Original Article

Dose volume histogram analysis and comparison of different radiobiological models using in-house developed software

Arun S. Oinam, Lakhwant Singh[1], Arvind Shukla, Sushmita Ghoshal, Rakesh Kapoor, Suresh C. Sharma

Department of Radiotherapy, PGIMER, Chandigarh, [1]Department of Physics, Guru Nanak Dev University, Amritsar, Punjab, India

ABSTRACT

The purpose of this study is to compare Lyman-Kutcher-Burman (LKB) model versus Niemierko model for normal tissue complication probability (NTCP) calculation and Niemierko model versus Poisson-based model for tumor control probability (TCP) calculation in the ranking of different treatment plans for a patient undergoing radiotherapy. The standard normal tissue tolerance data were used to test the NTCP models. LKB model can reproduce the same complication probability data of normal tissue response on radiation, whereas Niemierko model cannot reproduce the same complication probability. Both Poisson-based and Niemierko models equally reproduce the same standard TCP data in testing of TCP. In case of clinical data generated from treatment planning system, NTCP calculated using LKB model was found to be different from that calculated using Niemierko model. When the fractionation effect was considered in LKB model, the calculated values of NTCPs were different but comparable with those of Niemierko model. In case of TCP calculation using these models, Poisson-based model calculated marginally higher control probability as compared to Niemierko model.

Key words: Niemierko model, normal tissue complication probability, Poisson-based model and Lyman-Kutcher-Burman model, tumor control probability

Introduction

Evaluation of treatment plans for the determination of best plan among the different plans is done by analysis of dose volume histogram (DVH) as well as two-dimensional and three-dimensional spatial dose distributions. These plans are further evaluated by calculating the tumor control probability (TCP) and normal tissue complication probability (NTCP) of the treatment plans to determine the radiobiological ranking of different plans amongst them.[1-3] This final evaluation of treatment plans can be done by using both cumulative and differential DVH generated by treatment planning system (TPS). Various researchers developed their own in-house evaluation software for TCP and NTCP calculation.[3-6] Some of these models do not consider the fractionation effect in NTCP calculations,[2,7] whereas some of the models use the effect of fractionation in radiotherapy treatment in NTCP[5,6,8] and TCP[5,6,9] calculation. The purpose of this study is to develop a comprehensive and user-friendly in-house computer program for DVH analysis and clinical implementation of NTCP calculation based on Lyman-Kutcher-Burman (LKB) model and Poisson distribution model based TCP calculation and its comparison with those of calculations based on Niemierko models. Further, the incorporation of different dose per fraction sizes in LKB model will be tested.

Materials and Methods

Software requirements and data input/output

A MATLAB® software version 7.1 was used to develop this program. The differential and cumulative DVH data were exported from Eclipse TPS of Varian Medical System,

Palo Alto, USA, in ASCII format in dose bin size of 20 cGy and these DVH data were imported in MATLAB software for the estimation of different DVH parameters, TCP and NTCP.

Normal tissue complication probability based on dose response curve
Lyman-Kutcher-Burman model

Lyman's formula models the sigmoid-shaped dose response curve of NTCP as a function of dose (D) to a uniformly irradiated fractional reference volume (v_{ref}). The parameters used in this model are $TD_{50/5}$ (dose at which probability of complication becomes 50% in 5 years), m (tissue-specific parameter inversely proportional to the slope of response curve) and n [parameter to find the equivalent uniform dose (EUD) of inhomogeneous irradiation using DVH reduction method proposed by Kutcher-Burman model].[10,11] The expression of this NTCP is given as

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{t^2}{2}\right) \cdot dt \qquad ....(1)$$

$$\text{where } t = \frac{\left[D - TD_{50/5}(v)\right]}{m \cdot TD_{50/5}(v)} \qquad ....(2)$$

The volume-dependent parameter $TD_{50/5}(v)$ for fractional volume v can be expressed in terms of $TD_{50/5}(1)$ of full volume irradiation as

$$TD_{50/5}(v) = TD_{50/5}(1) \cdot v^{-n} \qquad ....(3)$$

where $0 < n < 1$ for all tissues fitted by Burman *et al.*[7] The above parameters are fitted on this model by Burman *et al.*[7] for the normal tissue tolerance data of high-grade complications associated with full or partial organ irradiation, compiled by Emami *et al.*[12] The values used in this study are summarized in Table 1. The dose response data of Emami *et al.* are derived mostly from nominal doses near to 2 Gy per fraction. Dose fractionation effects are not explicitly taken into account in this LKB model calculation of NTCP.

Application of fractionation in Lyman-Kutcher-Burman model

The raw data obtained from TPS are of different dose per fraction. The radiobiological effects of such different dose per fraction size are different from those of 2 Gy per fraction for the same radiation dose distribution in an organ. In order to consider the effect of fractionation and size of dose per fraction in the NTCP calculation, the DVH of different doses per fraction is converted into biologically equivalent physical dose of 2 Gy per fraction (EQD_2) using the linear quadratic (LQ) model as

$$EQD_2 = D \cdot \frac{\left(\frac{\alpha}{\beta} + \frac{D}{n_f}\right)}{\left(\frac{\alpha}{\beta} + 2\right)} \qquad ....(4)$$

where n_f and $d_f = D/n_f$ are the number of fractions and dose per fraction size of the treatment course, respectively. α/β are the tissue-specific LQ parameters of the organ being exposed. EQD_2 DVH data obtained using equation (4) were used to calculate the LKB model based NTCP by Kuperman *et al.*,[13] using equations (1)-(3).

