Journal of Radiotherapy in Practice

cambridge.org/jrp

Study of normal tissue dosimetric benefit using asymmetric margin-based biological fuzzy decision making: volumetric modulated arc therapy of prostate cancer

Santosh Kumar Patnaikuni[1,2], Sapan Mohan Saini[1], Rakesh Mohan Chandola[2], Pradeep Chandrakar[2], Rajeev Jain[2] and Vivek Chaudhary[2]

[1]Department of Physics, National Institute of Technology, Raipur, Chhattisgarh, India and [2]Department of Radiotherapy, Pt. JNM Medical College, Raipur, Chhattisgarh, India

Technical Note

Cite this article: Patnaikuni SK, Saini SM, Chandola RM, Chandrakar P, Jain R, and Chaudhary V. (2022) Study of normal tissue dosimetric benefit using asymmetric margin-based biological fuzzy decision making: volumetric modulated arc therapy of prostate cancer. *Journal of Radiotherapy in Practice* **21**: 129–137. doi: 10.1017/S1460396920000904

Received: 27 June 2020
Revised: 21 August 2020
Accepted: 22 September 2020
First published online: 4 November 2020

Key words:
asymmetric margins; fuzzy inference system; organ motion; prostate cancer; treatment planning; volumetric modulated arc therapy

Address for correspondence:
Dr. Sapan Mohan Saini, Associate Professor, Department of Physics, National Institute of Technology, Raipur 492010, Chhattisgarh, India. E-mail: smsaini.phy@nitrr.acin

Abstract

Aim: Radiation therapy has historically used margins for target volume to ensure dosimetric planning criteria. The size of margin for a given treatment site is still uncertain particularly for moving targets along with set-up variations leading to a fuzziness of target volume. In this study, we have estimated the dosimetric benefit of normal structures using biological-based optimal margins. The treatment margins are derived by knowledge-based fuzzy logic technique which is considering the radiotherapy uncertainties in treatment planning.

Materials and methods: All treatment plans were performed using stepped increments of asymmetric margins to estimate prostate radiobiological indices such as tumour control probability (TCP) and normal tissue complication probability (NTCP). An absolute NTCP of 5% was considered to be the maximum acceptable value while TCP of 85% was considered to be the minimal acceptable limit for each volumetric modulated arc therapy (VMAT) plan of localised prostate cancer radiotherapy. Results were used to formulate rules and membership functions for Mamdani-type fuzzy inference system (FIS). 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. The new margins were applied in VMAT planning of prostate cancer for standard displacement errors. The dosimetric results of normal tissue predictors were estimated such as organ mean doses, rectum V_{60} (volume receiving 60 Gy), bladder V_{65} (volume receiving 65 Gy) and other clinically significant dose–volume indicators and compared with VMAT plans using current margin formulations.

Results: Dosimetric results compared well to the results obtained by current techniques. Good agreement was obtained between proposed fuzzy model margins and currently used margins in lower error magnitude, but significant results were observed at higher error magnitude when organ toxicity concerned without compromising the target volumes.

Findings: The new margins may be helpful to estimate possible outcomes of normal tissue complications and thus may improve complication free survival particularly when organ motion errors are inevitable, case by case.

Introduction

The treatment of cancer using radiation therapy is the process of optimisation of maximising radiation dose to tumour cells while sparing healthy tissues and critical organs. In a course of treatment, target volumes and critical organs should be outlined accurately. Induction of adverse side effects on the normal tissues and critical organs depends on dose–volume relationship and hence development of complications. There is always a trade-off between complications and cure and it depends on best possible margins to achieve favourable treatment outcomes. Using the International Commission on Radiation Units and Measurements recommendations, there are margin formulations studied based on probabilistic dose distributions by considering a linear relationship between planning target volume (PTV) margin and radiotherapy errors.[1] This symmetric or linear nature of PTV margins may be applicable for all treatment strategies today. But in actual fractionated treatment phase, delivered dose may differ from planned dose due to the presence of organ motion and other radiotherapy set-up errors encountered in radiotherapy. The advantages of intensity-modulated radiotherapy and volumetric modulated arc therapy (VMAT) are limited due to these treatment uncertainties.[2,3] Also currently using margin recommendations is mostly based on geometrical or physical dose/volume considerations as they may not account for radiobiological effects of tumour and adjacent critical organs at planning level.

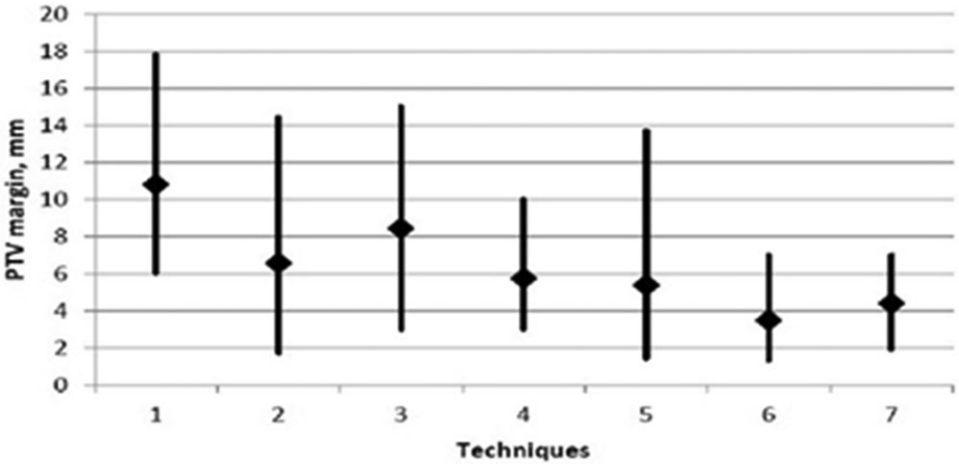

Figure 1. PTV margin values with max/min range proposed in the literature using different techniques: (1) positioning on external marks, (2) image-guided radiation therapy, (3) bone anatomy match, (4) soft tissue match, (5) fiducial markers, (6) electromagnetic tracking and (7) adapted delivery. (Yartsev S et al. 2016).

