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Original Article

Methods to calculate normal tissue complication and tumour control probabilities for fractionated inhomogeneous dose distribution of intensity-modulated radiation therapy

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Abstract

Objectives: This study is designed to present and evaluate radiobiological-based dose–volume histogram (DVH) reduction schemes to calculate normal tissue complication probability (NTCP) and tumour control probability (TCP) for intensity-modulated radiation therapy (IMRT).

Methods: The proposed DVH reduction schemes were derived for 2 Gy per fraction and prescribed dose per fraction for critical organs and tumours, respectively. Sample computed tomography scans were used to generate two IMRT plans to deliver 54 Gy to PTV1 and 24 Gy to PTV2 via sequential IMRT boost (SqIB) and simultaneous integrated IMRT boost (SIB) plans. Differential DVHs were used to calculate effective volumes using published values of related parameters of critical organs and prostate.

Results: NTCP values for bladder were almost zero for both IMRT plans. The plots between k and NTCP for rectum and femurs ($k = 0.1–1.0$) show higher NTCP for SqIB than that for SIB. The TCP decreases with increasing clonogenic cell density and is higher for SIB than that for SqIB for all clonogenic cell densities. The value of α proposed by Brenner and Hall shows very low radio sensitivity of clonogens of the prostate, which gives very low TCP for conventional doses of 70–80 Gy delivered in 7–8 weeks, even for very low clonogenic cell density in the prostate.

Conclusion: The presented DVH reduction schemes have radiobiological bearing and therefore seem to be effective in calculating fairly accurate NTCP and TCP.

Keywords

NTCP; TCP; DVH reduction; clonogenic cell density; normal tissue tolerance doses

INTRODUCTION

The aim of three dimensional (3D) conformal radiation therapy and intensity-modulated radiation therapy (IMRT) treatment planning is to maximise the dose to the tumour volume and to minimise the dose to the adjacent normal tissues and/or organ at risk (OAR) to the tumour, thereby increasing the therapeutic ratio.[1] The dose distribution within the tumour volume is aimed to be within +7 and −5%.[2] The dose distribution within the adjacent

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normal tissues and/or OARs to the tumour is highly heterogeneous and some of the portions may receive significantly higher dose, which may be equal to the tumour dose. The computation of normal tissue complication probability (NTCP) for such an inhomogeneous dose distribution within the normal tissue and/or OAR is a difficult task, because the tolerance doses for normal tissues and critical organs were reported for uniformly irradiated partial volumes for conventional fractionation schemes.[3] Various researchers have proposed different dose–volume-histogram (DVH) reduction methods to convert the volume of non-uniform dose distribution to an equivalent effective volume of uniform dose distribution for maximum dose received by the normal tissue/organ,[4–9] which may be different than that of the conventional fractionation dose of 1.8–2.0 Gy, and the equivalent effective volume were used to compute NTCP by different non-radiobiological models. Most of these models do not have radiobiological basis and their parameters were computed for normal tissue tolerance doses reported by Emami et al.[3] for conventional dose fractionation schemes. Hence, the use of these model parameters in the computation of NTCP of irradiated normal tissue or organ may not be accurate, because dose distribution within critical organ is highly non-uniform and receives doses in the range of almost zero dose per fraction to the maximum dose per fraction, which may be equal to that of the tumour dose.

Zaider and Amols[10] proposed a radiobiological NTCP model, equivalent to the Kallman et al.'s[11] 'Poisson model of cell kill', which was modified by Kehwar for the linear quadratic (LQ) model[12] and Kehwar and Sharma for the multiple component (MC) model.[13] The data on tolerance doses as a function of dose for partial volumes $v = 1/3$, 2/3 and 1, reported by Emami et al.,[3] were fitted to these models to determine model parameters. In this paper, new methods of DVH conversion to an equivalent effective volume have been proposed for the calculation of the NTCP for an irradiating normal tissues/organs, and tumour control probability (TCP) for tumours.

