Chapter 3

Development of an Indigenous Radiobiological Model Based TCP and NTCP Estimation Software for Routine Plan Evaluation in Clinics

Chapter-3 discussed the process of development of software/program used to calculate biological indices TCP and NTCP for biological model based plan evaluation. In addition, cross validation of output of developed software with Bio-suite software also performed. In radiotherapy, there is ongoing practice of plan evaluation is based on dose volume histogram (DVH). DVH is a two dimensional representation of three dimensional dose distribution. However, design of treatment plan outcome based on biological objective functions has the potential to improve clinical outcomes. The biological objective functions are usually expressed in the form of tumour control probability (TCP) & normal tissue complication probability (NTCP). To obtain more reliable outcome, it require the knowledge of parameter values of TCP/NTCP models.

1 Background

There are sufficient number of radiobiological (RB) models exists in literature and most of them failed to get recognition because lack of reliability and clinical validation of models for accurate TCP/NTCP prediction. Therefore, most of researchers in their study always take into account multiple models to get output in terms of TCP/NTCP. There are various studies which compared multiple models and showed limitations and benefits over each other.(Oinam *et al.* 2011) (Adamus-Górka *et al.* 2011) (Chang *et al.* 2016) (Seppenwoolde *et al.* 2003) Uncertainties in parameter estimation while using particular RB model in clinical practice had applied brake on transition of dose based treatment planning (DVH) to biological based treatment planning. Still some planning system like Eclipse, Pinnacle and Raystation provided option of biological based treatment plan optimization & evaluation with warning of precaution while applying results in actual clinical practice.(Allen Li *et al.* 2012)

We are well aware that there are several software (CERR, DRESS, DORES, RADBIOMOD, BIOSUITE, TCP_NTCP_CALC) designed with similar intention. Some of this software is not freely available and some of them which are in open access are complex in their application.(Deasy, Blanco, and Clark 200)(Tsougos *et al.* 2009) (El Naqa *et al.* 2006) (Warkentin *et al.* 2007) (Uzan and Nahum 2012) The above mentioned software used critical models which demand so many parameters. Our developed software employed simple models intended to build confidence amongst users those are little scared of RB models application. The initial aim of proposed thesis is to develop indigenously developed program for plan evaluation based on RB models. It is quite tough to perform manual calculation to get output from RB models because of their complex mathematical formulation. Manual calculation leads to high probability of error and lack of accuracy. Manual calculation cannot provide flexibility to compare different biological models outcome because it is time consuming process. The benefit of writing own codes is that we can modify mathematical equations according to need to simplify outcome and reduce complexity. It is easy to add or delete model parameters according to need and chance of improvisation, in short it provides flexibility. Therefore it is proposed to write own program although in literature discussed some of authors provided their developed software free on request. Personally, I experienced the application of free software is very complex and difficult to understand the idea. The input requirement of software is difficult to understand also. The ultimate goal

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is to develop a simple user friendly program for TCP and NTCP estimation. Program codes mentioned in appendices section.

2 Material and Methods

We have developed a simple application using MATLAB licensed version 2016b (Mathworks) for estimating TCP and NTCP named as RBMODELV1. The programme contains Niemierko free EUD programme code provided in authors research article (Gay and Niemierko 2007). This programme was initially validated as per guidelines of the author but we found error while running the code in MATLAB software which has been corrected. Author provided standard six inputs and six outputs for programme validation but it was found that three inputs were wrong and could not produce the right output. Hence by hit and trial method we corrected input for which output was matched. Corrected input given below.

Given = [0 100; 200 0] corrected= [0 100; 120 0]
Given = [0 100; 12000 0] corrected= [0 100; 120 0]
Given = [0 100; 14000 0] corrected= [0 100; 140 0]

For rest of RB models in the software separate coding is performed. Software has user friendly graphical user interface (GUI). The programme accepts cumulative DVH file in (.txt) format containing two columns, dose and volume with minimum bin size of 0.1 cGy. This application incorporated two most widely used TCP models of Poisson's and Niemierko and four NTCP models LKB, Niemierko EUD model or logit, logistic model & Weibull distribution model. A set of two radiobiological parameters dataset were prepared, default and recommended in excel sheet format named as RBDATA provided with software. User has freedom to choose any one of them for TCP & NTCP estimation and can modify or update. We cross validated results of our developed software with Biosuite software for Poisson TCP model and LKB model (Uzan and Nahum 2012). A set of total 20 patient's data of head & neck site took under study and respective TCP & NTCP calculated by all the RB models and compared variations against each other.

3 Radiobiological models

In this software simple RB models opted, as clinical dose response data have sufficient diversity; use of complex models with too many parameters typically results in significant parameter correlation and ambiguity in biological interpretation. The four models are briefly discussed in the following paragraphs, and the parameters used in each of the models are summarized in table 3.1 & 3.2.

3.1 Niemierko EUD or Logit model

The equivalent uniform dose (EUD) model is a simple model based on two equations (1) & (2). The unique thing is that same model can be used for both TCP and NTCP predictions.

$$\mathrm{EUD} = \left\{\sum_{i=1}(v_i D_i^a)\right\}^{\frac{1}{a}} \quad \text{---------- (1)}$$

Where, EUD is the equivalent uniform dose, which represents the dose that, if delivered uniformly to the entire organ, would produce the same effect as the given heterogeneous dose distribution.(Niemierko 1997) "**a"** is a unitless model parameter that is specific to the normal structure or tumor of interest, and $\mathbf{V_i}$ is unitless and represents the i^{th} partial volume receiving dose **Di** in Gy. Since the relative volume of the whole structure of interest corresponds to 1, the sum of all partial volumes $\mathbf{V_i}$ will equal to 1. The choice of parameter a will determine the behavior of the EUD-based model. Values of 'a' represents volume effect which can be understand by the example. For normal

tissues that exhibit a large volume effect (e.g., liver, parotids, and lungs), the dose response may be closer to the mean dose therefore 'a' should be small positive number.