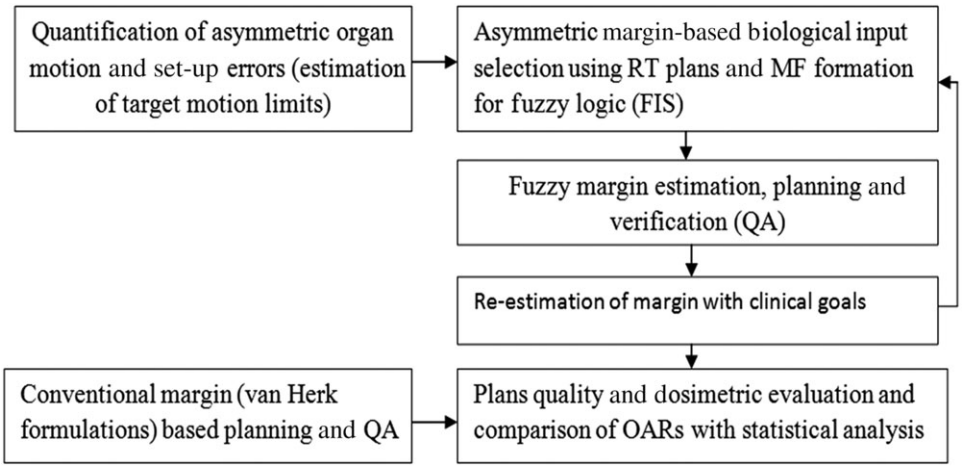

Figure 2. The workflow of study on estimating dosimetric impact with FIS.

The relationship is difficult between radiobiological parameters such as tumour control probability (TCP), normal tissue complication probability (NTCP) and radiotherapy margins as well as radiotherapy uncertainties to quantify mathematically or has a large degree of variability. This may be one of the possible reasons to consider only geometrical or dose/volume constraints in current margin formulations. Deasy et al.[4] highlighted that treatment optimisation and evaluation should be biologically and not physical dose/volume based.

In treatment planning, the clinical target volume (CTV) margin is incorporating the region of microscopic spread of the disease. This region is a diagnostic uncertainty in the definition of treatment volume. A minimal CTV definitely containing the tumour was outlined as well as a maximal CTV outside of which there was no tumour spread. The region of diagnostic uncertainty in between these two volumes is called fuzziness particularly in dynamic target volume. Fuzzy logic application was chosen in this study because it offers a methodology to link radiobiological parameters such as TCP, damage to healthy tissues (NTCP), geometrical parameters such as organ motion or deformations and other set-up errors. The required target volume margin is derived using linguistic rules and membership functions (MFs) which cannot be combined easily using statistical techniques. The strength of fuzzy logic is that it allows input patterns to belong to the output classes to a certain degree. However, this work focuses only on the outlining errors related to organ motion and set-up errors in the definition of the target volume.

A study was done by Yartsev et al.[5] on the possible variations in PTV margins with various approaches due to the presence of organ motion as shown in Figure 1, which illustrates fuzziness of target volume which may effect on nearby normal overlapped volumes. Also critical organs such as rectum and bladder volumes change during prostate cancer radiotherapy.[6] Hence the rigidity of currently using conventional margin formulation may be limited to adapt for many treatment scenarios such as prostate, like dynamic tumour volumes. Complex radiotherapy techniques such as VMAT require precise selection of treatment margins for optimisation and dose escalation. Also the difficulty in treatment planning in prostate cancer varies greatly case by case where there is organ motion near to the PTV. Thus, in such cases, possible treatment margins may be asymmetric in nature instead of conventional symmetric margins. Recently, Patnaikuni et al.[7] studied asymmetric margins and practical limitation on the margin size of prostate cancer using VMAT technique and compared with conventional van Herk margin using total displacement standard errors. In radiation dose planning, a predictor of rectal toxicity[6] is V_{60}, that is, rectal volume receiving more than 60 Gy of radiation dose.[8,9] The bladder is highly distensible organ; a predictor[6] for bladder toxicity is V_{60}, that is, bladder volume receiving more than 65 Gy of radiation dose.

https://doi.org/10.1017/S1460396920000904 Published online by Cambridge University Press

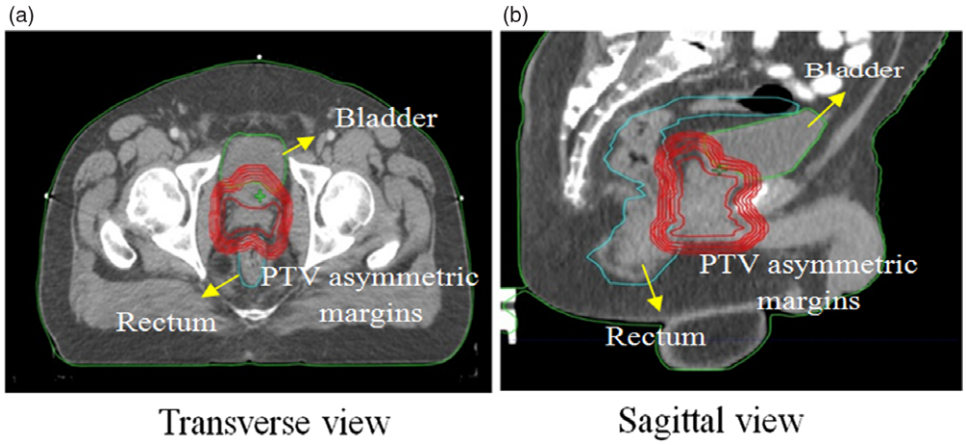

Figure 3. PTV asymmetric margins range used for treatment plans (LR: 0–12 mm, SI: 0–14 mm, AP: 0–14 mm and PA: 0–12 mm).

The present study is based on our earlier work.[7] In this study, we have estimated the dose-limiting parameters and dosimetric impact of rectum and bladder in VMAT treatment planning of prostate cancer. These parameters are compared between fuzzy margin VMAT planning and the conventional van Herk margin VMAT planning to assess the dosimetric benefit of treatment.

