approximately two times shorter than that in the non-CCRT group.

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Introduction

Radiation therapy plays an important role in the treatment of unresectable solid tumors [1, 2]. In most of cases, a combination of radiation therapy and chemotherapy is used to improve the outcome of the treatment [3]. The esophagus is one of the organs located along the thorax region. This organ can be irradiated as a normal tissue when other tumors, such as lung, nasopharynx, Hodgkin lymphoma, oral cavity, and spinal metastasis, are under treatment by three-dimensional (3D) conformal therapy or other new modalities (e.g., intensity-modulated radiation therapy [IMRT] and stereotactic treatment of thorax region).

Treatment planning software packages are equipped with precise and fast algorithms to provide dose distribution inside the treatment volumes, using dose distribution curves and dose-volume histograms. In recent years, other quantities have been proposed to provide more biological predictions, regarding the effectiveness and complication of the treatments. These two quantities are tumor control probability (TCP) and normal tissue complication probability

*Corresponding Author: Tel: : +98 9144114137; Fax: +9804133364660; E-mail: amirgasemijangjoo@yahoo.com

(NTCP). The indices are calculated based on the radiobiological parameters of tumor or normal tissue and a proper mathematical radiobiological model. These two quantities may help the selection of rival plans and management of acute complications after radiation therapy [4-6].

Radiobiological models exploit the dosimetric information of a treatment plan, including dose-volume histogram (DVH), total dose, dose per fraction, and radiosensitivity parameter, in order to calculate the incidence probability of a given endpoint after radiation therapy. The Lyman-Kutcher-Burman (LKB) and equivalent uniform dose (EUD) models have been widely used among the proposed ones [7-9].

The average length of the esophagus is 25 cm; accordingly, it may be affected during the treatment of the tumors located in the mediastinum, lung, and neck, as well as during the therapy of spinal metastasis. Depending on the received dose and treated volume of the esophagus, acute and chronic esophagitis can occur within a time interval of ≤ 3 and 6 months after radiation therapy, respectively [10,11].

To the best of our knowledge, acute esophagitis (AE) has been predicted by radiobiological models for lung tumors. This condition has not been studied extensively during the tumor treatment of other thoracic or neck regions [12-14]. In a follow-up study performed by Gomez et al., AE was studied after the radiation therapy of lung tumors with IMRT, 3D conformal therapy, and proton therapy. The AE (grade ≥3) was reported to have the incidence rates of 28%, 8%, and 6% for IMRT, 3D conformal therapy, and proton therapy, respectively [15].

In this regard, Alevronta et al. performed a radiobiological modeling study on chronic esophagitis after the radiation therapy of head and neck tumors; however, they did not study AE [16]. Moreover, in a study by Zhu et al., AE was predicted by the LKB model after the radiation therapy of lung cancers, and the results were compared with the clinical data. Their results indicated a higher complication in concurrent chemotherapy group, relative to the group only subjected to radiotherapy [17]. Chapet et al. proposed new parameters of *n*, *m*, and median toxic dose (TD_{50}) by fitting follow-up data for AE grade of ≥ 2 with the LKB model. They used the proposed parameters for the prediction of AE in patients with non-small cell lung cancers [18].

According to a study (2010) addressing the quantitative analysis of normal tissue effects in the clinic (QUANTEC), the incidence of AE V_{35} of < 50% and V_{50} of < 40% was indicated as a dose-volume threshold for the incidence of AE with a grade of ≥ 2. Consideration of the recommended dose-volume limits can significantly lower the complication and increase the quality of the treatment [19]. On the other hand, the incidence time of AE after radiation therapy has been investigated in a few studies [20]. However, conducting more studies on the onset of AE in different modalities, and the effect of chemotherapy on the severity and incidence of AE will provide invaluable information in the management of esophagus complications after radiation therapy.

To the best of our knowledge, there is no study applying EUD-based model for the estimation of AE and comparing the obtained results with the LKB model. Moreover, there were two newly proposed sets of parameters to estimate AE by LKB model, which needed to be evaluated by other investigations. Considering the above-mentioned reasons, the objective of the current study was to assess the incidence and associated factors of AE, following the treatment of tumors of Hodgkin lymphoma, metastatic spinal cord, nasopharynx, oral cavity, larynx, and lung. Moreover, this research aimed to compare the ability of two mathematical models in the prediction of grade ≥ 2 AE incidence.

Materials and Methods

This prospective study was performed in Shahid Madani and Valiasr Hospitals, Tabriz, Iran, for a period of one year (January 2017- the end of December 2017). It should be mentioned here that the project was approved by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (code No. 59507).

The present research was conducted on a total of 100 patients with lung, nasopharynx, larynx, oral cavity, and Hodgkin lymphoma cancers or spinal metastasis referring to the aforementioned hospital. All patients suffering from radiation-induced esophagitis were entered into the study. The exclusion criteria were previous radiation, chemotherapy, or active reflux. Before the treatment, the normal status of the esophagus was confirmed through objective observation and patient questioning.