METHODS AND MATERIALS

The NTCP model

The expression of the NTCP model[12] may be written as

$$\mathrm{NTCP}(D,\ v) = \exp\left[-N_0 v^{-k} \exp\{-\alpha \mathrm{BED}\}\right], \qquad (1)$$

where α is a radiobiological parameter which represents the radio sensitivity of irradiated tissue/organ and is the coefficient of lethal damage, BED is the biologically effective dose of a uniformly irradiated normal tissue or organ and the expression contains a tissue-specific parameter α/β. The N_0 and k are tissue specific, non-negative adjustable parameters, v is the uniformly irradiated partial volume of the tissue/organ (i.e., $v = V/V_0$, where V is uniformly irradiated volume of the normal tissue/organ and V_0 is the reference volume of the normal tissue/organ).

Previously, the equivalent effective volume from a DVH was obtained by two methods: (1) the Lyman's scheme[6] and (2) the Kutcher and Burman's scheme.[4] The Lyman's scheme is based on the step-by-step reduction of the cumulative DVH (cDVH), whereas Kutcher and Burman's scheme uses the differential DVH (dDVH) and is based on the assumption that each sub volume (voxel) contributes independently to the overall complication probability. In this study, the dDVH of a complicated 3D dose distribution of a normal tissue/organ is converted to a single volume 'V' of a uniform dose distribution irradiated to a single dose D_2 delivered with 2 Gy per fraction, using Kutcher and Burman's scheme.[4]

To derive an expression of effective volume, entire volume 'V_0' of a normal tissue/organ is divided into 'n' number of sub volumes, and is assumed that each sub volume irradiated to a uniform dose distribution. These sub volumes V_1, V_2, $V_3, \ldots,$ V_n are irradiated to D_1, D_2, $D_3, \ldots,$ D_n doses with corresponding d_1, d_2, $d_3, \ldots, d_n$ doses per fraction, respectively. The corresponding NTCP of these sub volumes are NTCP(D_1, V_1), NTCP(D_2, V_2), NTCP(D_3, V_3), …, NTCP(D_n, V_n). Let us take a sub volume V_i irradiated to a total dose of D_i with

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d_i dose per fraction. The NTCP for this sub volume may be written as

$$\mathrm{NTCP}(D_i,\ V_i) = \exp\left[-N_0\left(\frac{V_i}{V_0}\right)^{-k}\exp\{-\alpha \mathrm{BED}_i\}\right], \tag{2}$$

where $\mathrm{BED}_i = D_i[1 + d_i/(\alpha/\beta)]$, $v_i = V_i/V_0$ and α/β is the ratio of the coefficients of lethal and sub lethal damages in the tissue/organ and is tissue-specific parameter. Let us assume that '$V_{\mathrm{eff\_i}}$' will be the corresponding effective sub volume of 'V_i' exposed to the total dose D_2 with 2 Gy per fraction. The NTCP for this sub volume is written as

$$\mathrm{NTCP}(D_2, V_{\mathrm{eff\_i}}) = \exp\left[-N_0\left(\frac{V_{\mathrm{eff\_i}}}{V_0}\right)^{-k} \times\exp\{-\alpha \mathrm{BED}_2\}\right], \tag{3}$$

where $\mathrm{BED}_2 = D_2[1 + 2/(\alpha/\beta)]$. Because '$V_{\mathrm{eff\_i}}$' is the corresponding effective sub volume of 'V_i' exposed to the total dose D_2 with 2 Gy per fraction, the NTCPs for dose D_i and sub volume V_i, and dose D_2 and effective sub volume $V_{\mathrm{eff\_i}}$ are equal. By equating and rearranging the equations (2) and (3), the $V_{\mathrm{eff\_i}}$ can be written as

$$V_{\mathrm{eff\_i}} = V_i \exp\left[-\left(\frac{\alpha}{k}\right)(\mathrm{BED}_2 - \mathrm{BED}_i)\right]. \tag{4}$$