In normal tissues with a serial or ''links in a chain'' architecture like the spinal cord, breaking one of the links will likely rupture the functional tissue chain, therefore 'a' will usually be a large positive number.

The local control of a tumor will likely depend on the volume that received the minimum dose; since this is where the tumor clonogen survival should be highest therefore 'a' should be large negative number.

To calculate the EUD-based normal tissue complication probability (NTCP), Niemierko proposed parameterization of the dose response characteristics using the logistic function as shown below.

$$\mathrm{NTCP} = \frac{1}{\left[1-\left(\frac{\mathrm{TD_{50}}}{\mathrm{EUD}}\right)^{4\Upsilon 50}\right]} \qquad \text{---------- (2)}$$

Where, TD_{50} is the tolerance dose for a 50% complication rate at a specific time interval.

Υ_{50} is a unitless model parameter that is specific to the normal structure or tumor of interest and describes the slope of the dose-response curve.

Similarly, to calculate the tumor control probability (TCP), the EUD is substituted in the following equation.

$$\mathrm{TCP} = \frac{1}{\left[1-\left(\frac{\mathrm{TCD_{50}}}{\mathrm{EUD}}\right)^{4\Upsilon 50}\right]} \qquad \text{---------- (3)}$$

Where, TCD_{50} is the tumor dose to control 50% of the tumors when the tumor is homogeneously irradiated

3.2 Lyman-Kutcher-Burman model

Lyman's formula models the sigmoid dose-response (SDR) curve of NTCP as a function of dose (Di) to a uniformly irradiated fractional reference volume (Vref) (Kutcher *et al.* 1991). The expression of this NTCP is given as below

$$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} exp\left[\frac{-t^2}{2}\right].dt$$

$$Where, t = \frac{[D-TD50/5(v)]}{m.TD50/5(v)} \qquad \text{---------- (4)}$$

The SDR model has three parameters: *n*, *m*, and D_{50}; *n* determines the dose-volume dependence of a tissue and thus accounts for differences in tissue architecture; *m* controls the slope of the dose-response curve (in the case of homogeneous irradiation); and *D*50 represents the dose at which there is a 50% chance of complication, and thus dictates the position of the dose-response curve.

3.3 TCP model based on Poisson statistics

TCP models generally rely on the assumption that tumor control requires the killing of all tumor clonogens.(Oinam *et al.* 2011) Poisson statistics predict that the probability of this occurring presented as

$$TCP = \exp(-N\, p(D)) \quad \text{---------- (5)}$$

Where, N is the initial number of clonogens, and $p(D)$ is the cell survival fraction after a dose D. If it is assumed that cell survival can be described by single-hit mechanics,

$$p(D) = \exp(-\alpha D), \quad \text{---------- (6)}$$

The expression in Eq. (6) can be rewritten in terms of the two parameters describing the dose and normalized slope at the point of 50% probability of control, Υ_{50} and D_{50}

$$\boldsymbol{TCP = \left(\frac{1}{2}\right) e^{\left[2\gamma 50\left(1-\frac{D}{TCD50}\right)\right]/ln2}} \quad \textbf{---------- (7)}$$

Using the assumption of independent subvolumes, for the case of heterogeneous irradiation, the overall probability of tumor control is the product of the probabilities of killing all clonogens in each tumor sub-volume described by the CDVH:

$$\boldsymbol{TCP = \prod_i TCP(D_{i,} v_i)} \quad \textbf{---------- (8)}$$

Thus, for a given DDVH {Di,vi}, the TCP can be calculated using the following two-parameterl TCP formula:

$$\boldsymbol{TCP = \left(\frac{1}{2}\right)^{\sum_{i=1}^{N} V_i . Exp\left[2\gamma_{50}\left(1-\frac{D_i}{TCD_{50}}\right)/Ln2\right]}} \quad \textbf{---------- (9)}$$

3.4 Weibull distribution model

The mathematical form of the model is given below(Adamus-Górka *et al.* 2011)

$$P(D) = 1 - \exp\left[-\ln 2\left(\frac{D}{D_{50}}\right)^{\frac{2}{\ln 2}\Upsilon_{50}}\right] \quad \textbf{---------- (10)}$$

Where, P(D) is a normal tissue complication probability

3.5 Logistic Model

The mathematical form of the model represented as(PhD *et al.* 2018)

$$NTCP = \frac{1}{\left[1-e^{\left(1-D/D50\right)*4\Upsilon 50}\right]} \quad \textbf{---------- (11)}$$

D_{50} is the dose leading to 50% complication rate, D is the dose to organ and Υ_{50} is the relative change in complication rate per unit change in dose rate at the 50 % level.

Table 3.1: *Containing biological parameters used for NTCP calculation by four radiobiological models for head and neck cancer site.*

OAR	NTCP models	Used parameter values	Parameter description
Parotid	1. Gay and Niemierko Model 2. Logistic Model 3. Weibull distribution	a = 1, α/β=3 Υ_{50} = 2 TD_{50} = 31.40%	'a' is a unitless tissue specific parameter Υ_{50} is a slope of dose response curve TD_{50} (tolerance dose) is the uniform dose given to entire organ that results in 50% complication risk 'n' is a parameter which describes magnitude of the volume effect 'm' is a measure of slope of the sigmoid curve
	LKB or Probit model	n =1 , m= 0.53, TD_{50} =31.40%, α/β=3	
Oral cavity	1. Gay and Niemierko Model 2. Logistic Model **3.** Weibull distribution	a = 1, α/β=3 Υ_{50} = 2 TD_{50} = 55.9 %	
	LKB or Probit model	n =1 , m=0.541 , TD_{50}=55.9%, α/β=3	
Spinal cord	1. Gay and Niemierko Model 2. Logistic Model **3.** Weibull distribution	a = 13, α/β=2 Υ_{50} = 4 TD_{50} = 66.5%	
	LKB or Probit model	n=0.05, α/β=2, m=0.175, TD_{50}=66.5%	

