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ORIGINAL ARTICLE

Quantification of uncertainties in conventional plan evaluation methods in Intensity Modulated Radiation Therapy

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Summary

Purpose: *In Intensity Modulated Radiation Therapy (IMRT) dose distributions tend to be more complex and heterogeneous because of the modulated fluences in each beamlet of every single beam. These dose-volume (DV) parameters derived from the dose volume histogram (DVH) are physical quantities, thought to correlate with the biological response of the tissues. The aim of this study was to quantify the uncertainty of physical dose metrics to predict clinical outcomes of radiotherapy.*

Methods: *The radiobiological estimates such as tumor control probability (TCP) and Normal Tissue Complication Probability (NTCP) were made for a cohort of 40 cancer patients (10 brain;19 head & neck;11 cervix) using the DV parameters. Statistical analysis was performed to determine the correlation of physical plan quality indicators with radiobiological estimates.*

Results: *The correlation between conformity index (CI) and TCP was found to be good and the dosimetric parameters for optic nerves, optic chiasm, brain stem, normal brain and parotids correlated well with the NTCP estimates. A follow up study (median duration 18 months) was also performed. There was no grade 3 or 4 normal tissue complications observed. Local tumor control was found to be higher in brain (90%) and pelvic cases (95%), whereas a decline of 70% was noted with head & neck cancer cases.*

Conclusions: *The equivalent uniform dose (EUD) concept of radiobiological model used in the software determines TCP and NTCP values which can predict outcomes precisely using DV data in the voxel level. The uncertainty of using physical dose metrics for plan evaluation is quantified with the statistical analysis. Radiobiological evaluation is helpful in ranking the rival treatment plans also.*

Key words: *intensity modulated radiation therapy, equivalent uniform dose, normal tissue complication probability, tumor control probability*

Introduction

Radiotherapy is one of the cancer treatment modalities employed either alone or as concomitant/adjuvant therapy with surgery and/or chemotherapy. The main aim of radiotherapy is to deliver a therapeutic dose to target malignant tissues, while minimizing normal tissue complication risks. IMRT is an advanced form of radiotherapy delivery technique which has been practiced worldwide since three decades [1,2]. Physical metrics such as prescribed total dose and DV parameters are thought to correlate with the biological response of irradiated tissues based on clinical studies [3]. Hence, DV parameters from the DVH are used to evaluate the quality of treatment plans until recently. A DV parameter V20 from the treatment plan (percentage of lung volume receiving 20Gy) is used to gauge the incidence of grade ≥2 or grade ≥3 radiation pneumonitis, but the complications can be correlated to more than one point in the DVH (eg: V5, V40, D50) and it is treatment technique-dependent [4].The effectiveness of IMRT has to be studied extensively using radiobiological models. Evaluation of treatment plans with surrogate measure of the DV criteria should be replaced by actual biological indices which can reflect the clinical goals of radiotherapy [4]. Various radiobiological models for predicting the efficacy of radiotherapy were devised [5-9].

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A number of software programs were developed by different researchers based on various radiobiological models in the past decade to analyze the dose-response relationships [10-15], but their clinical usage is still inadequate. Generalized equivalent uniform dose (gEUD) concept of radiobiological modeling is more robust in reporting and analyzing the IMRT dose distributions that are heterogeneous in nature [16]. A free Matlab code for computing the TCP and NTCP based on the gEUD concept was developed by Gay et al. [17] which can use DVH parameters (D_i,v_i) available from treatment plans.

The EUD concept assumes that any two dose distributions are equivalent if they cause the same radiobiological effect in the tissues irradiated. The TCP and NTCP calculations are based mainly on two equations and the same model, unlike other models that are separately formulated for computing TCP and NTCP estimations. Emami et al. normal tissue tolerance data can be excellently fit with the model parameters, but tolerance doses estimated by these authors are applicable to conventional therapy evaluation only. The published QUANTEC (QUantitative Analysis of Normal Tissue Effects in the Clinic) reports have listed the normal tissue tolerance doses for three-dimensional (3D) and advanced conformal therapies. Hence, they can be used in IMRT plan evaluation to calculate TCP and NTCP estimates.

