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

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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.⁴⁻⁶ Some of these models do not consider the fractionation effect in NTCP calculations,⁶⁻⁷ whereas some of the models use the effect of fractionation in radiotherapy treatment in NTCP⁶⁻⁸ and TCP⁵⁻⁹ 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,
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 \((v)\). 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

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

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

\[
TD_{50/5}(v) = TD_{50/5}(1) \cdot v^{-n} \quad \text{........(3)}
\]

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.\(^{[3]}\) 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 \((EUD_v)\) using the linear quadratic (LQ) model as

\[
EUD_v = D \cdot \left(\frac{\alpha}{\beta} + \frac{D}{n_f}\right) \left(\frac{\alpha}{\beta} + 2\right) \quad \text{........(4)}
\]

where \(n_f\) and \(d_f = D/n_f\) are the number of fractions and dose per fraction size of the treatment course, respectively. \(\alpha/\beta\) are the tissue-specific LQ parameters of the organ being exposed. \(EUD_v\) 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 \(EUD\), 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\(_v\) obtained from the conversion of inhomogeneous dose distribution of different partial volume \(v\) receiving the dose \(D_v\) is given as

\[
EUD_v = \left[\sum_{i=1}^{N} v_i \cdot \{EUD_v\}^{\frac{1}{a}}\right] \quad \text{where } a = \frac{1}{n} \quad \text{........(5)}
\]

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

\[
NTCP = \frac{1}{1 + \left[\frac{TD_{50/5}}{EUD_v}\right]^{\gamma_{50}} \quad \text{........(6)}
\]

where \(\gamma_{50}\) is the slope of sigmoidal dose response curve of normal tissue at 50% complication probability

\[
= TD_{50/5} \frac{dNTCP}{dD} \bigg|_{D=TD_{50}} \quad \text{........(7)}
\]

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

\[
= \text{Exp}\left[-N_c \cdot p(D)\right] \quad \text{........(8)}
\]

where \(N_c, p(D)\) 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 \(N_c\) number of exposures of dose per fraction \(d_f\) 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) |
|------------------------|-------------------------------------|-----------|----------------------|------------|
|                        |                                     | $a$       | $\gamma_{50}$ (%) | $n$        | $m$ |
| 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                  | 3         | 3                    | 0.35       | 0.10  | 48 |
| Larynx                 | Laryngeal edema                     | 3         | 3                    | 0.35       | 0.10  | 48 |
| Heart                  | Pericarditis                         | 1         | 2                    | 0.87       | 0.18  | 24.5 |
| Lung                   | Pneumonitis                          | 3         | 3                    | 0.32       | 0.15  | 40 |
| Liver                  | Liver failure                       | 1         | 3                    | 0.70       | 0.10  | 28 |
| Kidney                 | Nephritis                           | 6         | 4                    | 0.15       | 0.16  | 55 |
| Intestine/Colon        | Obstruction/Perforation             | 2         | 4                    | 0.5        | 0.11  | 80 |
| Bladder                | Bladder contracture / Volume loss   | 8.33      | 4                    | 0.12       | 0.15  | 80 |
| Rectum                 | Severe proctitis/ necrosis/ stenosis/ fistula | 0.07 | 0.10 | 72 |
| Temporomandibular joint/Mandible | Reduced joint function            | 19        | 4                    | 72         | 70    | 68 |
| Esophagus              | Perforation                         |           |                      |            |      |

*If the value $\gamma_{50}$ (%) is not known, its value is taken as 4

\[ P_s(D) = \exp\left( -\sum_i N_i \beta_i d_i \left( 1 + \frac{d_i}{\alpha} \right) \right) \]  

(9)

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

\[ TCP = \exp\left( -N_s \exp\left( -\sum_i N_i \alpha_i d_i \left( 1 + \frac{d_i}{\alpha_i} \right) \right) \right) \]  

(10)

