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FULL PAPER

Dosimetric assessment of tumor control probability in intensity and volumetric modulated radiotherapy plans

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Objective: Radiobiological models have been used to calculate the outcomes of treatment plans based on dose-volume relationship. This study examines several radiobiological models for the calculation of tumor control probability (TCP) of intensity modulated radiotherapy plans for the treatment of lung, prostate, and head and neck (H&N) cancers.

Methods: Dose volume histogram (DVH) data from the intensity modulated radiotherapy plans of 36 lung, 26 prostate, and 87 H&N cases were evaluated. The Poisson, Niemierko, and Marsden models were used to calculate the TCP of each disease group treatment plan. The calculated results were analyzed for correlation and discrepancy among the three models, as well as different treatment sites under study.

Results: The median value of calculated TCP in lung plans was 61.9% (34.1–76.5%), 59.5% (33.5–73.9%) and 32.5% (0.0–93.9%) with the Poisson, Niemierko, and Marsden models, respectively. The median value of calculated TCP in prostate plans was 85.1% (56.4–90.9%), 81.2% (56.1–88.7%) and 62.5% (28.2–75.9%) with the Poisson, Niemierko, and Marsden models, respectively. The

median value of calculated TCP in H&N plans was 94.0% (44.0–97.8%) and 94.3% (0.0–97.8%) with the Poisson and Niemierko models, respectively. There were significant differences between the calculated TCPs with the Marsden model in comparison with either the Poisson or Niemierko model ($p < 0.001$) for both lung and prostate plans. The TCPs calculated by the Poisson and Niemierko models were significantly correlated for all three tumor sites.

Conclusion: There are variations with different radiobiological models. Understanding of the correlation and limitation of a TCP model with dosimetric parameters can help develop the meaningful objective functions for plan optimization, which would lead to the implementation of outcome-based planning. More clinical data are needed to refine and consolidate the model for accuracy and robustness.

Advances in knowledge: This study has tested three radiobiological models with varied disease sites. It is significant to compare different models with the same data set for better understanding of their clinical applicability.

INTRODUCTION

Intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) have become standard of care and increasingly used for the treatment of various tumor sites due to highly conformal dose distribution allowing better tumor control and more so the normal tissue sparing. In planning IMRT or VMAT cases, some dosimetric parameters are usually defined as the physical constraints, and treatment planning systems (TPS) employ an optimization algorithm that applies the given constraints in the cost function to meet the desired objectives. However, the treatment plans as such, designed by physical objectives, might not be directly correlated with the clinical outcomes.

Various radiobiological models^{1–3} are available to predict the radiation response using dose-volume histogram (DVH) data from a dosimetric plan. DVH is the summary of dose distribution in a defined structure representing the volume of structure receiving greater than or equal to that specified amount of radiation dose. The DVH has become one of the most useful tools to help clinicians understand how well a plan has met the desired dose objectives in terms of dose and volume relationship. However, the truly relevant end points in radiotherapy are not dose distributions, rather, the tumor control probability (TCP) and normal tissue complication probability (NTCP). Various models have been developed to assess the clinical results of a radiation treatment plan.^{4,5} Those models apply the fitting parameters acquired from clinical data sets and the

DVH information from plans in question to estimate the TCP and NTCP. Unfortunately, these models are variable and predict divergent outcomes depending on the model selected. Additionally, the lack of reliable biological data has largely limited the application of these models.

One important aspect of radiobiological models is that they can be used prospectively for dose escalation and de-escalation, particularly TCP models can be used for optimizing the planning parameters. Based on ICRU-50, ICRU-83 and ICRU-91, many dosimetric parameters *e.g.* DVH, conformity index (CI), homogeneity index (HI), gradient index (GI) etc. can be associated with tumor control. It is not intuitive to know from physical dose distribution which plans have better TCP because multiple points in the DVH can have an impact on the calculation of a radiobiological model. Few studies^{6,7} report a detailed analysis of the correlation between dosimetric parameters and calculated TCP. It can be clinically interesting and useful to see the relationship of physical dose metrics and TCP estimates from the perspective of clinical outcomes.

It is suggested⁸ that the optimization and evaluation of radiation treatment plans should be directly based on biological indices rather than physical dose parameters. Several publications^{9–11} have discussed the application of biological tools to evaluate and rank complex treatment plans. Most commercial TPS (Elekta Monaco, Varian Eclipse and Phillips Pinnacle etc.) have implemented biological tools for plan optimization and evaluation. Before the new mathematical tools can be safely used in clinic, more studies are needed to confirm their validity and reliability. The correlation of radiobiological models with physical dose parameters and clinical outcomes for various cancer sites and treatment modalities has yet to be well-established.