In this study, 80 patients were male, and the rest were female. The median age of the patients was 60 years (range: 20-70 years), and 45 patients were smokers. For 85% of the patients, the Karnofsky performance status (KPS) was 90, and 15% of them had a KPS lower than 90. Table 1 presents the histology and staging of tumors that are tabulated according to the American Joint Committee on Cancer criteria.

In this research, the patients were divided into two groups. Group one (n=50) received concurrent chemotherapy, while group two (n=50) was subjected to only radiation or had a chemotherapy treatment course before radiation therapy commencement. The purpose was to study the effect of concurrent chemotherapy on the incidence of AE. Table 2 presents data related to chemotherapy dosage and regimen.

Table 1. Patients' characteristics and histology and stage of patient tumors

Region of Tumors	Histology	Concurrent chemoradiotherapy cases	Sequential chemoradiotherapy and no chemotherapy cases	AJCC Staging	Patient
Spinal	Metastatic	-	10	S 4	10
nasopharynx	SCC	12	4	S 3	16
lymphoma	Hodgkin	-	15	S 1	6
				S 2	8
				S 3	1
Larynx	SCC	11	5	$S\ 4_a$	4
				S 3	2
				S 2	10
Oral cavity	SCC	7	3	S 2	6
				S 3	4
Lung	NSCLC (21 patients)+ +SCLC (12 patients)	20	13	$S\ 4_a$	5
				$S\ 4_b$	12
				$S\ 3_b$	16

AJCC: American Joint Committee on Cancer, S: Stage, SCC: squamous cell carcinoma, NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer

Table 2. Chemotherapy regimens based on dosage and days injected to patients

Types of Chemotherapy	Chemotherapeutic agent	Patient	Utilization (mg/m^2)	Days	Total Patient
Non					35
-concurrent	CIS	30	100	1,22,43	50
	CIS+NAV	14	25 + 25	(1,2,3) +(1,8)	
	CIS+ETO	6	25 + 100	1,2,3	
Sequential	ABVD	15	25 + 10 + 6 + 375	1,15	15
					100

CIS: Cisplatin, NAV: Navelbin, ETO: Etoposide, ABVD: Adriamycin, Bleomycin, Vinblastine, Dacarbazine

Table 3. Radiation therapy oncology group criteria for the classification of acute esophagitis

Score	Description
0	No changes
1	Mild dysphagia or odynophagia; may require topical anesthetic or nonnarcotic analgesics; may require soft diet
2	Moderate dysphagia or odynophagia; may require narcotic analgesics; may require puree or liquid diet
3	Severe dysphagia or odynophagia with dehydration or weight loss (>15% from baseline) requiring nasogastric tube, intravenous fluids, or hyper alimentation
4	Complete obstruction, ulceration, or perforation, fistula
5	Death

The radiation therapy was performed, using a Siemens Oncor linear accelerator (Seimens, Germany) by 6- and 18- MV photon beams, one session each day and 5 days a week. The Linac was equipped with 40 pairs of multi-leaf collimators. The planning was performed on X-ray computed tomography images with the slice thicknesses of 3 and 5 mm, acquired in a spiral mode with a pitch No. 1.2. In this research, the treatment planning system was TiGRT (Linatech, Sunnyvale, CA, USA). For all patients, the esophagus external wall was countered from the cricoid cartilage to the gastroesophageal junction.

The mean doses administered to the planning target volume of the tumors of Hodgkin's lymphoma, lung, spinal metastasis, nasopharynx, larynx, and oral cavity were 4392.99±725.2, 5333.52±1288.11, 4422.36±917.05, 5580.67±1002.36, 5522.84±1544.58, and 5048.29±990.33 cGy, respectively. The maximum, minimum, and mean doses that the esophagus received were 5317.64±1293.38, 205.17±669.35, and 2227.44±1226.35 cGy, respectively.

The esophageal status of the patients was checked by a planned questionnaire. In addition, the patients were physically examined during the treatment by two radiation oncologists 2 times a week up to 3 months after the initiation of the treatment. The time of AE commencement was recorded, and the complication grading was performed according to Table 3 and radiation therapy oncology group criteria [21].

