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A statistical quantification of radiobiological metrics in Intensity Modulated Radiation Therapy evaluation

A. Surega, J. Punitha, S. Sajitha, BS Ramesh, A. Pichandi, P. Sasikala

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Abstract

The dosimetric parameters from the DVH cannot predict the amount of tumor kill and normal tissue complications directly but it can assess the conformity and homogeneity of the physical dose distributions. For example, the D-V parameter V20 (Percentage of lung volume receiving 20Gy) is used to gauge the incidence of grade ≥2 or grade ≥3 radiation pneumonitis with the plan. But the complication can be correlated to more than one point in the DVH (eg. V5, V40, D50) and it is treatment technique dependent. The aim of this study is to quantify the uncertainty of physical dose metrics to predict the clinical outcomes of the radiotherapy treatments.

Methods:

The radiobiological estimates such as TCP and NTCP were made for a cohort of 50 patients (15-Brain; 20-H&N; 15-Pelvis) using the D-V parameters. A statistical analysis based on Spearman ranking coefficient correlation was performed to determine the correlation of the physical plan quality indicators with that of radiobiological estimates.

Results:

The correlation between the Conformity Index and the Tumor Control probability was found to be good and the dosimetric parameters for optic nerves, optic chiasm, brain stem, normal brain and parotids correlated well with the Normal Tissue Complication Probability estimates compared to other normal structures. A follow up study (median duration: 28 Months) was also performed. There was no grade 3 or grade 4 normal tissue complications observed. Local tumor control was found to be higher in brain (90%) and pelvic cases (95%) whereas a decline of 75% was noted with Head and Neck cases.

Conclusions:

The EUD concept of radiobiological model used in the software determines the TCP and NTCP values which can predict precise outcomes with the use of dose volume data in the voxel level. The uncertainty of using physical dose metrics for plan evaluation is quantified with the statistical analysis. It is also helpful in ranking rival treatment plans.

Keywords:
IMRT, EUD, radiobiology, TCP, NTCP, India

Introduction

In radiotherapy planning, the physical metrics such as the prescribed total dose and the dose – volume (DV) parameters are thought to correlate with the biological response of irradiated tissues based on clinical studies. Hence the DV parameters from the Dose Volume Histogram (DVH) are used to evaluate the quality of treatment plans until recently. The effectiveness of IMRT has to be studied extensively with the use of radiobiological models.

With the help of gEUD formalism, the amount of complications or tumor control can be assessed by Di and vi parameters of the DVH. Thus the biological response can be determined precisely.
The use of radiobiological plan evaluation metrics in IMRT, A. Surega, et. al.

from the dosimetric data. The correlation can be quantified using statistical methods like Spearman method.

**Materials and methods**

The evaluation of treatment plans with the surrogate measure of the DV criteria were replaced by actual biological indices which can reflect the clinical goals of radiotherapy (1-4). Various radiobiological models for predicting the efficacy of radiotherapy were devised (5-9). A number of software programs were developed by different researchers based on various radiobiological models in the past decade to analyze the dose response relations (10-15) but their clinical usage was limited. Generalized Equivalent Uniform Dose (gEUD) concept of radiobiological modeling is more robust in reporting and analyzing the IMRT dose distributions which are heterogeneous in nature (16). A free Matlab code for computing the Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) based on gEUD concept was developed by Gay et al (17). It can use the DVH parameters (Di, vi) 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 which are separately formulated for TCP and NTCP calculations. Emami et al have noted that normal tissue tolerance data fit excellently with the model parameters. But the tolerance doses estimated by Emami et al are applicable to conventional therapy evaluation only. The published QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) report lists the normal tissue tolerance doses for three dimensional conformal therapies. Hence they can be used in the clinical cases to arrive at the TCP and NTCP estimates for IMRT plan evaluation.

Eudmodel.m is a Matlab code available as an open source from the literature. It is a user friendly program which needs processed DVH data from any treatment planning system. The other software programs developed were based on LKB, Relative seriality and Poisson models have their inherent errors in execution. For e.g.: the DVH file format from the TPS was not found to be compatiblt with the program execution which resulted in run time errors. The eudmodel code is useful in calculating both TCP and NTCP whereas other programs calculate either TCP or NTCP based on the model used.