Understanding of biological models as the tool to evaluate complex and heterogeneous dose distributions in IMRT and VMAT plans is limited, particularly the relationship of the predicted outcomes and the model parameters, the uncertainties and factors affecting TCP predictions. In this study, we calculated TCP for IMRT/VMAT plans of various cancers in a cohort of patients with three different radiobiological models, namely, the Poisson Model,¹² the Niemierko Model³ and the Marsden Model.¹ The calculation parameters were taken from the literature,^{2,12} including the cell survival index (α , β), which can vary with tumor type and fractionation. We looked at the results of TCP calculation by varied models for different tumor sites, lung, prostate, and head and neck (H&N) cancer. We investigated the correlation of dosimetric parameters with TCP

models, discussed the TCP estimates in relation to published outcomes and the variations as well as the limitations of the models.

METHODS AND MATERIALS

IMRT or VMAT plans for the definitive treatment courses of 149 patients (36 lung, 26 prostate, and 87 H&N cancer) were selected from a de-identified institutional review board approved data set.¹³ The dose was calculated with heterogeneity correction at a calculation grid size of 0.25 cm from several commercial TPS (Pinnacle, Eclipse and CMS XiO). The DVH of each plan for planning tumor volume (PTV) was exported from the TPS with the default setting of a 1 cGy bin size. The calculation of TCP from each plan uses the differential dose volume histogram of PTV, which consists of pairs of partial volume (v_i) receiving dose greater than D_i (D_i , V_i) in PTV.

All plans were prescribed to 100% isodose line with a fraction size ranged from 1.80 to 2.12 Gy per fraction, which was corrected to 2 Gy per fraction equivalent dose. Dose prescription and DVH characteristics are provided in Table 1. The median prescription dose was 60.0 Gy (range, 40.0–70.0), 70.2 Gy (range, 50–79.2), and 70.0 Gy (range, 50.0–70.3) for lung, prostate and H&N, respectively. The H&N plans were prescribed to PTV for primary tumors, not including nodal regions. The mean dose for all tumor sites was 103.1% (91.8–114.6%) of prescription dose. The prescribed tumor coverage was variable from case to case as previously shown by Das et al.¹³ The lung cancer plans had a smaller mean D95% but a greater equivalent uniform dose (EUD) than those of the prostate or H&N cancer. The minimum dose had fairly large variation between plans with the ranges of (32.6–100.6%), (60.4–99.0%), and (8.5–101.3%) for the lung, prostate, and H&N plans, respectively. Figure 1 plotted the characteristics of tumor volume and plan fractionation.

The following three radiobiological models were employed in TCP calculations. The characteristics of each model are briefly described below. These models are all dependent on the tumor type and the biological parameters assumed.⁷ The main difference of the Marsden Model¹ is that it explicitly incorporates inter patient variation of radio-sensitivities by assuming a normal distribution amongst patient population with a standard deviation.¹⁴

Poisson Model⁹: Assumed cell survival from radiation dose D_i in independent subvolume v_i following Poisson distributions.

Table 1. Dose prescription and PTV dose–volume with $\pm$ standard deviation for the IMRT plans

Tumor site	Prescription (Gy)	Dosimetric characteristics of plans (% relative to prescription dose)				
		Min dose	Max dose	D95%	Mean dose	EUD
Lung	55.1 $\pm$ 8.0	78.7 $\pm$ 14.7	112.5 $\pm$ 5.4	97.7 $\pm$ 3.7	104.1 $\pm$ 3.9	102.0 $\pm$ 6.7
Prostate	69.3 $\pm$ 9.7	85.8 $\pm$ 9.3	107.6 $\pm$ 1.5	99.5 $\pm$ 1.3	102.4 $\pm$ 1.0	99.7 $\pm$ 2.4
H&N	65.6 $\pm$ 6.2	79.8 $\pm$ 19.6	110.1 $\pm$ 2.9	98.1 $\pm$ 4.3	102.8 $\pm$ 2.6	99.1 $\pm$ 15.4

EUD, equivalent uniform dose; H&N, head and neck; PTV, planning tumor volume;

Figure 1. Characteristics of tumor volume and plan fractionation. (a) Histogram of tumor volumes; (b) percentage frequency of fraction numbers of all plans.

$$TCP = \left(\frac{1}{2} \right)^{\sum_i \nu_i \exp \left[\frac{2}{\ln 2} \gamma_{50} \left(1 - \frac{D_i}{D_{50}} \right) \right]}$$

D_{50} and γ_{50} are the dose and normalized slope at the 50% of tumor control.

