Original Article

Study of Asymmetric Margins in Prostate Cancer Radiation Therapy Using Fuzzy Logic

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Abstract

Purpose: The purpose of present study is to estimate asymmetric margins of prostate target volume based on biological limitations with help of knowledge based fuzzy logic considering the effect of organ motion and setup errors. **Materials and Methods:** A novel application of fuzzy logic modelling technique considering radiotherapy uncertainties including setup, delineation and organ motion was used in this study to derive margins. The new margin was applied in prostate cancer treatment planning and the results compared very well to current techniques Here volumetric modulated arc therapy treatment plans using stepped increments of asymmetric margins of planning target volume (PTV) were performed to calculate the changes in prostate radiobiological indices and results were used to formulate the rule based and membership function for Mamdani-type fuzzy inference system. The optimum fuzzy rules derived from input data, the clinical goals and knowledge-based conditions imposed on the margin limits. The PTV margin obtained using the fuzzy model was compared to the commonly used margin recipe. **Results:** For total displacement standard errors ranging from 0 to 5 mm the fuzzy PTV margin was found to be up to 0.5 mm bigger than the vanHerk derived margin, however taking the modelling uncertainty into account results in a good match between the PTV margin calculated using our model and the one based on van Herk *et al*. formulation for equivalent errors of up to 5 mm standard deviation (s. d.) at this range. When the total displacement standard errors exceed 5 mm s. d., the fuzzy margin remained smaller than the van Herk margin. **Conclusion:** The advantage of using knowledge based fuzzy logic is that a practical limitation on the margin size is included in the model for limiting the dose received by the critical organs. It uses both physical and radiobiological data to optimize the required margin as per clinical requirement in real time or adaptive planning, which is an improvement on most margin models which mainly rely on physical data only.

Keywords: Fuzzy inference system, normal tissue complication probability, planning target volume, tumour control probability, volumetric modulated arc therapy

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Introduction

The treatment of cancer using radiation therapy is to kill all the cancerous cells whilst sparing the healthy tissues and critical organs. Prior to the treatment the volumes to be irradiated and avoided are outlined. In the treatment planning phase the beam placement and dose optimization is adapted to achieve the overall goal of treatment cure and sparing of normal tissue. There is sufficient evidence that the dose-volume (DV) relationship for the development of complication also exists and this results in the induction of adverse side effects on the normal tissue and critical organs. Optimal treatments thus depend on the selection of the best possible margins due to the inherent complex trade-off between complication and cure. The radiobiological concept of tumour control probability (TCP) describes the probability of killing all tumour cells in a volume whilst the concept of normal tissue complication probability (NTCP) describes the damage that occurs to normal tissues and critical organs. The radiation effects, in both tumour and surrounding healthy tissue, follow a typical sigmoid shape as function of dose. This relationship is illustrated in Figure 1. A cure without complication can only be achieved if the dose to the tumour is high enough for the destruction of all tumour cells and the tolerance doses of the normal tissues are not to be exceeded. In order to avoid side effects of radiotherapy the dose distribution is spatially conformed to the tumour

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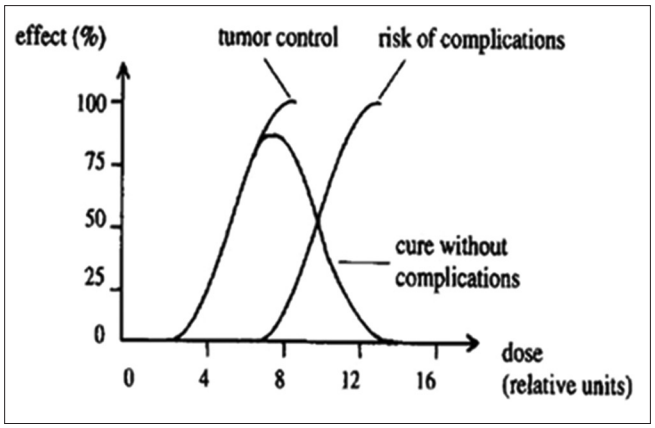

Figure 1: Dependence of the probability of cure without complication on dose, resulting from the probability of tumour control and the risk of complications in the normal tissues (Waschek T *et al*. 1997)

such that the normal tissues are spared as much as possible. Treatment margins have previously been derived based on these radiobiological considerations.[1-3]

During the actual fractionated patient treatment phase, the presence of organ motion, patient set-up and tumour delineation variations affect the planned treatment and may therefore result in the delivered dose which differs from the intended planned dose. Various recommendations are available for the derivation of margins for the use in radiotherapy treatment planning including the International Commission on Radiation Units and Measurements reports 50,[4] 62,[5] 71[6] and formulation based on probabilistic dose distributions.[7,8] The published margin formulations tend to assume a linear relationship between tumour margin and radiotherapy errors. This may be varying for all treatment strategies encountered in radiotherapy. New techniques such as dose escalations may be significant challenge which may limit the application of current margins. The rigidity of these formulations to adapt to changing patient condition also limits their applicability to all treatment scenarios.