With the help of the gEUD formalism, the amount of normal tissue complications or tumor control can be assessed by D_i and v_i parameters of the DVH. Thus the biological response can be determined precisely from dosimetric data.

Generalized Equivalent Uniform Dose (gEUD)

In 1997, Niemierko proposed a concept which uses a single metric for reporting non-uniform tumor dose distributions. Conventional radiotherapy involves the dose distributions which tend to be uniform across the target volume. High-end radiotherapy such as IMRT results in rather inhomogeneous dose distributions. EUD is defined as an uniform dose that, if delivered over the same number of fractions to the target volume as the non-uniform dose distribution of interest, yields the same radiobiological effect. It is the uniform dose which leads to the same probability of injury in normal tissue or tumor control in tumors as the examined in inhomogeneous dose distribution.A phenomenological formula was proposed by Niemierko extending the EUD concept to normal tissues referred as gEUD [6].

$$gEUD = \left[\sum_i v_i D_i^a\right]^{1/a}$$

Where: v_i=fractional organ volume receiving a dose D_i,a=volume effect describing tissue specific parameter (-ve for tumor, +ve for serial organs)

$$NTCP=1/\left(1+\left(TD_{50}/EUD\right)\right)^{4\gamma 50}$$

Where: TD_{50} is the tolerance dose for a 50% complication rate at a specific time interval (e.g. 5 years Emami et al. data) [18,19], and γ50 is a unitless model parameter that is specific to the normal structure or tumor of interest and describes the slope of the dose-response curve [17,18]. All normal tissues have a limit as to the amount of radiation they can receive and still remain functional; this is defined as radiation tolerance.

$$TCP=1/\left(1+\left(TCD_{50}/EUD\right)\right)^{4\gamma 50}$$

Where: TCD_{50} is the tumor dose to control 50% of the tumor when the tumor is homogeneously irradiated [19]. The TCP was assessed using the TCD_{50} value (the 50% tumor control dose) as an end point. The lowest TCD_{50} was found in the lymphoma with 24.9 Gy, whereas the TCD_{50} of soft tissue sarcomas and squamous cell carcinoma ranged from 57.8 to 65.6 Gy [20].

There was a highly significant correlation between TCD_{50} and the prescribed total dose (normalized to 2 Gy fractions).

The purpose of this research was to estimate the TCP and NTCP in IMRT plans and to correlate the conventional DV criteria evaluated along with the clinical outcomes.

Methods

Eudmodel.m is a Matlab code readily available as an open source from the literature. It is an user-friendly program that needs processed DVH data from any treatment planning system. The other software programs so far developed based on Lyman Kutcher Burman (LKB) relative seriality and Poisson models have some difficulty in their implementation. E.g., the DVH file format from the treatment planning system (TPS) was not found to be compatible with the program execution and resulted in run time errors. The EUD model code is useful in calculating both TCP and NTCP whereas other programs calculate either TCP or NTCP based on the model used.

The patient undergoing radiotherapy was simulated in the same treatment position on the CT couch as on the treatment couch and axial images were obtained. CT scans of 40 patients were transferred to Nucletron PLATO treatment planning system (v14.3.7). Ten pa-

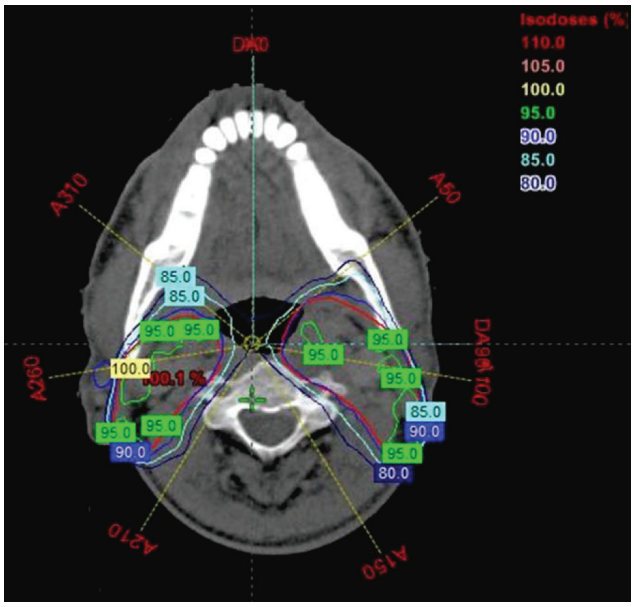


Figure 1. Axial dose distribution in a CT section.