Niemierko Model³: Assumed logistic dose response for the whole tumor after inhomogeneous dose distribution was reduced in EUD.

$$TCP = \frac{1}{\left[1 + \frac{D_{50}}{EUD} \right]^{4\gamma_{50}}}$$

Marsden Model¹: Incorporates inter patient response variation into Poisson-based cell survival from radiation. The model has been implemented in software Biosuite.²

$$TCP = \frac{1}{\sigma_{\alpha} \sqrt{2\pi}} \int_0^{\infty} \left(\exp \left(-\rho_{cl} \sum_i \{ \nu_i \exp(-\alpha D_i) \} \right) \right) \exp \left(-\frac{(\alpha - \bar{\alpha})^2}{2\sigma_{\alpha}^2} \right) d\alpha$$

Parameter α (in α/β) is the tumor-specific linear-quadratic (LQ) parameter. σ_{α} is standard deviation of the normal distribution of α among patient population, ρ_{cl} is the clonogenic cell density.

Model parameters from publication¹⁵ were summarized in Table 2 and the defaults for lung and prostate cancer in Biosuite were used.^{2,12} The dose fractionations were corrected with tumor specific α/β ratios in Table 2. The H&N cases were not calculated with the Marsden model due to unavailability of the parameters.

Table 2. Parameters for the TCP models

Tumor Site	Poisson/Niemierko model			Marsden model		
	D_{50}	γ_{50}	α/β	ρ_{cl}	α	σ_{α}
Lung	51.24	0.83	10	1.00E + 07	0.307	0.037
Prostate	46.29	0.95	3	1.00E + 07	0.301	0.114
H&N	51.77	2.28	10	NA	NA	NA

NA, not available; TCP, tumor control probability;

Statistical analysis was performed by linear regression and paired *t*-tests for the correlation of TCP results among different models.

RESULTS

Figure 2 and Table 3 summarize the results of TCP calculation with the three different models for the plans of each specified tumor type. The median value of TCP calculated from the lung IMRT plans was 61.9% (34.1–76.5%), 59.5% (33.5–73.9%) and 32.5% (0.0–93.9%) with the Poisson, Niemierko, and Marsden model, respectively. The median value of TCP calculated from the prostate plans was 85.1% (56.4–90.9%), 81.2% (56.1–88.7%) and 62.5% (28.2–75.9%) with Poisson, Niemierko and Marsden model, respectively. The median value of TCP calculated from the H&N plans was 94.0% (44.0–97.8%) and 94.3% (0.0–97.8%) with Poisson and Niemierko model, respectively. The spread in TCP results is likely related to a combination of different target sizes and non-uniformity in dose distributions.

The TCP was significantly different with the Marsden model (lower TCP) in comparison with either Poisson or Niemierko model ($p < 0.001$) for both lung and prostate plans. The calculated TCPs between Poisson and Niemierko were significantly correlated for all three cancer types ($r^2 = 0.97, 0.99, 0.92$ for lung, prostate and H&N, respectively).

Figure 3 shows the relationship of the TCP calculated with different models for each plan. For both lung and H&N plans, the TCPs calculated with the Niemierko or Marsden model can be much lower than the TCPs calculated with the Poisson model. There were some H&N plans showing greater differences between the Poisson model and Niemierko model. The Marsden model shows a sharper slope than the Poisson model for TCPs greater than 40% in the lung treatment plans. Figure 4 shows the

Figure 2. TCPs (Mean $\pm$ standard deviation) calculated using the three models for IMRT plans. H&N, head and neck; IMRT, intensity modulated radiotherapy; TCP, tumor control probability.

difference of the TCPs for the plans of all tumor sites under study between Poisson model and Niemierko model versus the difference between PTV mean dose and minimum dose. The difference in TCPs was negligible when the difference in PTV mean dose and minimum dose was less than 20 Gy as highlighted by ellipse in Figure 4. The Niemierko model TCP was substantially less than the Poisson model TCP when the difference in PTV mean and minimum dose was greater than 20 Gy, and the difference appeared linearly related to the difference between PTV mean and minimum dose. Figure 5 are some example DVHs of H&N tumor cases showing the strong dependence of Niemierko model-calculated TCP on minimum dose. Figure 6 demonstrated the correlation of TCP with the dosimetric parameters of PTV for each model and treatment site. Physical dose parameters all showed a good correlation with the models in general whereas volume parameters including CI and HI presented a weak correlation.