Radiobiological models

In order to calculate the NTCP of esophagitis by the LKB model, the BioSuite software (version 12) was used [22]. The equations used in this software are as follows:

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

$$t = \frac{EUD - \mathrm{TD50}}{\mathrm{mTD50}} \quad (2)$$

$$EUD = \left(\sum_i \mathrm{Vi} * (\mathrm{EQD2i})^{1/n}\right)^n \quad (3)$$

$$\mathrm{EQD2i} = \mathrm{Di} * \frac{\left(\frac{\alpha}{\beta}\right)+\mathrm{d}}{\left(\frac{\alpha}{\beta}\right)+2} \quad (4)$$

Where TD_{50} indicates the dose which causes 50% of complications in the studied organs at risk. The parameter *'m'* shows the slope of the dose-response curve in a point where 50% of complications are observed, and *n* is the indicator of volume effect in dose-response curves. In addition, D_i and V_i are the doses and volumes in each voxel, which are obtained from dose-volume histograms. In this equation, the *d* shows the dose per faction, and α/β ratio is defined as the ratio of intrinsic radiosensitivity to repair capability, which was considered 10 according to a study performed by Wijsman et al. [13].

Following a study carried out by Chapet et al. [18], NTCP for the esophagus was calculated for both groups based on a volume effect of 0.44, slope of 0.32, and TD_{50} of 51 Gy. Additionally, the parameters proposed by Zhu et al. were used separately for the chemoradiation (i.e., Group 1; n=0.29, m=0.15, and TD_{50}=46 Gy) and radiation therapy groups (i.e., Group 2; n=0.09, m=0.42, and TD_{50}=36 Gy) [17].

For NTCP calculation using the EUD-based methods, a MATLAB-based file written by Gay et al. was used [23]. The equations used in this execution file are as follows:

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

$$EUD = \left(\sum_i \mathrm{Vi} * (\mathrm{EQD2i})^a\right)^{\frac{1}{a}} \quad (6)$$

$$\mathrm{EQD2i} = \mathrm{Di} * \frac{\left(\frac{\alpha}{\beta}\right)+\mathrm{d}}{\left(\frac{\alpha}{\beta}\right)+2} \quad (7)$$

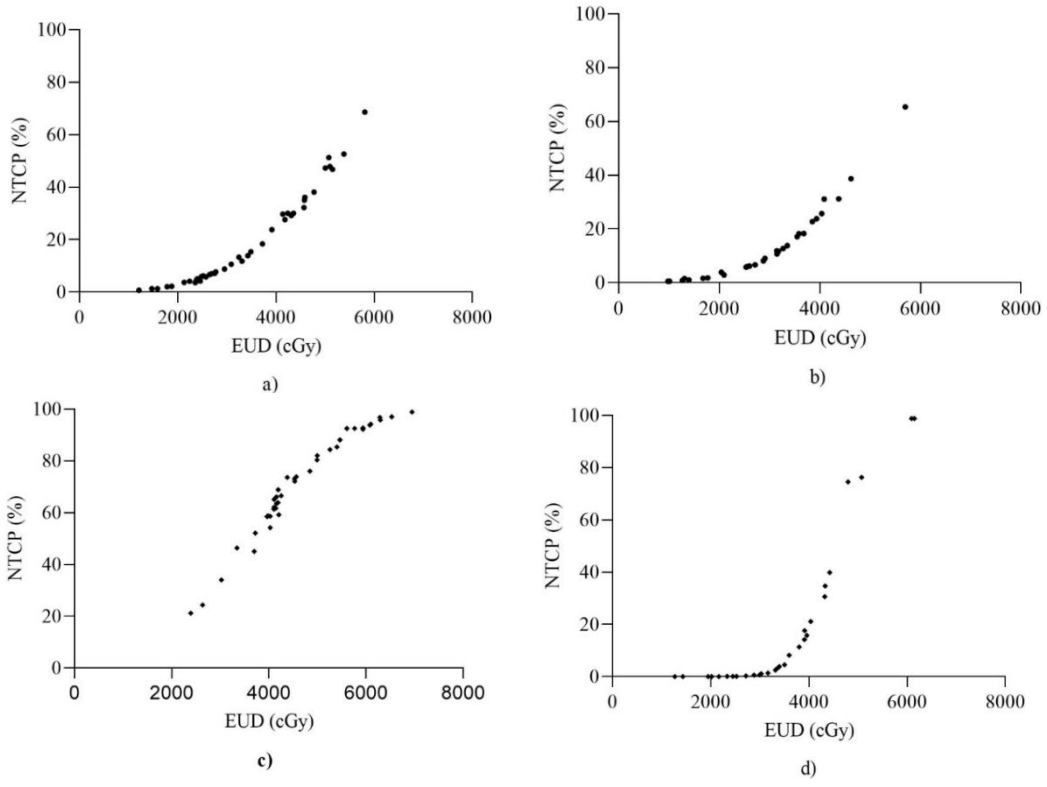
Where *'γ_{50}'* indicates the slope of the dose-response curve, and *'a'* denotes the volume effect.

The parameters proposed by Gay and Niemieriko (TD_{50}=68Gy, γ_{50}=3, and a=8) were used [23]. Before the calculation of NTCP, the delivered doses were changed to equivalent 2 Gy per session, using linear quadratic method (eq.$EQD2_i$) for all patients.