**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 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 the 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 inhomogeneous dose distribution. A phenomenological formula was proposed by Niemierko extending the EUD concept to normal tissues referred to as generalized EUD (gEUD) (6).

\[ gEUD = \left( \sum vi Dia \right) ^{1/a} \]

Where,

\[ vi = \text{Fractional organ volume receiving a dose } Di \]

\[ a = \text{Volume effect describing tissue specific parameter} \]

\[ (-ve \text{ for tumor, +ve for serial organs}) \]

**Normal Tissue Complication Probability (NTCP)**

NTCP is the probability that a given dose of radiation will cause an organ or structure to experience complications considering the specific biological cells of the organ or structure. It is used in treatment planning as an evaluation tool to differentiate among treatment plans.

\[ NTCP=1/ \left(1 + (TD50/EUD) \right)^{450} \]
**TD50:** Tolerance dose for a 50% complication rate at a specific time interval (e.g., 5 years Emami et al data)\(^{(18,19)}\).

γ50: is a unit-less 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 which is defined as Radiation Tolerance.

**Tumor Control Probability (TCP)**

Tumor control probability is a radiobiological estimate that takes tissue parameters into consideration to estimate the regression/relapse of malignancy after irradiation. TCP thought to be more relevant in evaluating the tumor control compared to dosimetric parameters.

\[
TCP=\frac{1}{1+(\frac{TCD50}{EUD})^{\gamma50}} \tag{3}
\]

**TCD50:** Tumor dose to control 50% of the tumors when the tumor is homogeneously irradiated\(^{(19)}\). The TCP was assessed using the TCD50 value (the 50% tumor control dose) as an end point. The lowest TCD50 was found in the lymphoma with 24.9 Gy, whereas the TCD50 of the soft tissue sarcomas and the squamous cell carcinoma ranged from 57.8 Gy to 65.6 Gy\(^{(20)}\).

**TCD50 assay**

Irradiated tumors were examined twice weekly and scored as locally controlled if regrowth was not observed within 90 days after the radiation treatment. The percentage of locally controlled tumors was plotted versus prescription dose, and the TCD50 value was determined by probability regression analysis. There is a highly significant correlation between TCD50 and the prescribed total dose (Normalized to 2Gy fractions)\(^{(21)}\).

**Methods**

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. The CT scans of 50 patients were transferred to Eclipse treatment planning system (Varian Medical Systems Inc, USA, Version 8.2). Among the 50 patients, 15 patients were diagnosed with brain tumors, 20 were with head and neck carcinoma and remaining 15 were cervical cancer patients (Table 2). Evenly spaced gantry angle arrangement around the patient anatomy was planned and inversely optimized with Anisotropic Analytical Algorithm (Version: v11.0.31). Dose was calculated with a grid size of about 2mm and the Dose Volume Histograms was generated for each case.

The DV parameters such as TVref (Reference target volume receiving the prescribed dose), TV (Target volume delineated), D95 (Dose received by 95% of tumor volume) and D5 (Dose received by 5% of tumor volume) of the corresponding target volume (Brain, Head & Neck, and Cervix) were obtained from the DVH data.

The Conformity Index (CI) which is a dosimetric quality metric was calculated using the formula (22):

\[
CI=\frac{TV_{ref}}{TV} \tag{4}
\]

The Maximum/Mean dose value of each associated organs 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 (Text Format) were then exported to windows based computer system. The cumulative DVH file format is as follows: The first column corresponds to increasing absolute dose or percentage dose values, and the second column to the corresponding absolute or relative volume values. Text file format is converted and saved as MS excel file. To account for cold spot and hot spot in the dose distributions radio biologically, dose in each voxel or voxel element should be converted into biologically effective uniform dose (BED).

\[
BED=D\left(1+\frac{d}{(\alpha/\beta)}\right) \tag{5}
\]
From the data, the X and Y coordinates corresponding to the Biologically Effective Dose (Di) and Volume (vi) (Voxel element of 2mm calculation grid) were then fed as a two column matrix into the EUD program in the MATLAB environment for computing the radiobiological metrics such as TCPs and NTCPs. The input variable DVH was created by typing `dvh = ( )` in
Results

The dose distribution in the transverse section of the CT scan is shown in Figure 1. This cumulative dose volume histogram was generated using Treatment Planning System’s inbuilt algorithm. The cumulative DVHs of three different cases viz., Brain, Head and Neck and Cervix were shown in Figures 2, 3 and 4.