Table 3.2: *Containing biological parameters used for TCP calculation by four radiobiological models for head and neck cancer site*

	TCP models	Used parameter values	Parameter discription
PTV	1. Gay and Niemierko Model 2. Logistic Model 3. Weibull distribution	a = -13 Υ_{50} = 4.41 TCD_{50} = 51.77%, α/β = 10	'a' is a unitless tissue specific parameter TCD_{50} (tumour control dose) is the uniform dose given to entire organ that results in 50% tumour control probability
	Poisson model	Υ_{50} = 4.41 TCD_{50}=51.77%, α/β = 10	

4 Application Architecture

The RBMODELV1 was developed in MATLAB 2016b version (Mathworks) programming environment and is designed for use on a windows based computer. RBMODELV1 is a menu driven user interface designed to use conveniently. The framework of the application is simple as shown in **fig.(2)** The user has to browse input file in .txt format which should be cumulative DVH as it is most preferably form of plan evaluation. The rest of model parameters need to enter manually from the database provided with software. TCP or NTCP calculations are performed based on these parameter values for different RB models embedded into the application. Further details of the application functionality explained below.

4.1 Input section

The programme accepts cumulative dose volume histogram (CDVH) file in (.txt) format with two columns in the form of [Di,Vi]. There is one browse option for PTV and separate browse option for OAR CDVH files, therefore simultaneously TCP & NTCP can be calculated. While extracting CDVH file from the treatment planning system, it should be noted that DVH plot should be in absolute dose (cGy) versus absolute volume (cubic centimetre).

4.2 Parameter database and parameter selection

One of the prime purposes of the RBMODELV1 is to provide a convenient means of accessing and archiving current and future radiobiological knowledge as it pertains to treatment plan evaluation. The program package contains parameter databases for two TCP and four NTCP models described above. For each of these models two databases were maintained: a "default" one, which is recommended for user and a "user dependent" database, which gives flexibility to user to add or delete entries. This parameter database separately provided in the form of excel sheet named as "RBDATA" in addition with software package. The table 3.3 contains biological parameter values for TCP model from Okunieff *et al* study for various tumours of head & neck site. The table 3.4 contains biological parameters values for NTCP model of different organ at risk of head & neck site with 95% confidence interval where available. Radiobiological parameters (a, Υ_{50}, TCD_{50},TD50, α/β, m,n) collected from meta-analysis studies as well as proposed model parameters based on cumulative experience at various institutions which assume to be more representative and readily incorporated into clinical use.(PhD *et al.* 2018) (Okunieff *et al.* 1995) (van Leeuwen *et al.* 2018) (Semenenko and Li 2008) (Lee *et al.* 2012) (Luxton, Keall, and King 2008)

Table 3.3: *Radiobiological model parameters of head and neck site for TCP calculation from Okunieff et al*

Tumor site	Comments	TCD50 (%)	ϒ50 (%)
Nasopharynx	Node<3 cm	50.01	17.54
Nasopharynx	All node +	50.27	32.22
Nasopharynx	Node 3-6 cm	55.12	1.82
Nasopharynx	T1 + T2	58.79	47.26
Nasopharynx	T1 - 4	61.59	3.38
Nasopharynx	T4	67.23	3.25
Nasopharynx	Node > 6 cm	68.81	1.67
Supraglottic	T1	50.44	1.83
Supraglottic	T2 + T3	63.28	4.01
Supraglottic	T4	62.92	0.63
Tonsil	N1 -3	54.02	1.03
Tonsil	T1 – 4	57.27	1.29
Pyriform sinus	Nodes < 3 cm	60.76	3.80
Pharyngeal wall	T3 + 4	72.18	0.80
Squamous cell (microscopic)	-	51.77	4.41
Pyriform sinus	All Nodes	63.40	2.85

*These are values for head & neck site for other site, reader should refer Okunieff et al complete report.

Table 3.4: *Radiobiological model parameters reported in literature for head and neck site organ at risk (OAR).*

OAR	Model parameters with 95% CI where available			ϒ50 (%)	a	Clinical endpoint	References
	n	m	TD50				
Brainstem	0.16	0.14	65	3	7	Necrosis	Chang et al & Oinam et al
Spinal cord	0.05	0.175	66.5	-	13	Myelitis/ncrosis	Oinam et al & Chang et al
Parotids	1	0.53 (0.45,0.65)	31.40 (29.1,34.0)	-	-	Xerostomia expressed as stimulated salivary flow≤25% at 6 months	Semenenko et al
Larynx	0.45 (-0.10,1.0)	0.16 (0.06,0.26)	46.3 (42.77,49.83)	2.6 (0.8,4.5)	-	Laryngeal edema	Chang et al & Brodin et al
TM joint & mandible	0.07	0.1	72	-	-	Marked limitation of joint function	Chang et al
Oral cavity	-	-	51(40,61)	1(0.6,1.5)	-	Mucositis	Brodin et al

*If the value of Υ_{50}(%) is not known, recommended value is 4.

*If value of "a" is not known then for parallel organ, recommended value is 1.

*If value of "n" is not known then for parallel organ, recommended value is 1.

4.3 Display and Output

The graphical user interface (GUI) based display is shown in figure 2, the display divided into main four panels, patient information panel, instructions & software version details, TCP section and NTCP section. There are clear option for erasing the input & output entries. User has to click on Target file & OAR file button to browse the respective CDVH file. Push button is provided in TCP & NTCP section to enable calculation. User can take an output in .txt file by pressing print button.