Material and Methods

In the present study, Mamdani-type fuzzy inference system (FIS) was used in a biological-based PTV margin derivation procedure using eight localised prostate radiotherapy patients ($n = 08$). The Mamdani-type FIS has an expected output suited to human thinking. So the Mamdani-type FIS is widely accepted for capturing expert knowledge which is expected as significant in real-time adaptive treatment. The basic workflow of the current study is shown in Figure 2.

Fuzzy-based PTV margin framework

The preferred method was VMAT for prostate cancer patients using adopted asymmetrical PTV margins, which were estimated statistically as asymmetrical (LR: 0–12 mm, SI: 0–14 mm, AP: 0–14 mm and PA: 0–12 mm) using image guidance analysis,[7] external marks, image-guided radiation therapy with cone beam computed tomography (CBCT), soft tissue match-volume assessment of normal structures and ultrasound guided tracking which were consistent with the study by Yartsev et al.[5] In treatment planning, 1 mm stepped size was added to subsequent asymmetric PTV margin from minimum (LR: 0–3 mm, SI: 0–5 mm, AP: 0–5 mm and PA: 0–3 mm) to maximum limit (LR: 0–12 mm, SI: 0–14 mm, AP: 0–14 mm and PA: 0–12 mm) for fuzzy input data. For each 1 mm stepped sized PTV, there is a VMAT plan and hence up to margin order 10, there are 10 VMAT plans in 1 patient case. Total 8 patients are considered, and 80 VMAT plans were performed with plan passing criteria as PTV will be covered by the isodose of 95% of prescription dose. All VMAT plans were used in calculating baseline TCP and NTCP corresponding to minimum acceptable value of PTV margin. After each 1 mm stepped increment margin of PTV, recalculation of new TCP and NTCP values was done. The fuzzification of inputs (TCP and NTCP) and defuzzification of output were done in Mamdani-type FIS using adopted rules and MFs. Finally, the margin obtained from fuzzy model was applied in VMAT treatment planning.

Table 1. Planning objectives and parameters used for modelling (Mzenda et al. 2010 and AAPM Task Group 166, AAPM)

Sample characteristics	Parameter value
Clinical details	
Number of patients	8
Age (years)	45–65
Tumour staging	T1–T2/N0/M0
Dose prescription/no. of fractions	73·5 Gy/33
Organ/structure objectives	
PTV-prostate	73·5 Gy (uniform dose), V95% > 95%,
TCP parameters	
EDU/γ_{50}/a/D_{50}	Target EUD = 69·3 Gy, a = −10
OAR-rectum constraints	V50 Gy < 65%, V65 Gy < 50%, V70 Gy < 35%,
NTCP parameters	
EDU/γ_{50}/a/TD_{50}	EUD = 58 Gy, a = 8
OAR-bladder constraints	V50 Gy < 60%, V65 Gy < 35%, V70 Gy < 25%,
NTCP parameters	
EDU/γ_{50}/a/TD50	EUD = 59 Gy, a = 8

PTV, planning target volume; TCP, tumour control probability; NTCP, normal tissue complication probability; EUD, equivalent uniform dose; OAR, organ at risk.

Planning and biological fuzzy margin estimation

All VMAT plans were performed with dose prescription of 73·5 Gy for treating localised prostate radiotherapy patients ($n = 08$). The position and shape of the bladder and rectum vary throughout the course of prostate radiotherapy treatment. The most significant variation in dose area is caused by the air bubbles, which expands the rectum closer to the target. Moreover, the image quality of CBCT suffers from the air bubbles, which blurs the boundary of the rectum and causes uncertainty in contouring and further dose evaluation. Bladder shrinkage and expansion are two key factors for volume and dose variances, but may be difficult to control. Some patients may not feel comfortable holding urine and did not realise the importance of drinking water to keep the bladder full so they may not always drink sufficient water. Furthermore,

https://doi.org/10.1017/S1460396920000904 Published online by Cambridge University Press

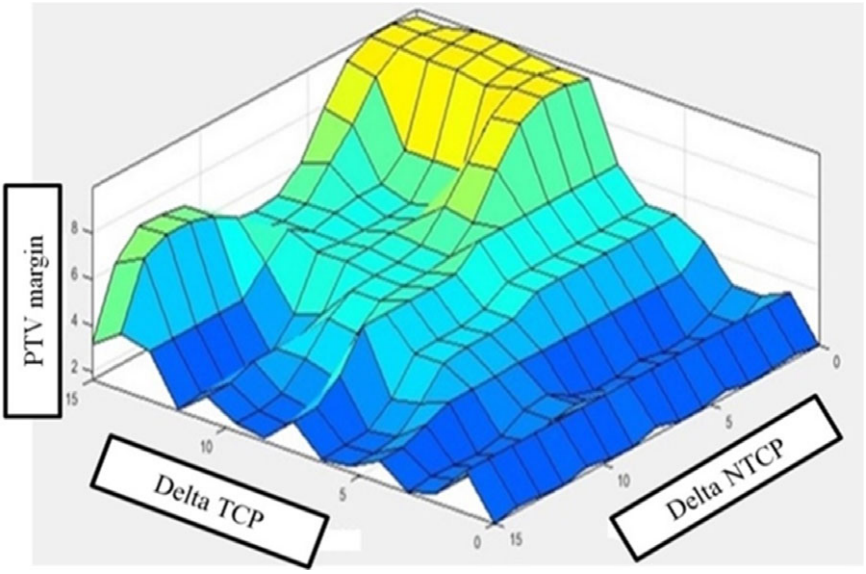

Figure 4. Fuzzy output as 3D surfaces (Patnaikuni et al. J Med Phys 2020).

some patients may be too nervous and therefore drank more water, making the bladder full. Some patients could not keep the bladder volume constant during each fraction treatment. So before simulation, all patients were advised to empty their bowel and drank more water so that bowel and bladder preparation was reasonably considered to maintain their position during treatment. PTV with magnetic resonance imaging co-registrations was outlined by expanding each CTV as per guidelines.[10] All VMAT plans were generated using asymmetric PTV margins to CTV using Eclipse 15.6 treatment planning system (Varian Medical Systems, Palo Alto, CA, USA) with gEUD-based parameters setting,[11] as shown in Figure 3. Sample characteristics, planning objectives and dose constraints are mentioned in Table 1. The radiobiological parameters TCP and NTCP were calculated in Matlab R 2018a (Mathworks, Natick, MA, USA) based simulation tool[12] using the equivalent uniform dose (EUD) modelling with required statistical values from all plans. The TCP and NTCP can be calculated as follows:

$$\mathrm{TCP} = \frac{1}{1 + \left(\frac{\mathrm{D}_{50}}{\mathrm{EUD}}\right)^{4\gamma_{50}}} \quad (1)$$

$$\mathrm{NTCP} = \frac{1}{1 + \left(\frac{\mathrm{TD}_{50}}{\mathrm{EUD}}\right)^{4\gamma_{50}}} \quad (2)$$

where D_{50} is absorbed dose producing a 50% control rate of tumour exposed to uniform radiation, γ_{50} is unit less model parameter for describing the slope of tumour dose–response curve and TD_{50} is tolerance dose producing a 50% complication rate.

