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Analytical approach to estimate normal tissue complication probability using best fit of normal tissue tolerance doses into the NTCP equation of the linear quadratic model

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ABSTRACT

Aims and Objectives: Aims and objectives of this study are to get the best fit of the normal tissue tolerance doses to the NTCP model of the linear quadratic model.

Methods and Materials: To compute the NTCP, the modified form of the Poisson cell kill model of NTCP, based on linear-quadratic model, is used. The model has been applied to compute the parameters of the NTCP model using clinical tolerance doses of various normal tissues / organs extracted from published reports of various authors. The normal tissue tolerance doses are calculated for partial volumes of the organs using the values of above-said parameters for published data on normal tissue tolerance doses. In this article, a graphical representation of the computed NTCP for bladder, brain, heart and rectum is presented.

Results and Conclusion: A fairly good correspondence is found between the curves of 2 sets of data for brain, heart and rectum. Hence the model may, therefore, be used to interpolate clinical data to provide an estimate of NTCP for these organs for any altered fractionated treatment schedule.

Key words: Normal tissue complication probability, Normal tissue tolerance dose, Linear-quadratic model, External beam radiotherapy, volume effect

INTRODUCTION

Estimation of the normal tissue complication probability (NTCP) of critical organs is an essential factor prior to the delivery of external beam radiotherapy (EBRT), because very often critical organs, within the vicinity of the tumour, receive a radiation dose equal to that of the tumour, which is generally based on the published data on normal tissue complications and clinical experience of the radiation oncologist.[1, 2] First set of normal tissue tolerance doses was published by Rubin and Cassarett,[3] in terms of $TD_{5/5}$ and $TD_{50/5}$ (the NTCP at 5% and 50%, respectively, within 5 years after radiotherapy) for a large number of normal tissues and organs. Some other investigators had also done in this direction but their work was little comprehensive and systematic.[4, 5, 6, 7]

Similar concept of $TD_{5/5}$ and $TD_{50/5}$ has been adopted by Emami et al [8] to report the normal tissue tolerance doses for selected organs. The normal tissue tolerance doses were defined for uniformly irradiated 1/3, 2/3 and 3/3 partial volumes of the organs only for conventional fractionation schedules of 1.8 to 2 Gy per fraction, 5 fractions a week. The work of many other researchers is sparsely scattered in the literature and are for limited organs with varied end points.[9-51]

Because of radiobiological bearings of the empirical model based on linear-quadratic (LQ) model, proposed by Kallman et al [52] and modified by Zaider & Amols,[53] has been used, in this study, to fit these data with consideration of quadratic term. A method of least square fit was used to compute the values of the parameters of the model for the normal tissue tolerance doses. The values of the tissue specific LQ parameters, α and β, are determined using the value of a factor, $\alpha\Gamma$, of the NTCP equation obtained from the above said least square fit and other researches using

the published values of the α/β ratio for different normal tissue and organs extracted from the literature, where $\Gamma = [1 + d/(\alpha/\beta)]$. A set of representative curves have also been plotted between dose and computed NTCP to demonstrate the applicability of the NTCP model.

METHODS AND MATERIALS

NTCP Model

The proposed equation of the NTCP model has radiobiological bearings and is similar to that proposed by Zaider & Amols.[53] The expression of the equation of the NTCP model may be written as

$$NTCP(D, v) = \exp[-N_0 v^{-k} \exp\{-\alpha D\Gamma\}] \quad (1)$$

Where $\Gamma = [1+d/(\alpha/\beta)]$, a is the coefficient of lethal damage and α/β is the ratio of the coefficients of lethal and sublethal damages. The N_0 and k are non-negative adjustable parameters, v is the uniformly irradiated partial volume of the tissue/organ (i.e. $v = V/V_{ref}$, where V is uniformly irradiated volume of the normal tissue/organ and V_{ref} is the reference volume of the normal tissue/organ). D is the normal tissue dose in terms of $TD_{5/5}$ or $TD_{50/5,}$ delivered with d dose per fraction. The expression in the exponent, exp ($-\alpha D\Gamma$), is the reminiscent of the LQ model for cellular survival.

The expression of the relative effectiveness (RE) per unit dose can be written as

$$RE = \Gamma \quad (2)$$

Using equation (2) into equation (1) the expression of NTCP may be written as

$$NTCP(D, v) = \exp[-N_0 v^{-k} \exp\{-\alpha D^*RE\}]$$

Or

$$NTCP(D, v) = \exp[-N_0 v^{-k} \exp\{-\alpha BED\}] \quad (3)$$

Where $BED = D^*RE$. In equation (1), if N_0 is considered to be the clonogenic cell density of the tumour cells, and the exponent of the partial volume v is taken as $k = -1$, then the product of $N_0 v$ represents the total number of the clonogenic cells in the tumour volume and the expression will be of the tumour control probability (TCP) model. But here in equation (1) the N_0 and k are assumed to be non-negative adjustable parameters and are allowed to vary depending on the type of the tissue / organ. To get the best fit of normal tissue tolerance doses, it is required that parameter k should be greater than zero, i.e. $k > 0$, and as the volume of the irradiated tissue / organ increases, the NTCP of the tissue must also increase.

Normal Tissue Tolerance Doses

To get the best fit of equation (1) the published normal tissue tolerance doses of Emami et al [8] and other investigators [9-51] have been used. The Emami et al's data are in the form of TD5/5 and TD50/5 defined for 1/3, 2/3, and 3/3 partial volumes or a reference volume (length or area) of the organs. The partial volume of a organ is presented in terms of fraction of the reference volume V_{ref}. In many cases the reference volume of the organ is considered to be the whole volume of the organ while in some it is assumed to be a part of the organ or length of the organ, such as spinal cord.

Many other workers have also reported normal tissue tolerance doses for different organs / tissue, but these are widely scattered in the literature and is very difficult to extract from all reports.[9-51] Hence, in this study, an attempt is made to collect normal tissue tolerance doses from published reports for the organs for which Emami et al [8] have compiled. I have chosen only those reports which have tolerance doses at different NTCP levels for fractional (partial) volumes of the organs or at different NTCP levels for whole organ or at same NTCP level for fractional volumes. The references of the reports from where data have been extracted, other than Emami et al,[8] are listed in [Table 1]. There has not been any control on the tolerance data and these may be of less severe endpoints.

RESULTS

Normal tissue tolerance data of Emami et al [8] used to fit into the equation (1) to obtain the values of $\alpha\Gamma$, k and N_0. The method of least square fit is used to compute the parameters using transformed linear expression of the equation (1). The values of aG, k and N_0 for Emami et al [8] are listed in Table 2 along with the end points of corresponding normal tissues / organs. In case of 2 point data, the tolerance doses, $TD_{5/5}$ and $TD_{50/5}$, are given only for single volume. Hence these parameters can not be computed, because for the purpose more than 2 point data are required. Due to unavailability of adequate data no attempt can be made to set correlation between NTCP and volume. To solve this problem, for simplicity, it is assumed that the organs which have only 2 point data do not show volume dependency with NTCP. So the value of k, for these organs, is set equal to zero. Using the computed values of $\alpha\Gamma$, k and N_0 parameters, the values of the tolerance doses for partial volumes of the organs are computed and are listed in Table 3 along with the tolerance doses compiled by Emami et al.[8] Since the parameter $\alpha\Gamma$ is a factor of the coefficients α and β (or α/β), so to determine the values of these coefficients, an accurate value of α/β for a tissue/organ must be known. Hence, the published values of α/β, for different organs, are extracted from the literature,[54-81] and are used to calculated the values of α and β. The extracted values of α/β of different tissues/organs, along with their reference(s) of the publication, and calculated values of α and β are listed in [Table 5]. In the calculation of the values of α and β from the factor $\alpha\Gamma$, it is assumed that the dose per fraction is 2Gy for the conventional treatment schedule.