In the present study we propose the use of fuzzy logic technique to derive asymmetric radiotherapy treatment margins. The use of fuzzy logic technique for the derivation of radiotherapy margins was initially used by Waschek *et al*.[9] Their technique relied on expert knowledge to derive the clinical target volume (CTV) margins. However they did not consider the effect of organ motion and setup errors in order to derive planning target volume (PTV) margins. Study by Mzenda *et al*.[10] was based on delineation, set-up and organ motion errors to deduce the treatment margins, but they did not consider the asymmetric nature of motion of PTV and other nearby multiple critical organ effects around target volume whereas these also play significant role and hence they should not be neglected.

In the present study we consider the asymmetric nature of target volume motion and hence effect of nearby critical organs along with the setup-errors and delineation errors to deduce asymmetric margins based on biological limitations with help of fuzzy logic. The input rules used in fuzzy inference system (FIS) are based on the analytical simulations thus removing the subjective nature of inter-observer variation. In the present study fuzzy logic application is adopted because fuzzy model features make it robust for modelling to derive treatment margins that are too complex to be modelled by means of conventional mathematical techniques. The relationship between radiobiological parameters (TCP and NTCP), radiotherapy margins as well as radiotherapy uncertainties is difficult to quantify mathematically or has a large degree of variability. However fuzzy logic has a distinct advantage in allowing the linkage of these geometrical and radiobiological parameters through use of fuzzy rules and membership functions.[11-13] In the present study Mamdani-type FIS is used for modelling because it allows to describe the problem in more intuitive manner with suitable environment to correlate target motion estimation which is significant particularly in adaptive radiotherapy planning and treatment. Further the main disadvantage of currently used margin formulations[4,5,8] is that they do not consider the effects of organ motion and surrounding organ at risk (OAR) when deriving PTV margins. From the clinical cases it was found that fuzziness region to derive exact PTV margin. In the current study the fuzziness region of PTV along with physical and radiobiological factors is considered in determining the asymmetric nature of PTV margins. Complex radiotherapy treatment delivery techniques such as volumetric modulated arc therapy (VMAT) require precise selection of treatment margins for optimization and dose escalation and also the difficulty in treatment planning for prostate cancer varies greatly case by case and hence the application of derived fuzzy margins is assessed in the current study to shape their perspective on clinical decisions.

Materials and Methods

Brief description of modelling procedure and modelling input data

The PTV margin modelling procedure using the Mamdani-type knowledge based fuzzy logic system involved a number of steps. The procedure started with the creation of treatment plans using variable PTV margins asymmetrically (LR: 0–12 mm, SI: 0–14, AP: 0–14 mm, PA: 0–12 mm) with the help of pre-and in-treatment image guidance[14-18] analysis for tighter margins with improved OARs sparing. These plans were used to calculate baseline TCP and NTCP. The above step was followed by simulation technique to displace the prostate and critical organs using typical incremental error magnitude as obtained during radiotherapy treatment. This allowed the recalculation of new TCP and NTCP values after each stepped increment margin. The output obtained provides the basic dosimetric information for use in deriving the fuzzy linguistic rules and membership functions for use in the knowledge based fuzzy logic system. The inputs were then fuzzified using mamdani-type FIS with help of formulated rules and membership functions. The defuzzification stage provided

the initial crisp output. A Gaussian convolution kernel was then applied to optimize the initial fuzzy output. Finally the margin obtained as output from the fuzzy model was compared with currently used margins and applied in current VMAT treatment planning.

The preferred method for treating Prostate cancer patients (n = 08) with radiation is VMAT and all VMAT plans were generated with treatment planning system using Eclipse 15.6, Varian Medical Systems with photon optimization with maximum dose rate and dose prescription of 73.5 Gy. All treatment were generated using asymmetric PTV margins as mentioned earlier with 1 mm stepped size to calculate input data for fuzzy model as shown in Figure 2. Most VMAT planning systems apply DV based objective functions[19] for dose optimization and an acceptable plans can be generated in most cases. For more complex plans, more iteration are required because many Parameters need to be finely tuned. A successful improvement tool-generalized equivalent uniform dose (gEUD) was developed with fewer parameters setting[20-23] to improve the quality of plans. However gEUD based optimization cannot demonstrate such advantages on first run, more iteration are required to share the dose distribution.[24] To overcome the disadvantages mentioned above, here treatment planning started with DV-based optimization, and then improved it by adding gEUD-based improvement. Current study based on strategies and choice of volume effect parameters and weightage of cost function by standard recommendations. The superposition dose calculation algorithms were used for plan calculation. The dose distribution of the treatment plans was optimized such that 95% isodose covered the PTV on all slices.