Statistical analysis was performed using the SPSS software (version 23). Moreover, the receiver operating characteristic (ROC) analysis was used to compare the radiobiological models with the follow-up results. The obtained results were considered in a binary format. It means that the incidence of esophagitis with a grade of ≥ 2 was assigned a value of 1, while grade 1 esophagitis or lack of esophagitis were given a value of 0 in the ROC analysis. The relationship between volumes of V_5-V_{60}, percentage of patient weight loss after treatment, and mean esophageal dose with follow-up of grade ≥ 2 AE were evaluated, using logistic regression. The time of AE occurrence was also analyzed using the Cox proportional hazards regression.

Results

Among 100 patients in the study, 40, 38, and 22 patients showed AE grades 1, 2, and 3, respectively. However, there was no case with AE grades 0, 4, or 5. Figure 1 depicts the results of grade ≥ 2 AE prediction in terms of the EUD of the esophagus, using the LKB model and EUD-based model. For the LKB model, the parameters proposed by Zhu et al. and Chapet et al. were used, respectively. For the EUD-based model, the parameters recommended by the model developer were used. Group 1 consisted of concurrent chemoradiotherapy (CCRT) patients and Group 2 was radiotherapy only group.



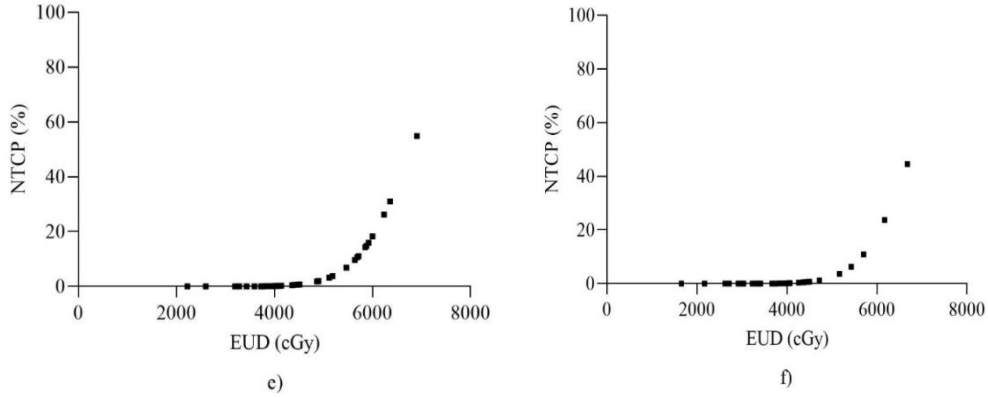


Figure 1: Normal tissue complication probability based on equivalent uniform dose curves for: a) Lyman-Kutcher-Burman model using Chapet et al. parameters for group 1, b) Lyman-Kutcher-Burman model using Chapet et al. parameters for group 2, c) Lyman-Kutcher-Burman model using Zhu et al. parameters for group 1, d) Lyman-Kutcher-Burman model using Zhu et al. parameters for group 2, e) equivalent uniform dose-based model using Niemieriko parameters for group 1, and f) equivalent uniform dose-based model using Niemieriko parameters for group 2

Table 4. Normal tissue complication probability and equivalent uniform dose for acute esophagitis grade ≥ 2 described (mean±SD)

Cases	EUD-based parameters		LKB With CHAPET et al. parameters		LKB With ZHU et al. parameters	
	NTCP	EUD (cGy)	NTCP	EUD (cGy)	NTCP	EUD (cGy)
Concurrent chemo radiotherapy group						
	5.10±10.14	4428.64±1110.82	18.10±17.49	3277.67±1227.38	70.00±20.84	4640.56±1091.95
Sequential chemo radiotherapy and No chemotherapy group						
	2.95±9.38	3861.68±1114.45	13.14±14.27	2886.46±1129.63	13.41±24.24	3248.27±1089.61
Hodgkin Lymphoma						
NCCC	2.62±6.21	4250.07±886.13	11.85±6.99	3094.67±495.60	10.72±18.60	3493.47±556.41
Metastatic Spinal Cord						
NCCC	0.08±0.09	3301.10±917.25	12.31±10.03	2872.62±1119.23	7.08±9.72	3033.96±1020.87
Nasopharynx						
TC	0.91±2.32	3326.13±1069.89	3.82±4.26	1954.15±773.94	40.34±31.44	3360.56±1332.64
CCC	1.21±2.64	484.17±449.25	4.84±4.49	2209.18±719.25	53.78±23.65	3915.02±1027.24
NCCC	0.003±0.003	75±28.87	0.75±0.29	1189.05±239.54	0	1697.20±302.88
Oral Cavity						
TC	1.90±5.75	3821.70±877.07	7.04±7.90	2536.76±652.45	47.60±34.49	3831.55±1170.51
CCC	2.71±6.86	881.43±902.60	8.81±9.03	2726.39±706.19	67.96±13.15	4423.81±831.26
NCCC	0.005±0	290±0	2.9±0	2094.3±0	0.1±0	2449.6±0
Larynx						
TC	0.52±0.95	3959.88±644.84	7.85±7.50	2523.86±830.81	46.98±29.90	3779.02±998.44
CCC	0.36±0.56	1375.64±1411.25	7.31±6.24	2566.15±677.65	63.09±17.41	4128.95±768.18
NCCC	0.86±1.54	1569±1403.27	9.04±10.54	2430.82±1193.58	11.52±17.59	3009.16±1088.78
Lung						
TC	9.72±14.67	4938.21±1119.26	30.42±18.39	4122.56±1086.93	62.62±37.01	4822.75±1306.35
CCC	10.87±13.66	3610.25±1459.04	35.23±14.55	4503.06±692.59	84.26±13.14	5433.13±879.09
NCCC	7.94±16.52	2301.54±2165.37	23.02±21.65	3537.18±1333.59	29.32±37.4	3883.72±1323.25