Initial TCP and NTCP values were calculated for all treatment plans based on various PTV margins from margin order 1–10 using above equations. The effect of margin order on prostate ΔTCP, rectum ΔNTCP and bladder ΔNTCP using CTV only margin. For the effect on TCP, increasing the errors resulted in the increased loss of TCP. Also for the effect on NTCP, the increase in magnitude of margin order was found to increase the NTCP values. This variation may be expected to be linear or nonlinear depending on organ type and sub-volumes overlapping. Subsequent changes[7] in TCP and NTCP due to target volume displacements standard deviation (SD) were calculated using these initial TCP and NTCP values to estimate subsequent loss in TCP (i.e., ΔTCP) and increase in NTCP (i.e., ΔNTCP).

In the present study, the Mamdani-type FIS consisted of two inputs as ΔTCP and ΔNTCP while one output as PTV margin. MFs were chosen in modelling for assessment of outputs. For implementing the rules in fuzzy system, an absolute NTCP of the maximum acceptable value was considered.[13,14] Fuzzy rules were devised based mainly on limitation that increase in NTCP is compensated for by reducing PTV margin while loss in TCP is compensated for by increasing PTV margin size. Optimum number of fuzzy rules[14,15] was selected using clinical goals imposed on margin limits using permutations of MFs for ΔTCP, ΔNTCP and PTV margin. The 3D output surface[7] of FIS is adopted in the current study which was generated in Matlab R 2018a. Figure 4 represents combination of ΔTCP, ΔNTCP and PTV margin values that indicate uneven changes in PTV margin with required TCP/NTCP relation while a standard uncertainty 0·5 ± 0·2 mm was considered as error in PTV margin.

As current van Herk et al. formulations in theory, PTV margin was continuous linear increasing irrespective of organ motion. PTV margin was studied[7] as greater than 13 mm using current margin techniques, while the fuzzy margin remained below 12 mm depending on displacement errors SD It was observed that the PTV margin results were consistent for both conventional margin technique and fuzzy margin model at low error SD (< 5 mm SD approximate). At higher standard errors (> 5 mm SD approximate), the fuzzy margin remained below 12 mm and van Herk et al. formulations were greater than 13 mm margin size. This trend was attributed to the effect of introducing volume-based TCP/NTCP in the margin formulation. However, the resulting PTV margin conditions may vary from case to case while considering confounding factors such as organ motion, deformation and other clinical factors.

Implementation of fuzzy margin and dosimetric predictors of normal structures

The VMAT plans using fuzzy PTV margin were performed to assess organ at risk's (OAR) dosimetric benefit. Using the SD of total displacement errors, fuzzy PTV margins of 6 mm and 10 mm corresponding to 4 mm (low error SD) and 6 mm (high error SD) standard errors were selected respectively.[7] The selection

https://doi.org/10.1017/S1460396920000904 Published online by Cambridge University Press