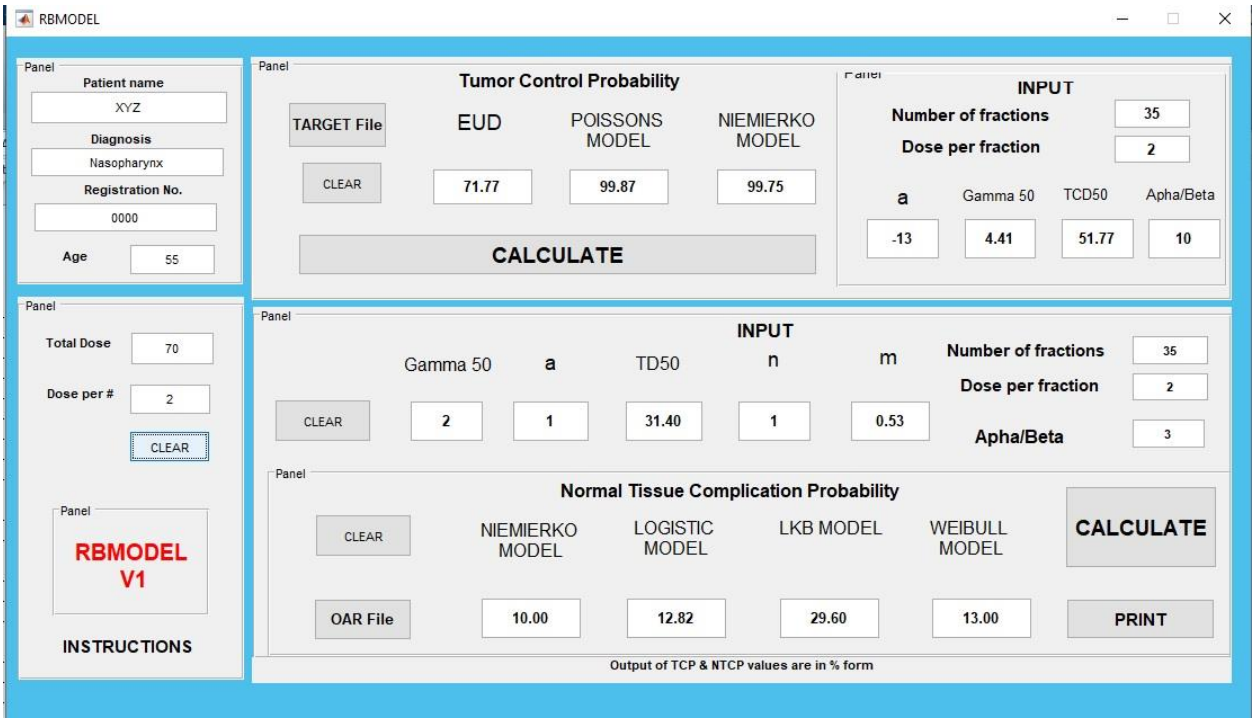

Figure 2: *Graphical user interface of the developed program.*

4.4 Advantages and Disadvantages of the software

In this software we used very simple models demanding radiobiological parameters which accept common input amongst the incorporated models. This surely reduces confusion for the enduser and once you entered all parameters you will find results of all models output simultaneously. In this study we cross calibrated our results with Biosuite software for LKB model and Poisons TCP model. The most important thing which included in this software package is radiobiological parameters generated after quantitative analysis of normal tissue effects in the clinic (QUANTEC) dose report summary.(Marks *et al.* 2010) We also archived old parameter database for the enduser. The speed of TCP and NTCP calculation is very fast, even for input DVH file having 0.1 cGy dose binning.

Input file creation is a little time taking process as user has to export DVH file for individual OAR and PTV. This software is developed in MATLAB platform therefore user should have the MATLAB software and MATLAB is not a freely available software. Work is in progress to provide software in MATLAB compiler format or can say in application form so that no need for MATLAB installation will be required. The user has to simply download the application and run into his/her system. We are trying to develop software in Python platform, as Python is freely available software and now a day's popular in scientific community.

5 Results

We cross validated the results of predicted NTCP by LKB model and predicted TCP by Poisson model with Biosuite software developed by Uzan *et al* as these two models common in both the software (Uzan and Nahum 2012).

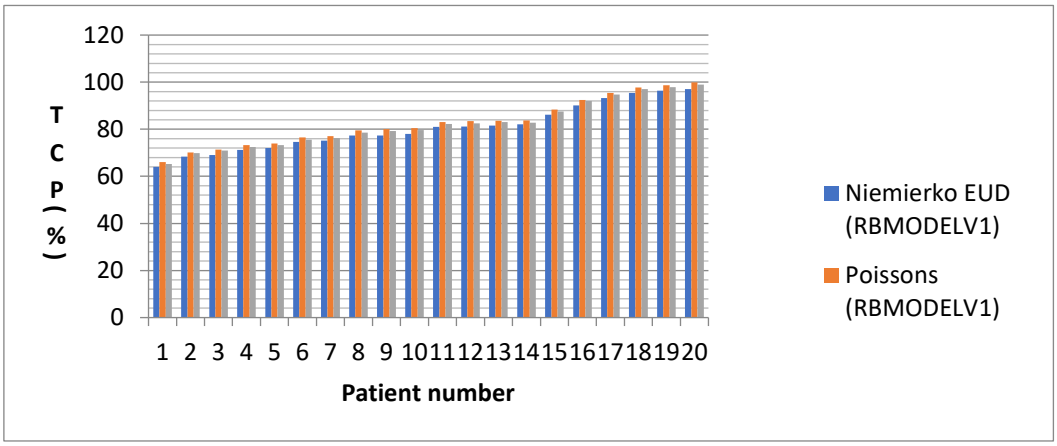

Figure 2.1: *Graph showing % variation of calculated TCP for two different models by two different programs.*

The difference in TCP calculated for Niemierko or logit model and Poisson model by RBMODELV1 program is found to be less than 3%. There is less than 1% variation observed in calculated TCP for Poisson model by Biosuite and RBMODV1 software as shown in figure 2.1. The sigmoid dose response curve plotted for both the models as shown in figure 2.2.