Survey of the literature reveals that there is a wide scattering in the normal tissue tolerance doses and no consensus on the issue among the radiation oncology community. In

Table 1: Parameters $\alpha\Gamma$, k and N_0, for different organs [8-51]

Organ	$\alpha\Gamma$	k	N_0	References
Kidney	0.0962	2.3462	15.55	[8,9,10,11,12]
Brain	0.0683	0.7031	75.43	[8,9,10,13,14]
Brain stem	0.1062	0.6210	814.40	[8,9,15]
Ear(Mid/Ext)	0.1464	0	241.84	[8]
Ear(Mid/Ext)	0.1289	0.1647	4033.12	[8,16,15]
Esophagus	0.0976	0.1811	748.82	[8,9,10,17]
Heart	0.1158	2.5685	183.67	[8,9,10]
Bladder	0.0476	0.1582	42.61	[8,9,10,18,19]
Larynx(Cartilage necrosis)	0.1291	1.1778	19147.40	[8]
Larynx (Edema)	0.0613	-1.2949	153.94	[8,20]
Liver	0.1050	1.6023	56.491	[8,9,21]
Lung	0.0468	1.0299	3.93	[8,9,22,23]
Skin-> *Necrosis*:	0.0857	0.6015	283.51	*Necrosis*:- [8,9,24]
Telangiectasia:	0.0885	0	219.39	*Telangiectasia*:- [8,24]
Small intestine	0.1071	0.3737	345.60	[8,9,10]
Colon	0.1464	1.3323	2172.96	[8]
Spinal cord	0.0614	-0.0489	56.12	[8,9,10,25,26,27,14,28,29]
Stomach	0.0968	1.0179	277.26	[8,9]
Temporomandibular joint & mandible	0.0796	0.0227	361.39	[8,9,10,15,30,31,32,33,34,35,36,37]
Cauda equine	0.0885	0	538.20	[8,9]
Brachial plexus	0.0832	0.2908	351.65	[8,38]
Femoral head & neck	0.0842	0	280.26	[8,9]
Eye lens	0.1450	0	7.99	[8,10,39]
Optic nerve	0.0828	0	177.81	[8,9,40,41,42]
Optic chiasma	0.0418	0	23.73	[8,43]
Retina	0.0866	0	143.02	[8,44,45]
Rectum	0.0490	0.2001	42.44	[8,9,10,46,47,18,48,49,50]
Rib cage	0.0944	0	415.08	[8,51]
Parotid	0.0569	0.0192	13.16	[8,9]
Thyroid	0.0139	0	4.39	[8,9]

Table 2: Parameters $\alpha\Gamma$, k and N_0, for different organs. [8]

Organ	$\alpha\Gamma$	k	N_0	End Point
Kidney	0.0177	4.6091	123.37	Clinical nephritis
Brain	0.0975	1.3390	235.36	Necrosis / infraction
Brain stem	0.0956	0.8815	345.81	Necrosis / infraction
Ear(Mid/Ext)	0.1464	0	241.84	Acute serious otitis
Ear(Mid/Ext)	0.1464	0	9391.38	Chronic serious otitis
Esophagus	0.1180	0.4681	2132.37	Clinical stricture/ perforation
Heart	0.1395	2.5911	669.16	Pericarditis
Bladder	0.1171	2.9239	7007.99	Symptomatic bladder contracture and volume loss
Larynx	0.1291	1.1778	19147.40	Cartilage necrosis
Larynx	0.0418	0	19.67	Laryngeal edema
Liver	0.1587	2.5643	349.84	Liver failure
Lung	0.0977	3.0007	11.90	Pneumonitis
Skin	0.0886	0.5867	351.42	Necrosis / ulceration
	0.0976	0	393.94	Telangiectasia
Small intestine	0.1126	0.7617	302.92	Obstruction / perforation
Colon	0.1464	1.3323	2172.96	Obstruction / perforation / ulceration / fistula
Spinal cord	0.0714	0.1211	90.68	Myelitis / necrosis
Stomach	0.1151	0.7637	1118.77	Ulceration / perforation
Temporomandibular joint & mandible	0.1195	0.5782	3508.31	Marked limitation of the joint function
Cauda equine	0.0976	0	1045.23	Clinically apparent nerve damage
Brachial plexus	0.0976	0.1736	1054.43	Clinically apparent nerve damage
Femoral head & neck	0.1126	0	1045.23	Necrosis
Eye lens	0.1824	0	18.67	Cataract requiring intervention
Optic nerve	0.0976	0	393.94	Blindness
Optic chiasma	0.0976	0	393.94	Blindness
Retina	0.0732	0	80.68	Blindness
Rectum	0.0732	0	241.84	Severe proctitis / necrosis / stenosis / fistula
Rib cage	0.0975	0	393.94	Pathologic fracture
Parotid	0.1046	0	85.01	Xerostomia
Thyroid	0.0419	0	19.76	Clinical thyroiditis

Table 3: Calculated tolerance doses by the proposed model and tolerance doses of Emami et al [8]

Organ	$TD_{5/5}$ (Gy) Volume 1/3		2/3		3/3		$TD_{50/5}$ (Gy) Volume 1/3		2/3		3/3		End point
	Clinical	Calc.	Clinical	Calc.	Clinical	Calc.	Clinical	Calc.	Clinical	Calc.	Clinical	Calc.	
Kidney	50	49.64	30	31.38	23	21.06	—	57.88	40	39.63	28	29.30	Clinical nephritis
Brain	60	59.90	50	50.27	45	44.82	75	74.91	65	65.28	60	59.83	Necrosis/ infraction
Brain stem	60	59.86	53	53.39	50	49.73	—	75.14	—	68.67	65	65.02	Necrosis/ infraction
Ear(Mid/Ext)	30	30	30	30	30	30	40	40	40	40	40	40	Acute serious otitis
Ear(Mid/Ext)	55	55	55	55	55	55	65	65	65	65	65	65	Chronic serious otitis
Esophagus perforation	60	60	58	57.23	55	55.66	72	72.41	70	69.63	68	68.07	Clinical stricture/
Heart	60	59.26	45	46.23	40	38.86	70	69.69	55	56.66	50	49.29	Pericarditis
Bladder	—	93.93	80	76.25	65	66.25	—	106.43	85	88.75	80	78.75	Symptomatic bladder contracture and loss
volume													
Larynx	79	78.02	70	71.56	70	67.90	90	89.36	80	82.90	80	79.25	Cartilage necrosis
Larynx	—	45	45	45	45	45	—	80	—	80	80	80	Laryngeal edema
Liver	50	47.60	35	36.27	30	29.86	55	56.78	45	45.45	40	39.04	Liver failure
Lung	45	47.88	30	26.36	17.5	14.19	65	62.93	40	41.41	24.5	29.24	Pneumonitis
Skin	$10cm^2$	$10cm^2$	$30cm^2$	$30cm^2$	$100cm^2$	$100cm^2$	$10cm^2$	$10cm^2$	$30cm^2$	$30cm^2$	$100cm^2$	$100cm^2$	Necrosis/ulceration
	70	69.07	60	61.79	55	53.81	—	85.60	—	78.32	70	70.34	
Small intestine	50	48.50	—	43.71	40	41.00	60	61.50	—	56.71	55	54.00	Obstruction/ perforation
Colon	55	55	—	48.61	45	45	65	65	—	58.61	55	55	Obstruction/ perforation/ ulceration/ fistula
Spinal cord	5cm	5cm	10cm	10cm	20cm	20cm	5cm	5cm	10cm	10cm	20cm	20cm	Myelitis/necrosis
	50*	50.14*	50	48.96	47	47.78	70*	70.64*	70	69.47	—	68.29	

Table 3: (Cont.) Calculated tolerance doses by the proposed model and tolerance doses of Emami et al [8]