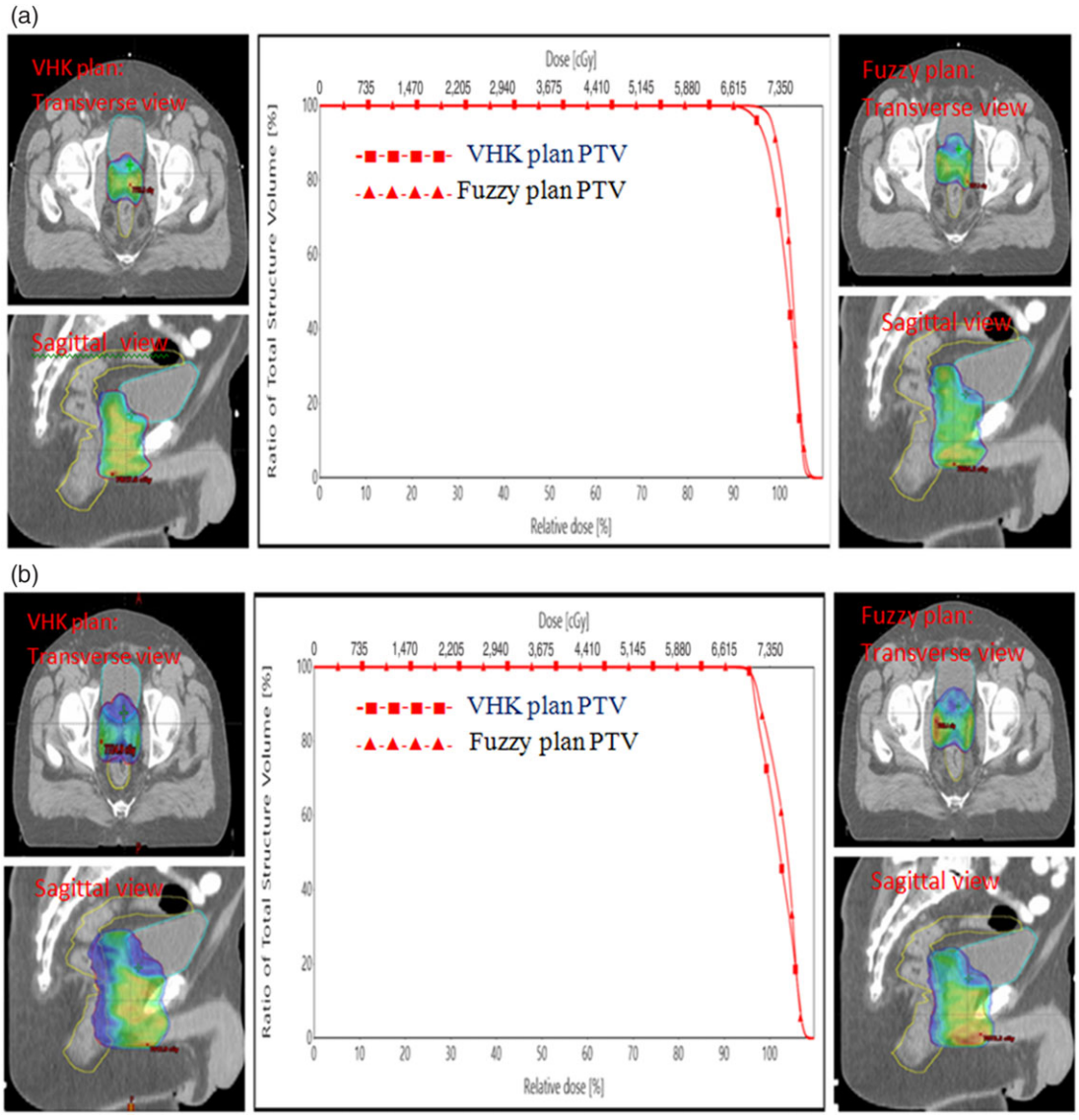

Figure 5. Target volume dose distributions and dose–volume histogram (DVH) at (a) 4 mm SD standard errors and (b) 6 mm SD standard errors: conventional margin plan versus fuzzy margin plan.

of fuzzy PTV margins was arbitrary to compare dosimetric results with conventional van Herk margins at low and high SD errors, respectively. All VMAT plans (using fuzzy PTV margin as well as conventional PTV margin) were planned and compared statistically to assess OARs dosimetric predictors of normal structures corresponding to low SD as well as high SD error regions. The biological dose–volume evaluations for fuzzy VMAT plans were estimated for OARs such as mean dose and dose–volume predictors (V30, V50 and V60 Gy for rectum; V30, V50 and V65 Gy for bladder). Also other OARs dose receiving volumes were observed for better quality plans while maintaining 95% isodose of prescription dose will covered by CTV. For PTV, the conformity index (CI) and homogeneity index (HI) were used.[16] The CI was used to evaluate conformal coverage of PTV by isodose volume, prescribed in treatment plan. $CI = \frac{V_{PTV} \times V_{TV}}{TV^2_{PV}}$ (V_{TV}, volume of actual prescribed dose; V_{PTV}, volume of PTV; T_{VPV}, volume and V_{PTV} within V_{TV}). The HI was used to determine dose homogeneity of PTV. $HI = D_{5\%}/D_{95\%}$ ($D_{5\%}$ and $D_{95\%}$ are minimum doses delivered to 5 and 95% of PTV, respectively). Dosimetric results were analysed using a two-tailed *t*-test for patient-specific dose–volume histogram (DVH) values. Statistical significance was set at $p \leq 0{\cdot}05$. Data processing was done with Statistical Package for Social Science. Final dosimetric results were compared with currently using van Herk margin formulations.

Results and Discussions

Dosimetric predictors of normal structures and comparison to current margins

The VMAT plans were performed with 6 and 10 mm fuzzy PTV margins corresponding to total displacement standard errors 4 and 6 mm SD, respectively. PTV dose distribution and DVH of fuzzy PTV plan were compared to current van Herk margin, as shown is Figure 5. All plans were clinically acceptable in the present study in view of PTV conformity so there were no significant changes found in PTV objectives as shown in Table 2. The statistical analysis of bladder and rectum dosimetric predictor results is shown in Tables 3 and 4, respectively, corresponding

https://doi.org/10.1017/S1460396920000904 Published online by Cambridge University Press

Table 2. PTV dosimetric results for all plans: conventional margin plan (VHK) versus fuzzy margin plan

Parameter	Conventional plan	Fuzzy plan
$V_{95\%}$ (%)	98·4 ± 0·45 (97·95–98·85)	98·5 ± 0·8 (97·7–99·3)
CI	0·86 ± 0·15 (0·71–1·01)	1·01 ± 0·1 (0·91–1·11)
HI	1·10 ± 0·03 (1·07–1·15)	1·11 ± 0·03 (1·06–1·10)
TCP (%)	89·80 ± 2·5 (92·3–87·3)	89·95 ± 1·2 (88·45–91·45)

CI, conformity index; HI, homogenate index; TCP, tumour control probability; $V_{x\%}$, volume receiving ≥ x% of the prescribed dose.

Table 3. Dosimetric results of bladder (volume = 16,030 ± cc): conventional VHK plan versus fuzzy plan at (a) 4 mm SD standard errors and (b) 6 mm SD Standard errors