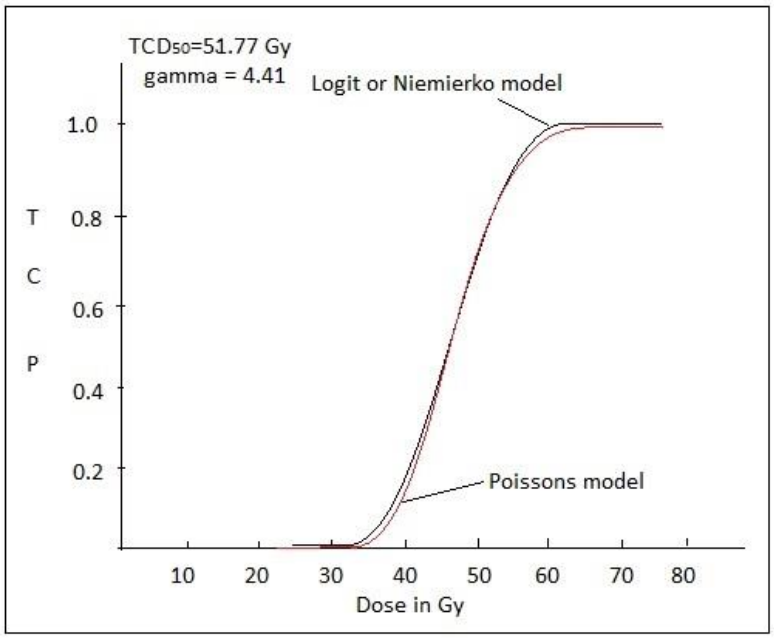

Figure 2.2: *Statistical distribution used to describe the shape of dose response curve for two different TCP models.*

The difference in predicted NTCP of parotid gland and oral cavity from LKB model by two different programs is observe to be less than 4% as shown in figure 2.5 & 2.8. The dose response curve plotted for both organs parotids and oral cavity which helps to understand variations of outcome of different NTCP models as shown in figure 2.6 & 2.7. Graph is plotted between predicted NTCP by four different models as a function of equivalent uniform dose (EUD) for parotid as shown in figure 2.3. Graph indicating calculated NTCP values against equivalent uniform dose (EUD) of parotid organ for LKB model by two different programs as shown in figure 2.4.

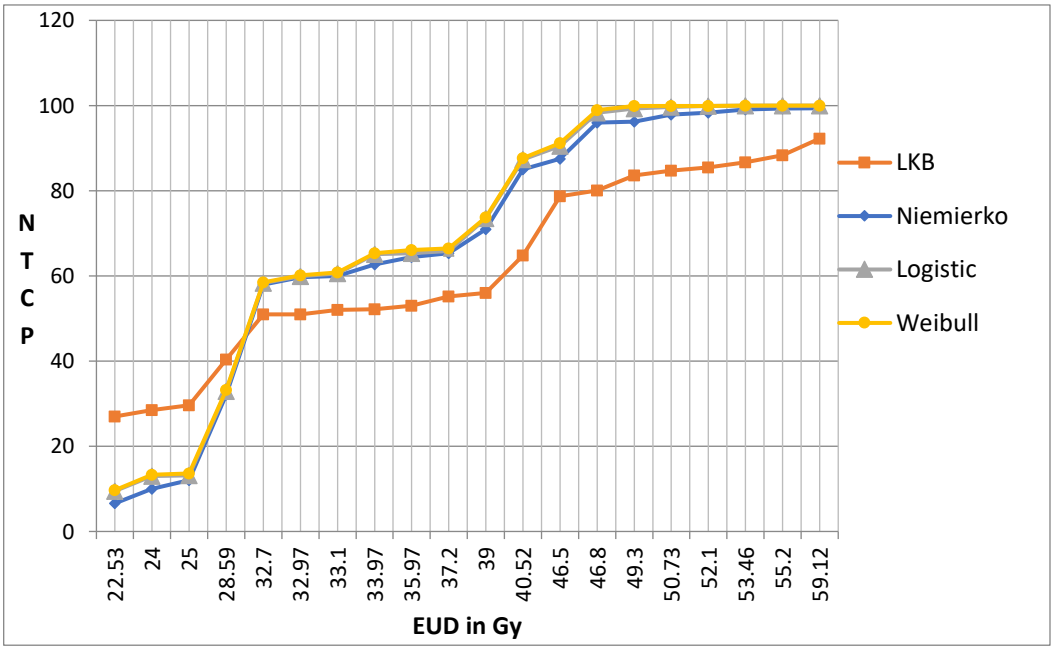

Figure 2.3: *Graph indicating calculated NTCP values by four different models as a function of equivalent uniform dose (EUD) for parotid organ.*