Converting all sub volumes to a single equivalent effective volume '$V_{\mathrm{eff\_2}}$' that receives a dose D_2

$$V_{\mathrm{eff\_2}} = \sum V_{\mathrm{eff\_i}} = \sum\left[V_i \exp\left\{-\left(\frac{\alpha}{k}\right)(\mathrm{BED}_2 - \mathrm{BED}_i)\right\}\right]. \tag{5}$$

The total fractional effective volume can be calculated as

$$v_{\mathrm{eff\_2}} = \frac{V_{\mathrm{eff\_2}}}{V_0}. \tag{6}$$

With equation (6), the NTCP is calculated by

$$\mathrm{NTCP}(D_2, v_{\mathrm{eff\_2}}) = \exp\left[-N_0 v_{\mathrm{eff\_2}}^{-k}\exp\{-\alpha \mathrm{BED}_2\}\right]. \tag{7}$$

Equation (7) depends on N_0 and k non-negative adjustable parameters, α, BED_i and BED_2.

For maximum dose received by the normal tissue/organ, the equivalent effective volume may be written as

$$V_{\mathrm{eff\_m}} = \sum^{n} V_{\mathrm{eff\_i}} = \sum_{i=1}\left[V_i \exp\left\{-\left(\frac{\alpha}{k}\right)\left(\mathrm{BED}_m - \mathrm{BED}_i\right)\right\}\right] \tag{8}$$

and NTCP expression for maximum dose received by normal tissue/organ may be written as

$$\mathrm{NTCP}(D_m, v_{\mathrm{eff\_m}}) = \exp\left[-N_0 v_{\mathrm{eff\_m}}^{-k}\exp\{-\alpha \mathrm{BED}_m\}\right]. \tag{9}$$

The TCP model

The TCP is defined by a Poisson statistics model,[14–16] and is written by

$$\mathrm{TCP}(D, V) = \exp[-\rho V \exp\{-\alpha \mathrm{BED}\}], \tag{10}$$

where ρ is the clonogenic cell density, V is the tumour volume, α is a radio sensitivity parameter and is the coefficient of lethal damage, BED is the biologically effective dose of a uniformly irradiated tumour.

To derive an expression for equivalent effective volume of the tumour from its dDVH, similar methodology is used as adopted for normal tissue/organ. For the purpose, entire tumour volume is divided into 'n' number of sub volume, and is assumed that each sub volume receives a uniform dose. These sub volumes, V_1, V_2, $V_3, \ldots$, V_n, are irradiated to D_1, D_2, $D_3, \ldots$, D_n doses with corresponding d_1, d_2, $d_3, \ldots$, d_n doses per fraction, respectively. The TCP of these sub volumes are $\mathrm{TCP}(D_1, V_1)$, $\mathrm{TCP}(D_2, V_2)$, $\mathrm{TCP}(D_3, V_3), \ldots$, $\mathrm{TCP}(D_n, V_n)$, respectively. Let us suppose that a sub volume V_i exposed to a total dose of D_i delivered with d_i dose per fraction. The TCP for this sub volume is written as

$$\mathrm{TCP}(D_i, V_i) = \exp[-\rho V_i \exp\{-\alpha \mathrm{BED}_i\}], \tag{11}$$

where $\mathrm{BED}_i = D_i[1 + d_i/(\alpha/\beta)]$, and α/β is the ratio of the coefficients of lethal and sub lethal damages of the tumour. Suppose $V_{\mathrm{eff\_i}}$ will be the equivalent effective sub volume exposed to the total dose of D_p delivered with

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d_p Gy per fraction. The TCP for this sub volume is written as

$$\mathrm{TCP}(D_p, V_{\mathrm{eff\_i}}) = \exp\left[-\rho V_{\mathrm{eff\_i}} \exp\{-\alpha \mathrm{BED}_p\}\right]. \quad (12)$$