The radiation dose received to prostate target, rectum and bladder was calculated for all plans and output data was used to calculate the radiobiological parameters TCP and NTCP [Appendex-A]. The TCP was calculated with using Matlab R2018a-based simulation tool based on the concept of EUD modelling.[25] The concept of EUD is defined as the uniform dose that, if delivered over the same number of fractions as the nonuniform dose distribution of interest, yields the same biological effect. To extend the Concept of EUD, a phenomenological formula referred to as the generalized EUD (DVH-based) or gEUD has been used.

$$gEUD = \left(\sum V_i D_i^a\right)^{\frac{1}{a}} \quad (1)$$

Where V_i is the fractional organ volume receiving a dose D_i and "a" is a tissue-specific parameter that describes the volume effect. For a-->-∞, gEUD approaches the minimum dose; thus negative values of "a" are used for tumour. For a--> + ∞, gEUD approached the maximum dose. For a = 1, gEUD is equal to the arithmetic mean dose, for a = 0, gEUD is equal to the geometric mean dose. gEUD objective options can be generally selected in TPS Eclipse 15.6 (VMS) as target EUD selected for the PTV, while max. EUD selected for OARs. The resolution of the dose calculation grid bin size considered unbiased for subsequent computation of various indices. In this way the EUD based TCP and NTCP can be calculated as follows:

$$TCP = \frac{1}{1+\left(\frac{D_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (2)$$

and

$$NTCP = \frac{1}{1+\left(\frac{TD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (3)$$

Where D_{50} is the absorbed dose producing a 50% control rate of the tumour exposed to uniform radiation, γ_{50} is the unit less model parameter for describing the slope of the tumour dose-response curve, and TD_{50} is the tolerance dose producing a 50% complication rate. For radiobiological modelling, the recommended parameters from prostate radiotherapy treatment studies[26-29] were used in the above equations for the calculation of the tissue control probability and the normal tissue control probability together with the parameters shown in Table 1 were used for calculation according to the relation.Initial TCP and NTCP values were calculated using the above equations for all the treatment plans based on various PTV margins. Subsequent changes in TCP and NTCP due to target volume

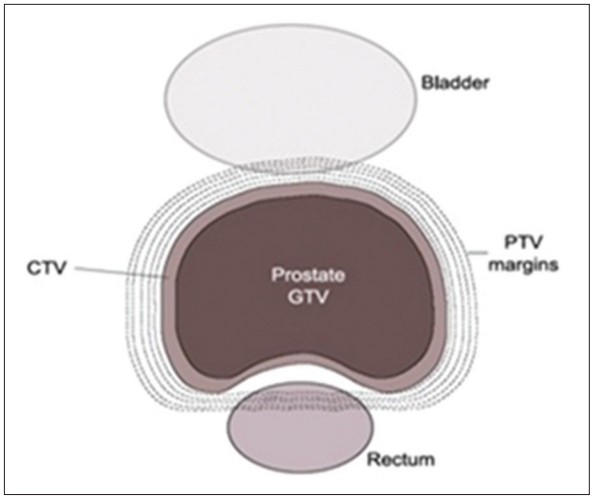

Figure 2: Schematic diagram showing variable planning target volume asymmetric margins used in treatment plans to calculate input data for fuzzy model (B Mzenda *et al*. 2010)

Table 1: Parameters used for prostate tumour control probability and for rectum normal tissue complication probability modelling (Mzenda B *et al*. 2010 and AAPM Task Group 166, AAPM)

Structure	D_{50} (Gy)	γ_{50}	a	Dose per fraction	TD_{50} (Gy)
Prostate	46.3	0.95	-10	2.2	-
Rectum	-	-	8.33	2.2	80
Bladder	-	-	2	2.2	80

displacements used these initial TCP and NTCP values to deduce the subsequent loss in TCP and increase in NTCP.