Organ	$TD_{5/5}$ (Gy) Volume 1/3		2/3		3/3		$TD_{50/5}$ (Gy) Volume 1/3		2/3		3/3		End point
	Clinical	Calc.	Clinical	Calc.	Clinical	Calc.	Clinical	Calc.	Clinical	Calc.	Clinical	Calc.	
Stomach	60	58.83	55.0	54.13	50	51.47	70	71.55	67	66.85	65	64.19	Ulceration/ perforation
Temporomandibular joint & mandible	65	64.46	60	61.06	60	59.13	77	76.70	72	73.29	72	71.37	Marked limitation of the joint function
Cauda equina	—	60	—	60	60	60	—	75.01	—	75.01	75	75.01	Clinically apparent nerve damage
Brachial plexus	62	62.06	61	60.82	60	60.11	77	77.07	76	75.82	75	75.12	Clinically apparent nerve damage
Femoral head & neck	—	52	—	52	52	52	—	65	—	65	65	65	Necrosis
Eye lens	—	10	—	10	10	10	—	18	—	18	18	18	Cataract requiring intervention
Optic nerve	—	50	—	50	50	50	—	65	—	65	65	65	Blindness
Optic chiasma	—	50	—	50	50	50	—	65	—	65	65	65	Blindness
Retina	—	45	—	45	45	45	—	65	—	65	65	65	Blindness
Rectum	—	61.38	—	60.50	60	60	—	81.38	—	80.50	80	80	Severe proctitis/ necrosis/ stenosis/ fistula
Rib cage	50	50	—	50	—	50	65	65	—	65	—	65	Pathologic fracture
Parotid	—	32	32	32	32	32	—	46	46	46	46	46	Xerostomia
Thyroid	—	45	—	45	45	45	—	79.91	—	79.91	80	79.91	Clinical thyroiditis

this study suitable tolerance dose data, for the organs, have been extracted from the literature and combined together with Emami et al's [8] data to compute the values of above said parameters. [Table 1] enlists the values of these parameters, i.e. $\alpha\Gamma$, k and N_0, for the listed organs, for the combined tolerance doses along with the source of references. With use of the values of $\alpha\Gamma$, k and N_0 parameters, from Table 1, the values of the tolerance doses for 1/3, 2/3 & 3/3 partial volumes of all listed organs are computed and are listed in [Table 4]. In the brackets of the Table 4 along with computed values of the tolerance doses, the 95 % confidence interval (CI) limits for published data are given. The limits of 95% CI are calculated using computed tolerance doses($TD_{5/5}$ or $TD_{50/5}$) and standard errors (s) of the published tolerance doses. The parameter $\alpha\Gamma$ is used to compute the values of α and β, for combined data set of the tolerance doses for each organ, the published values of α/β for different organs, as used for Emami et al's [8] data, have taken into account. The extracted values of α/β of different tissues/organs, along with their reference (s) of the publication, and calculated values of α and β are listed in Table 5.

Using the values of $\alpha\Gamma$, k and N_0, from Tables 1 & 2, 2 set of curves have been plotted between dose and computed NTCP for bladder, brain, heart and rectum for partial and whole volume and are shown in Figures 1 - 4. The solid lines of the curves are for the Emami et al's [8] data and broken lines are for combined data. In the curve fitting, a method of least square fit has been used. To plot the curve for Emami et al's [8] data with 2 points tolerance doses the parameter k is set to zero, because there is no conclusion could be made on volume dependency of the organ, and rest of the parameters are calculated from these data.

DISCUSSION

A number of models have been proposed to predict the NTCP of normal tissues/critical organs by many authors [52,82,53]. All the models predict an increase in NTCP with increasing absorbed dose and irradiated volume. The model, presented in this study, is the Kallman's[52] Poisson cell kill model, modified by Zaider and Amols,[53] which had a radiobiological base, because it is based on the linear quadratic model. Normal tissue tolerance doses of Emami et al's[8] and other authors (in combination of Emami et al's data[8]) have been used to fit into the transformed expression of the equation (1) to determine the values the parameters $\alpha\Gamma$, k and N_0. The values of these parameters were used to calculate the values of the tolerance doses for partial volumes of the organs and were named as the theoretically calculated tolerance doses, and are listed in Tables 3 & 4 for both set of data. The theoretically calculated tolerance doses, for Emami et al's[8] data, are very close to the compiled tolerance doses[8] [Table 3]. The theoretical tolerance doses are also calculated for 1/3, 2/3 & 3/3 partial volumes of the organs using the values of $\alpha\Gamma$, k and N_0 from Table 1 for the combined set of data. Values of k [Tables 1 & 2] indicate that the organs which has higher value of k have high volume dependency than that of the lower value of k. i.e. the volume dependency of the organs is directly proportional to the value of the k. No volume dependency could be estimated for the organs where only 2 point data are given. Such organs are femoral head and neck, rib cage, skin (telangiectasia), optic nerve, optic chiasma, cauda equina, eye lens, retina, ear (middle/external), parotid, larynx (edema), rectum and thyroid. The value of parameter, k, for these organs, is adjusted to zero. For the combined set of data, the correlation between tolerance dose and volume is similar to that for Emami et al's [8] data, except for 2 organs such as spinal cord and larynx (edema), where the value of k is negative which show that the tolerance dose increases with increasing the irradiated volume of these organs which is contradictory to the available data and our own experience.

The accuracy of the computed values of the parameters of the model depends on the accuracy of the complied tolerance doses and their end points, which are used to compute the parameters. The organs for which all 6 point tolerance doses are provided the calculated values of the parameters have better confidence. On the other hand, the values of the parameters became less accurate for the tolerance doses, where the tolerance doses are not provided for one or more partial volumes either at 5% or at 50% or at both NTCP levels. For these organs, the dependency of the parameters is more skewed towards data provided for the partial volumes and NTCP. For example, in case of Emami et al's [8] data of skin (necrosis) and brain stem, the tolerance doses at NTCP level of 5% are provided for all 3 partial volumes, while at NTCP level of 50% the data are provided only for whole organ. Hence the parameters, $\alpha\Gamma$, k and N_0, have more dependency on the tolerance doses provided for NTCP level of 5%. Similarly the dependency of the parameters can be seen for other data set. In the cases for which the tolerance doses are provided only for one partial volume for NTCPs at 5% and 50%, the volume dependent parameter, k, could not be computed, and hence there will be much less confidence in the results. For the cases for which only 2 point data are provided, the computation of the parameters, $\alpha\Gamma$ and N_0, is done by adjusting $k = 0$ for the simplification. The values of the parameters, $\alpha\Gamma$ and N_0, for 2 point data have less confidence. When other author's data were combined with the Emami et al's [8] data and the parameters, $\alpha\Gamma$, k and N_0, were computed, then it is seen that the values of these parameters become highly inaccurate. Because most of the data are for single volume of the organ and have a wide variation in their values, and even some of the data do not have their same endpoints, or may have different endpoint definition.

To get more accurate values of the parameters, $\alpha\Gamma$, k and N_0, it is necessary to have accurate and some more additional tolerance doses for all the organs. The best use of

Table 4: Tolerance doses with 95% (Calc TD5/5 or TD50/5 ±1.96s) confidence interval (Gy) [8-51].