TC = Total cases; CCC= concurrent chemotherapy cases; NCCC= Non concurrent chemotherapy cases; NTCP= normal tissue complication probability; EUD= equivalent uniform dose; LKB= Lyman-Kutcher-Burman; SD: =Standard Deviation

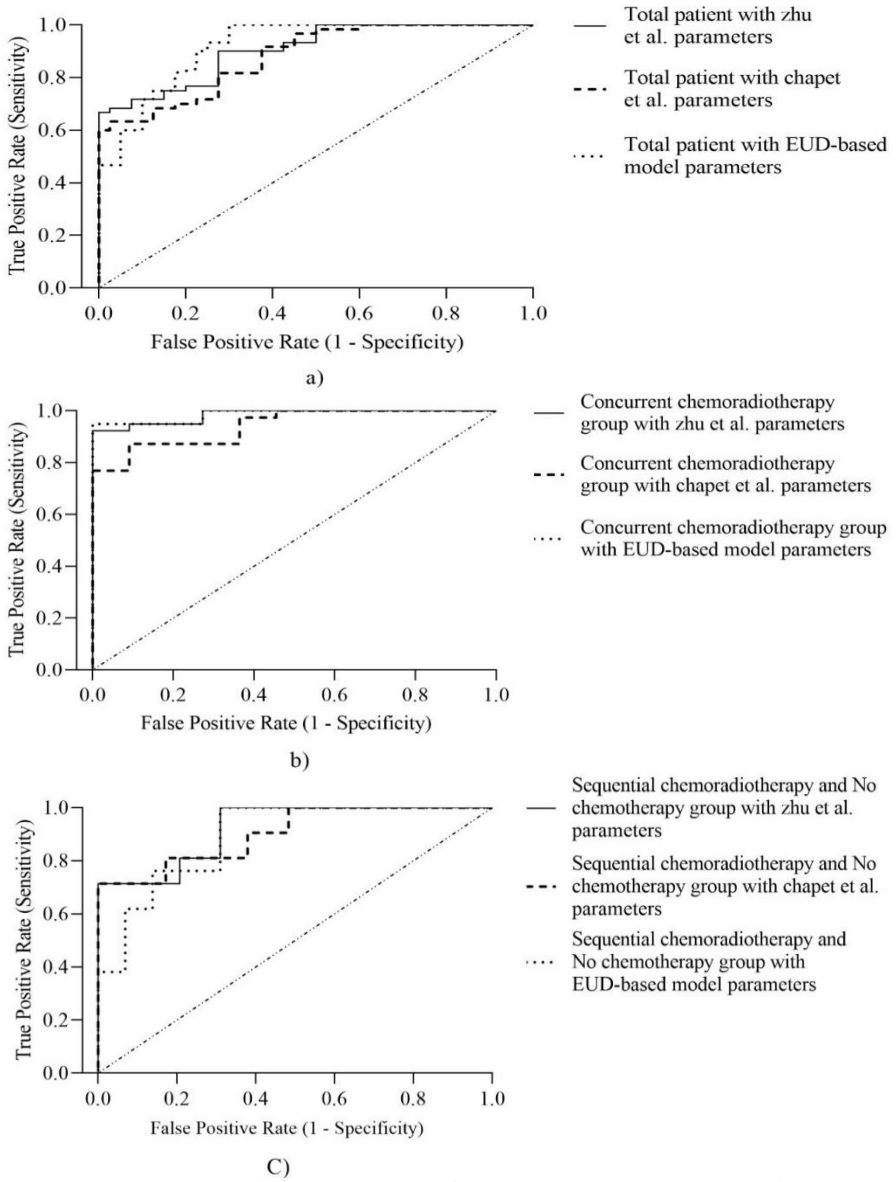


Figure 2: Receiver operating characteristics curves for the compatibility of radiobiological models with patient follow-up results; a) all patients**.** b) concurrent chemoradiotherapy group, c) sequential chemoradiotherapy and only radiotherapy group