The number of clonogenic cells can be found out using the following relation according to Niemierko and Goiten 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

\[ TCP = \left( \frac{1}{2} \right)^{\frac{2\gamma_{50}}{\ln 2}} \exp\left( 2\gamma_{50} \left( 1 - \frac{D}{TD50/5} \right) \right) \]  

(11)

where $TD50/5$ is the tumor dose required to produce 50% TCP and $\gamma_{50}$ is the slope of dose response at 50% TCP, which is $TD50/5 \frac{dTCP}{dD} \bigg|_{D=TD50/5}$. For a heterogeneous irradiation of independent subvolumes $v_i$ of tumors with dose $D_i$, the overall TCP is given by

\[ TCP = \prod_{i=1}^{N} TCP(D_i \cdot v_i) \]  

(12)

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

\[ TCP = \left( \frac{1}{2} \right)^{\sum_i v_i \exp\left( 2\gamma_{50} \left( 1 - \frac{D_i}{TD50} \right) \right)} \]  

(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 $D$ 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 of such dose distribution is given by

\[ TCP = \frac{1}{1 + \left( \frac{TD50/5}{EUD} \right)^{\gamma_{50}}} \]  

(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  |

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.

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.\textsuperscript{[12]} NTCP calculation of LKB model for bladder using normal tissue tolerance dose data points of TD\textsubscript{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.\textsuperscript{[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\textsubscript{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 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\textsubscript{5/5} and TD\textsubscript{50/5} of rectum was found to be 4.78% and 50%, respectively, whereas Niemier...
Table 4: Validity checking of normal tissue complication probability calculation using Emami et al. (1994) data

| Organ          | Tolerance dose for volume | NTPC calculated (LKB) % | NTPC calculated (Niemierko) % | NTPC (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 5.35               | 13.58 5                 |                               |                       |
| Brain stem     | 65* 65* 50.00            | 48.18 50                |                               |                       |
| Parotid        | 33* (44*) 32 (43) 4.16   | 0.25 (12.28) 5          |                               |                       |
| Parotid        | 47* (63*) 46 (46) 47.62  | 45.69 (98.93) 50        |                               |                       |
| Larynx         | 55 52 5.00               | 4.95 5                  |                               |                       |
| Larynx         | 76 72 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       | 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 18.17%, 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 % |
|--------------|---------------------------------|---------------------------------------------|--------------|---------------------|---------------------------|
| Prostate     |                                 | D100 | D2/3 | D1/2 | D1/3 | Dmean (*D1cc) | D100 | D2/3 | D1/2 | D1/3 | Dmean (*D1cc) | D100 | D2/3 | D1/2 | D1/3 | Dmean (*D1cc) |
| Prostate     | 1 (37)                          | 46.30| 64.87| 68.34| 71.55| 68.55         | 0.77| 5.82| 0.18 |
| Prostate     | 2 (27)                          | 29.90| 48.90| 53.82| 58.61| 55.00         | 0.00| 0.00| 0.00 |
| Prostate     | 3 (37)                          | 29.90| 57.58| 63.15| 68.26| 61.41         | 0.02| 0.86| 0.00 |
| Prostate     | 4 (27)                          | 32.50| 47.05| 50.52| 54.19| 52.40         | 0.00| 0.21| 0.00 |
| Bowel        | 1 (37)                          | 1.3  | 25.77| 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| 1 (33)                          | 2.25 | 36.37| 37.97| 40.40| 42.87         | 0.73| 0.00| 0.17 |
| Head and Neck| 2 (33)                          | 2.25 | 38.24| 39.50| 41.02| 43.80         | 0.92| 0.00| 0.23 |
| Head and Neck| 3 (33)                          | 2.00 | 4.45 | 10.57| 26.60| 37.77         | 0.00| 0.00| 0.00 |
| Head and Neck| 4 (33)                          | 3.00 | 9.04 | 23.66| 32.48| 41.48         | 0.005| 0.004| 0.000 |
| Ipsilateral  | 1 (33)                          | 55.00| 68.47| 69.13| 70.04| 72.07         | 94.39| 99.84| 93.55 |
| Ipsilateral  | 2 (33)                          | 37.75| 59.51| 63.50| 66.83| 71.37         | 54.87| 98.44| 38.90 |
| Ipsilateral  | 3 (33)                          | 12.75| 18.76| 22.78| 36.31| 62.76         | 0.02| 0.00| 0.01 |
| Ipsilateral  | 4 (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 |
| Esophagus    | 1 (27)                          | 0.00 | 0.83 | 29.65| 40.13| 44.29         | 0.93| 0.00| 0.30 |
| Esophagus    | 2 (27)                          | 0.20 | 1.89 | 35.99| 43.02| 46.25         | 1.35| 0.01| 0.47 |
| Liver        | 1 (27)                          | 0.20 | 3.337| 5.34 | 10.03| 11.94         | 0.00| 0.06| 0.00 |
| Liver        | 2 (27)                          | 0.60 | 5.12 | 7.81 | 10.63| 13.29         | 0.02| 0.13| 0.00 |
| Liver        | 3 (27)                          | 0.80 | 21.58| 36.02| 38.37| 18.63         | 0.00| 0.32| 0.00 |
| Liver        | 4 (27)                          | 2.00 | 46.17| 47.00| 48.35| 43.47         | 6.16| 13.76| 9.31 |