DISCUSSION

Statistical analysis has shown positive and strong correlations of TCP with some physical dosimetric parameters. A good correlation was found for all dose variables, including prescribed dose, minimum, maximum, mean and median dose as well as EUD, D100, D98, D95, D50 and D2 in PTV. It is a known property of EUD that as “ α ” approaches negative infinity to TCP prediction, EUD approaches the minimum dose therefore the higher correlation between TCP and minimum dose as well as D95% is expected. The Poisson and Niemierko models appeared strongly

correlated while the Marsden model was somewhat of an outlier. The correlation was better for lung plans than for prostate plans. The implication of these correlations means that both minimum and mean dose delivered to PTV is important for the TCP calculation. This is contradictory to the clinical data by Terahara et al¹⁶ which support the treatment of inhomogeneous dose distributions in the TCP model. On the other hand, a negative correlation ($r < 0.3$ and $p > 0.5$) was found for CI, HI, V100, V95 and V90. Our results are in agreement with the findings^{6,17} that, for a given mean dose, TCP increases with a more uniform dose distribution. None of these three models in our calculation include effects such as hypoxia and variation of clonogenic cell density (ρ_{cl}) across the target volume. The latter has been postulated to be of only modest consequence.¹⁸ It's essential to see how well each model agrees with the clinical data specific to different tumors.

All these three radiobiological models have their formula defined more by physical dose and less by volume. As a result, we see a less correlation of TCP with dose-volume parameters in all three models, such as V100, V95, V90, CI and HI. H&N tumors have some plans with very low minimum dose that resulted in those TCP outliers of small values. But HI was calculated as (D2-D98)/D50 in treatment planning system, which might not appreciate the small minimum doses (Figure 5 for the added DVH curves). These outlier points likely led to the negative correlation with HI, but the correlation coefficient is ~ -0.5 without significance.

Santiago et al¹⁹ did an interesting meta-analysis out of 31 published studies on non-small cell lung cancer with a total of 2319 patients, including both conventional fractionation and hypofractionated treatment plans. The median value of the 3 year local control rate was 63% (50–91%) for patients treated with conventional fractionation and 86% (55–100%) for the hypofractionated series. They also found both the linear-quadratic (LQ) and linear-quadratic-linear (LQ-L) fits can model the local tumor control and predict clinical outcomes for non-small cell lung cancer, but the model breaks down at higher doses. A comparison study of clinical outcomes between three-dimensional conformal radiotherapy and IMRT for prostate cancer by Shimizuuchi et al²⁰ showed little difference in biochemical failure survival, 93.2% for the three-dimensional conformal radiotherapy group vs 95.4% for the IMRT group. The prescription dose was 76 Gy in 38 fractions for both groups. The biochemical failure survival rates for low-, intermediate- and high-risk groups were 100, 94.5 and 91.5%, respectively. For H&N cancer, Bibault et al²¹ performed a prospective evaluation of the clinical outcomes comparing helical Tomotherapy with RapidArc across 14 centers. The locoregional control rate at 18 months was 83.3% (range, 72.5–90.2%) in the Tomotherapy group and 72.7% (range, 60.1–80.8%) in the RapidArc group with the same prescription dose of 70 Gy in 35 fractions.

For the results of our calculation in this study, the mean TCP in lung was 58.4% (± 11.1) calculated with the Poisson model, 56.4% (± 11.5) using the Niemierko model, and 36.3% (± 30.3) with the Marsden model. The mean TCP in prostate was 81.9% (± 10.1) calculated with the Poisson model, 80.2% (± 9.5) with

Table 3. TCPs (mean $\pm$ standard deviation) calculated using the three models for IMRT plans

Tumor site	TCP (%)		
	Poisson	Niemierko	Marsden
Lung	58.4 $\pm$ 11.1	56.4 $\pm$ 11.5	36.3 $\pm$ 30.3
Prostate	81.9 $\pm$ 10.1	80.2 $\pm$ 9.5	60.9 $\pm$ 14.2
H&N	87.0 $\pm$ 13.9	82.8 $\pm$ 24.0	NA