Organ motion, set-up and delineation error effects on radiobiological parameters

With the help of pre-and in-treatment image guidance[14-18] for tighter margins with improved OARs sparing, the prostate target displacement has been found asymmetrical (LR: 0–12 mm, SI: 0–14, AP: 0–14 mm, PA: 0–12 mm) in all axial views. To avoid interobserver variations in target volumes delineations, the same oncologist outlined all cases. Combined organ motion and setup error with 5 mm added 1 mm step sized asymmetrical margins up to maximum of PTV were used in our study to calculate the changes in radiobiological parameters TCP and NTCP. This was performed using Matlab-based simulation tool,[30] where translation and rotation followed Gaussian distribution data. A stepwise increase in the combined delineation, set-up and organ motion error was used to shift the organ with respect to the dose distribution and compute the resulting loss of prostate TCP (i.e., ΔTCP) and the increase in rectal NTCP (i.e., ΔNTCP) after each step increment. This procedure was repeated for each of the treatment plans using the different PTV margins. In radiotherapy prostate cancer treatment, an absolute NTCP of 5% is considered to be the maximum acceptable value if rectal complications are to be avoided.[27] The range of treatment plans and simulated errors in our study produced absolute NTCP values which were all within the 5% absolute limit. In implementing the rules for the fuzzy system for ΔNTCP values above 10%, the PTV margin was not permitted to exceed 5 mm to avoid rectal complications due to margin selection. A further consideration in implementing the fuzzy rules was that for a tubular structure such as the rectum, the irradiated fraction of the circumference is correlated to rectal bleeding.[31] As such the fraction of irradiated rectal wall was also calculated for each margin as a function of combined errors, and used in the formulation of the fuzzy membership rules.

Implementation of Mamdani Fuzzy Logic System

Mamdani-type fuzzy system was chosen for modelling as shown in Figure 3. It gave results which were consistent with the expected output suited to human input and so widely accepted for capturing expert knowledge which is very significant particularly in real time adaptive treatment. The final number of membership functions and fuzzy rules used in this study were chosen to fulfil the applied model conditions described below. The system consisted of 2 inputs, namely ΔTCP and ΔNTCP, and 1 output, i.e., PTV margin. Six membership functions i.e., almost zero, very small, small, medium, high and very high were chosen for the input and output terms resulted in the functions shown in Figures 4 and 5. The widths of the functions were based on the gradient of the different sections of the input data. The output membership functions were defined using constants.

The Gaussian type membership functions were chosen for modelling following an assessment of the outputs from triangular, trapezoidal, generalized bell and Gaussian membership functions. The output surfaces from all functions other than the Gaussian function showed steep variations which imply uneven changes in PTV margin with changes in TCP and NTCP, which did not correspond to the known relationships from the input data. The output surface for the Gaussian function however showed relatively continuous and even transitions which correspond well with the input data variation.

The rules of the Mamdani FIS were formulated as shown below:

Ri: If $(x_1$ is $f_{i1})$ and … $(xj$ is $fij)$… and $(xm$ is $fim)$

then $yi = gi$ (4)

Where i = 1, n; j = 1, m;

m is the number of inputs, n is the number of rules, xj represents the jth input, fij the membership function of the ith rule, yi is the output of rule Ri and gi represents the analytical function of the inputs xj, and gi is a real number. The fuzzy rules were devised based mainly on the condition that the increase in NTCP is compensated for by reducing the PTV margin whilst the loss in TCP is compensated for by increasing the PTV margin size. Preselected ΔNTCP values as well as the irradiated volume of the anterior wall were chosen so as to allow the algorithm to select margins that would avoid rectal complications. Therefore the fraction of irradiated rectal wall was also calculated for each margin as a function of total displacement, and used in the formulation of the fuzzy membership rules. The optimum fuzzy rules[32,33] derived from input data and using the clinical goals and knowledge-based conditions imposed on the margin limits are as shown in Table 2. The Permutations of the membership functions for ΔTCP, ΔNTCP and PTV margin resulted in 36 fuzzy rules. However these conditions vary from case to

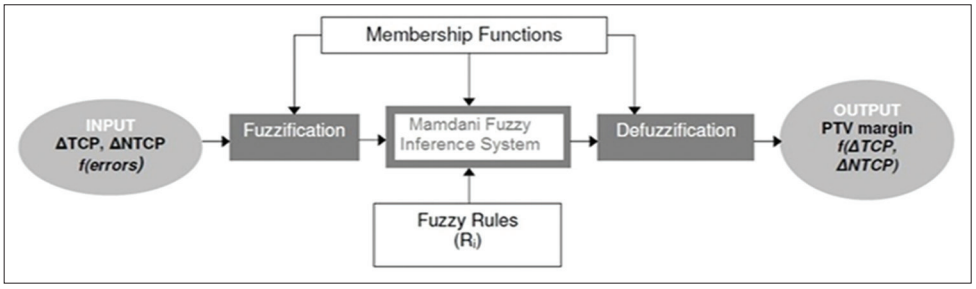

Figure 3: Basic operation principle of the Mamdani type fuzzy inference system used to calculate the planning target volume margin output function

case taking into account organ motion and deformation of target and surrounding normal structures as one of the major confounding factors for prostate tumour site.