Niemierko model

In this model also, the raw data from TPS are converted into the biological equivalent physical EQD_2 DVH using equation (4). Then, this DVH is converted into the DVH of the whole volume of the organ receiving an EUD, using the DVH reduction method proposed by Kutcher *et al.*[10] The EUD, obtained from the conversion of inhomogeneous dose distribution of different partial volume v_i receiving the dose D_i, is given as

$$EUD = \left[\sum_{i=1}^{N} v_i \cdot \left\{EQD_{2i}\right\}^a\right]^{\frac{1}{a}} \text{ where } a = \frac{1}{n} \qquad ....(5)$$

The value of a is equal to 1 when EUD is equal to mean dose. The "a" is a large negative value for tumor as the tumor control depends on the minimum dose received by the tumor. In case of normal tissues such as serial and parallel architectures, the values of a are large positive and small positive values depending on small and large volume effects, respectively. Then, the NTCP of such organ is determined using a logistic function as

$$NTCP = \frac{1}{1 + \left[\frac{TD_{50}}{EUD}\right]^{4\gamma_{50}}} \qquad ....(6)$$

where γ_{50} is the slope of sigmoidal dose response curve of normal tissue at 50% complication probability

$$= TD_{50} \cdot \left.\frac{dNTCP}{dD}\right|_{D=TD_{50}} \qquad ....(7)$$

The tissue-specific parameters given in Table 1 are used for NTCP calculation based on Niemierko model.[8]

Tumor control probability
Poisson's model of cell killing

Survival of cell killing by radiation exposure follows the Poisson's distributions.[14] The probability of survival of clonogenic cell that does not receive any hit ($N = 0$) after the exposure of radiation dose D is given by

$$= Exp\left[-N_c \cdot p(D)\right] \qquad ....(8)$$

where $N_c \cdot p(D)$ is the average number of hits on N_c (clonogenic cells) due to small $p(D)$ (probability of hit per cell). If it is assumed that cell killing follows two-target model of single-track and multiple track events, the probability of survivability of clonogenic cells after N_f number of exposures of dose per fraction d, is given by

Table 1: Parameters of sigmoidal dose response curve and dose volume histogram reduction scheme used in normal tissue complication probability calculation (LKB and Niemierko model)

Organ	End points	Niemierko		Lyman Kutcher Burman		TD50/5(Gy)
		a	γ50 (%/%)	n	m	
Brain	Necrosis	5	3	0.25	0.15	60
Brain stem	Necrosis	7	3	0.16	0.14	65
Spinal cord	Myelitis/necrosis	13		0.05	0.175	66.5
Ear (mid/exter)	Chronic serous otitis	31	3	0.01	0.095	65
Ear (mid/exter)	Acute serous otitis	31	4	0.01	0.15	40
Optic chiasma	Blindness	25	3	0.25	0.14	65
Optic nerve	Blindness	25	3	0.25	0.14	65
Retina	Blindness	15	2	0.20	0.19	65
Lens	Cataracts	3	1	0.30	0.27	18
Parotid	Xerostomia	0.5/ <0.5		0.7	0.18	46
Larynx	Cartilage necrosis			0.11	0.075	80
Larynx	Laryngeal edema			0.08	0.17	70
Heart	Pericarditis	3	3	0.35	0.10	48
Lung	Pneumonitis	1	2	0.87	0.18	24.5
Liver	Liver failure	3	3	0.32	0.15	40
Kidney	Nephritis	1	3	0.70	0.10	28
Intestine/Colon	Obstruction/Perforation	6	4	0.15	0.16	55
Bladder	Bladder contracture/ Volume loss	2	4	0.5	0.11	80
Rectum	Severe proctitis/ necrosis/ stenosis/ fistula	8.33	4	0.12	0.15	80
Temporomandibular joint/Mandible	Reduced joint function			0.07	0.10	72
Esophagus	Perforation	19	4	72	70	68

*If the value γ50 (%/%) is not known, its value is taken as 4

$$P_s(D) = Exp\left(-\sum_i N_f . \alpha . d_i \left(1 + \frac{d_i}{\alpha/\beta}\right)\right) \quad \text{........(9)}$$

Similarly, TCP depends on the number of survived clonogenic cells N_s and small survival fraction $p_s(D)$, and TCP is given by the probability of average number of clonogenic cells survived ($N_s = 0 = N_c.p_s(D)$) as

$$TCP = Exp\left(-N_c.Exp\left(-\sum_i N_f . \alpha . d_i \left(1 + \frac{d_i}{\alpha/\beta}\right)\right)\right) \quad \text{....(10)}$$

The number of clonogenic cells can be found out using the following relation according to Niemierko and Goiten[9] and Stavrev *et al.*[15,16] [Appendix A]. If the clonogenic cell data are not available, the expression of TCP in equation (10) can also be rewritten in terms of sigmoidal dose response parameters according to Warkentin *et al.*[4] and Stavrev *et al.*[15,16] as

$$TCP = \left(\frac{1}{2}\right)^{Exp\left[2\gamma_{50}\left(1-\frac{D}{TCD_{50}}\right)/ln2\right]} \quad \text{........(11)}$$

where TCD_{50} is the tumor dose required to produce 50% TCP and γ_{50} is the slope of dose response at 50% TCP, which is $= TCD_{50}.\left.\frac{dTCP}{dD}\right|_{D=TCD_{50}}$. For a heterogeneous irradiation of independent subvolumes v_i of tumors with dose D_i, the overall TCP is given by

$$TCP = \prod_{i=1}^{N} TCP(D_i \cdot v_i) \quad \text{........(12)}$$

Using equation (11), the TCP using Poisson-based model is given by

$$TCP = \left(\frac{1}{2}\right)^{\sum_{i=1}^{N} v_i \cdot Exp\left[2\gamma_{50}\left(1-\frac{D_i}{TCD_{50}}\right)/ln2\right]} \quad \text{........(13)}$$

The tumor-specific parameters used in this study are given in Table 2.[17]