tients were diagnosed with brain tumors, 19 with head & neck carcinoma and the remaining 11 patients with cervical cancer (Table 1). Evenly spaced gantry angle arrangement around the patient anatomy was planned and inversely optimized with ITP Lightning workspace (v1.2 .3) (Figure 1). Dose was calculated with a grid size of about 2mm and DVHs were generated for each case. DVH of brain case is shown in Figure 2.

Figure 3 shows the schematic diagram of computation workflow.

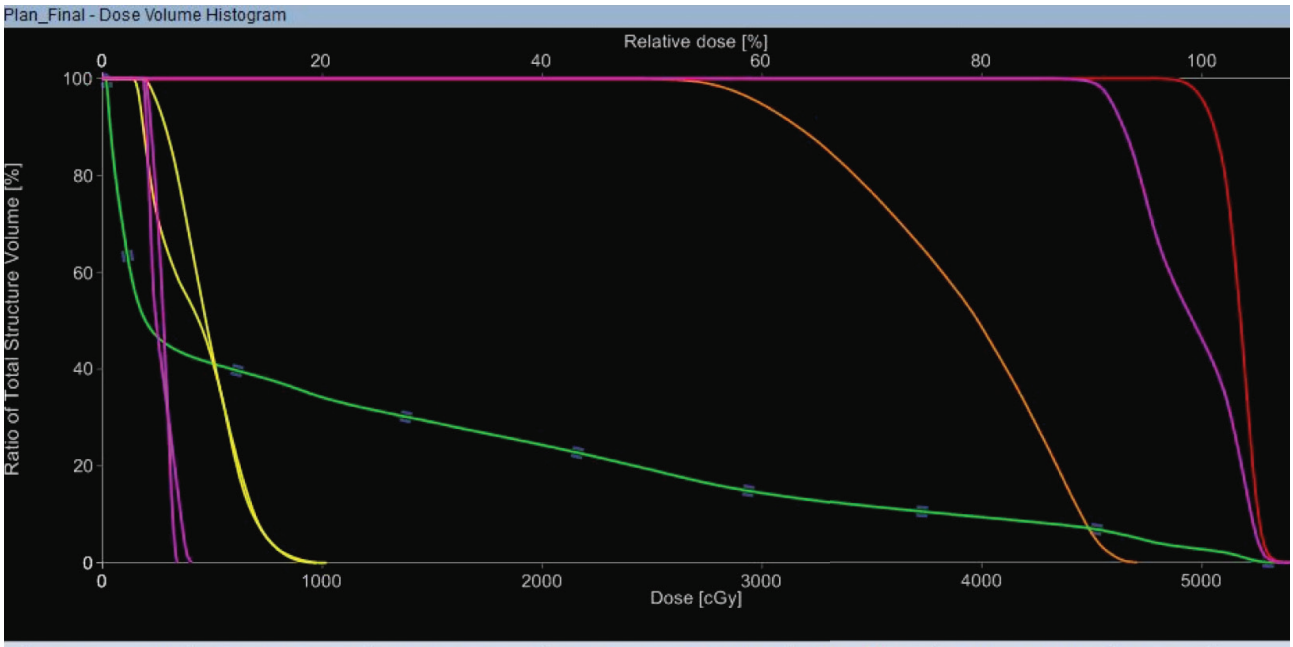
DV parameters such as TVref (reference target volume receiving the prescribed dose), TV (target volume delineated), D_{95} (dose received by 95% of tumor volume) and D_5 (dose received by 5% of tumor volume) of the corresponding target volume (brain, head & neck and cervix) were obtained from the DVH data.