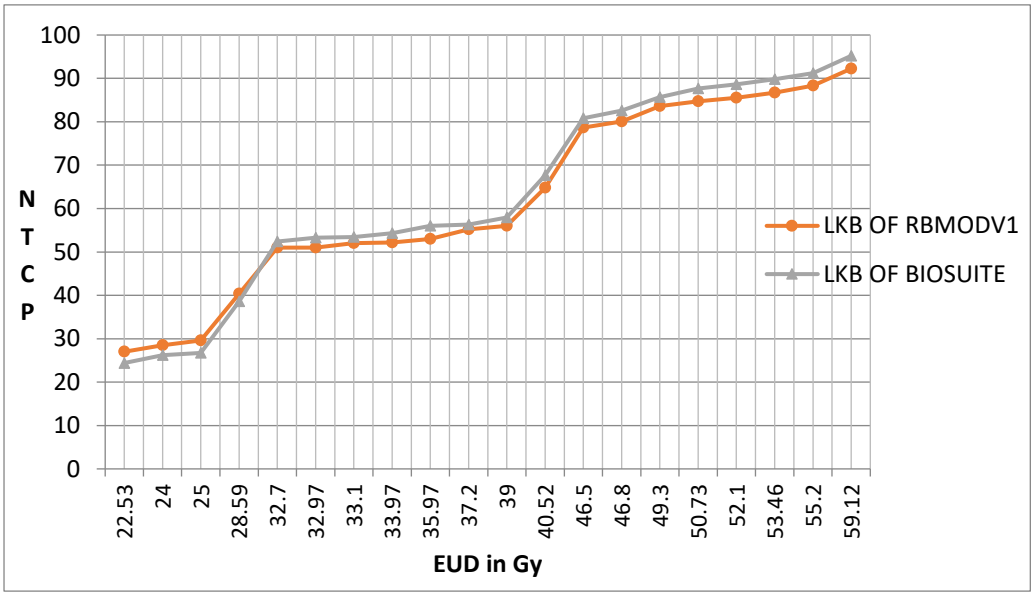

Figure 2.4: *Graph indicating calculated NTCP values against equivalent uniform dose (EUD) of parotid organ for LKB model by two different programs.*

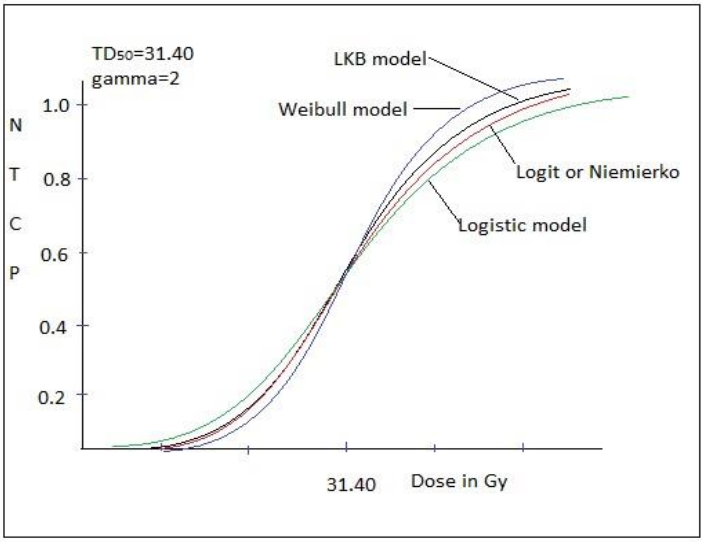

Figure 2.5: *Statistical distribution used to describe the shape of dose response curve of parotid organ for four different NTCP models.*

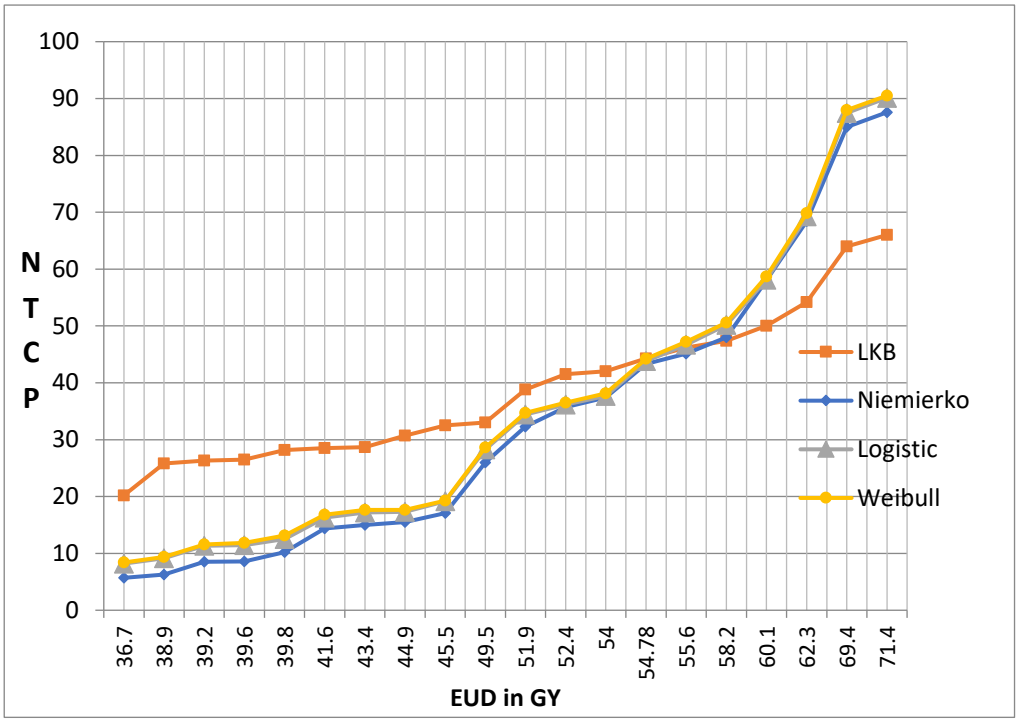

Figure 2.6: *Graph indicating calculated NTCP values by four different models as a function of equivalent uniform dose (EUD) for oral cavity*