Niemierko model based on equivalent uniform dose

After converting the tumor DVH data of different dose per fraction size into equivalent physical DVH of 2 Gy per fraction using equation (4), the inhomogeneous dose distribution of different dose bin D_i irradiating small volume v_i is reduced into an EUD of the whole volume of the tumor using equation (5). The TCP of the tumor[9] of such dose distribution is given by

$$TCP = \frac{1}{1 + \left[\frac{TCD_{50}}{EUD}\right]^{4\gamma_{50}}} \quad \text{........(14)}$$

Results and Discussion

Dose volume analysis

The flow charts of MATLAB programs for dose volume

Table 2: Parameters of sigmoidal dose response curve of tumor from Okunieff *et al* data for TCP calculation

Organ	Parameters used in TCP calculation				
	TCD50 (Gy)	γ50 (%/%)	a (Niemierko)	Slope50 (%/Gy)	α/β
Prostate (T3)					
Macroscopic	46.29	0.95	-10	2.06	3
Microscopic	35.4	2.6	-10	4.2	3
Head and Neck					
Squamous cell (Macroscopic)	51.77	2.28	-13	4.41	10
Supraglottic (Macroscopic)	50.44	1.83	-13	3.62	10
Microscopic (Squamous cell)	35.4	2.6	-13	4.2	10
Esophagus (Squamous cell)	49.09	2.16	-13	4.41	10

analysis and TCP and NTCP calculation software are shown in Appendix B. For DVH analysis and LKB model based NTCP calculation software, the required input data is cumulative DVH, whereas Poisson's model based TCP calculation software uses the differential DVH. In NTCP and TCP calculation using Niemierko model, differential DVHs are used. This software is compatible for any type of DVH. It can convert any type of DVH into a particular DVH depending on the requirement of model to be used for analysis. Figure 1 shows the output of cumulative DVH of this software, reconstructed from the differential DVH of TPS. This figure also shows percentage difference of calculated cumulative DVH from that of original DVH. The deviations of both the calculated DVHs from those of original DVHs are less than 0.006% except a small spike of -2.35% at an initial dose bin of differential DVH, reconstructed from cumulative DVH. The output of DVH analysis parameters is shown in Table 3. The DVH parameters calculated using this software are D_{100}, D_{95}, $D_{2/3}$, $D_{1/2}$, $D_{1/3}$, and D_{1cc}, (dose to 100%, 95%, 66.66%, 50%, 33.33%, 1 cc volume of the organ, respectively). Mean, maximum and minimum dose (D_{mean}, D_{max} and D_{min}) to the organ are also calculated by it.

Validity checking of NTCP calculation using Emami et al.'s data

The output of this comprehensive in-house developed m-file program of MATLAB software for NTCP and TCP calculation is shown in Figure 2. Table 4 shows the validity checking of normal tissue tolerance data of Emami *et al.*[12] NTCP calculation of LKB model for bladder using normal tissue tolerance dose data points of $TD_{5/5}$ (normal tissue tolerance dose of 80 Gy and 65 Gy to 2/3 volume and whole volume of bladder, respectively, for 5% complication occurrence within 5 years of radiation exposure) of Emami *et al.*[12] was found as 4.76%, which is approximately equal to 5%, whereas Niemierko model calculated it to be 40.96%. 50% complication of bladder for the data of tolerance dose ($TD_{50/5}$ of 85 Gy and 80 Gy to 2/3 volume and whole volume of bladder, respectively) was found exactly as NTCP of 50% was obtained using LKB model, whereas Niemierko model calculated higher complication probability of 70.12%. In selecting the data point of dose corresponding to volume

Table 3: The difference of MATLAB calculated DVH parameters of an organ from those of TPS

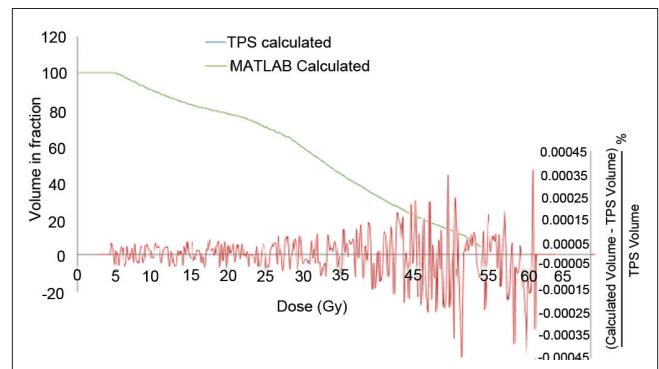| SIB IMRT	TPS	MATLAB	Percent difference normalized TPS
D_{100} (Gy)	23.46	23.50	0.18
D_{95} (Gy)	33.55	33.65	0.28
$D_{2/3}$ (Gy)	47.18	47.42	0.50
$D_{1/2}$ (Gy)	51.94	52.03	0.18
$D_{1/3}$ (Gy)	59.35	59.59	0.41
D_{1cc} (Gy)	77.85	77.96	0.14
Mean dose (Gy)	54.27	54.27	0.00
Maximum dose (Gy)	79.77	79.70	-0.08
Modal dose (Gy)	77.02	77.30	0.36
Absolute volume (cc)	49.30	49.25	-0.09

Figure 1: Dose volume histogram comparison of TPS calculated cumulative DVH and MATLAB calculated cumulative DVH from differential DVH for bowel. Fractional volume difference between the TPS calculated and MATLAB calculated DVHs

lesser than 2/3 volume of bladder, it is assumed that any volume lesser than 2/3 volume of bladder receiving the dose corresponding to 2/3 volume of bladder will produce the same radiobiological effects.