Organ	TD5/5(1/3)(95%CI)	TD5/5(2/3)(95% CI)	TD5/5(3/3)(95%CI)	TD50/5(1/3)(95% CI)	TD50/5(2/3)(95% CI)	TD50/5(3/3)(95% CI)
Kidney	43.92 (41.31–46.54)	27.02 (24.40-29.63)	17.12 (14.51-19.74)	59.14 (56.53-61.76)	42.23 (39.62-44.85)	32.34 (29.73-34.95)
Brain	58.56 (55.34–61.78)	51.42 (48.21-54.64)	47.25 (44.03-50.46)	80 (76.78-83.21)	72.86 (69.64-76.07)	68.68 (65.47-71.90)
Brain stem	59.20 (56.10–62.31)	55.15 (52.05-58.26)	52.78 (49.67-55.89)	72.99 (69.88-76.09)	68.93 (65.83-72.04)	66.56 (63.46-69.67)
Ear(Mid/Ext)	29.99 (29.99-30)	29.99 (29.99-30)	29.99 (29.99-30)	39.99 (39.99-40)	39.99 (39.99-40)	39.99 (39.99-40)
Ear(Mid/Ext)	57.30 (54.74-59.86)	56.41 (53.85-58.98)	55.9 (53.33-58.46)	68.66 (66.06-71.22)	67.77 (65.21-70.33)	67.25 (64.69-69.81)
Esophagus	59.10 (57.34-60.87)	57.82 (56.05-59.58)	57.07 (55.3-58.83)	74.1 (72.34-75.87)	72.82 (71.05-74.58)	72.07 (70.30-73.83)
Heart	59.91 (58.25-61.56)	44.53 (42.88-46.19)	35.54 (33.88-37.20)	72.54 (70.89-74.20)	57.17 (55.51-58.83)	48.18 (46.52-49.84)
Bladder	59.40 (54.71-64.09)	57.1 (52.41-61.79)	55.75 (51.06-60.44)	90.14 (85.45-94.83)	87.84 (83.15-92.53)	86.49 (81.80-91.18)
Larynx (Cartilage necrosis)	77.90 (76.52-79.26)	71.57 (70.19-72.96)	67.88 (66.49-69.26)	89.24 (87.85-90.62)	82.91 (81.53-84.29)	79.21 (77.83-80.60)
Larynx (Edema)	41.05 (37.14-44.96)	55.69 (51.78-59.60)	64.25 (60.34-68.17)	64.92 (61.01-68.84)	79.56 (75.65-83.48)	88.13 (84.21-92.04)
Liver	44.73 (42.51-46.94)	34.15 (31.94-36.37)	27.96 (25.75-30.18)	58.66 (56.45-60.88)	48.09 (45.87-50.30)	41.9 (39.69-44.12)
Lung	29.93 (21.51-38.34)	14.69 (6.269-23.10)	5.771 (-2.65-14.19)	61.18 (52.76-69.60)	45.94 (37.52-54.35)	37.02 (28.6-45.44)
Skin-> Necrosis:	60.84 (58.48-63.20)	55.97 (53.61-58.33)	53.12 (50.76-55.48)	77.92 (75.57-80.28)	73.06 (70.70-75.42)	70.21 (67.85-72.57)
Telangiectasia:	48.54 (47.51-49.58)	48.54 (47.51-49.58)	48.54 (47.51-49.58)	65.09 (64.06-66.13)	65.09 (64.06-66.13)	65.09 (64.06-66.13)
Small intestine	48.17 (45.77-50.56)	45.75 (43.36-48.14)	44.33 (41.94-46.73)	61.83 (59.44-64.23)	59.41 (57.02-61.81)	58 (55.61-60.39)
Colon	55.00 (0.0-0.0)	48.69 (0.0-0.0)	45 (0.0-0.0)	65 (0.0-0.0)	58.69 (0.0-0.0)	55 (0.0-0.0)
Spinal cord	46.89 (43.58-50.19)	47.44 (44.13-50.75)	47.76 (44.45-51.07)	70.74 (67.44-74.05)	71.30 (67.99-74.61)	71.62 (68.31-74.93)
Stomach	58.33 (56.10-60.55)	51.04 (48.81-53.26)	46.77 (44.55-49.00)	73.45 (71.22-75.67)	66.16 (63.93-68.39)	61.9 (59.67-64.12)
Temporomandibular joint & mandible	60.51 (57.75-63.27)	60.32 (57.56-63.08)	60.2 (57.44-62.96)	78.90 (76.14-81.66)	78.7 (75.94-81.46)	78.58 (75.82-81.35)
Cauda equine	58.65 (47.06-70.25)	58.65 (47.06-70.25)	58.65 (47.06-70.25)	75.19 (63.60-86.79)	75.19 (63.60-86.79)	75.19 (63.60-86.79)
Brachial plexus	61.09 (59.70-62.48)	58.67 (57.27-60.06)	57.25 (55.86-58.64)	78.67 (77.28-80.06)	76.25 (74.86-77.64)	74.83 (73.44-76.23)
Femoral head & neck	51.61 (41.56-61.66)	51.61 (41.56-61.66)	51.61 (41.56-61.66)	63.70 (53.65-73.74)	63.7 (53.65-73.74)	63.7 (53.65-73.74)
Eye lens	6.762 (4.29-9.23)	6.762 (4.294-9.229)	6.762 (4.294-9.229)	16.86 (14.39-19.32)	16.86 (14.39-19.32)	16.86 (14.39-19.32)
Optic nerve	49.34 (46.06-52.62)	49.34 (46.06-52.62)	49.34 (46.06-52.62)	67.02 (63.74-70.31)	67.02 (63.74-70.31)	67.02 (63.74-70.31)
Optic chiasma	49.54 (37.54-61.54)	49.54 (37.54-61.54)	49.54 (37.54-61.54)	84.57 (72.57-96.57)	84.57 (72.57-96.57)	84.57 (72.57-96.57)
Retina	44.67 (43.04-46.29)	44.67 (43.04-46.29)	44.67 (43.04-46.29)	61.58 (59.95-63.20)	61.58 (59.95-63.20)	61.58 (59.95-63.20)
Rectum	58.56 (55.15-61.97)	55.73 (52.32-59.14)	54.08 (50.66-57.49)	88.42 (85.00-91.83)	85.59 (82.17-89.00)	83.93 (80.52-87.35)
Rib cage	52.23 (49.78-54.69)	52.23 (49.78-54.69)	52.23 (49.78-54.69)	67.74 (65.29-70.19)	67.74 (65.29-70.19)	67.74 (65.29-70.19)
Parotid	26.38 (9.74-43.02)	26.14 (9.501-42.78)	26 (9.364-42.65)	52.09 (35.45-68.73)	51.86 (35.22-68.50)	51.72 (35.08-68.36)
Thyroid	27.50 (-2.21-57.20)	27.5 (-2.2-57.2)	27.5 (-2.2-57.20)	132.5 (102.8-162.2))	132.5 (102.8-162.2)	132.5 (102.8-162.2)

Table 5: Values of the α/β and calculated values of α & β for listed organs

	Emami et al (8)			Emami et al (8) + others			
Organ	**α/β (Gy)**	**α (Gy^{-1})**	**β (Gy^{-2})**	**α (Gy^{-1})**	**β (Gy^{-2})**	**End point**	**Reference**
Kidney	3.0 - 3.5	0.0106 - 0.0113	0.0036 - 0.0032	0.0577 - 0.0612	0.0192 - 0.0175	Clinical nephritis	[54,55,56][57]
	2.5	0.0099	0.0039	0.0534	0.0214		
Brain	2.1	0.0499	0.0238	0.0350	0.0167	Necrosis/ infraction	[58,59]
Brain stem	2.1	0.0491	0.0234	0.0544	0.0259	Necrosis/ infraction	[58,59]
Ear(Mid/Ext)	3.0*	0.0878	0.0293	0.0878	0.0293	Acute serious otitis	[60]
Ear(Mid/Ext)	3.0*	0.0878	0.0293	0.0773	0.0258	Cronicserious otitis	[60]
Esophagus	3.0*	0.0708	0.0236	0.0585	0.0195	Clinical stricture /perforation	[61]
Heart	2.0	0.0702	0.0351	0.0579	0.0290	Pericarditis	[62,63,64]
Bladder	6.0	0.0878	0.0146	0.0357	0.0060	Symptomatic	[55,56][65,66]
	3.4 - 4.5	0.0737 - 0.0811	0.0217 - 0.0780	0.030 - 0.033	0.0088 - 0.0073	bladder contracture and volume loss	
Larynx [69,70]	»3.4	» 0.0813	» 0.0239	» 0.0813	» 0.0239	Cartilage necrosis	[67] [68]
	< 4.4	0.0888	0.0202	0.0888	0.0202		
	< 4.2	0.0875	0.0208	0.0875	0.0208		
Larynx	3.8	0.0274	0.0072	0.0402	0.0106	Laryngeal edema	[71]
Liver	1.5	0.0683	0.0455	0.045	0.030	Liver failure	[72]
Lung	< 3.8	£0.0637	³0.0168	£0.0307	³0.0081	Pneumonitis	[73] [74,51]
	4.4 - 6.9	0.0669 - 0.0754	0.0152 - 0.0109	0.0322 - 0.0363	0.0073 - 0.0093		
Skin	1.9 - 2.3	0.0432 - 0.0474	0.0227 - 0.0206	0.0417 - 0.0458	0.022 - 0.0199	Necrosis/ulceration	[74,51]
Small intestine	6.0 - 8.3	0.0845 - 0.0907	0.0141 - 0.0109	0.0803 - 0.0863	0.0134 - 0.0104	Obstruction/ perforation	[75]
Colon	3.1 - 5.0	0.0890 - 0.1046	0.0287 - 0.0209	0.0890 - 0.1046	0.0287 - 0.0209	Obstruction/ perforation/ ulceration/fistula	[76]
Spinal cord	< 3.3	0.0445	0.0135	£0.0382	³0.0116	Myelitis/necrosis	[77]
	2.0	0.0357	0.0179	0.0307	0.0153		[57]
Stomach	7-10	0.0895 - 0.0959	0.0128 - 0.0096	0.0753 - 0.0807	0.0108 - 0.00807	Ulceration/ perforation	[57]
Temporomandibular & mandible	3.5	0.0761	0.0217	0.0507	0.0145	Marked limitation of the joint function	[78] joint
Cauda equina	2.0 - 3.0	0.0488 - 0.0586	0.0244 - 0.0195	0.0443 - 0.0531	0.0221 - 0.0177	Clinically apparent nerve damage	[79]
Brachial plexus	< 5.3	0.0709	0.0134	£0.0604	³0.0114	Clinically apparent nerve damage	[38]
Femoral head & neck	0.8	0.0349	0.0388	0.0346	0.0432	Necrosis	[30,31]
Eye lens	1.2	0.0686	0.0572	0.0544	0.0453	Cataract requiring intervention	[80]
Optic nerve	3.0*	0.0586	0.0195	0.0497	0.0166	Blindness	—
Optic chiasma	3.0*	0.0586	0.0195	0.0251	0.0084	Blindness	——
Retina	3.0*	0.0439	0.0146	0.0519	0.0173	Blindness	——
Rectum	3.9	0.0484	0.0124	0.0324	0.0083	Severe proctitis necrosis/stenosis/ /fistula	[81]
Rib cage	1.8 - 2.8	0.0462 - 0.0569	0.0257 - 0.0203	0.0447-0.0551	0.0248-0.0197	Pathologic fracture	[74,75]
Parotid	3.0*	0.0628	0.0209	0.0341	0.0114	Xerostomia	—
Thyroid	3.0*	0.0251	0.0084	0.0084	0.0028	Clinical thyroiditis	—