Simultaneous Integrated Boost (SIB) method delivered with Step and Shoot technique was followed to plan the IMRT cases in our institution. The tumor control correlation data for treatment sites such as Brain, Head and Neck and Cervix are listed in Table 2. The dosimetric parameters correlating with normal tissue complications were listed in Table 3.

The TCP and NTCP calculations were performed using the EUD Model software program (Figures 2 and 3). The Mean TCP value for Glioma-Brain (Volume: 115.6cc to 413.6cc) was 89.8%, Head and Neck tumors (Volume was 65.7cc to 125.5cc) was 65.5% and Cervix tumors (Volume: 918.8cc to 2880.1cc) was 93.2%. A Spearman correlation coefficient (r) of 0.376 was obtained for correlating the two plan evaluation metrics (CI and TCP) with a statistically significant value (p=0.07, CI=95%) for pelvic cases. Figure 4 shows the correlation between the Conformity Index calculated for each plan and the Tumor Control Probability estimated irrespective of the treatment sites, using the EUD model based calculation program in a 2D scatter plot diagram.

Statistical Analysis

An attempt to correlate the routine plan evaluation metrics with the TCP and NTCP was made based on statistical analysis. Spearman ranking coefficient method was used to deduce the correlation between the physical plan quality metrics (CI, D50, Dmax) with the radiobiological indices such as TCP and NTCP using a Statistics computation environment STATISTICA 5.0 (StatSoft Inc, USA). Thus the uncertainties involved with the conventional plan evaluation metrics can be quantified.
The correlation data between the dose volume parameters for the ten normal structures and their corresponding Normal Tissue Complication Probabilities were tabulated (Table 3). The parallel organs such as parotids and optic nerves evaluated with the maximum 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). The NTCP correlation with the maximum dose obtained for the serial organs 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 50 IMRT patients was conducted with a median duration of 28 months. Local control of the disease for the sites such as Brain, H&N and Pelvis are 90%, 75% and 95% respectively. No severe normal tissue complications such as Grade 3 or Grade 4 are observed.

**Discussion**

The dose constraints recommended by physicians 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 (Tolerance Doses) alone. DVHs happen to be the only available plan evaluation tool with which the probability risks cannot be assessed completely.

The Conformity index (CI) of Brain, Head & Neck and Cervix cases listed in Table 2

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients</th>
<th>Median Age(Yr)</th>
<th>TV(cc)</th>
<th>DP(Gy)</th>
<th>TVref (%)</th>
<th>Mean CI</th>
<th>Mean TCP(%)</th>
<th>r(x,y)</th>
<th>p</th>
<th>Observed Local Control(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>10</td>
<td>49.5</td>
<td>45.8 – 432.5</td>
<td>1.8,2.2,2</td>
<td>95.50</td>
<td>0.955</td>
<td>89.8</td>
<td>0.495</td>
<td>0.63</td>
<td>90</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>19</td>
<td>51</td>
<td>65.7-404.9</td>
<td>1.8,2.2,12</td>
<td>95.06</td>
<td>0.949</td>
<td>65.5</td>
<td>0.117</td>
<td>0.15</td>
<td>75</td>
</tr>
<tr>
<td>Pelvis</td>
<td>11</td>
<td>51</td>
<td>148.1-2611.8</td>
<td>1.8,2</td>
<td>94.07</td>
<td>0.940</td>
<td>93.2</td>
<td>0.318</td>
<td>0.07</td>
<td>95</td>
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Table 2. Tumor Control correlation data