Results and Discussion

Effect of input data on asymmetric margin order of planning target volume and defuzzified output

The effect of magnitude of organ motion and set-up errors on prostate ΔTCP, rectum ΔNTCP and bladder ΔNTCP using CTV only margin, are generated with MatlabR2018a as shown in Figures 6-8, respectively. For the effect on TCP, Increasing the errors resulted in the increased loss of TCP. For combined errors with magnitude of margin order up to 10 used in our study. It was found that increasing the PTV margin resulted in a nonlinear decrease in the loss in TCP. Also for the effect on NTCP, the increase in magnitude of margin order was found to increase the NTCP values. This variation of ΔNTCP with increasing asymmetric margin order from 0 to 10 was found to be approximately nonlinear. This variation may be expected linear or nonlinear depends on organ type and sub volumes overlapping.

Based on the ΔTCP/ΔNTCP input data, the output function was calculated for the Mamdani-FIS as shown in Figure 9, as a three dimensional surface generated in MatbalR2018a, where each point corresponds to a specific ΔTCP, ΔNTCP and PTV margin value. From this output function it was observed that the increase in the ΔNTCP results in a decrease in the PTV margin. Correspondingly an increase in the ΔTCP results in an increase in the PTV margin. This result satisfies the imposed margin requirements as the increase in the loss in TCP gives rise to an increase in the PTV margin as required. Also, in compensation, an increase in critical organ dose results in

Table 2: Fuzzy rules used in the Mamdani-fuzzy inference system (Mzenda B *et al*. 2010)

Rule	If inputs		Output
	ΔTCP	ΔNTCP	PTV margin
R1	Almost zero	Almost zero	Almost zero
R2	Very small	Almost zero	Small
R3	Very small	Very small	Small
R4	Small	Small	Medium
R5	Small	Medium	Medium
R6	Medium	Medium	Medium
R7	Medium	High	Small
R8	High	High	Very small
R9	High	Very high	Almost zero
R10	Very high	Very high	Almost zero

TCP: Tumour control probability, NTCP: Normal tissue complication probability, PTV: Planning target volume

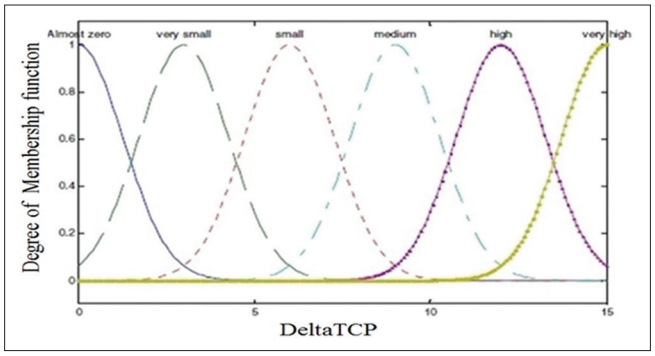

Figure 4: Membership function for Δ tumour control probability

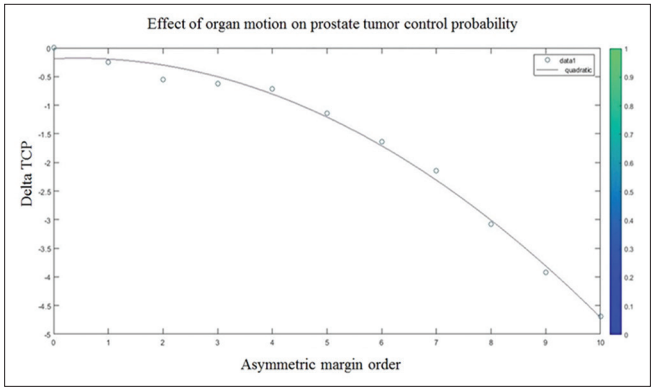

Figure 6: Delta tumour control probability versus asymmetric margin order: Effect of organ motion and setup errors on prostate tumor control probability