*Assumed values of alpha/beta for late reacting tissues

these parameters can be obtained if radiation oncologist compares the NTCP with his own experience. If the values the parameters match with his own values, then this suggests that the computed values of the parameters are reasonable and can be used to estimate the NTCP of critical organs. But if the computed values of the parameters consistently differ from that of the radiation oncologist, then new values of the parameters could be used to reflect the local experience.

The proposed model is connected with three variables viz. NTCP, delivered dose (D) and partial volume (v) of the irradiated organ. In 2 D graphical representation, a curve can be plotted between any two quantities while keeping the third one constant. To demonstrate the applicability of the model, a set of curves have been plotted between dose and NTCP for 1/3, 2/3 and 3/3 partial volumes for bladder, brain, heart and rectum and are shown in Figure 1 to 4 respectively . It is clear from these Figures that the organs demonstrate threshold type behavior. In other words, the NTCP of the organ does not appreciate until a certain amount of radiation dose is delivered. The dose beyond that the NTCP is

the function of dose is known as the 'threshold dose'. The pattern of the NTCP variation with dose depends on the behavior of the organ. The plot of the NTCP Vs dose for these organs have sigmoid shape. There is only difference in the threshold doses and increment in the NTCP with dose (after crossing the threshold dose) and can be seen between the curves of the organs. The 2 point tolerance data for rectum are reported only for one partial volume, hence the curve between NTCP and dose is a single line and does not show volume dependency [Figure 4].

Figure 1 shows that the calculated the NTCP, for Emami et al's [8] data, increases sharply with dose than that of the combined data. The threshold doses for 1/3, 2/3 and 3/3 partial volumes of combined data are in the range of 35-40 Gy, which are quite lower than that predicted for Emami et al's [8] data. For Emami et al's [8] data, the threshold doses are 85 Gy, for 1/3 volume; 70 Gy, for 2/3 volume and 60 Gy for 3/3 volume and the window of variation of tolerance doses between the partial volumes, at all NTCP levels, is wider than that of the combined data set, which demonstrates that the NTCP in bladder is highly volume dependent. On the other hand, a narrow window for combined data set indicates that the NTCP in bladder is less volume dependent. At all dose levels there is a wide variation in the predicted NTCP for both the data sets, which is highly confusing to decide that which data set should be used in the practice. This is also a problem to consider whether the NTCP in bladder is a highly volume dependent or less volume dependent. Hence it is recommended that to predict NTCP in bladder, the radiation oncologist should use his own experience.

It is seen in Figure 2 that the predicted the NTCP in brain for 2 sets of data in the therapeutic range is reasonably accurate. The threshold dose, for these sets of data, are almost at the same level and window of variation of tolerance doses is similar between partial volumes. The gap between the curves for the partial volumes reveals that the NTCP of the brain is the function of the volume, i.e. the brain NTCP is having volume dependency. From these curves, it can be suggested that any set of predictions can be used in the clinical practice, if the doses are in the therapeutic range. At higher doses, beyond the therapeutic range, the predicted NTCP, for Emami et al's [8] data, is higher than that of the combined set of the data, hence this portion of the curves left physician indecisive.

Curves, in Figure 3, show that the predicted NTCP in heart, for 2 sets of data, is fairly accurate at all doses. The threshold doses are almost same for both sets of data and window of variation of tolerance doses is similar between partial volumes. Hence any set of prediction can be used in the practice. Here also the gap between the curves for the partial volumes of the heart indicates that the NTCP of is the

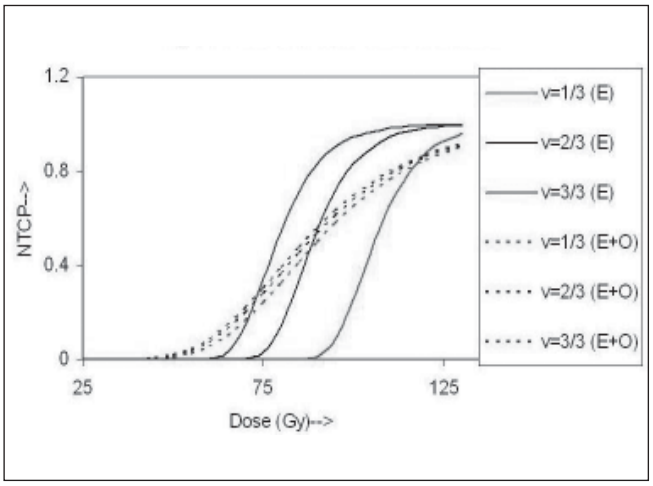

Figure 1: Curves between bladder NTCP and dose for 2 data sets are plotted. The solid lines are for Emami et al [8] tolerance doses and broken lines for combined set of data [8-51]. In both the sets, the thin, thick and thicker are for 1/3, 2/3 and 3/3 partial volumes respectively

function of the volume, i.e. the heart NTCP is volume dependent.

In case of rectum, Emami et al's [8] have provided 2 point tolerance doses from which no correlation could be made between the NTCP and volume. Hence for simplification, it is assumed that the rectum NTCP may not be volume dependent, so the value of the parameter k is adjusted equal to zero. While some other reports show that the NTCP increases with increasing the volume of the rectum.[49, 83, 50, 48, 18] Using combined set of tolerance data of Emami et al's [8] and other author's, the value of k was found equals to 0.2001, which shows that the NTCP is a function of irradiated volume of rectum. The values of all 3 parameters, aG, k and N_0, of 2 sets of data, are used to generate the curves

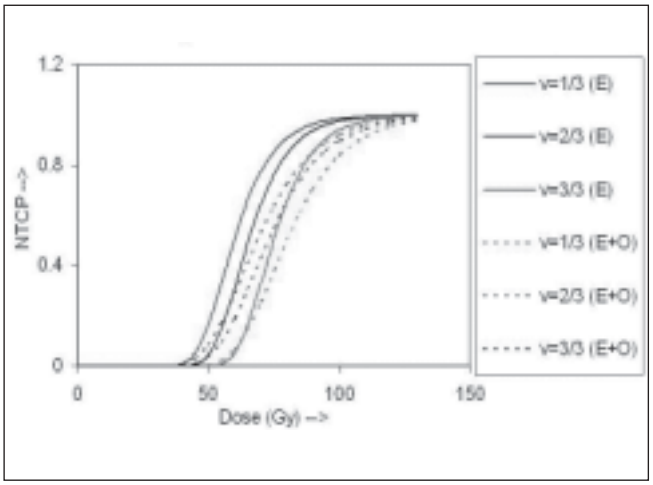

Figure 2: Curves between brain NTCP and dose for 2 data sets are plotted. The solid lines are for Emami et al [8] tolerance doses and broken lines for combined set of data [8-51]. In both the sets, the thin, thick and thicker are for 1/3, 2/3 and 3/3 partial volumes respectively

between dose and NTCP [Figure 4]. In Figure 4, the solid line is for Emami et al's [8] data, while broken lines are for combined set of data.[8-51] It is clear from these curves that tolerance doses of Emami et al's [8] do not show volume dependency for rectum which is contrary to our own experience. While combined data set have shown volume dependency, but the window of tolerance doses between partial volumes is narrow, hence the NTCP in rectum could be considered to be volume independent. The Emami et al's [8] data predicts a sharp increase in NTCP and at higher doses and is more than that of the combined set of data [9-51]. While in therapeutic range of doses, both set of data predict NTCP reasonably accurate.