	4 mm SD standard error		6 mm SD standard error	
Dosimetric parameters	Conventional VHK margin	Fuzzy margin	Conventional VHK margin	Fuzzy margin
Mean dose (Gy)	25·5 ± 2·5	26·0 ± 3·0	43·0 ± 2·5	38·0 ± 2·0
V_{30Gy} (%)	40·0 ± 3·0	42·0 ± 1·5	68·0 ± 3·0	57·0 ± 1·3
V_{50Gy} (%)	22·0 ± 4·5	26·0 ± 5·5	34·0 ± 3·0	25·0 ± 2·0
V_{60Gy} (%)	10 ± 3·0	12·0 ± 2·5	25·0 ± 2·5	18·5 ± 1·5
V_{65Gy} (%)	8·5 ± 3·0	9·0 ± 4·0	22·0 ± 2·0	17·0 ± 1·0
$V_{5\%}$ (%)	95·5 ± 0·5	96·5 ± 1·5	99·0 ± 0·5	99·0 ± 0·5
$V_{10\%}$ (%)	85·0 ± 3·0	88·5 ± 3·5	96·0 ± 1·0	95·0 ± 0·5
$V_{50\%}$ (%)	26·5 ± 2·5	29·0 ± 3·0	54·0 ± 2·5	45·0 ± 1·5
$V_{90\%}$ (%)	6·5 ± 1·5	10·5 ± 3·0	20·0 ± 1·5	15·0 ± 1·0
$V_{100\%}$ (%)	0·5 ± 0·2	0·6 ± 0·2	0·5 ± 0·0	0·5 ± 0·0
D_{1cc} (Gy)	72·3 ± 0·3	72·5 ± 0·5	76·0 ± 0·2	75·0 ± 0·1
D_{5cc} (Gy)	70·0 ± 0·5	71.±1·0	72·0 ± 0·3	71·0 ± 0·5
D_{10cc} (Gy)	63·0 ± 2·5	64·5 ± 2·5	71·0 ± 0·5	71·0 ± 0·1
D_{20cc} (Gy)	49·0 ± 2·0	50·5 ± 1·5	71·0 ± 1·5	67·0 ± 1·0
D_{30cc} (Gy)	40·0 ± 1·5	43·0 ± 2·0	68·0 ± 3·0	59·0 ± 1·5
D_{40cc} (Gy)	33·0 ± 1·0	34·5 ± 1·5	60·0 ± 1·5	50·0 ± 1·0
D_{50cc} (Gy)	29·0 ± 0·5	30·0 ± 0·5	53·0 ± 2·5	45·9 ± 1·5
D_{100cc} (Gy)	14·5 ± 0·5	15·0 ± 1·0	32·0 ± 2·5	27·0 ± 1·5
D_{150cc} (Gy)	4·0 ± 1·0	4·0 ± 1·5	4·0 ± 0·5	4·0 ± 0·1

$V_{x\%}$, volume receiving ≥ x% of prescribed dose; $V_{z\%}$, volume receiving ≥ Z% of prescribed dose. D_{Ycc}, dose of Ycc volume (all decimals were round figured).

to 4 mm SD (below 5 mm SD was considered as lower error region) and 6 mm SD errors (greater than 5 mm SD was considered as high error region). Also the differential DVHs of bladder and rectum were shown in Figures 6 and 7, respectively. In lower error region (Figures 6a and 7a), no significant changes in dosimetric predictors were found except bladder mean dose ($p = 0{\cdot}03$) and rectum mean dose ($p = 0{\cdot}04$). This may be due to fuzzy margin that was found to be similar or 0·5 mm larger compared to conventional van Herk margin. However, taking the modelling uncertainty into account, results showed good match between fuzzy PTV margin calculated and van Herk et al.'s formulation of up to error 5 mm SD But at higher error region (Figures 6b and 7b), significant changes in dosimetric predictors were found in mean dose ($p \sim 0{\cdot}002$), V_{30Gy} ($p \sim 0{\cdot}003$), V_{50Gy} ($p \sim 0{\cdot}005$), V_{65Gy} ($p \sim 0{\cdot}0010$) for bladder

Table 4. Dosimetric results of rectum (volume = 15,915 ± cc): conventional VHK plan versus fuzzy plan at (a) 4 mm SD standard errors and (b) 6 mm SD standard errors

	4 mm SD standard error		6 mm SD standard error	
Dosimetric parameters	Conventional VHK margin	Fuzzy margin	Conventional VHK margin	Fuzzy margin
Mean dose (Gy)	22·5 ± 1·5	23·5 ± 1·0	36·5 ± 2·0	30·0 ± 1·5
V_{30Gy} (%)	30·5 ± 1·5	31·5 ± 1·0	58·0 ± 2·5	50·0 ± 1·5
V_{50Gy} (%)	15·0 ± 1·0	15·0 ± 1·5	45·0 ± 3·0	28·0 ± 1·0
V_{60Gy} (%)	8·0 ± 0·5	8·5 ± 0·5	30·0 ± 2·5	20·0 ± 1·5
V_{65Gy} (%)	5·0 ± 0·5	5·5 ± 0·5	25·0 ± 1·5	15·0 ± 2·0
$V_{5\%}$ (%)	78·5 ± 3·0	79·0 ± 4·0	97·0 ± 0·5	95·0 ± 0·5
$V_{10\%}$ (%)	58·0 ± 3·5	59·0 ± 4·0	69·1 ± 1·0	63·0 ± 2·0
$V_{50\%}$ (%)	24·5 ± 0·5	25·0 ± 0·5	52·0 ± 2·0	45·0 ± 1·5
$V_{90\%}$ (%)	5·5 ± 0·5	6·5 ± 0·5	25·0 ± 2·0	15·0 ± 0·5
$V_{100\%}$ (%)	0·5 ± 0·1	0·6 ± 0·1	0·0 ± 0·5	0·0 ± 0·2
D_{1cc} (Gy)	71·5 ± 0·3	78·5 ± 0·5	72·0 ± 0·5	72·0 ± 0·2
D_{5cc} (Gy)	69·5 ± 0·5	70·0 ± 0·2	71·5 ± 0·5	71·0 ± 0·0
D_{10cc} (Gy)	65·5 ± 1·0	65·5 ± 0·5	71·0 ± 0·5	70·0 ± 0·5
D_{20cc} (Gy)	52·5 ± 1·0	54·5 ± 0·5	71·0 ± 0·5	66·0 ± 1·0
D_{30cc} (Gy)	43·0 ± 1·0	44·0 ± 0·5	69·5 ± 1·0	58·0 ± 0·5
D_{40cc} (Gy)	35·5 ± 1·0	37·0 ± 1·5	66·5 ± 1·5	52·0 ± 0·5
D_{50cc} (Gy)	31·0 ± 0·5	29·5 ± 1·0	60·0 ± 2·0	45·0 ± 1·5
D_{100cc} (Gy)	5·0 ± 0·5	6·0 ± 1·0	9·0 ± 1·0	7·0 ± 0·5
D_{150cc} (Gy)	2·5 ± 0·5	2·9 ± 0·5	6·0 ± 0·5	4·0 ± 0·5

$V_{x\%}$, volume receiving ≥ x% of prescribed dose; $V_{z\%}$, volume receiving ≥ Z% of prescribed dose. D_{Ycc}, dose of Ycc volume (all decimals were round figured).

and mean dose ($p \sim 0{\cdot}0012$), V_{30Gy} ($p \sim 0{\cdot}0014$), V_{50Gy} ($p \sim 0{\cdot}0011$), V_{65Gy} ($p \sim 0{\cdot}0013$) for rectum, respectively. This was due to optimal dose-received volume benefit in dosimetric predictors based on biological volume–dose relationship. Because at higher SD errors (>5 mm) the fuzzy margin was limited than current margin formulations. Therefore, present FIS technique may be expected as suitable for radiotherapy margin modelling. The resulting margins were providing better OAR sparing without compromising target dose coverage and so FIS technique is at least as good as current methods in dose escalation applications.