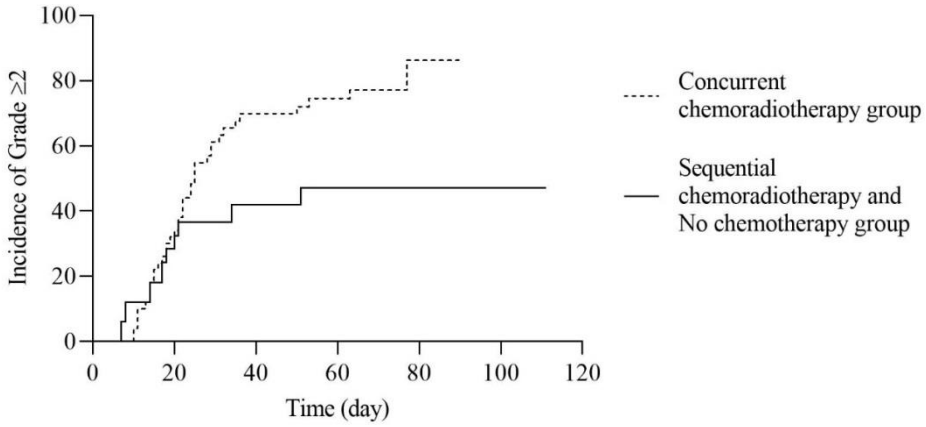


Figure 3: Kaplan-Meier curve of acute esophagitis grade ≥ 2 based on the time of treatment onset for sequential chemoradiotherapy, no chemotherapy, and concurrent chemoradiotherapy groups

Table 5. Results of receiver operating characteristics curves regarding the correlation of radiobiological models with patient follow-up data

Patients	Test Result Variables	AUC	SE
Total Patients			
	NTCP- EUD-based model	0.919	0.027
	NTCP- LKB-Chapet et al. model	0.880	0.032
	NTCP-LKB-Zhu et al. model	0.905	0.028
Concurrent chemoradiotherapy group			
	NTCP-EUD-based model	0.986	0.013
	NTCP-LKB-Chapet et al. model	0.942	0.032
	NTCP-LKB-Zhu et al. model	0.984	0.014
Sequential chemoradiotherapy and no chemotherapy group			
	NTCP- EUD-based model	0.890	0.044
	NTCP-LKB-Chapet et al. model	0.901	0.044
	NTCP-LKB-Zhu et al. model	0.921	0.037

AUC: area under curve, SE: Standard error, ROC: receiver operating characteristics

Table 6. Univariate logistic regression and receiver operating characteristics analysis for grade ≥2 acute esophagitis

Variable	Total patients			Concurrent chemoradiotherapy group			Sequential chemoradiotherapy and no chemotherapy group		
	OR(95%CI OR)	p	AUC	OR(95%CI OR)	p	AUC	OR(95%CI OR)	p	AUC
WLP	1.289 (1.120-1.480)	<0.001	.709	1.770 (1.201-2.600)	.003	.89	1.060 (.870-1.290)	.520	.52
V5	1.022 (1.003-1.040)	.022	.644	1.010 (.980-1.040)	.340	.59	1.040 (1.010-1.070)	.007	.75
V10	1.030 (1.011-1.050)	.002	.698	1.030 (1.000-1.070)	.052	.71	1.040 (1.010-1.070)	.005	.78
V15	1.035 (1.015-1.056)	.001	.721	1.060 (1.010-1.110)	.016	.76	1.040 (1.010-1.070)	.004	.77
V20	1.039 (1.018-1.060)	<0.001	.746	1.090 (1.020-1.170)	.005	.84	1.040 (1.010-1.070)	.005	.78
V25	1.040 (1.020-1.062)	<0.001	.758	1.100 (1.020-1.180)	.005	.85	1.040 (1.010-1.070)	.004	.80
V30	1.045 (1.023-1.067)	<0.001	.788	1.100 (1.020-1.180)	.006	.85	1.040 (1.010-1.070)	.002	.82
V35	1.101 (1.060-1.143)	<0.001	.890	1.120 (1.030-1.220)	.006	.86	1.180 (1.060-1.320)	.003	.94
V40	1.108 (1.067-1.151)	<0.001	.910	1.210 (1.060-1.390)	.006	.95	1.110 (1.050-1.180)	<.001	.92
V45	1.094 (1.052-1.138)	<0.001	.848	1.310 (1.100-1.570)	.003	.95	1.060 (1.020-1.100)	.002	.75
V50	1.109 (1.031-1.109)	.006	.756	2.230 (0.660-7.510)	.190	.77	1.080 (1.006-1.150)	.030	.73
V55	1.262 (0.951-1.676)	.108	.703	-	-	-	1.140 (0.920-1.410)	.210	.61
V60	1.881 (0.948-3.374)	.071	.709	-	-	-	1.810 (0.800-4.110)	.150	.65
Mean dose	1.142 (1.081-1.208)	<0.001	.826	1.002 (1.000-1.004)	.017	.86	1.002 (1.001-1.003)	.001	.91