TCP, tumor control probability;

Figure 3. Scatter plots of Niemierko and Marsden model calculated TCPs vs Poisson model TCPs for each plan.

the Niemierko model, and 60.9% (± 14.2) with Marsden model. The TCP for patients treated for H&N cancer was 87.0% (± 13.9) with the Poisson model and 82.8% (± 24.0) with the Niemierko model. Our calculated TCP values appear to agree with some but deviate in general from those reported series in clinic.^{19–21} A direct analysis of the known clinical outcomes and the model-based TCP results for the same group of patients and treatment plans is necessary to validate a given biological model. Of the note, TCP calculated with the Marsden model for both lung and prostate plans was predicted to be about 20% lower than that calculated for the same prescription dose with either the Poisson model or the Niemierko model. The reason is that the TCP result from the Marsden model was the average of patient populations with varied radio-sensitivities (different α values) and its dose response curves is naturally shallower due to the normal distribution of radiosensitivity.

Figure 4. Relationship of the difference in Poisson and Niemierko model TCPs with the difference between PTV mean and minimum dose of a plan. PTV, planning tumor volume; TCP, tumor control probability.

A remarkable and significant discrepancy in estimating TCP can occur depending on the radiobiological parameters and TCP models. However, without any solid and recent clinical data, it is difficult to constrain radiobiological models and obtain more appropriate parameters prediction from any particular radiotherapy. It can be seen that the choice of TCP model with radiobiological parameters as (D_{50} , γ_{50} , α/β etc.) can significantly modify the TCP scores. The endpoint of clinical interest in radiation therapy is to know the true TCP. It is the ultimate goal for clinicians to review and compare treatment plans with known biologic effect to the organs at risk as well as the target. The development of biological based planning has been slow but quite promising. Several vendors have implemented plan optimization algorithms incorporating biological models in their TPS. Traditional planning technique utilizes dose-volume variables in the cost function for optimization and DVH for plan evaluation. Biological-based planning algorithms would eventually employ TCP/NTCP in the cost functions for both optimization and evaluation.

Due to the uncertainty of the model parameters, the published biological tools are only recommended being used to rank radiotherapy plans^{22,23} at this stage. It is essential to have the accurate TCP/NTCP models if the absolute values are to be applied for planning and decision-making. Current commercial TPSs employ the combination of EUD and dose-volume for optimization and of DVH and relative TCP/NTCP for evaluation.⁸ As demonstrated in this study, calculated TCP may or may not correlate with some dose-volume parameters the same way as the dose-volume based optimization would. The absolute values of TCP calculated by these biological models must be tested by good clinical data with explicit information on outcomes, radio-sensitivity, clonogenic cell density, dose calculation algorithm etc. Additionally as the biological models get integrated in the TPS, clinical trials should implement biological endpoint rather than physical ones. However, for this to be meaningful, all available models should provide the same end results in TCP and NTCP such that outcome can be clinically compared.

All three models under the study are well-established and widely accepted in radiation oncology community. These models were based on radiological assumption, and derived with statistic

Figure 5. Example DVHs for H&N tumor plans. The table shows that Niemierko model-calculated TCP substantially depended on minimum dose. DVH, dose volume histogram; H&N, head and neck; TCP, tumor control probability.

formulation. Varying the formula may violate their biological assumptions and lead to difficulty in data interpretation. However, we may be able to generate models completely based on quality outcomes data using machine learning techniques. Data-based models can be more clinically relevant but less biologically understandable in comparison with statistics-based models.

CONCLUSION

This study evaluated three commonly used radiobiological models for TCP calculation in lung, prostate and H&N cancer IMRT treatment plans. Differences are observed among models and disease sites investigated. There is a strong correlation of calculated TCP with dosimetric parameters such as minimum, maximum, mean and median dose as well as EUD, D100, D98,

Figure 6. Correlation coefficient of TCP with physical parameters for each model and treatment site. CI, conformity index; HI, homogeneity index; H&N, head and neck.

D95, D50 and D2 in PTV, but little dependence on CI, HI, V100, V95 and V90. Better understanding of the biological models in relation with dose optimization can help develop outcome driven planning to achieve desired tumor control and lower toxicity.

Our data can be an additional contribution to and a thorough demonstration of the usefulness and limitations of those biological tools. More planning and clinical data are required to refine and validate the implementation of biological based planning.

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