Similarly, in case of rectum, NTCP calculation of LKB model using $TD_{5/5}$ and $TD_{50/5}$ of rectum was found to be 4.78% and 50%, respectively, whereas Niemierko

Table 4: Validity checking of normal tissue complication probability calculation using Emami *et al*. (1994) data

Organ	Tolerance dose for volume			NTCP calculated (LKB) %	NTCP calculated (Niermierko) %	NTCP (Emami et al.) %
	1/3	2/3	1			
Bladder		80	65	4.76	40.96	5
Bladder		85	80	50.00	70.12	50
Rectum			60	4.78	0.99	5
Rectum			80	50.00	50.00	50
Spine	50	50	47	6.63	0.40	5
Spine	70	70	68*	45.44	48.17	50
Brain stem	60	53	50	5.35	13.58	5
Brain stem	65*	65*	65	50.00	48.18	50
Parotid	33* (44*)	32 (43)	32 (32)	4.16 (4.57)	0.25 (12.28)	5
Parotid	47* (63*)	46 (61)	46 (46)	47.62 (47.62)	45.69 (98.93)	50
Larynx	55	52	50	4.95	4.95	5
Larynx	76	72	70	50.00	50.00	50
Lung	45	25	17	5.80	86.48	5
Lung	64	35	25	54.51	99.12	50
Heart	60 (59)	45	40	6.81 (5.13)	49.60	5
Heart	70	55	48	50.00	90.29	50

*Data points of doses (of volume lesser than the available volume) equal or higher than the dose corresponding to volume of the available dose data points were assume that any volume lesser than the available volume of the organ receiving the dose corresponds to the same volume or higher dose will produce the same radiobiological effects.
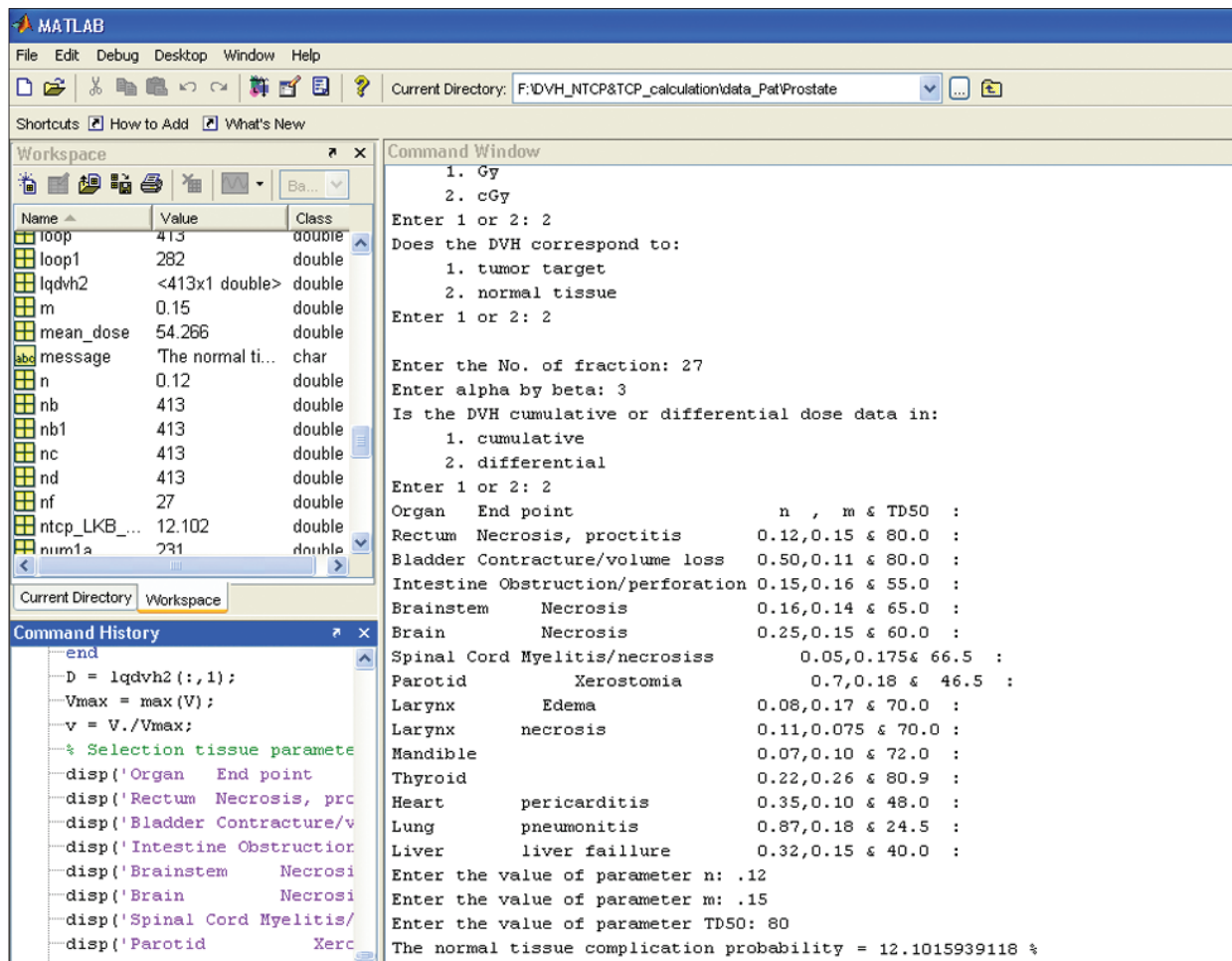

Figure 2: Output of NTCP and TCP calculation software based on Lyman-Kutcher-Burman, Niemierko and Poisson-based model

model underestimated NTCP to be 0.99% for $TD_{5/5}$ and 50% complication was exactly calculated for $TD_{50/5}$. The complication probability calculation of spine using LKB model corresponding to $TD_{5/5}$ and $TD_{50/5}$ was found as 6.63% and 45.44%, respectively, whereas those calculated using Niemierko model were found to be 0.40% and 48.17%, respectively. Both $TD_{5/5}$ and $TD_{50/5}$ were overestimated by Niemierko model in case of lung and heart. The overestimations of lung were 86.48% and 99.12% for $TD_{5/5}$ and $TD_{50/5}$, respectively. Similarly, for heart, $TD_{5/5}$ and $TD_{50/5}$ are calculated as 49.60% and 90.29%, respectively. The values for parotid,[18,19] spine and rectum were found to be underestimated as 0.25%, 0.40% and 0.99%, respectively, for $TD_{5/5}$. However NTCPs of bladder and brainstem were overestimated as 37.91% and 13.58%, respectively, corresponding to $TD_{5/5}$. In all cases of normal tissues, LKB model reproduces the same complication probabilities of normal tissue tolerance data of Emami *et al.*[12]