It can be seen from above said Tables 3 and 4 that some of the organs show wider window of variation in the tolerance doses between partial volumes, and some have very narrow window, while others do not have any variation in the tolerance doses with the change in partial volume. The organs which have very narrow window of tolerance dose variation with the change in partial volume or no window of tolerance dose variation, show that even if a small volume of a organ is irradiated to a sufficiently high dose, a whole organ NTCP will occur, which is independent of the irradiation to the rest of the organ. On the other hand, the organs where window of tolerance doses is wider and vary with the change in partial volume, show that the NTCP is a function of dose and volume. In other words, the intensity of the NTCP depends on the amount of radiation dose and irradiated volume of the organ i.e. a smaller volume of the organ could tolerate a higher amount of radiation dose than does a large volume in order to cause same NTCP.

Burman et al [84] used Emami et al's [8] data to generate the NTCP curves for these organs. In their study, the Lyman's[82]

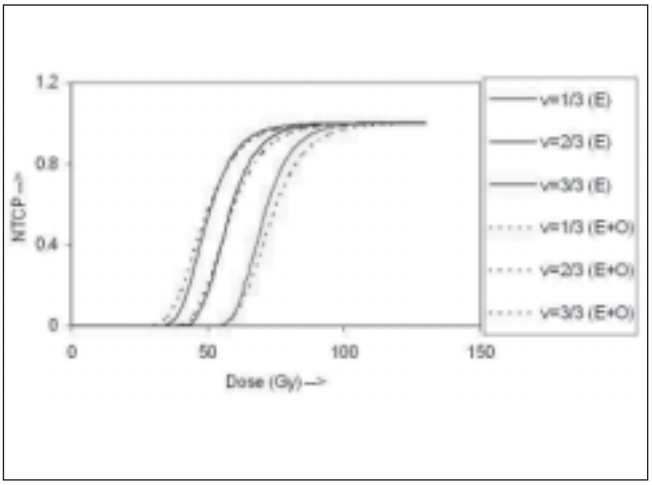

Figure 3: Curves between heart NTCP and dose for 2 data sets are plotted. The solid lines are for Emami et al [8] tolerance doses and broken lines for combined set of data [8-51]. In both the sets, the thin, thick and thicker are for 1/3, 2/3 and 3/3 partial volumes respectively

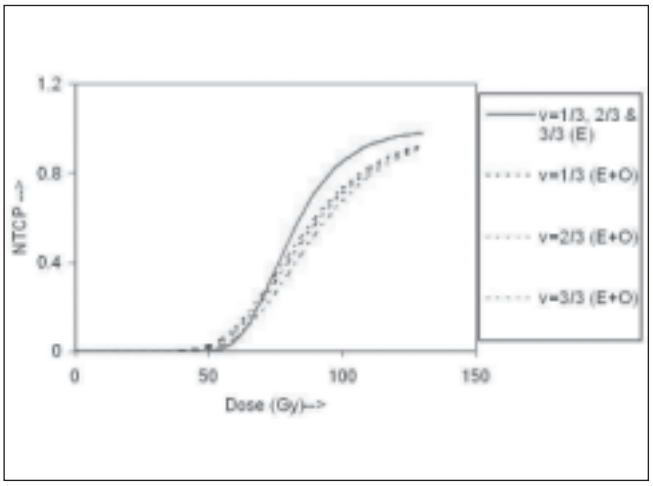

Figure 4: Curves between rectum NTCP and dose for 2 data sets are plotted. The single solid line is for Emami et al [8] tolerance doses and broken lines for combined set of data [8-51]. In 2nd sets, the thin, thick and thicker are for 1/3, 2/3 and 3/3 partial volumes respectively

NTCP model has been used to compute its parameters and to generate the NTCP curves. Since the Lyman's [82] model is based on the normal distribution of the tolerance data and do not have any correlation with radiobiological processes and findings, hence can not be accounted for varying tissue specific radiobiological parameters. In the present model, the factor aG has two tissue specific radiobiological coefficients, such as α and β, which account for α-cell kill (lethal damage) and α-cell kill (sublethal damage) of the LQ model. For a conventional treatment schedule where 2 Gy per fraction radiation dose is delivered to the organ, the value of the factor $\alpha\Gamma$ can directly be used from Tables 1 & 2 to interpret the NTCP of the organ, for any amount of the radiation dose and partial volume of the organ, if the delivered dose is uniform throughout the irradiated volume of the organ. When an altered dose fractionation schedule is used to irradiate the organ, then radiobiological coefficients, α & β (α/β), play an important role in the prediction of the NTCP for a particular dose and volume of the organ. Burman et al [84] did not say any thing about altered fractionation schedules that by using Lyman's [82] model how one could predict NTCP.

To compute the values of α & β from the factor $\alpha\Gamma$, the published values of α/β extracted from the literature, are used and listed in Table 5 along with their source of reference. The main difficulty with the choice of α/β is that in the literature there is no definite value of α/β is reported. Always one can find a range of α/β values reported by different researchers, which made our work somewhat difficult during the search of the literature. We have taken the values of α/β from the published reports, but in the prediction of NTCP for altered fractionation schedules the radiation oncologist must use the value of α/β of his own choice with careful selection to match his own experience.

CONCLUSION

A radiobiological model of NTCP, presented in this study, was used to fit the normal tissue tolerance data compiled by Emami et al's [8] and combined data of Emami et al [8] and some other investigators.[9-51] These data sets have provided reasonable estimate of the values of the parameters ($\alpha\Gamma$, k and N_0) of the model for all the listed organs. In this model volume correction factor is represented by a power-law and the curves between dose and NTCP are presented. However, volume wise response of the tissue is a complicated process and is not well understood. There have been attempts other than the power-law to understand the volume dependent complication process.[85] It has been discussed that in some cases there are insufficient data to determine the values of the parameters ($\alpha\Gamma$ k and N_0) more accurately. Hence the calculated values of the parameters represent a substantial extrapolation of the normal tissue tolerance data, like in case of rectum the tolerance data are given only for one volume which show no volume effect which is not true, because in some studies [49,83,50,48,18] it is seen that rectum has volume dependency. In case of spinal cord and larynx (edema) the value of k, for combined data set, is negative which shows that the tolerance dose, for these organs, increases with increasing the volume of the organ, which is contrary to our experience. This is because of wider variation in tolerance doses of these organs. Hence to find out appropriate reasonable values of the tolerance doses for the organs, more normal tissue tolerance data are required, and widely accepted values of the tolerance doses will be estimated. The model used in this study can be used to estimate the outcome of altered multifractionation schedules because it has a radiobiological basis. The generated curve can be used to estimate the NTCP for a fractional (partial) volume of the organ if it is being irradiated uniformly and match with local experience. The values of a and b along with two other parameters of the model could be used to compute the value of the NTCP for an altered fractionation schedules.