The CI (a dosimetric quality metric), was calculated using the formula [22],

$$CI=TVref/TV$$

The Maximum /Mean dose value of each organ at risk such as brain stem (BS), right optic nerve (RON), left optic nerve (LON), normal brain, optic chiasm (OC), right parotid (RP), left parotid (LP), spinal cord (SC), bladder and rectum were also extracted from the DVHs.

The DVH files (Unix Format) were then exported to a windows-based computer system. The cumulative DVH file format was as follows: the first column corresponded to increasing absolute dose or percent dose values, and the second column to the corresponding absolute or relative volume values . UNIX file format was converted to MS excel file and the data were saved. To



Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

DVH Line	Structure	Approval St...	Plan	Course	Volume [cm³]	Dose Cove...	Sampling ...	Min Dose [...	Max Dose [...	Mean Dos...
	BODY	Approved	Plan_Final	C1	3368.5	100.0	100.0	7.0	5409.4	1129.8
	CTV	Approved	Plan_Final	C1	196.2	100.0	100.0	4220.9	5409.4	4944.9
	GTV	Approved	Plan_Final	C1	81.7	100.0	100.0	4725.3	5409.4	5164.0
	RT EYE	Approved	Plan_Final	C1	9.5	100.0	100.0	126.9	1026.1	428.3
	LT EYE	Approved	Plan_Final	C1	6.6	100.0	99.9	120.1	975.9	481.6
	OPTIC CHI...	Approved	Plan_Final	C1	0.7	100.0	100.1	2401.9	4711.8	3884.7
	RT LENS	Approved	Plan_Final	C1	0.1	100.0	100.4	181.7	410.4	263.2
	LT LENS	Approved	Plan_Final	C1	0.1	100.0	100.3	192.1	345.6	272.3

Figure 2. Dose volume histogram in a brain case.

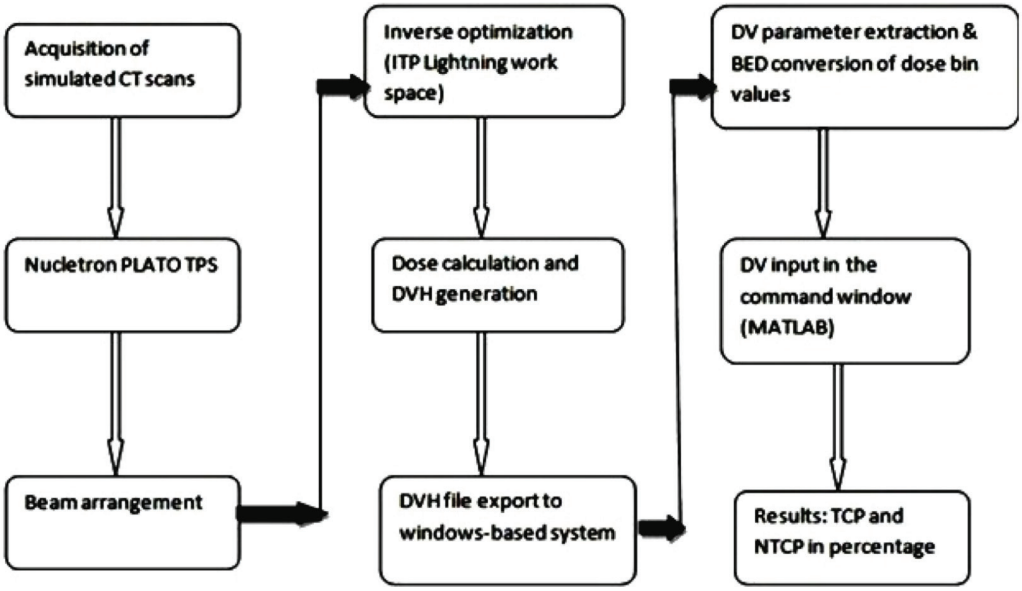


Figure 3. Schematic diagram of the computation workflow.