NTCP calculation output using TPS data

A few brief examples of the output of this software are shown in Table 5. These consist of DVH parameters and NTCPs calculated by this software using the normal tissue dose response and tumor dose response parameters. Figure 3 and Table 5 show DVH calculation of rectum for four different prostate adenocarcinoma treatment plans. According to relative cumulative DVHs and DVH parameters of rectum, plan (2) has to produce the minimum NTCP and NTCP has to be increased in the order: plan (2), plan (4), plan (3) and plan (1). The NTCPs calculated using LKB models are 2.73%, 2.88%, 3.07% and 4.66%, respectively, in the increasing order for the above order of plans, whereas Niemierko models

Table 5: Normal tissue complication probability for the treatment of different sites from tumor control probability data

	Organ at risk	Plan no. (Number of fractions)	Dose (Gy) to percent volume of organ at risks					NTCP (LKB) %	NTCP (Niemierko) %	NTCP (LKB fractionation) %
			D100	D2/3	D1/2	D1/3	Dmean (*D1cc)			
Prostate	Bladder	1 (37)	46.30	64.87	68.34	71.55	68.55	0.77	5.82	0.18
	Bladder	2 (27)	29.90	48.90	53.82	58.61	55.00	0.00	0.75	0.00
	Bladder	3 (37)	29.90	57.58	63.15	68.26	61.41	0.02	0.86	0.00
	Bladder	4 (27)	32.50	47.05	50.52	54.19	52.40	0.00	0.21	0.00
	Bowel	1 (37)	1.3	28.57	30.11	36.64	31.78	5.26	0.38	1.59
	Bowel	2 (27)	4.1	30.22	39.72	46.16	37.50	5.55	11.07	5.76
	Bowel	3 (37)	1.1	21.38	28.16	31.71	26.11	1.76	0.04	0.45
	Bowel	4 (27)	2.7	20.26	25.66	30.11	25.29	0.80	0.12	0.67
	Rectum	1 (37)	37.1	61.68	63.85	67.20	63.71	4.66	5.76	4.95
	Rectum	2 (27)	23.50	47.42	59.59	59.64	54.27	2.73	16.48	12.10
	Rectum	3 (37)	39.30	55.24	62.44	64.36	61.99	3.07	3.17	3.04
	Rectum	4 (27)	31.50	51.64	53.47	56.78	57.01	2.88	15.84	12.25
Head and Neck	Spinal cord	1 (33)	2.25	36.37	37.97	40.40	*42.87	0.73	0.00	0.17
	Spinal cord	2 (33)	2.25	38.24	39.50	41.42	*43.80	0.92	0.00	0.23
	Brain stem	1 (33)	2.00	4.45	10.57	26.60	*37.77	0.00	0.00	0.00
	Brain stem	2 (33)	3.00	9.04	23.66	32.48	*41.48	0.005	0.004	0.000
	Ipsi parotid	1 (33)	55.00	68.47	69.13	70.04	72.07	94.39	99.84	93.55
	Ipsi parotid	2 (33)	37.75	59.51	63.50	66.83	71.37	54.87	98.44	38.90
	Opposite parotid	1 (33)	12.75	18.76	22.78	36.31	62.76	0.02	0.00	0.01
	Opposite parotid	2 (33)	12.25	19.36	23.21	35.58	64.74	0.02	0.00	0.01
	Larynx	1 (33)	37.75	52.42	54.81	57.79	67.33	9.85	28.84	7.87
	Larynx	2 (33)	51.22	54.68	55.89	57.55	63.27	7.54	6.89	4.85
Eshophagus	Spinal cord	1 (27)	0.00	0.83	29.65	40.13	*44.29	0.93	0.00	0.30
	Spinal cord	2 (27)	0.20	1.89	35.99	43.02	*46.25	1.35	0.01	0.47
	Lung	1 (27)	0.20	3.337	5.34	10.03	11.94	0.00	0.06	0.00
	Lung	2 (27)	0.60	5.12	7.81	10.63	13.29	0.02	0.13	0.00
	Heart	1 (27)	0.80	21.58	36.02	38.37	18.63	0.00	0.32	0.00
	Heart	2 (27)	2.00	46.17	47.00	48.35	43.47	6.16	13.76	0.93
	Liver	1 (27)	0.000	0.32	0.43	2.78	20.07	0.00	0.00	0.00
	Liver	2 (27)	0.20	3.89	5.52	11.67	11.75	0.12	0.15	0.04

*Dose to 1 cc volume of the organ at risk

calculated the NTCPs to be 16.48%, 15.84%, 3.17% and 5.76%, respectively. The first two plans used the number of fractions of 27, whereas the last two plans used the number of fractions of 37. Since the fractionation effect is not taken into account in the LKB model, the first two plans produce lesser NTCPs as compared to the last two plans. But when the fractionation effect is taken into account using equation (4) by converting the cumulative dose of different dose per fraction into the equivalent dose of 2 Gy per fraction, the first two plans predict

NTCPs of 12.10% and 12.25%, respectively, whereas the last two plans are estimated to predict 3.04% and 4.95%, respectively, which are approximately predicted by Niemierko model.

NTCPs of different organs at risk (bowel and bladder for four different cases of prostate adenocarcinoma treatments; spinal cord, brainstem, ipsilateral parotid, larynx and contralateral parotid for two cases of a head and neck radiotherapy treatment, and spinal cord, heart, liver and lung for two treatment cases of squamous cell carcinoma of esophagus) are also shown in Table 5. Similarly, the DVH parameters [Table 5] and cumulative DVH [Figures 4 and 5] of these organs can predict NTCPs in LKB model. Considering the fractionation effect by Niemierko and LKB models, the calculated NTCPs were comparable to each other in all organs at risk.