REFERENCES

1. Rubin P, Cassarett GW. Urinary tract: The kidney. *In*: Rubin P, Casserett GW, editors. Clinical radiation pathology. Philadelphia: WB Saunders; 1968. p. 293-333.
2. Rubin P, Cassarett GW. Urinary tract: The kidney. *In*: Rubin P, Casserett GW, editors. Clinical radiation pathology. Philadelphia: WB Saunders; 1968. p. 423-70.
3. Rubin P, Cassarett GW. A direction for clinical radiation pathology. *In*: Vaeth JM, editors. Frontiers of radiation therapy and oncology VI. Baltimore: University Park Press; 1972: p. 1-16.
4. Mah K, Dan Dyuk J, Keane T. Quantitative measurement of lung density changes following lung irradiation. Proc. Of 8th International Conference on the use of Computers in Radiation Therapy 1984:255-9.
5. Mah K, Poon PY, Van Dyk J, Keane T, Majesky IF, Rideout DF. Assessment of acute radiation-induced pulmonary changes using computed tomography. J. Comput. Assist. Tomogr 1986;10:736-43.
6. Wara WM, Phillips TL, Margolis LW, Smith V. Radiation pneumonitis: A new approach to the derivation of time-dose-factors. Cancer 1973;32:547-52.
7. Wara WM, Phillips TL, Sheline GE, Schwade IG. Radiation tolerance of the spinal cord. Cancer 1975:35;1558-62.
8. Emami B, Lyman J, Brown A, Coia L, Goiten M, Munzenride JE, *et al*. Tolerance of normal tissue to therapeutic radiation. Int J Radiat Oncol Biol Phys 1991;21:109-22.
9. In: Rubin P, Cooper RA, Phillips TL, editors. Radiation biology and radiation pathology syllabus. Set RT1: Radiation Oncology. Ammerican College of Radiology, Chicago; 1975. p. 2-7.
10. Rubin P. The law and order of radiation sensitivity, absolute vs relative. *In*: Vaeth JM, Meyer TL, editors. Radiation tolerance of normal tissues. Frot Radiat Ther Oncol. Basel Switzerland Karger; 1989. p. 7-40.
11. Rubin P, Casserett GW. Concept of clinical radiation pathology, *In*: Dalrymple G, Gaulden M, Kallomogen G, Vogel H, editors. Medical radiation biology, Philadelphia: WB Saunders; 1973. p. 160-89.
12. Willett CG, Tepper JE, Orlow EL, Shipley WU. Renal complications secondary to radiation treatment of upper abdominal malignancies. Int J Radiat Oncol Biol Phys 1986:12;1601-4.
13. Marks RD, Agarwal SK, Constable WC. Increased rate of complications as a result of treating only one prescribed field daily. Radiology 1972;107:615-9.
14. Schultheiss TE, Kun LE, Ang KK, Stephens DVM. Radiation response of the central nervous system. Int J Radiat Oncol Biol Phys 1995;31:1093-112.
15. Lee AWM, Law SCK. Retrospective analysis of nasopharyngeal carcinoma treated during 1976-85: Late complications following megavoltage irradiation. Br J Radiol 1992;65:918-28.
16. Devineni VR. Ear. *In*: Perez CA, Brady LW, editors. Principles and Practice of Radiation Oncology. 3rd edn. Lippincott-Raven: Philadelphia; 1997. p. 889-96.
17. Coia LR, Myerson RJ, Tepper JE. Late effects of radiation therapy on the gastrointestinal tract. Int J Radiat Oncol Biol Phys 1995;31:1213-36.
18. Storey MR, Pollack A, Zagars G, Smith L, Antolak J, Rosen I. Complications from radiotherapy dose escalation in prostate cancer: Preliminary results of a randomized trial. Int J Radiat Oncol Biol Phys 2000:48;635-42.
19. Marks LB, Carroll PR, Dugan TL, Anscher MS. The response of the urinary bladder urethra and ureter to radiation and chemotherapy. Int J Radiat Oncol Biol Phys 1995:31;1257-80.
20. Mendenhall WM, Parsons JT, Mancuso AA, Stringer SP, Cassisi NJ. Larynx. *In*: Perez CA, Brady LW, editors. Principles and Practice of Radiation Oncology. 3rd edn. Lippincott-Raven: Philadelphia; 1997. p. 1069-3.
21. Jirtle RL, Anscher MS, Alati T. Radiation sensitivity of liver. Adv. Radiat Biol 1990:14;269-311.
22. Emami B, Graham MV. Lung. *In*: Parez CA, Brady LW, editors. Principles and Practice of Radiation Oncology. 3rd edn. Philadelphia; 1997. p. 1181-220.
23. McDonald S, Rubin P, Phillips TL, Marks LB. Injury to the lung from cancer therapy: Clinical syndromes, measurable endpoints, and potential scoring systems. Int J Radiat Oncol Biol Phys 1995:31;1187-203.
24. Archambeau JO, Pezner R, Wasserman T. Pathophysiology of irradiated skin and breast. Int J Radiat Oncol Biol Phys 1995:31;1171-85.
25. Marcus RB, Million RR. The incidence of myelitis after irradiation of the spinal cord. Int J Radiat Oncol Biol Phys 1990;19:3.
26. Schultheiss TE, Stephens LC, Jiang GL, Ang KK, Peters LJ. Radiation myelopathy in primates treated with conventional fractionation. Int J Radiat Oncol Biol Phys 1990;19:935-40.
27. Fowler JF, Bentzen SM, Bond SJ, Ang KK, van der Kogel AJ, van den