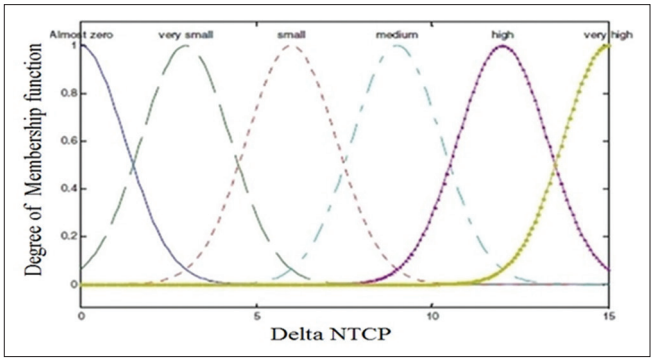

Figure 5: Membership function for Δ normal tissue complication probability

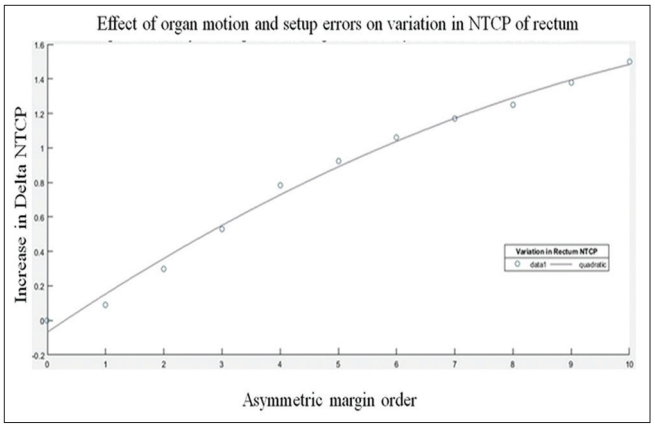

Figure 7: Delta normal tissue complication probability versus asymmetric order: Effect of organ motion and setup errors on the variation in normal tissue complication probability of rectum

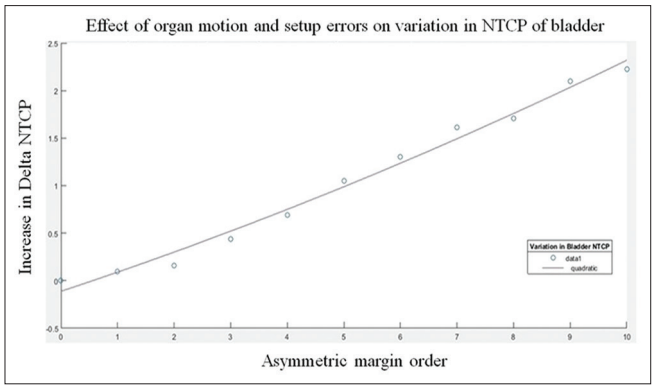

Figure 8: Delta normal tissue complication probability versus asymmetric order: Effect of organ motion and setup errors on the variation in normal tissue complication probability of Bladder

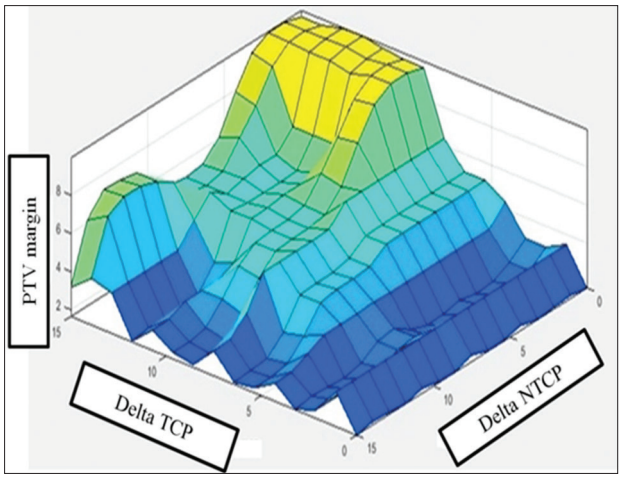

Figure 9: Output function from fuzzy system

a decrease in the PTV margin. The output function satisfied the applied system rules and also the conditions regarding predefined ΔNTCP tolerance levels on the margin limitations.

Fuzzy margin comparison to current margins

The PTV margin obtained using the fuzzy model was compared to the commonly used margin recipe proposed by van Herk *et al*.[8] For total displacement standard errors ranging from 0 to 5 mm, the fuzzy PTV margin was found to be up to 0.5 mm bigger than the van Herk derived margin, however taking the modelling uncertainty into account results in a good match between the PTV margin calculated using our model and the one based on van Herk *et al*. formulation for equivalent errors of up to 5 mm standard deviation (s. d.) at this lower range. When the total displacement standard errors exceed 5 mm s. d. the van Herk margin was higher because the van Herk *et al*. theoretical formulation shows a continuous linearly increasing PTV margin. In practice the combined treatment errors encountered in prostate radiotherapy seldom result in PTV margins that exceed 12 mm whilst the fuzzy margin remained below 12 mm. This trend is attributed to the effect of introducing TCP and NTCP in the margin formulation and the dominance of the constraint for rectal sparing in the margin formulation. This variation is dependent on the chosen TCP and NTCP tolerances as well as the proximity between the tumour volume and the OARs. A standard uncertainty of ± 0.5 mm was computed as the error in the PTV margin values obtained using the fuzzy model in this study.