Here $\mathrm{BED}_p = D_p[1 + d_p/(\alpha/\beta)]$. It is assumed that if the TCP for dose D_i, sub volume V_i, dose D_p and sub volume $V_{\mathrm{eff\_i}}$ are equal. By equating and rearranging the equations (11) and (12), the total $V_{\mathrm{eff\_p}}$ can be written as

$$V_{\mathrm{eff\_p}} = \sum_{i=1}^{n} V_{\mathrm{eff\_i}} = \sum_{i=1}^{n} \left[V_i \exp\{-\alpha(\mathrm{BED}_i - \mathrm{BED}_p)\}\right]. \quad (13)$$

The total effective volume is calculated with equation (13) and the TCP is calculated by

$$\mathrm{TCP}(D_p, V_{\mathrm{eff\_p}}) = \exp\left[-\rho V_{\mathrm{eff\_p}} \exp\{-\alpha \mathrm{BED}_p\}\right]. \quad (14)$$

Equation (14) is an expression of TCP for the tumour exposed with non-uniform dose distribution.

IMRT treatment plans

To examine the applicability of equations (7), (9) and (14), sample computed tomography scans of pelvis region were used to generate the IMRT plans using Eclipse treatment planning system. The bladder, rectum, femurs, prostate and seminal vesicles were contoured and planning target volumes (PTVs) were created for the IMRT planning. The PTV1 created with 1 cm margin to prostate and seminal vesicles (prostate + seminal vesicles + 1.0 cm), and PTV2 with 0.75 cm to the prostate (prostate + 0.75 cm). Two IMRT plans were generated: (1) IMRT initial to PTV1 (IMRT1) followed by an IMRT boost to PTV2 (IMRT2), that is, the sequential IMRT boost (SqIB), and (2) simultaneous integrated IMRT boost (SIB) to both PTV1 and PTV2. The prescription doses to PTV1 and PTV2 were 54 Gy and 24 Gy, respectively. The maximum dose limits to the critical organs were set to 50 Gy for bladder and femurs and 45 Gy for rectum. The priorities for these organs were set to 80% and limiting volume to 10%. The dDVH of critical organs and prostate of both the IMRT plans were used for effective volumes using proposed dDVH reduction schemes, which were used in the computation of NTCP and TCP.

RESULTS AND DISCUSSION

In the computation of equivalent effective volume and the NTCP for critical organs, the values of the parameters, N_0, k, α, α/β were used from earlier publication,[12] where N_0, k and α were derived from Emami et al.'s[3] normal tissue tolerance doses and published values of α/β. The values of these parameters are given in Table 1.

The values of α/β for bladder, rectum, and femoral head and neck were taken from the reports of Withers et al. (1995),[16,17] Stewart et al. (1984),[18,19] and Deore et al. (1993),[20] respectively. The value of k in Table 1, for rectum and femoral head and neck is zero, because Emami et al.[3] had provided $\mathrm{TD}_{5/5}$ and $\mathrm{TD}_{50/5}$ values only for single volume, that is, two point tolerance dose data, hence the value of k could not be derived but was set to zero. In this analysis, the NTCP for rectum and femurs is calculated for k varies from 0.1 to 1.0. The value of NTCP for bladder is almost zero for both SqIB and SIB plans, calculated using equations (7) and (9). Because, the value of k, for rectum and femurs, is set from 0.1 to 1.0, the plots between k and NTCP, calculated for 2 Gy/fraction and d_m Gy/fraction, are shown in Figures 1a,b for rectum and in Figures 2a,b for femurs, respectively. It is clear from Figure 1a, b that the values of NTCP are higher for SqIB plan than that for SIB for rectum, irrespective to the value of k. Figures 2a,b reveals that values of NTCP of femurs are higher for SqIB plans when k is <0.2.