ROI Name	DVH Type	Dose Unit	DVH Volume Units	DVH Nr Of Bins	X	Y
RT PAROTID	CUMULATIVE	GY	PERCENT	404	0	100
RT PAROTID	CUMULATIVE	GY	PERCENT	404	22	100
RT PAROTID	CUMULATIVE	GY	PERCENT	404	44	100
RT PAROTID	CUMULATIVE	GY	PERCENT	404	66	100
RT PAROTID	CUMULATIVE	GY	PERCENT	404	88	100
RT PAROTID	CUMULATIVE	GY	PERCENT	404	110	100
RT PAROTID	CUMULATIVE	GY	PERCENT	404	132	100
RT PAROTID	CUMULATIVE	GY	PERCENT	404	154	100
RT PAROTID	CUMULATIVE	GY	PERCENT	404	176	100
RT PAROTID	CUMULATIVE	GY	PERCENT	404	198	100
RT PAROTID	CUMULATIVE	GY	PERCENT	404	220	100
RT PAROTID	CUMULATIVE	GY	PERCENT	404	242	100
RT PAROTID	CUMULATIVE	GY	PERCENT	404	264	100

Figure 4. Raw data from the treatment planning system converted to XML table in Windows system.

account for cold spot and hot spot in the dose distributions radiobiologically, the dose in each voxel or voxel element should be converted into biologically effective uniform dose (BED).

$$BED=D(1+d/(\alpha/\beta))$$

From the data, the X and Y coordinates corresponding to BED (Di) and Volume (v_i) (Voxel element of 2mm calculation grid) were fed as a two column matrix into the EUD program in MATLAB environment. An input variable DVH was created by typing dvh = [ ] in the command window. EUD model calculation requires the input data as differential DVH data. Since the cumulative DVH is the most commonly used plan evaluation tool, it can be given as the program input directly. The software internally converts input data into differential DVH data. For the 40 patients, a total of 129 raw DVH files from TPS were processed and evaluated radiobiologically with the input parameters (Figure 4).

Tumor kill dose to control 50% of the tumor (TCD_{50}) was used for calculating TCP [21]. According to that, irradiated tumors were examined twice weekly and scored as locally controlled if no growth was observed within 90 days after the radiation treatment. The percentage of locally controlled tumors was plotted vs the prescription dose. The TCD_{50} values determined by probability regression analysis for squamous cell carcinoma of head & neck, cervix and brain glioma were used to compute TPC in this study.

Statistics

An attempt to correlate the routine plan evaluation metrics with the TCP and NTCP was made based on statistical analysis. Pearson product moment method was

Table 1. Normal tissue complications correlation data

S.No	*Normal tissue*	*Mean Dmax/D_{50}(Gy)*	*Mean NTCP %*	*r(x,y)*	*p-value*
1	Brain stem	42.270	0.099	0.649	0.0400
2	Right optic nerve	16.780	0.940	0.882	0.0007
3	Left optic nerve	24.632	1.131	0.681	0.0200
4	Normal brain	58.276	8.176	0.673	0.0300
5	Optic chiasma	34.315	19.220	0.870	0.0010
6	Right parotid	30.385	21.667	0.657	0.0020
7	Left parotid	28.553	13.252	0.427	0.0600
8	Spinal cord	43.366	0.001	0.395	0.0900
9	Bladder	51.896	0.025	-0.012	0.9700
10	Rectum	51.424	0.015	0.407	0.2100

r (x,y): Pearson correlation coefficient, NTCP: normal tissue complication probability

used to deduce the correlation between the physical plan quality metrics (CI, D50, Dmax) with the radiobiological indices TCP and NTCP using a Statistics computation environment STATISTICA 5.0 (StatSoft Inc, USA). Thus the uncertainties involved with the conventional plan evaluation metrics could be quantified.

Results

The cumulative dose volume histogram was generated using Treatment Planning System's inbuilt algorithm. The simultaneous integrated boost (SIB) method (delivered with Step & Shoot technique) was followed to plan IMRT cases in our institution.

TCP and NTCP calculations were performed using the EUD model software program. (Figures 5,6). The mean TCP value for glioma-brain (volume : 115.6 - 413.6cc) was 89.8%, for head & neck tumors (volume 65.7-125.5cc) it was 65.5% and for cervix tumors (volume:918.8-2880.1cc) it was 93.2%. A Pearson correlation coefficient (r) of 0.376 was obtained for correlating the two plan evaluation metrics (CI & TCP) with a statistically significant value (p=0.017). Figure 7 shows the correlation between CI calculated for each plan and TCP estimated irrespective of the treatment sites, in a 2D scatter plot diagram. Dosimetric parameters correlating with normal tissue complications are listed in Table 1.