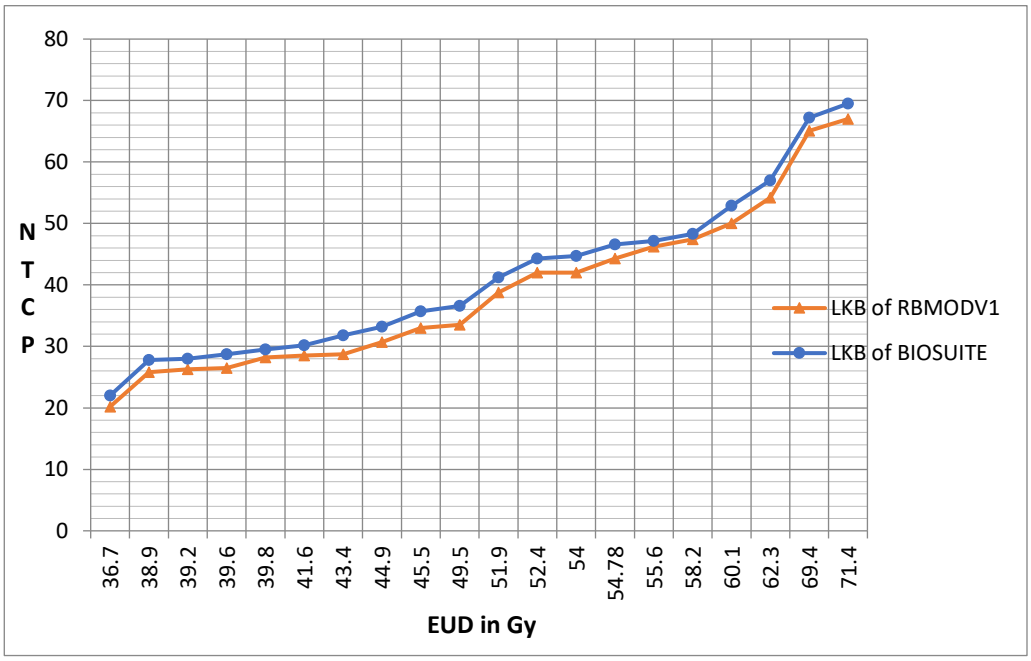

Figure 2.7: *Graph indicating calculated NTCP values against equivalent uniform dose (EUD) of oral cavity for LKB model by two different programs.*

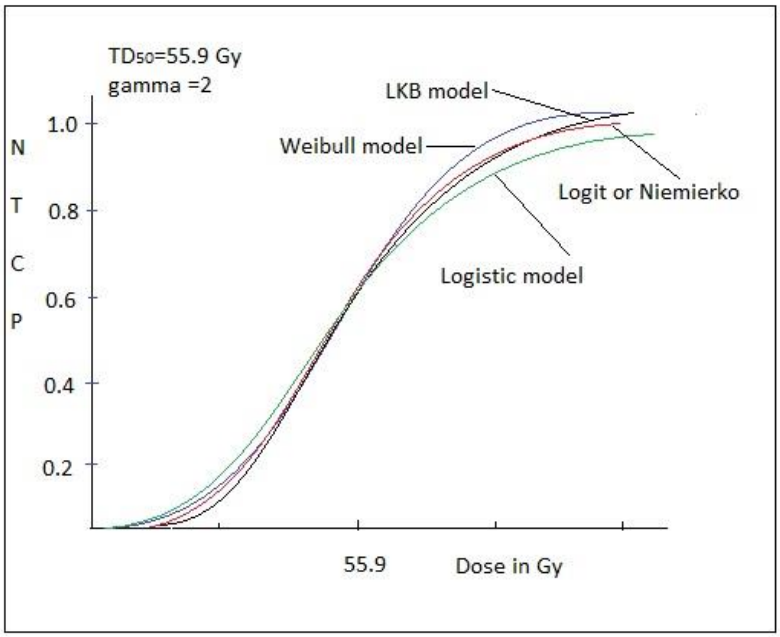

Figure 2.8: *Statistical distribution used to describe the shape of dose response curve of oral cavity organ for four different NTCP models.*

The results of predicted TCP & NTCP by Gay and Niemierko EUD model is cross validated as per the author guidelines mentioned in his study which is found to be no variation with software calculated program. Weibull distribution model and logistic model results could not be cross validate as we do not have any reference software or program. The maximum percentage variation between Weibull distribution model and logistic model is less than 1% whereas there is less than 3% variation between Weibull, logistic and Gay and Niemierko EUD model for parotid gland and oral cavity as shown in figure 2.4 & 2.8. The maximum percentage variation between predicted NTCP by all the models for the serial organ spinal cord is less than 1% as shown in table 3.5. This shows that there is good correspondence in predicted NTCP values for serial structure as compare to parallel structure; this may be because volume effect is predominant in parallel structure (Marks *et al.* 2010) (Rutkowska, Baker, and Nahum 2010).

The NTCP predictions estimated by the four RB models for all twenty patients are in-line with the QUANTEC guidelines for radiation induced myelopathy of spinal cord. Oral cavity excluded from comparison as it is not a part of the summary. In case of bilateral whole parotid gland, according to QUANTEC mean dose $\leq$ 25 Gy results in less than 20 % rate of incidence of xerostomia. There are five patients who received mean doses less than 25 Gy and results of predicted NTCP by models are less than 20 %, LKB prediction is on higher side as compare to rest three models.

This is the first study in which we tried to establish correlation between the mean doses received by parallel structure (parotid gland and oral cavity) and predicted percentage of NTCP values. It is found that mean dose in the range of 35-40 Gy for parotid gland can result in more than 50% NTCP predicted by all four RB models. Similarly oral cavity receiving mean dose in the range of 53-58 Gy can results in more than 35 % NTCP predicted by all the four models.

Table 3.5: *Calculated NTCP values for spinal cord (serial organ) by RBMODELV1 & BIOSUITE software*

Patient	Physical Maximum Dose(Gy)	EUD (Gy)	LKB model (By Biosuite) (%)	Niemierko Model (%)	LKB Model (%)	Logistic Model (%)	Weibull Model (%)
P-1	33.5	21.0	0.00	0.00	0.00	0.00	0.00
P-2	37.3	24.0	0.00	0.00	0.009	0.00	0.00
P-3	37.5	22.5	0.00	0.00	0.005	0.00	0.00
P-4	38.2	22.9	0.00	0.00	0.01	0.00	0.00
P-5	39.5	23.6	0.009	0.00	0.012	0.00	0.00
P-6	41.1	26.4	0.01	0.00	0.032	0.00	0.00
P-7	42.5	29	0.04	0.00	0.065	0.00	0.00
P-8	43.57	27.7	0.04	0.00	0.043	0.00	0.00
P-9	44.10	30.5	0.07	0.00	0.11	0.00	0.00
P-10	44.29	32.96	0.15	0.00	0.20	0.00	0.00
P-11	45.30	35.01	0.29	0.00	0.34	0.00	0.00
P-12	45.42	34.23	0.22	0.00	0.28	0.00	0.00
P-13	45.56	35.0	0.31	0.00	0.37	0.00	0.00
P-14	46.2	36.6	0.36	0.00	0.44	0.00	0.00
P-15	47.4	38.1	0.47	0.00	0.52	0.00	0.00
P-16	48.50	35.70	0.42	0.00	0.54	0.00	0.00
P-17	48.75	36.59	0.38	0.00	0.48	0.00	0.00
P-18	49.0	38.0	0.55	0.013	0.69	0.015	0.012
P-19	51.50	37.32	0.54	0.02	0.60	0.03	0.03
P-20	52.80	37.60	0.58	0.02	0.65	0.03	0.03