The fuzzy PTV margin was applied in VMAT treatment planning example to assess its performance against current margins. Using the standard deviation of total displacement errors, treatment margins corresponding to 4 mm standard errors were selected. This led to a 9 mm margin for the fuzzy PTV and 8 mm margin for the van Herk PTV. Equivalent treatment plans were produced using these margins, together with a prescription dose of 73.5 Gy. Similar biasing were applied to these plans and the effects on the critical organs were evaluated. The results obtained from the VMAT plans for the prostate PTV are shown in Figure 10a. As it can be seen very small differences were observed between the plans. No significant differences were found in the prostate PTV, rectum, and bladder DVHs between the two plans when equal displacement errors were introduced. This is due to the small differences in these parameters in the original plans and the application of a reduced error magnitude due to the reduction of systematic and random errors from the applied image-guided radiation therapy protocol. Similarly equivalent treatment plans were produced using 12 mm margin for the fuzzy PTV and 14 mm margin for the van Herk PTV for treatment margins corresponding to 6 mm standard errors and the results obtained from the VMAT plans for the prostate PTV are shown in Figure 10b. Noticeable differences were found in the prostate, rectum, and bladder DVHs due to effect of introducing TCP and NTCP in the margin formulation and due to the dominance of the constraints for bladder and rectal sparing embedded in the margin selection procedure. Thus in the region of large errors, the rate of PTV margin increase is seen to decrease significantly for the fuzzy case compared to the conventional method.

The advantage of using mamdani-fuzzy logic is that a practical limitation on the margin size is imposed in the model for limiting the dose received by the critical organs. It uses both physical and radiobiological data to optimize the required margin as per clinical requirement in real time or adaptive planning, which is an improvement on most margin models which mainly rely on physical data only. The fuzzy model is also relatively simple to implement and gives accurate margin sizes and can thus be extended to other treatment sites as required. The main objective of this work was to show the feasibility of the computational methods for deriving patient margins, and this has been supported by the findings. Whilst the proposed methods have been compared together, it is worth pointing out that without a "gold standard," this comparison is relevant only for the sample of patient data used in this study. The novelty of the method proposed in this study lies more in that they allow for the calculation of individualised patient margins and prospective purpose, which

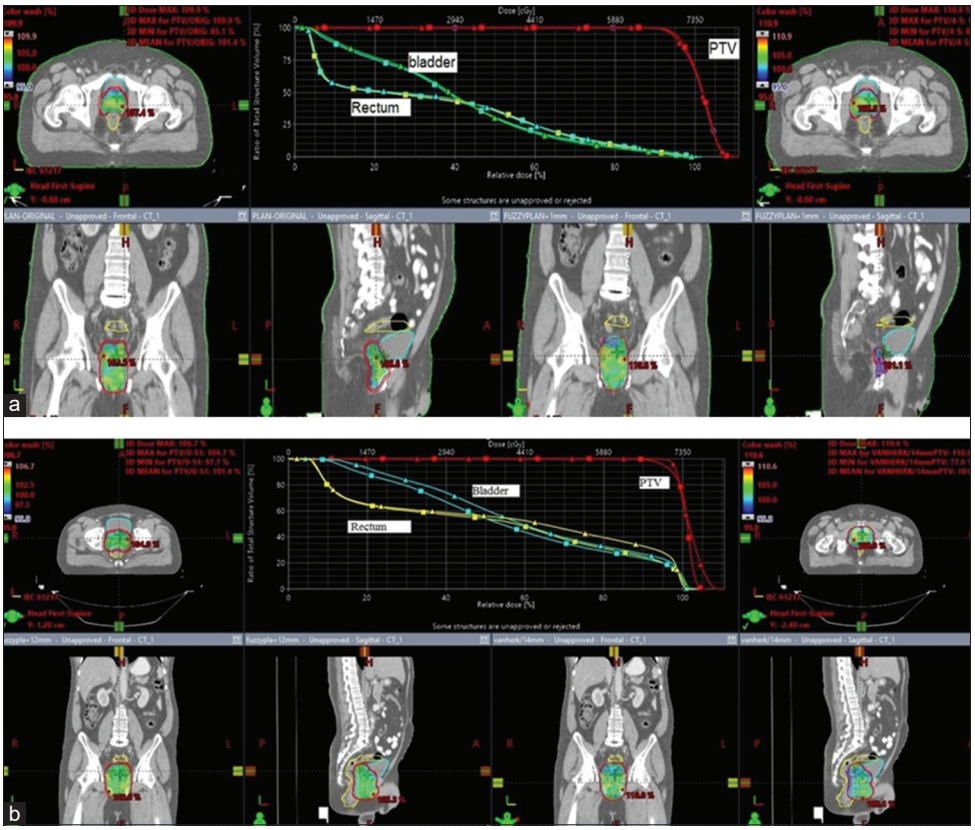

Figure 10: (a) Volumetric modulated arc therapy plan and dose volume histogram for planning target volume, Bladder, Rectum using the van Herk (-▲-▲-▲-▲-) and fuzzy (-■-■-■-■-) derived margins corresponding to 4 mm standard error standard deviation (b) Volumetric modulated arc therapy plan and Dose volume histogram for planning target volume, Bladder, Rectum using the van Herk (-▲-▲-▲-▲-) and fuzzy (-■-■-■-■-) derived margins corresponding to 6 mm standard error standard deviation

is currently very difficult to accomplish with manual setup of current techniques which result in low patient efficiency due individualised patient setup corrections particularly in busy radiotherapy departments.