Bogaert W, *et al*. Clinical radiation doses for spinal cord: the 1998 international questionnaire. Radiother. Oncol 2000:55;295-300.
28. Schultheiss TE, Stephens LC. Permanent radiation myelopathy. Br J Radiol 1992:65;737-53.
29. Schultheiss TE. Radiation 'tolerance' of spinal cord: doctorine vs data. Int J Radiat Oncol Biol Phys 1990;19: 219-21.
30. Withers HR, Peters LJ, Taylor JM, Owen JB, Morrison WH, Schultheiss TE, *et al*. Local control of carcinoma of the tonsil by radiation therapy: an analysis of pattern of fractionation in nine institutions. Int J Radiat Oncol Biol Phys 1995;33:549-62.
31. Withers HR, Peters LJ, Taylor JM, Owen JB, Morrison WH, Schultheiss TE, *et al*. Late normal tissue sequelae from radiation therapy for carcinoma of the tonsil: patterns of fractionation study of radiobiology. Int J Radiat Oncol Biol Phys 1995;33:563-8.
32. Beumer J, Curtis TA, Morrish RB Jr. Radiation complications in edentulous patients. J Prosthet Dent 1976;36:193.
33. Bedwinek JM, Shukovsky LJ, Fletcher GH, Daley TE. Osteonecrosis in patients treated with definitive radiotherapy for squamous cell carcinoma of the oral cavity and naso- and oropharynx. Radiology 1976;119: 665.
34. Murry CG, Herson J, Daly TE, Zimmerman S. Radiation necrosis of the mandible: A 10 year study. Part_I. Factors influencing the onset of necrosis. Int J Radiat Oncol Biol Phys 1980;6:543-8.
35. Murry CG, Herson J, Daly TE, Zimmerman S. Radiation necrosis of the mandible: A 10 year study. Part_II. Dental factors, onset, duration and management of necrosis. Int J Radiat Oncol Biol Phys 1980;6:549-67.
36. Morrish RB, Chan E, Silverman S Jr, Meyer J, Fu KK, Greenspan D. Osteonecrosis in patients irradiated for head and neck carcinimas. Cancer 1981;47:1980-8.
37. Cooper JS, Fu K, Marks J, Silverman S. Late effects of radiation therapy in the head and neck region. Int J Radiat Oncol Biol Phys 1995;31:1141-64.
38. Powell S, Cooke J, Parsons C. Radiation induced brachial plexus injury; follow-up of two different fractionation schedules. Radioth. Oncol 1990;18:213–20.
39. Marriam GR, Focht E. A clinical study of radiation cataracts and their relationship to dose. Am. J. Roentgenol. Radium. Therapy Nucl Med 1957;77:564-759.
40. Parsons JT, Bova FJ, Fitzgerald CR, Mendenhall WM, Million RR. Radiation optic neuropathy after megavoltage external-beam irradiation: analysis of time-dose factors. Int J Radiat Oncol Biol Phys 1994:30;755-63.
41. Parsons JT, Bova FJ, Fitzgerald CR, Mendenhall WM, Million RR. Radiation retinopathy after external-beam irradiation: analysis of time-dose factors. Int J Radiat Oncol Biol Phys 1994;30;765-73.
42. Harrish JR, Levens MB. Visual complications following irradiation for pitutary adenomas and craniopharyngiomas. Radiology 1976;120:167-71.
43. Jiang GL, Tusker SL, Guttenberger R, Peters LJ, Morrison WH, Garden AS, *et al*. Radiation-induced injury to the visual pathway. Radiother Oncol 1994;30:17-25.
44. MacFaul PA, Bedford MA. Ocular complications after therapeutic irradiation. Br J Opthalmol 1970;54:237-44.
45. Gordan KB, Char DH, Sagerman RH. Late effects of radiation on the eye and ocular adnexa. Int J Radiat Oncol Biol Phys 1995;31:1123-39.
46. Chen SW, Liang JA, Yang SN, Liu RT, Lin FJ. The prediction of late rectal complications following the treatment of uterine cervical cancer by high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 2000;47:955-61.
47. Wachter S, Gerstner N, Dorner D, Goldner G, Colotto A, Wambersie A, *et al*. The influence of a rectal balloon tube as internal immobilization device on variation of volumes and dose-volume histograms during treatment course of conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2002;52:91-100.
48. Schultheiss TE, Lee WR, Hunt MA, Hanlon AL, Peters RS, Hanks GE. Late GI and GU complications in the treatment of prostate cancer, Int J Radiat Oncol Biol Phys 1997;37:3-11.
49. Boersma LJ, Van der Brink M, Bruce AM, Shouman T, Gras L, Velde AT, *et al*. Estimation of the incidence of late bladder and rectum complications after high-dose (70-78 Gy) conformal radiotherapy for prostate cancer, using dose – volume histograms. Int J Radiat Oncol Biol Phys 1998;41:83-92.
50. Kutcher GJ, Leibel SA, Ling CC, Zelefsky M, Fuks Z. New wine in an old bottle? Dose escalation under dose volume constraints. A model of conformal therapy of the prostate. Int J Radiat Oncol Biol Phys 1996;35:415-6.
51. Overgaard M. Spontaneous radiation-induced rib fractures in breast cancer patients treated with postmastectomy irradiation. Acta Oncologica 1988;27:117-22.
52. Kallman P, Agren A, Brahme A. Tumour and normal tissue responses to fractionated non-uniform dose delivery. Int J Radiat Biol 1992;62:249-62.
53. Zaider M, Amols HI. Practical considerations in using calculated healthy - tissue complication probabilities for treatment - plan optimization. Int J Radiat Oncol Biol Phys 1999;44:439-47.
54. Turesson I, Notter G. Normal tissue reactions - clinical relevant end points. Int J Radiat Oncol Biol Phys 1985;11:1226-7.
55. Stewart FA, Randhawa VS, Michael BD. Multifraction irradiation of mouse bladders. Radioth Oncol 1984;2:131-40.
56. Stewart FA, Soranson JA, Alpen EL, Williams MV, Denekamp J. Radiation induced renal damage. The effect of hyperfractionation. Radiat Res 1984;98:407-20.
57. van der Kogel AJ, Ruifrok ACC. Calculation of isoeffect relationships. *In*: Steel GG, Edwaed Arnold, editors. Basic Radiobiology for Radiation Oncologists. London; 1991. p. 72-80.
58. Meek SL, Buatti JM, Foote KD, Friedman WA, Bova FJ. Calculation of cranial nerve complication probability for acoustic neuroma radiosurgery. Int J Radiat Oncol Biol Phys 2000;47:597-602.
59. Hornsey S, Morris CC, Myers R. Relative biological effectiveness for damage to the central nervous system by neutrons. Int J Radiat Oncol Biol Phys 1981;7:185-90.
60. Silva JJ. Tsang RW, Panzarell T, Levin W, Wells W. Results of radiotherapy for epithelial skin cancer of the pinna: the princess margaret hospital experience, 1982–1993. Int J Radiat Oncol Biol Phys 2000;47;451-9.
61. Akagi Y, Hirokawa Y, Kagemoto M, Matsuura K, Ito A, Fujita K, *et al*. Optimum fractionation for high-dose-rate endo-esophageal brachytherapy following external irradiation of early stage esophageal cancer. Int J Radiat Oncol Biol Phys 1999;43:525-30.
62. Martel MK, Sahijdak WM, Ten Haken RK, Kessler ML, Turrisi AT. Fraction size and dose parameters related to the incidence of pericardial effusions. Int J Radiat Oncol Biol Phys 1998;40:155-61.
63. McChesney SL, Gillette S, Gillette EL, Shida T, Boon J, Miller CW, *et al*. Late radiation response of canine mediastinal tissues. Radioth Oncol 1992;23:41-52.
64. Stewart JR, Farardo IF, Gillette SM, Constine LS. Radiation injury to the heart. Int J Radiat Oncol Biol Phys 1995;31:1205-11.
65. Perez CA, Brady LW, Roti JLR. Overview. *In*: Perez CA, Brady LW, editors. Principles and practice of radiation oncology. 3rd edn. Philadelphia, New York: Lippincott-Raven Publishers; 1997. p. 1-78.
66. Perez CA. Uterin cervix. *In*: Perez CA, Brady LW, editors. Principles and practice of radiation oncology. 3rd edn. Philadelphia, New York: Lippincott-Raven; 1997. p. 1143-202.
67. Henk JM, James KW. Comparative trial of large and small fractions in the radiotherapy of head and neck cancers. Clin Radiol 1978;29: 611-6.
68. Horiot JC, Fletcher GH, Ballantyne AJ, Lindberg RD. Analysis of

failures in early vocal cord cancer. Radiology 1972;103:663-5.
69. Fletcher GH, Barkley HT, Shukovsky LJ. Present status of the time factor in clinical radiotherapy II. The nominal standard dose formula. J Radiol Electrol 1974:55;745-51.
70. Stell PM, Morrison MD. Radiation necrosis in the larynx. Arch. Otolaryngol 1973;98:111-3.
71. Maciejewski B, Taylor JMG, Withers HR. Alpha/beta value and the importance of size of dose per fraction for late complications in supraglottic larynx. Radioth Oncol 1986;7:323-6.
72. Lawrence TS, Ten Haken RK, Kessler ML, Robertson JM, Lyman JT, Lavigne ML, *et al*. The use of 3-D dose volume analysis to predict radiation hepatitis. Int J Radiat Oncol Biol Phys 1992;23:781-8.
73. Cox JD. Presidential Address: Fractionation. A paradigm for clinical research in radiation oncology. Int J Radiat Oncol Biol Phys 1987;13:1271-81.
74. Overgaard M. The clinical implication of non-standard fractionation. Int J Radiat Oncol Biol Phys 1985;11:1225-6.
75. Withers HR, Chu AM, Reid BO. Response of mouse jejunum to multifractionation radiation. Int J Radiat Oncol Biol Phys 1975;1:44.
76. Terry NH, Denekamp J. RBE values and repair characteristics for colorectal injury after caesium 137 gamma-ray and neutron irradiation. II. Fractionation up to ten doses. Br J Radiol 1984;57:617-29.
77. Dische S, Martin WMC, Anderson P. Radiation myelopathy in patients treated for carcinoma of bronchus using a six fraction regime of radiotherapy. Br J Radiol 1981;54:29-35.
78. Bentzen SM, Thames HD, Overgaard M. Latent time for late cutaneous & subcutaneous radiation reactions in a single follow-up clinical study. Radioth Oncol 1989;15:267-70.
79. Roos DE, O'Brien PC, Smith JG, Spry NA, Hoskin PJ, Burmeister BH, *et al*. A role for radiotherapy in neuropathic bone pain: preliminary response rates from a prospective trial (Trans-Tasman Radiation Oncology Group, TROG 96.05). Int J Radiat Oncol Biol Phys 2000;46:975-81.
80. Schenken LL, Hagemann RF. Time/dose relationship in experimental radiation cataractogenesis. Radiology 1975;117:193.
81. Deore SM, Shrivastava SK, Supe SJ, Viswanathan PS, Dinshaw KA. Alpha/beta value and importance of dose per fraction for the late rectal and recto-sigmoid complications. Stehlentherapie und Onkologie 1993;169:521-6.
82. Lyman JT. Complication probability as assessed from dose volume histograms. Radiat Res 1985;104:513-9.
83. Dale E, Hellebust TP, Skjonsberg A, Hogberg T, Olsen DR. Modeling of normal tissue complication probability from repetitive computed tomography scans during fractionated high-dose-rate brachytherapy and external beam radiotherapy of the uterine cervix. Int J Radiat Oncol Biol Phys 2000;47:963-71.
84. Burman C, Kutcher GJ, Emami B, Goiten M. Fitting of normal tissue tolerance data to an analytic function. Int J Radiat Oncol Biol Phys 1991;21:123-35.
85. Schultheiss TE, Orton CG, Peck RA. Models in radiotherapy, Volume effects. Med Phys 1983;10:410-25.

Books Received

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