6 Discussion

Out of four NTCP models & two TCP models, LKB model & Poisson TCP model cross validated against Biosuite software. The Biosuite accepts differential DVH file in Microsoft excel format whereas RBMODV1 accept cumulative DVH file in txt format. It is found maximum variation of 1% in case of Poisson model and maximum 5 % variation in case of LKB model; this may be due to several reasons e.g dose binning error, use of different EQD2 formula and variation in program coding. The variation in NTCP outcome between Logit or Neimierko, Logistic & Weibull model is not significant because of small variation in mathematical formulation and all are using same input parameters. It is observed that there is significant difference in outcome of LKB model & rest three NTCP models and this variation is direct function of dose.

The TCP/NTCP models incorporated in RBMODELV1 are based on assumptions of linear quadratic model. LQ model overestimated for higher dose per fraction (usually >3.2 Gy) hence it is advised to the enduser that results of the software are not reliable in such fractionation schedules. Besides this the biological parameters (TD_{50}, $\Upsilon 50$) which are derived from conventional fractionation should not be used directly for evaluation of higher dose per fraction treatment plans which can results uncertainty. It has been suggested that in such cases revised biological parameters should be applied for biological

model based plan evaluation. The TCP/NTCP outcome is greatly affected by treatment gaps and accelerated fractionation treatment schedules specifically for early responding tissues (tumour, skin & oral mucosa). This is because overall treatment time changes and above discussed models are not corrected for phenomenon of repopulation effect occurs in tumour tissue and normal tissue. It is well understood that radiotherapy outcomes may also be affected by multiple clinical and biological prognostic factors such as stage, volume, tissue sensitivity, tumour hypoxia, concurrent chemotherapy etc.(El Naqa, Pater, and Seuntjens 2012) Besides this there are external factors like tumor delineation uncertainties, treatment delivery and set up uncertainties can affect clinical outcome. Hence, it is impossible to predict pattern of treatment failure or success. Bearing this into mind we limited our approach of TCP calculation to two simple models for the sake of curiosity and research. Therefore clinical validation of RB models for TCP calculation is difficult to establish.

RB models predicted NTCP cannot provide any direct relationship between complication grading (CTCAE, RTOG) and calculated percentage NTCP, hence toxicity assessment purely based on clinical experience. RB model based predictions are only as good as large data available. RB model based predictions are based on DVHs input. DVH are not ideal representations of the 3D dose distribution as they discard all organ specific spatial information. Lawrence B Marks *et al* well explained and discussed various limitations of NTCP models e.g. fractionation schedules, lack of spatial dose information in DVH, combined modality therapy etc.(Marks *et al*. 2010). RB models are highly sensitive to parameters involved in the formulation and there is scarcity of studies which can quantify the variations while using them. Organ at risk delineation found to have differences which directly affect NTCP outcome therefore in our study we followed consensus guidelines for CT-based delineation of organ at risk for head and neck region.(Brouwer *et al.* 2015) The NTCP models presents more reliability if large data is available and we can say that data driven decision support system becoming reality in modern day of radiation oncology.(PhD *et al.* 2018)

Application RB models for particle therapy is quite interesting and opened a way to explore. There is a major difference in dose distributions achieved by photon therapy and proton therapy. Photon therapy deliver significant low dose to large volume of healthy normal tissue and organ whereas proton therapy restricts dose distribution to very short range. Blanchard *et al* tested several NTCP models for proton treated patient plans and observed that performance of photon derived models is acceptable for estimating the risk of dysphagi, xerostomia and hypothyroidism, but not satisfactory for acute mucositis. Chaikh *et al* performed comparison study between proton & photon based on EUD values. Author found that the available NTCP models may underestimate the real benefit from proton based treatment plans. It is demanding that existing RB models needs to be modified by taking into account RBE & LET of particle therapy for better and accurate results.

Though the software is a research tool but if clinically validated NTCP models at the institutional level with updated biological model parameters, it can serve as a decision support system, designing new fractionation schedules as well as in clinical circumstances where risk versus benefit can be evaluate logically. The developed software RBMODELV1 is the first version of the software and next version will include new NTCP models with additional feature of dose response curve.

7 Conclusion

We created simple software RBMODELV1 which can be used as a research tool as well as decision support system. This software can assist in the treatment plan evaluation based on radiobiological models. It also provides utility of common radiobiological models by facilitating comparison of model

predictions to actual clinical outcomes. This software provides platform to test sensitivity of model predictions to uncertainties associated with RB model parameters. Present chapter explained that how author have developed indigenous program in MATLAB (Version: 2016b) platform for biological model based plan evaluation. The developed program has simple user friendly interface to operate conveniently. The program accepts the organ specific DVH file in .txt format (for each PTV and OAR one file needs to be generate) for obtaining the result in terms of TCP and NTCP. In addition with program, database of biological input parameters were also provided. The program contains RB models which are commonly used and there enough data of parameters are available in literature. This is because less data more uncertainty and more data less uncertainty. The program contains Gay Niemierko EUD, Poisson, LKB models. In support author cross validated the outcome of the developed program with Biosuite software which found in acceptable range of ±3%.

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