Conclusion

Fuzzy logic has the potential to be combined with existing algorithms in radiotherapy planning, leading to intelligent solutions to the complexities encountered in current and emerging radiotherapy treatment techniques. New treatment strategies e.g., VMAT and Cyberknife, are capable of delivering highly conformal dose distributions to the tumour volume. This inevitably involves steep dose gradients lying next to the critical organs. Using the same margin size for the same tumour type for all patients as is currently the case will not be ideal in such treatments. This is due to physiological variations from patient to patient. Using the models from this study it is possible to compute margins on a patient-by-patient basis using individual measured errors. This way the most reliable margins will always be used. A Matlab based software tool is in development for the practical implementation of this fuzzy margin in radiotherapy treatment planning.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendex-A

The MATLAB based algorithm is to calculate target and OARs EUD-based NTCP and TCP for inputs in our fuzzy model study.

A free program for calculating EUD-based NTCP and TCP in external beam radiotherapy (Reference-25) may be downloaded from http://www.ecu.edu/radiationonco logy/downloads.htm

```
%Save this file in Matlab as eudmodel.m
% EUDMODEL (DVH), where DVH is a 2 column matrix corresponding to the cumulative, not
% differentiaI, dose volume histogram. The 1st column corresponds to increasing absolute dose or
% percentage dose values, and the 2nd column to the corresponding absolute or relative volume value.
%The matrix must have a minimum of two rows, and both columns must be of equal length.
function probability = eudmodel (dvh)
%user input section
clc; disp('Welcome to the Equivalent Uniform Dose (EUD)-Based Model Program'); disp(' ');
disp ('Please note that: 1) the variable dvh should be a CUMULATIVE, not differential, DVH');
disp (' 2) the program assumes that all treatment fractions are equal');
disp(' '); disp(' ');
%end of user input section
%verifying that the cumulative DVH has at least 2 rows and columns
```

```
[nb, N]=size (dvh);
if (nb < 2)
disp('Error: Cumulative dvh must have at least 2 rows.'); return;
end
if (N < 2)
disp('Error: Cumulative dvh must have at least 2 columns.'); return;
end
%converting percentage dose bins into absolute dose bins
for i = 1:nb
dvh (i, 1)=dvh (i, 1)*nf*normalized fraction/100;
end
%if DVH dose data is in cGy it is converted to Gy
%EUD mathematical model parameters input section
clc; disp('Does the DVH correspond to:');
disp('     1. tumor target');
disp(' 2. normal tissue')
tissue type = input('Enter 1 or 2: '); disp(' ');
if (tissue type==l)
c1c
disp ('* = Niemierko'); disp(' ');
a = input ('Enter the value of parameter a: ');
gamma50 = input ('Enter the value of parameter gamma50 (recommend 2 if unknown): ');
tcd50 = input ('Enter the TCD50 (Gy): ');
ab = input ('Enter the tumor alpha/beta ratio (Gy): ');
elseif (tissue type ==2)
clc
disp ('Normal tissue EUD Parameters:'); disp(' ');
td50 = input('Enter the TD50 (Gy): ');
ab = input('Enter the normal tissue alpha/beta ratio (Gy): ');
else
disp ('Error: Invalid choice. Exiting program.'); return;
end
%calcu1ating the biologically equivalent dose and the total volume
%normalizing volume data to 1 (therefore, total volume corresponds to 1)
for I = l: nb
dvh (i, 2) = dvh (i, 2)/total volume;
bndvh (i, 2) = dvh (i, 2);
end
```

```
%calculating the EUD
for I = l: nb
eud = eud+(bndvh (i, 2))*(bndvh (i, l))^a;
end
%Results section
If (tissue type == l)
% ca1culating tumor contol probability
tcp = 1/(1+((tcd50/eud)^(4*gamma50)));
tcp = mcp*100;
message = sprintf('The tumor control probability = %10.10f %%', tcp);
% ca1culating normal tissue complication probability
tcp = 1/(1+((td50/eud)^(4*gamma50)));
ntcp = ntcp*100;
message = sprintf('The normal tissue complication probability = %10.10f %%', ntcp);
% end of Results section.
```