<table>
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<tr>
<th>S. No.</th>
<th>Normal Tissue</th>
<th>Mean Dmax/D50(Gy)</th>
<th>Mean NTCP (%)</th>
<th>r(x,y)</th>
<th>p</th>
</tr>
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<tr>
<td>1</td>
<td>Brain Stem</td>
<td>42.270</td>
<td>0.099</td>
<td>0.649</td>
<td>0.0400</td>
</tr>
<tr>
<td>2</td>
<td>RON</td>
<td>16.780</td>
<td>0.940</td>
<td>0.882</td>
<td>0.0007</td>
</tr>
<tr>
<td>3</td>
<td>LON</td>
<td>24.632</td>
<td>1.131</td>
<td>0.681</td>
<td>0.0299</td>
</tr>
<tr>
<td>4</td>
<td>NB</td>
<td>58.276</td>
<td>8.176</td>
<td>0.673</td>
<td>0.0327</td>
</tr>
<tr>
<td>5</td>
<td>OC</td>
<td>34.315</td>
<td>19.220</td>
<td>0.870</td>
<td>0.0010</td>
</tr>
<tr>
<td>6</td>
<td>RP</td>
<td>30.385</td>
<td>21.667</td>
<td>0.657</td>
<td>0.0023</td>
</tr>
<tr>
<td>7</td>
<td>LP</td>
<td>28.553</td>
<td>13.252</td>
<td>0.427</td>
<td>0.0605</td>
</tr>
<tr>
<td>8</td>
<td>SC</td>
<td>43.366</td>
<td>0.001</td>
<td>0.395</td>
<td>0.0943</td>
</tr>
<tr>
<td>9</td>
<td>Bladder</td>
<td>51.896</td>
<td>0.025</td>
<td>-0.012</td>
<td>0.9710</td>
</tr>
<tr>
<td>10</td>
<td>Rectum</td>
<td>51.424</td>
<td>0.015</td>
<td>0.407</td>
<td>0.2140</td>
</tr>
</tbody>
</table>

Table 3. Normal tissue complications correlation data

Abbreviation: r(x,y)= Correlation Coefficient, SD=Standard Deviation
gives the idea of tumor coverage with the dose prescribed by the oncologists. It helps them to comparatively score the 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 D-V constraints. The tumor coverage assessed using the CI should ideally be one indicating the 100% coverage by the physical dose distribution or the reference isodose line. This evaluation method does not depend on the tumor type and their volume effect. Hence there is a need for an external evaluation tool for the ultimate assessment of biological outcomes with the help of probability estimates such as TCP and NTCP.

The 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 was inadequate and further studies should be made for partial irradiation and organ movement phenomenon.

There are eleven TCP/NTCP calculation software programs presented in the literature. Among them, only five are freely distributed for the research studies (three for dose response regression analysis and two for direct TCP, NTCP computations). Apart from the BIOPLAN (Visual Basic workspace), developed by Nahum et al in 2000, others run in MATLAB environment. The free EUD based calculation program uses the unified formula for TCP and NTCP calculations. Thus, it can do the computation more easily compared to other radiobiological models e.g.: Lyman Kutcher Burman (LKB) model based software programs. LKB model calculation requires three radiobiological parameters such as n, m and TD50 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 this simple EUD program which requires TCD50, TD50, EUD, a, α/β and the dosimetric parameters (Di, vi). EUD model has the remarkable capability in fitting the normal tissue tolerance values (TD50) published in Emami et al data.

The conformity index 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 γ50, 50% tumor control dose (TCD50) and Equivalent Uniform Dose (EUD). From this study, CI is found to be correlating with the estimated TCP from the statistical analysis. Hence the calculation of Conformity Index can determine the plan quality effectively 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. For e.g., maximum normal brain dose is 67.46Gy which is 7.46Gy more than the TD50 for normal brain i.e. 60Gy. It can be evaluated that there may be a chance of 50% complication resulting in brain necrosis in the 5 year survival time. The exact amount of probability for the 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 56.35Gy (patient No.2). When there is a rival plan with a lesser complication probability, clinician can choose that plan for treatment delivery. Table 3 gives the NTCP estimates of the normal tissues such as Brain Stem, Rt. Optic Nerve, Lt. Optic Nerve, Optic Chiasma and Normal brain (Glioma Cases), Rt. Parotid, Lt. Parotid and Spinal cord (H&N cases) and Bladder and Rectum (Ca. Cervix cases).

The evaluation of mean doses in parotid may be effective since there is a statistically significant correlation found with the NTCP estimates. The complication probabilities for serial organs such as brain stem, normal brain, 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 SC. Conventional plan evaluation tool (DVH) stops with the assessment of physical metrics before proceeding to the treatment delivery. It has certain limitations in absolute assessment of biological outcomes because of the uncertainty exhibited in correlating the outcomes with more than one particular D-V parameter.

**Conclusion**

Dosimetric parameters can be further evaluated radiobiologically using an external work space running under the MATLAB environment. The dosimetric evaluation indices such as Conformity Index and Mean dose in case of parallel organs, 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. Thus, two treatment plans can be compared based on TCP and NTCP along with other physical dose metrics.

**References**