*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.

### 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) |
|-------------------------------|---------|-------------------------------------|----------------|------------------|
| Prostate Prostate and semina vesicle | 1 | $D_{0.0}$ $D_{0.9}$ $D_{0.5}$ $D_{0.2}$ $D_{0.1}$ $D_{0.0}$ | 95.26 | 92.92 |
| | 2 | 90.48 | 88.38 |
| Prostate and semina vesicle | 1 | 98.84 | 98.91 |
| | 2 | 98.39 | 98.45 |
| Lymph node | 1 | 55.37 | 55.37 |
| | 2 | 59.38 | 59.38 |
| Lymph node | 1 | 98.84 | 98.91 |
| | 2 | 98.39 | 98.45 |
| Head and neck GTV | 1 | 95.91 | 96.22 |
| | 2 | 96.81 | 97.01 |
| GTV | 1 | 92.49 | 92.41 |
| | 2 | 88.59 | 87.99 |
| CTV | 1 | 99.59 | 99.55 |
| | 2 | 99.74 | 99.69 |
| CTV lymph node | 1 | 70.35 | 70.85 |
| | 2 | 70.98 | 71.53 |
| CTV lymph node | 1 | 90.11 | 85.32 |
| | 2 | 96.78 | 94.31 |

![Figure 3: Cumulative dose volume histograms of rectum of four different plans showing the different dose delivery to rectum](image)

![Figure 4: Cumulative dose volume histograms of bowel of four different plans showing the different dose delivery to bowel](image)

![Figure 5: Cumulative dose volume histograms of bladder of four different plans showing the different dose delivery to bladder](image)
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 occurred 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.[10] The decrease in the values of NTCPs of both the LKB models[12,13] 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 EQD2. But in case of plan (1), EQD2 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[19] 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 is given by

\[ N_c = \ln(2) \cdot \frac{1}{10} \left( \frac{TCD_{50}}{1} \right) \]

Where

\[ 1 = \frac{TCD_{50}(V_1) - TCD_{50}(V_2)}{\log_{10} \left( \frac{V_1}{V_2} \right)} \]

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

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

\[ N_c = \ln 2 \cdot \exp \left( \gamma_{50} \cdot \frac{2}{\ln 2} \right) \] (Stavrev et al.)[18]

Where \( \alpha/\beta \) and \( \gamma_{50} \) are the tissue specific parameter of linear quadratic models and slope of dose response curve respectively of the organ under consideration. \( d \) is the dose per fraction of the treatment schedule. \( \ln \) is the natural logarithmic to base \( e \) (\( \approx 2.31 \)).
Appendix B

Flow chart for DVH analysis

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

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