The complication probabilities of ipsilateral parotids were found to be 94.38%, 99.84% and 93.55% for plan (1) and 54.87%, 98.44% and 38.90% for plan (2), when they were calculated using LKB, Niemierko and LKB fractionation models, respectively. DVH parameters also showed relatively larger volume of parotid irradiated
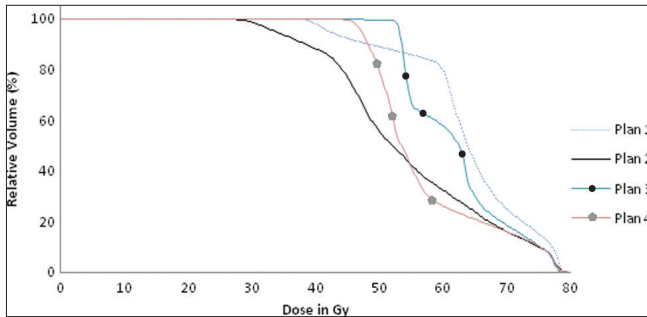

Figure 3: Cumulative dose volume histograms of rectum of four different plans showing the different dose delivery to rectum
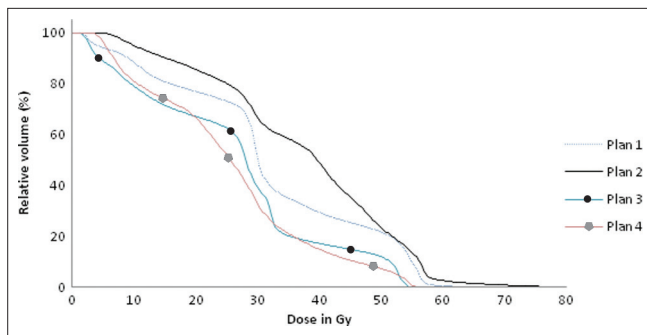

Figure 4: Cumulative dose volume histograms of bowel of four different plans showing the different dose delivery to bowel
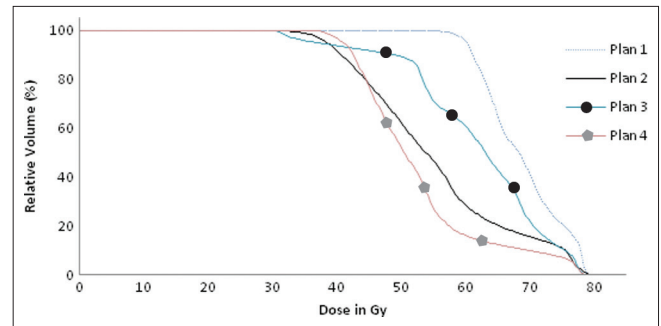

Figure 5: Cumulative dose volume histograms of bladder of four different plans showing the different dose delivery to bladder

Table 6: TCP for the treatment of different sites from TPS data

	PTV of different type of tumor	Plan no.	Dose (Gy) to percent volume of tumor						TCP% (Poisson)	TCP% (Niemierko)
			D_{100}	D_{95}	$D_{2/3}$	$D_{1/2}$	$D_{1/3}$	D_{mean}		
Prostate	Prostate and semina vesicle	1	72.60	76.57	77.35	77.61	77.91	77.63	95.26	92.92
	Prostate and semina vesicle	2	74.20	76.86	77.32	77.48	77.70	77.52	90.48	88.38
	Lymph node	1	45.60	52.28	54.30	54.71	55.14	55.37	98.84	98.91
	Lymph node	2	49.80	52.22	53.74	54.33	62.55	59.38	98.39	98.45
Head and neck	GTV	1	68.50	71.32	72.33	72.67	73.02	72.05	95.91	96.22
	GTV	2	69.50	73.06	74.04	74.38	74.73	73.88	96.81	97.01
	CTV	1	56.50	67.09	70.14	70.94	71.84	67.11	92.49	92.41
	CTV	2	51.50	62.12	66.18	67.55	69.15	63.21	88.59	87.99
	CTV lymph node	1	52.00	57.51	60.08	60.84	61.76	57.89	99.59	99.55
	CTV lymph node	2	50.50	59.34	62.24	63.04	63.93	60.01	99.74	99.69
Eshophagus	GTV	1	52.80	54.25	54.95	55.16	55.40	55.20	70.35	70.85
	GTV	2	53.40	54.59	55.14	55.36	55.62	55.37	70.98	71.53
	CTV	1	35.00	36.95	50.25	53.31	54.73	49.99	90.11	85.32
	CTV	2	35.20	40.23	54.24	54.87	55.26	53.31	96.78	94.31

to higher dose in plan (1) as compared to plan (2). The magnitudes of NTCPs amongst these three models were comparable in plan (1) but varied largely. Both the LKB models calculated smaller than that of Niemierko model in case of plan (2). This is occrred due to the use of a single value of EUD for the whole volume of organ, derived using Kutcher-Burman DVH reduction method in Niemierko model.[5] The decrease in the values of NTCPs of both the LKB models[2,7] is due to the considerations of every fractional volumes and the corresponding equivalent doses reduced from physical doses using the same DVH reduction method. Complication probability calculated using LKB fractionation model was lesser than that of LKB model due to the reduction of the physical dose of parotid into a relatively lesser dose of EQD_2. But in case of plan (1), EQD_2 dose of different fractional volumes of DVH was approximately equal to the physical dose.