In radiotherapy, dose escalation can carry a substantial risk of late toxicity particularly when there is internal organ motion was considered. So far, existing DVH analyses were indicated the presence of volume effect with respect to grade 2 or higher complications across doses of 60–78 Gy for prostate cancer. This risk grows exponentially as greater volumes of OARs are irradiated and resulting co-morbidities may be enhanced significantly. These complications may be severe when planning targets are defined with margins symmetrically irrespective of movement and shape of tumour and OARs. Hence, the above results on asymmetric margin-based fuzzy approach may helpful to estimate and reduce the risk of OARs toxicities by estimating appropriate interplay between TCP/NTCP values versus acceptable risk of complications even at higher doses. This variation may be dependent on proximity between tumour volume and OARs as well as preselected TCP and NTCP tolerances in FIS.

https://doi.org/10.1017/S1460396920000904 Published online by Cambridge University Press

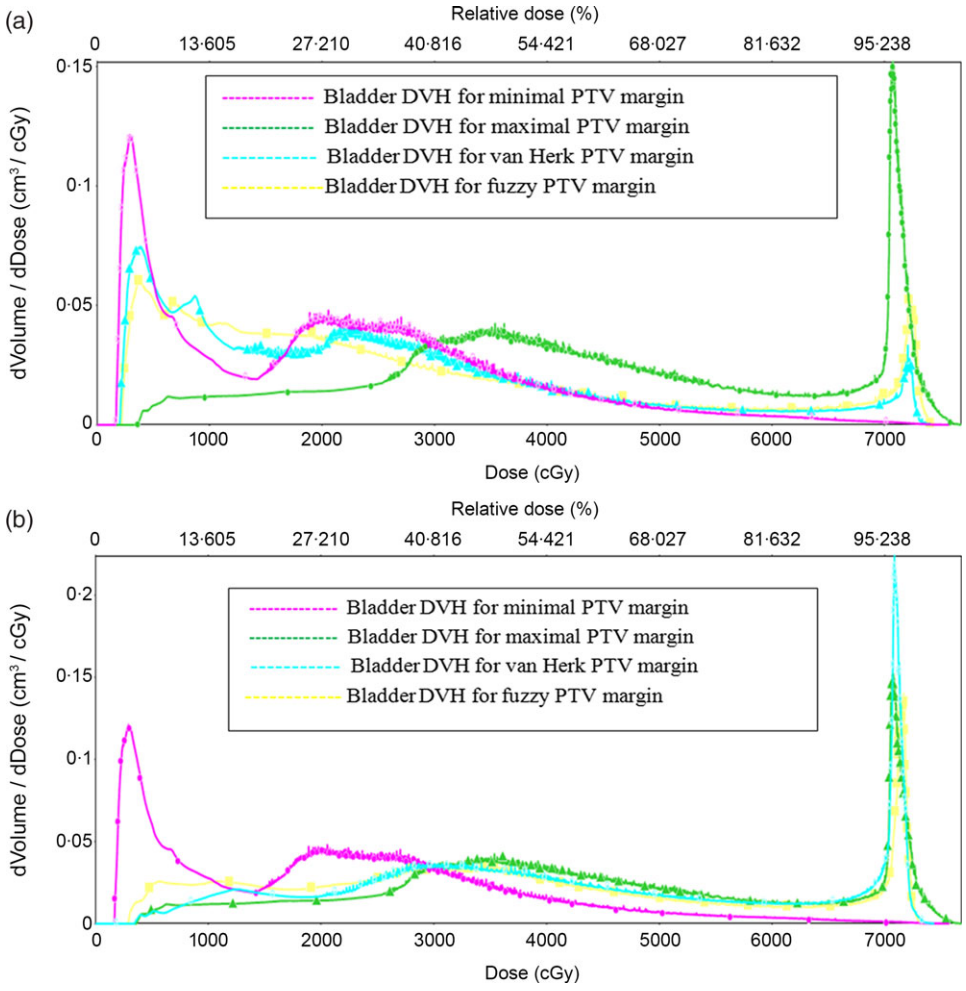

Figure 6. Bladder differential dose–volume histogram at (a) 4 mm SD standard errors and (b) 6 mm SD standard errors: conventional margin plan versus fuzzy margin plan.

The proposed method combines the radiobiological data, the proximity of the surrounding critical structures by considering dose effects to these organs with increasing margin size and knowledge using linguistic (clinician's intensions) relationships to produce the output margins. The resulting treatment margins may explicitly express the assumed margin variations for treatment planning and dose escalation with computational efficiency. The present study also allows the calculation of individualised patient margins and prospective purpose based on true expected biological outcomes. Individualised patient margins calculation is currently very difficult to accomplish with manual set-up of current techniques. Also due to the range of variability in patient anatomy and organ motion such as prostate target, OARs like bladder and rectum vary between patients. So the current margins may not be suitable in some cases. This biological fuzzy approach may be expected as an efficient tool for estimating the risk of gastrointestinal toxicity for rectum and gastrourinary toxicity for bladder in retrospective analysis of dose–volume and OARs toxicity relationship. Also fuzzy approach may take minimal additional set-up time so it is expected as effective in busy radiotherapy centres. In the present study, the dosimetric results were discussed for localised prostate target volume only. But in advanced cases, it involves multiple targets such as prostate, seminal vesicle and LN targets. In such cases also, fuzzy approach would be expected as a helpful tool for judgement of toxicity estimation by considering individual clinical case history.