The values of NTCP calculated for 2 Gy and d_m Gy per fraction using equations (7) and (9) are identical and demonstrates that the proposed

Table 1. *Values of NTCP parameters derived for Emami et al.[3] data*

Organ	k	N_0	α	α/β
Bladder	2.924	7007.99	0.0878	6.0
Rectum	0.0	241.84	0.0484	3.9
Femoral head and neck	0.0	1045.23	0.0349	0.8

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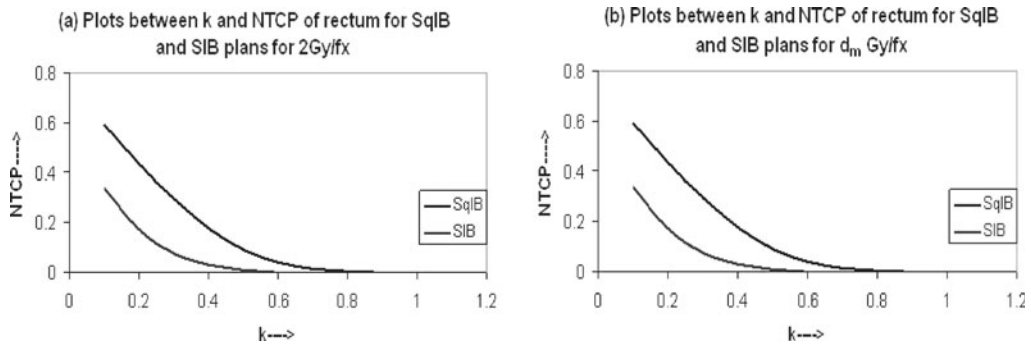

Figure 1. Represents the curves between parameter k, ranges from 0.1 to 1.0, and NTCP of rectum for SqIB and SIB IMRT plans with reference dose per fraction of (a) 2 Gy, and (b) d_m Gy.

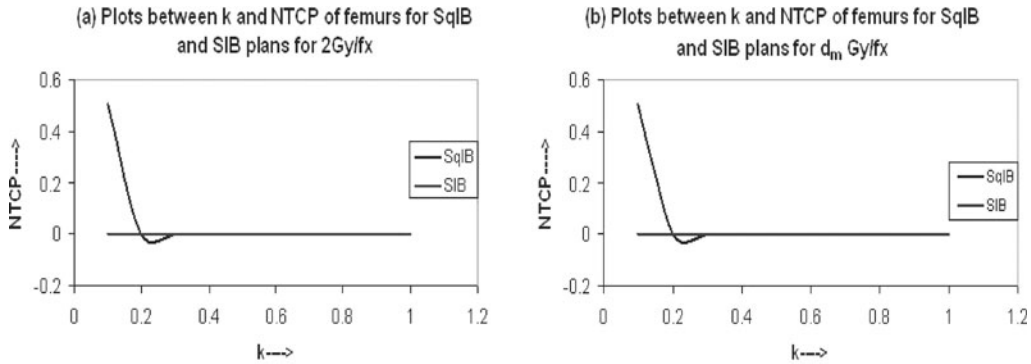

Figure 2. Represents the curves between parameter k, ranges from 0.1 to 1.0 and NTCP of the femurs for SqIB and SIB IMRT plans with reference dose per fraction of (a) 2Gy, and (b) d_m Gy.

Table 2. *TCP calculated using $\alpha = 0.04\ Gy^{-1}$ and $\alpha/\beta = 1.5$ Gy*

	Brachytherapy	External beam radiation therapy		
		PSA <10	PSA 10–20	PSA >20
IMRT plan	$\rho = 15.3$	$\rho = 53.4$	$\rho = 95.3$	$\rho = 302.3$
SqIB	51.5%	9.7%	1.6%	1.8×10^{-4}%
SIB	100%	93.6%	88.8%	68.6%

Table 3. *TCP calculated using $\alpha = 0.15\ Gy^{-1}$ and $\alpha/\beta = 3.1$ Gy*

	Brachytherapy	External beam radiation therapy		
		PSA <10	PSA 10–20	PSA >20
IMRT plan	$\rho = 15.3$	$\rho = 53.4$	$\rho = 95.3$	$\rho = 302.3$
SqIB	98.3%	94.2%	89.8%	71.2%
SIB	100%	100%	100%	100%

dDVH conversion method to get equivalent effective volume is accurate irrespective of reference dose and dose per fraction.