TCP calculation

Table 6 presents the calculated values of TCPs of TPS DVH data using Poisson-based model and Niemierko model for the treatment of adenocarcinoma of prostate, squamous cell carcinoma of oropharynx and esophagus tumor. The TCP values calculated using Poisson-based model were marginally larger than those of Niemierko model (within 5%), except the lesser estimation (within 0.6%) for macroscopic tumor of oropharynx and esophagus tumor and microscopic tumor of adenocarcinoma of prostate (within 0.06%). When the DVHs reconstructed from Okunieff *et al.*'s data[17] were used for TCP calculation, 50% TCPs of microscopic[20] and macroscopic tumor of adenocarcinoma[17,21] of prostate were reproduced as 48.31% and 50.25% by both Poisson and Niemierko models. Both the TCP calculation models calculated the same TCP values of 49.32% for all microscopic tumors of squamous cell carcinoma.[17] In case of squamous cell carcinoma of macroscopic tumor of head and neck[22-25] and esophagus,[26-28] TCP values were calculated as 49.86% and 49.32%, respectively, by both Poisson and Niemierko TCP calculation models.

Conclusion

This software developed using MATLAB platform can be used as a user-friendly program to estimate the DVH parameters, TCP and NTCP values, for the ranking of different plans. From the above discussion, it can be concluded that Niemierko model cannot predict the same normal tissue complication data of Emami *et al.*,[12] whereas LKB model can predict the same complication data. Both Poisson-based model and Niemierko model for TCP calculation equally reproduced the same TCP of Okunieff *et al.*'s data.[17] But in case of clinical data generated from TPS, NTCPs calculated using LKB model

were found to be different from those of Niemierko model. When the fractionation effect is considered in LKB model, the calculated NTCPs were lesser than those of LKB model which does not take into account fractionation, but both LKB and Niemierko models were comparable to each other. In case of TCP calculation using these models, Poisson-based model calculated marginally higher control probability as compared to Niemierko model.

Appendix A

Clonogenic cell density of tumor using Niemierko and Goitein modelling[9] is given by

$$N_c = \ln(2).10^{(TCD_{50} / 1)}$$

Where $1 = \dfrac{TCD_{50}(V_1) - TCD_{50}(V_2)}{\log_{10}\left(\dfrac{V_1}{V_2}\right)}$

and is the slope of TCD_{50} response curve as a function of volume. This is the difference in dose needed to achieve 50% TCP for tumors whose volumes differ by a factor of 10.

The clonogenic cell data can also be derived from the sigmoidal dose response curve using as

$$N_c = \ln 2 \ e^{TCD_{50}.(\alpha + \beta.d_f)} \qquad \text{(Poisson approximation by Stavrev N. } et\ al.)[17]$$

$$N_c = \frac{-\ln 2}{\ln\left[1 - e^{-TCD_{50}.(\alpha + \beta\, d_f)}\right]} \quad \text{(Stavrev. } et\ al.)[17]$$
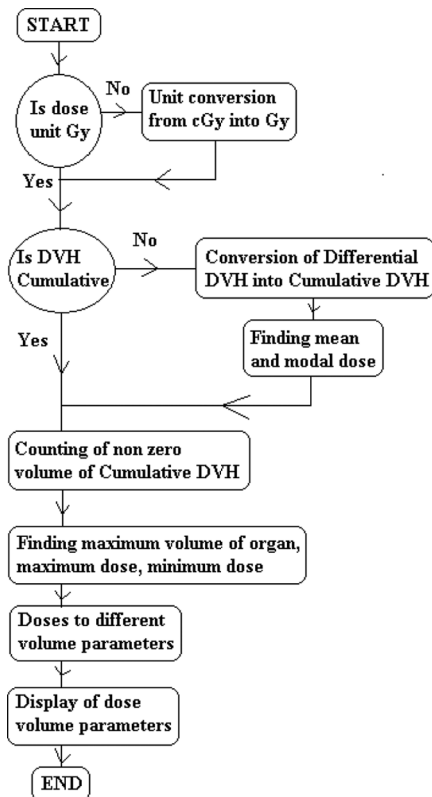
$$N_c = \ln 2 . \exp\left\{\gamma_{50} . \frac{2}{\ln 2}\right\} \quad \text{(Stavrev. } et\ al.)[18]$$

Where α/β and γ_{50} are the tissue specific parameter of linear quadratic models and slope of dose response curve respectively of the organ under consideration. df is the dose per fraction of the treatment schedule. ln is the natural logarithmic to base e (= 2.31).

Appendix B
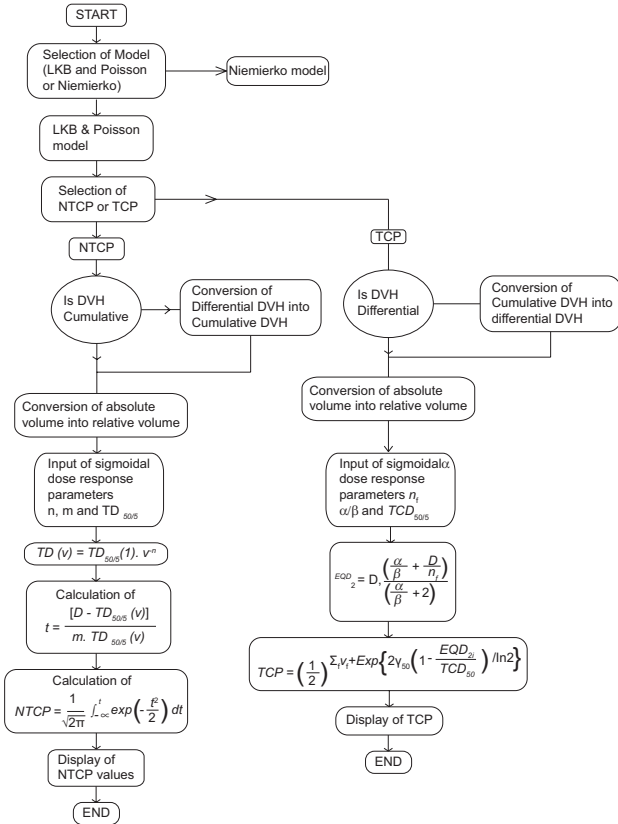
Appendix B.1: Flow chart for DVH analysis