OR: odds ratio, CI: confidence interval, Vx: volume of the esophagus receiving x dose, WLP: weight loss percentage, AUC: area under curve

Table 4 tabulates the calculated NTCPs and EUDs for the AE grade of ≥ 2 for all patients and categories. It can be seen that except for larynx tumors, spinal metastasis, and Hodgkin lymphomas, all patients with CCRT experienced AE more frequently. According to both models, most of AE cases were found in patients treated for lung tumors. For larynx tumors, using the parameters of Chapet et al., the NTCP of the non-concurrent chemotherapy cases (NCCC) was higher than that of the concurrent chemotherapy cases (CCC). Patients with spinal metastasis and Hodgkin's lymphomas treated by sequential chemoradiation therapy (SCRT) and non-chemotherapy were predicted to have the highest frequency of AE incidence, applying the model LKB with the parameters adopted by Chapet et al. For patients with nasopharynx and oral cavity tumors in the CCC, the LKB model showed the highest probability of AE using the parameters proposed by Zhu et al. However, in the NCCC, the LKB model with the study parameters of Chapet et al. showed the highest AE probability. For patients with lung and larynx tumors in both CCC and NCCC, the highest probability was indicated by the LKB model using the study parameters of Zhu et al.

Results of ROC curves analysis are presented in Figure 2 and Table 5. The EUD-based model had a higher predicting efficiency for all patients with the highest predictive value, including an area under the curve (AUC) of 0.919±0.027, compared to other models. For the chemoradiotherapy group, the EUD-based model showed a higher agreement with clinical data with an AUC of 0.986±0.013. Utilizing the parameters used by Zhu et al. for the LKB model, AUC was 0.92±0.037.

Results of univariate logistic regression are illustrated in Table 6, where the highest predictive value was seen for V_{40} for all patients. For Group 1, the highest score was seen for V_{45}, while for Group 2, V_{35} showed a higher predictive value. The overall incidence time of grade ≥ 2 AE was 52.24±4.58 days for all patients. In addition, this value was obtained as 37.92±4.07 and 68.39±7.08 days for the CCRT and non-CCRT groups, respectively. Kaplan-Meier curve for the incidence of grade ≥ 2 AE is shown in Figure 3. The incidence of AE ≥ 2 in the CCRT group was

significantly higher than in the radiochemotherapy group (HR=1.92; 95% CI: 1.12-3.27; P=0.016).

Discussion

The aim of our study was to select an optimal mathematical model according to the clinical datasets. Moreover, the factors affecting the occurrence of AE were evaluated through univariate logistic regression and ROC curve. In the present research, the EUD-based model was selected as the optimal model for predicting the AE grade of ≥ 2 for total patients, according to the statistical results. Based on the results of the survival analysis, the AE grade of ≥ 2 occurred significantly faster (about two times) in the CCRT group than in the radiotherapy only group. Considering all calculated NTCPs by two models, it was found that the EUD-based model estimations were significantly lower than those of the two LKB models. In addition, the LKB estimations performed based on Zhu et al. parameters showed remarkably higher NTCPs for all cases.

According to the data of the mean value of EUDs and NTCPs for groups 1 and 2 (Figure 1 and Table 4), with the increase in EUD, the probability of AE grade ≥ 2 increased for all models, except for larynx cases. However, it should be noticed that for very close values of EUDs, two models of EUD-based and LKB-Zhu et al. presented a significant difference in NTCP values for both groups. Based on Table 4, among the treatments of various tumors, the treatment of lung tumors was most likely to indicate the AE grade of ≥ 2, which justified recent studies in this regard [17, 18].

Our methodology was similar to the those of the studies by Zhu et al., Chapet et al., and Gay et al. [17, 18, 23], who studied the AE grade of ≥ 2 following 3D-CRT. Thus, the parameters of the mentioned studies were adopted in our research. Consequently, our results showed that LKB and EUD-based models resulted in very different estimations for the same DVH of patients, when the used parameters were taken from different studies, especially for the radiochemotherapy group. It should be reminded here that the above-mentioned studies proposed different model parameters based on their own patients' populations and clinical conditions; consequently, they reported various parameters.

If our NTCP estimations were compared with the results obtained by Chapet et al., Zhu et al., and Gay et al., there would be a significant discrepancy between our results and their reported data. These differences can be attributed to different patients' groups. In the current research, a wide spectrum of patients was considered, including nasopharynx and larynx, the aforementioned studies only worked on patients treated for lung tumors, and their proposed parameters were based on their patient dataset.