The parallel organs such as parotids and optic nerves evaluated with mean doses were found to be in good correlation with the NTCPs computed (RP: p=0.002; LP: p=0.06; RON: p=0.0007; LON: p=0.02). NTCP correlation with the maximum dose of serial organs was not statistically significant for the spinal cord, bladder and rectum (BS p=0.04; NB p=0.03; SC p=0.09; bladder p=0.97; rectum p=0.21).

A follow up study of the 40 IMRT patients was

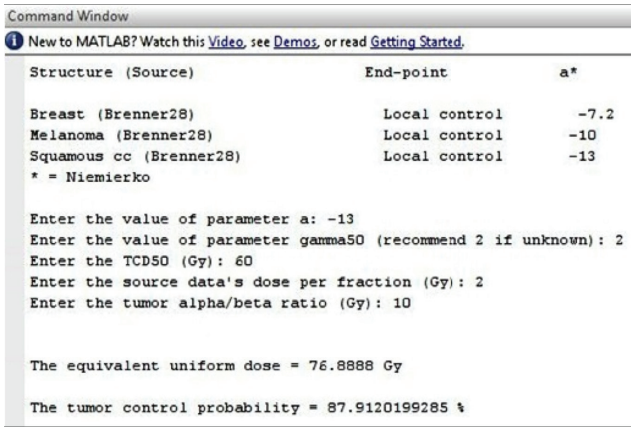


Figure 5. Tumor control probability calculation.

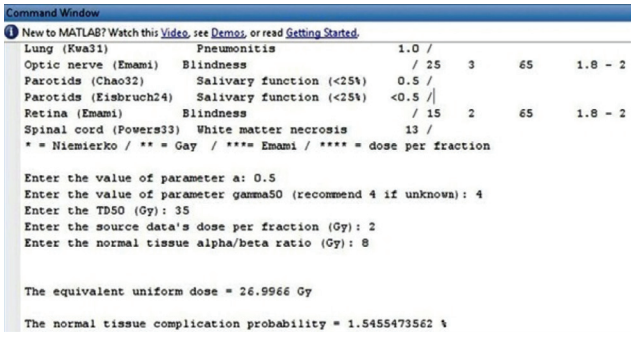


Figure 6. Normal tissue complication probability calculation.

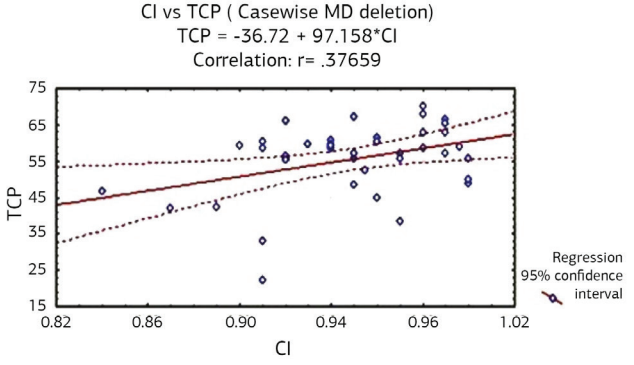


Figure 7. Conformity index (CI) vs tumor control probability (TCP)

conducted with a median duration of 18 months. Local disease control for the sites such as brain, head & neck and cervix were 90,70 and 95%, respectively. No severe normal tissue complications such as grade 3 or grade 4 were observed.

Discussion

The dose constraints physicians recommend are usually of the type "no more than x Gray, to no more than y percentile of the organ". From the available DVH information of the treatment planning system, treatment plans are evaluated based on the dosimetric parameters (tissue tolerance dose) alone. DVHs happen to be the only available plan evaluation tool with which the probability risks cannot be assessed completely.