Appendix B.2: Flow chart for NTCP and TCP calculation based on LKB and Poisson based models

References

1. Langer M, Morrill SS, Lane R. A test of the claim that plan rankings are determined by relative complication and TCP. Int J Radiat Oncol Biol Phys 1998;41:451-7.
2. Lyman JT. Complication probability as assessed from dose volume histogram. Radiat Res Suppl 1985;8: S13-9.
3. Wu Q, Mohan R, Niemierko A, Schmidth-Ullrich R. Optimization of IMRT plans based on equivalent uniform dose. Int J Radiat Oncol Biol Phys 2002;52:224-35.
4. Warkentin B, Stavrev P, Stavreva N, Field C, Fallone BG. A TCP and NTCP estimation module using DVHs and known radiobiological models and parameter sets. J Appl Clin Med Phys 2004;5:50-63.
5. Gay H, Niemierko A. A free program for calculating EUD-based NTCP and TCP calculation in external beam radiotherapy. Physica Medica 2007;2:115-25.
6. Sanchez-Nieto B, Nahum AE. BIOPLAN: Software for biological evaluation of radiotherapy treatment plans. Med Dosim 2000;25:71-6.
7. Burman C, Kutcher GJ, Emami, Goiten M. Fitting of normal tissue tolerance data to an analytic-function. Int J Radiat Oncol Biol Phys 1991;21:123-35.
8. Niemierko A, Goiten M. Modeling of normal tissue response to radiation critical volume model. Int J Radiat Oncol Biol Phys 1993;25:135-45.
9. Niemierko A, Goiten M. Implementation of a model for estimating TCP for an inhomogeneously irradiated tumor. Radiother Oncol 1993;29:140-7.
10. Kutcher GJ, Burman C, Brewster L. Histogram reduction method for calculating complication probabilities for three dimensional treatment planning evaluations. Int J Radiat Oncol Biol Phys 1991;21:137-46.
11. Kutcher GJ, Burman C. Calculation of complication probability factors for non-uniform normal tissue irradiation: The effective volume method. Int J Radiat Oncol Biol Phys 1989;16:1623-30.
12. Emami B, Lyman, Brown A. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1994;21:109-22.
13. Kuperman VY. General properties of different models used to predict normal tissue complications due to radiation. Med Phys 2008;35:4831-6.
14. Feller W. An introduction to probability theory and its applications. Vol. 1, 2nd ed. New York: NY: Wiley and Sons; 1957. p. 142-3.
15. Stavrev N, Stavrev P, Warkentin B, Fallone BG. Derivation of the expression for γ50 and D50 for different individual TCP and NTCP models. Phys Med Biol 2002;47:3591-604.
16. Stavrev P, Stavrev N, Niemierko A, Goiten M. Generalization of a model of tissue response to radiation based on the idea of functional subunits and binomial statistics. Phys Med Biol 2001;46:1501-18.
17. Okunieff P, Morgan D, Niemierko A, Suit HD. Radiation dose-response of human tumors. Int J Radiat Oncol Biol Phys 1995;32:1227-37.
18. Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 1999;45:577-87.
19. Chao KS, Deasy JO, Markman J, Haynie J, Perez CA, Purdy JA. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: Initial results. Int J Radiat Oncol Biol Phys 2001;49:907-16.
20. Chu FC, Lin FJ, Kim JH, Huh SH, Garmatis CJ. Locally recurrent carcinoma of the breast. Cancer 1976;37:2677-81.
21. Burstein FD, Calcaterra TC. Supraglottic laryngectomy: Series report and analysis of results. Laryngoscope 1995;95:833-6.
22. Hanks GE. Optimizing the radiation treatment and outcome of prostate cancer. Int J Radiat Oncol Biol Phys 1985;11:1235-45.
23. Khafif RA, Rafla S, Tepper P. Effectiveness of radiotherapy with radical

neck dissection in cancers of the head and neck. Arch Otolaryngol Head Neck Surg 1990;117:1960-9.

24. North CA, Lee DJ, Piantadosi S, Zahurak M, Johns ME. Carcinoma of the major salivary glands treated by surgery or surgery plus postoperative radiotherapy. Int J Radiat Oncol Biol Phys 1990;18:1319-26.

25. Fletcher GH. Clinical dose-response curves of human malignant epithelial tumours. Br J Cancer 1973;46:1-12.

26. Akakura I, Nakamura Y, Kakegawa T, Nakayama R, Watanabe H, Yamashita H. Surgery of carcinoma with preoperative radiation. Chest 1970;57:47-57.

27. Kasai M, Mori S, Watanabe T. Follow-up results after resection of thoracic esophageal carcinoma. World J Surg 1978;2:543-51.

28. Whittington R, Coia LR, Haller DG, Rubenstein JH, Rosato EF. Adenocarcinoma of the esophagus and esophago-gastric junction: The effects of single and combined modalities on the survival and patterns of failure following treatment. Int J Radiat Oncol Biol Phys 1990;19:593-603.

Staying in touch with the journal

1) **Table of Contents (TOC) email alert**
   Receive an email alert containing the TOC when a new complete issue of the journal is made available online. To register for TOC alerts go to **www.jmp.org.in/signup.asp.**

2) **RSS feeds**
   Really Simple Syndication (RSS) helps you to get alerts on new publication right on your desktop without going to the journal's website. You need a software (e.g. RSSReader, Feed Demon, FeedReader, My Yahoo!, NewsGator and NewzCrawler) to get advantage of this tool. RSS feeds can also be read through FireFox or Microsoft Outlook 2007. Once any of these small (and mostly free) software is installed, add **www.jmp.org.in/rssfeed.asp** as one of the feeds.