To compute the TCP, for both the plans, the values of α, α/β and clonogenic cell density for the prostate have been extracted from various published reports. Brenner and Hall[21] proposed that α and α/β for prostate cancer were 0.036 Gy^{-1} ($\approx$0.04 Gy^{-1}) and 1.5 Gy, but in the analysis the clonogenic cell density was not reported. Therefore, King and Mayo[22] have repeated the analysis of Brenner and Hall[21] using same equation and data and found that the number of clonogenic cells, for brachytherapy data, is 15.3, whereas for external beam therapy (EBRT) data, the values were 53.4, 95.3 and 302.3 for PSA <10, PSA between 10–20, and PSA >20, respectively. The TCP for these values of α, α/β and clonogenic cell density are listed in Table 2.

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Table 4. TCP calculated using $\alpha = 0.346\ Gy^{-1}$ and $\alpha/\beta = 4.96\ Gy$

	Brachytherapy	External beam radiation therapy		
		PSA <10	PSA 10–20	PSA >20
IMRT plan	$\rho = 3.4 \times 10^8$	$\rho = 1.9 \times 10^8$	$\rho = 3.3 \times 10^8$	$\rho = 1.05 \times 10^9$
SqIB	100%	100%	100%	100%
SIB	100%	100%	100%	100%

Wang et al.[23] have determined the values of α and α/β for prostate cancer were 0.15 Gy^{-1} and 3.1 Gy, respectively. These values of α, α/β were used to compute TCP using dDVH of prostate for above-described number of clonogenic cells for brachytherapy and EBRT data sets, and are listed in Table 3.

King and Mayo[22] proposed that α/β should be constant for all clonogenic cells in a tumour, which implies that mathematically α and β obey Gaussian distribution with mean value and standard deviation. They used same brachytherapy data, used by Brenner and Hall,[21] to determine the values of α and number of clonogenic cells, and found mean $\alpha = 0.346$ Gy^{-1} with standard deviation of 0.049, and number of clonogenic cells $= 3.4 \times 10^8$. Using these values of α and standard deviation, the EBRT data were used to calculate the value of α/β and number of clonogenic cells. The α/β was found to be 4.96 Gy, and number of clonogenic cells were 1.9×10^8, 3.3×10^8 and 1.05×10^9 for PSA <10, PSA between 10 and 20 and PSA >20, respectively. These values were used to calculate the TCP, for both the IMRT plans of the prostate, and are shown in Table 4.

In this analysis, it is clear from Tables 2 and 3 that the TCP decreases with clonogenic cell density and is higher for SIB than that for SqIB for all clonogenic cell densities. The value of α is also a critical parameter in the estimation of equivalent effective volume as well as TCP. The value of α proposed by Brenner and Hall[21] represents very low radio sensitivity of the clonogens of the prostate, which gives very low TCP for conventional doses of 70–80 Gy delivered in 7–8 weeks, even for very low clonogenic cell density in the prostate.

CONCLUSION

The DVH reduction schemes presented in this paper are having radiobiological bearing and calculate fairly accurate NTCP and TCP. The schemes take into account the effect of variation in dose per fraction in normal tissues/organs and tumour. The cell sensitivity is taken into account in the formulation in the form of LQ parameters, such as α and α/β parameters. The reference dose per fraction taken in this study is 2 Gy or d_m per fraction for normal tissues and d_p (prescribed dose per fraction) for tumours. The use of 2 Gy per fraction for normal tissues advocates direct use of the Enami et al.'s[3] data of normal tissue tolerance doses.

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