The CI of brain, head & neck and cervix cases gives the idea of tumor coverage, resulting from the dose prescribed by clinical oncologists. It helps them to comparatively score various treatment plans for the same patient and select the best one to execute. But this type of evaluation is based only on the photon beam energy used for the irradiation and the DV constraints. The tumor coverage assessed using the CI should ideally be one that can indicate 100% coverage by the physical dose distribution. This evaluation method does not depend on the tumor type and its volume effect. Hence there is a need for an external evaluation tool for the complete assessment of biological outcomes using probability estimates such as TCP and NTCP.

Radiation dose volume effects for the whole organ irradiation were studied and reviewed in the QUANTEC reports for various normal tissues [23-26], but the follow up data were inadequate and further studies should be made for partial irradiation and the organ movement phenomenon.

There are 11 TCP /NTCP calculation software programs available in the literature. Among them, only 5 are freely distributed for the research studies (3 for dose response regression analysis and 2 for direct TCP, NTCP computations). Apart from BIOPLAN (a Visual Basic workspace), developed by Nahum et al. in 2000, others run in MATLAB environment. The free EUD based calculation program uses an unified formula for TCP and NTCP calculations. Thus, it can do the computation more easily compared to other radiobiological models e.g. the Lyman Kutcher Burman (LKB) model based software programs. The LKB model calculation requires 3 radiobiological parameters such as n, m and TD_{50} in which the tissue specific parameter (m) and the equivalent uniform dose parameter (n) have no reliable estimates. Hence the uncertainty can be avoided by eliminating the use of other radiobiological parameters with simple EUD program that requires TCD_{50}, TD_{50}, EUD, a, α/β and the dosimetric parameters (D_i, vi).

CI is widely used to rank the treatment plans on the basis of target volume dose coverage. It merely depends on the radiation beam used and the radiotherapy technique followed. But the TCP calculation is based on the radiobiological parameters describing the volume effect (a) of irradiation, dose response slope factor ($\gamma 50$), 50% tumor control dose (TCD_{50}) and EUD. From this study, CI is found to be correlated with the estimated TCP. Hence, the calculation of CI can determine the plan quality similar to TCP estimates.

Normal tissue's maximum or mean dose obtained from the DVH are usually compared with the Emami tolerance data to select the optimal plan for execution. E.g, maximum normal brain dose is 67.46 Gy which is 7.46 Gy more than the TD_{50} for normal brain i.e. 60 Gy. From this, one can evaluate that there may be a chance of 50% complication rate, resulting in brain necrosis in 5-year survival time.The exact amount of probability of occurrence of brain necrosis can be estimated as 24.017% using the EUD-based software calculation of NTCP. Similarly, a complication probability of 0.873% was calculated for the incidence of brain necrosis when it receives a maximum dose of 56.35 Gy (observed in patient No.2). When there is a rival plan with a lower complication probability, clinicians can choose that particular plan treatment delivery.

Evaluation of mean doses in the parallel structures such as parotids and optic nerves in comparing two treatment plans may be effective since there was a statistically significant correlation found with the NTCP estimates. The complication probabilities for serial organs such as brain stem, normal brain, and optic chiasm are correlated well with the maximum dose. But spinal cord, rectum and bladder correlations deviated more with the radiobiological estimates. There may be an uncertainty in using maximum dose alone for the treatment plan evaluation of bladder,rectum and spinal cord.

Conclusion

Standard radiotherapy treatment plan evaluation tool (DVH) confines with the assessment of physical metrics before proceeding to treatment delivery. It has certain limitations in the absolute assessment of biological outcomes because of the

uncertainty exhibited in correlating the outcomes with more than one particular DV parameter. These parameters can be further evaluated radiobiologically by means of an external work space. Dosimetric evaluation indices such as the CI and mean dose in case of parallel organs, and maximum dose for the serial organs, correlate with their corresponding tumor control and normal tissue complication probabilities calculated. The EUD concept of radiobiological model used in the software determines the TCP and NTCP values that can predict the outcomes precisely. The uncertainty of using physical dose metrics for plan evaluation is quantified with a statistical analysis. Any two treatment plans can be effectively compared based on TCP and NTCP along with other physical dose metrics.

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