A part of the observed differences in the calculation of EUD and NTCP estimations in our data can be due to the EUD calculation method. As it can be seen in Table 4, although the same DVHs were used for the calculation of EUD in all models, the resultant EUDs were not the same. It was for the reason that three different values of *'n'*, which indicates volume effect, have been used by three models. Another reason for the differences in calculated NTCP originates from the dose-response curve slope parameters and TD_{50}.

According to Figure 2 and Table 5, the EUD-based model showed the highest correlation with clinical results for all patients, as well as for those in the CCRT group. However, the LKB model with the parameters of Zhu et al. indicated the highest correlation with the follow-up results just in the SCRT and only radiotherapy groups. To the best of our knowledge, no study has been conducted on the prediction of AE and its correlation with LKB and EUD-based models. However, there are a few studies on the modeling of AE in the literature. For instance, in a similar study by Zehentmayr et al., it was reported that for AE due to the treatment of non-small cell lung cancer (NSCLC), SCRT, and Lyman-MED model had the highest correlation with clinical results following accelerated radiotherapy [24].

Additionally, Huang et al. modeled the probability of acute esophageal complications, using multivariate regression logistics. They reported a correlation between the modeling results and clinical outcomes (AUC=0.83) [25]. In other studies carried out by Alevronta et al. and Mavroidis et al., the stricture of the esophagus was investigated after the treatment of head and neck tumors using the relative seriality model and estimation of its radiobiological parameters [16, 26]. Alevronta et al. proposed new parameters for the relative seriality model; however, they were not able to show a higher volume dependence for all the studied patients, except for a group of patients treated within 2001-2005. On the other hand, Mavroidis et al., working on the 5-cm proximal part of esophagus, found a strong volume dependence (i.e., low relative seriality) in the studied population (AUC=0.84).

Based on Table 6 showing the results of ROC and univariate logistic regression analyses, variables V_{50}-V_{60}, V_5-V_{10}/V_{50}-V_{60}, and weight loss percentage plus V_{50}-V_{60} were not statistically significant for all patients, group 1, and group 2, respectively. Moreover, V_{40} (AUC=0.91), V_{45} (AUC=0.95; P=0.003), and V_{35} (AUC=0.94) were the most predictive variables for AE grade ≥ 2 for all patients, group 1, and group 2, respectively. Our results regarding volumes were comparable with those reported by Belderbos et al., who concluded that for patients with concurrent and non-concurrent chemoradiation therapy, V_{35} was the best predictor of AE grade ≥ 2 [27]. However, according to the studies performed by Caglar et al. and Kim et al., who examined AE grade ≥ 3 following the CCRT of lung tumors, V_{55} and V_{60} were identified as the best predictors of esophagitis [28, 29].

It can be seen that our study was in agreement with the studies carried out by Belderbos et al.; however, it is slightly different from that of Caglar et al. The reason for the observed discrepancy is that in these studies, lung tumor treatment-induced AE was investigated. If

the treatment of lung tumors was compared with that of other tumor types, a higher percentage of the esophagus would be irradiated for lung cancer treatments. In our study, the volumes of esophagus, which received a noticeable absorbed dose during the treatment of nasopharynx, larynx, and oral cavity, were smaller compared to those of lung cases.

In a survival analysis addressing the incidence of esophagitis, the radiochemotherapy group was reported to have a significantly shorter time. However, our approach and results were different from those adopted by Wu et al. They investigated the incidence of AE grade ≥ 2 due to the treatment of lung tumors with stereotactic body radiotherapy, using survival analysis. In their study, the incidence of AE grade ≥ 2 with respect to time was based on the maximum dose received by the esophagus, and the effect of chemotherapy was not considered [20].

The limitation of our study was the lack of endoscopy results for all patients, which influenced the accuracy of our follow-up data. Moreover, the number of patients was limited for each type of cancer, which could be optimized by increasing the number of all patients. Therefore, future studies are recommended to adopt a higher number of patients and more accurate clinical data based on endoscopy.

Conclusion

Our study revealed that the EUD-based model had the highest level of consistency with the clinical follow-up data in predicting AE grade ≥ 2 for all patients and group 1. Nevertheless, the LKB model had the highest correlation with clinical outcomes for the radiotherapy only group. Tumor treatment using CCRT caused AE grade ≥ 2 with higher intensity and shorter incidence time than SCRT and only radiotherapy approaches.

It can be concluded that the prediction of AE by different models results in diverse scores for NTCP values. Regarding this, it is recommended to apply the EUD-based model for the estimation of AE. However, the authors think that more clinical follow-ups, model purification, and optimization are needed for the practical usage of EUD-based model.

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