In radiotherapy, fuzzy logic application was studied using uniform or symmetrical margins of PTV in the literature. Mzenda et al. studied fuzzy logic application using organ motion related considering uniform motion and they did not consider the asymmetric nature of motion of PTV and other nearby multiple critical organ effects around target volume. But in nature, dynamic targets and adjacent OARs have irregular motion, so their treating margins not always symmetric or uniform. However, as there are lot of radiotherapy uncertainties. So under small error deviation, the results of the present study were consistent with current margin formulations studied by Van Herk et al. But at high error deviations, the results of the present study may be expected as superior clinical/survival benefit, though all plans are clinically acceptable in terms of dose–volume statistics. Hence, it would be expected the fuzzy approach may helpful to estimate actual risk of OARs and reduce toxicities by estimating appropriate interplay between TCP/NTCP values versus acceptable risk of complications even at higher doses, by considering individual clinical case history.

The computational intelligence methods such as fuzzy logic have proved to be consistent and accurate in calculating the required treatment margins of prostate target volumes with real time. The computational intelligence methods such as fuzzy logic may also applicable in treating other target volumes where organ motion involves. The proposed fuzzy margins method is inherently more accurate as they include all the factors that affect the PTV. In comparison to manual or conventional techniques, the proposed

https://doi.org/10.1017/S1460396920000904 Published online by Cambridge University Press

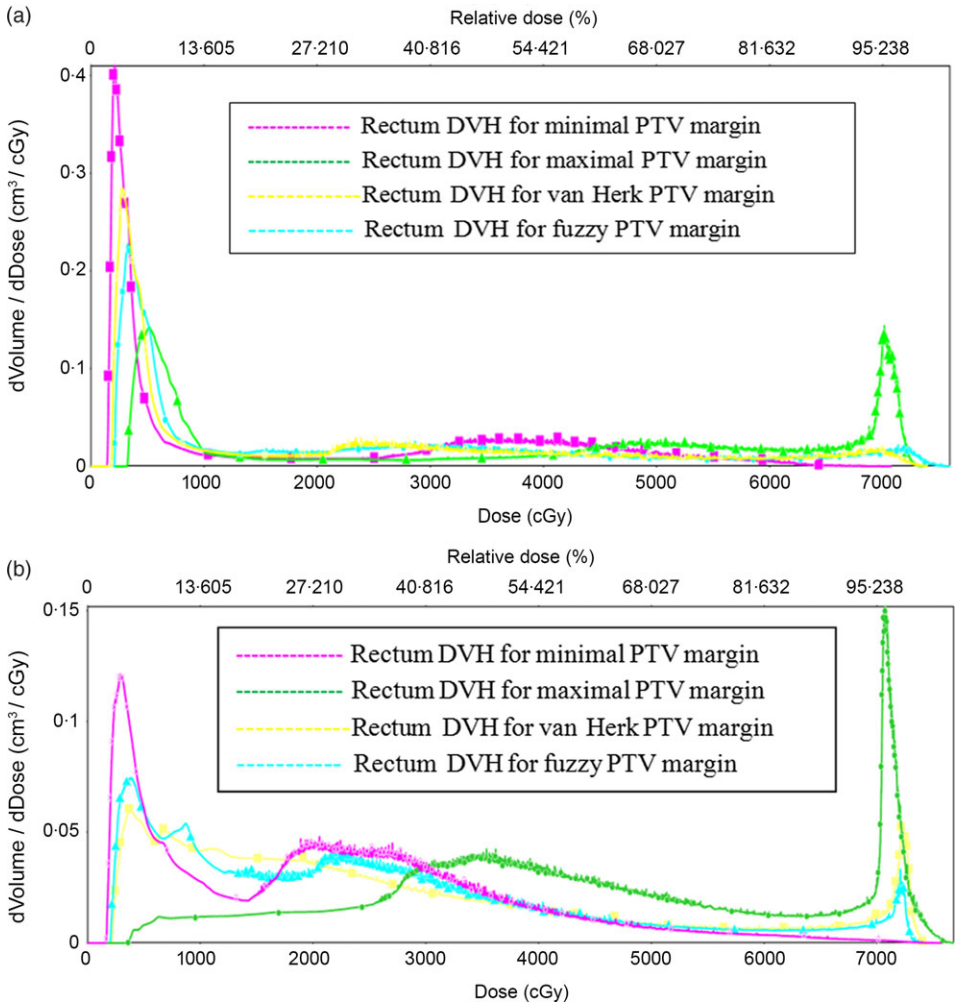

Figure 7. Rectum differential dose–volume histogram at (a) 4 mm SD standard errors and (b) 6 mm SD standard errors: conventional margin plan versus fuzzy margin plan.

model is computationally more efficient. The possibility of margins computation may be faster and accurate with proposed model, whereas conventional techniques are time taking due to manual statistical techniques. With the immense demands on radiotherapy in terms of high patient numbers and the required quick turn-around, it is important to reduce the time in all the steps in the process. The limitation of the current study was the estimation of standard errors SD at the patient realignment performance in all axial views (SI, AP and LR directions) only with small number in the sampleover course of treatment in estimation of fuzzy margin. The performance of the current study may be improved with the identification of relevant factors (co-morbidities, lifestyle, etc.) which can affect the normal tissue complications and incorporation of these factors into fuzzy rules at the planning level.

Conclusions

Advanced treatment technologies such as VMAT are options for dose escalation which inevitably involves critical organs lying next to steep dose gradients. Using the conventional margins for same tumour type for all patients may not be ideal due to physiological variations from patient to patient. The advantage of using the proposed fuzzy logic model is its ability to combine measured input/output data with radiobiological data using linguistic relationships to predict possible results in order to avoid complexities in current and emerging radiotherapy treatment techniques. Being closer agreement to statistical models, fuzzy margins were expected to be clinically more applicable to reduce late complications normal structures for survival benefit.

Acknowledgements. The authors are thankful to Department of Radiotherapy, Pt JNM Medical College and Department of Physics, National Institute of Technology, Raipur for providing support at each level to complete this work.

Financial Support. None.

Conflicts of Interest. There are no conflicts of interest.

References

1. Byrne TE. A review of prostate motion with considerations for the treatment of prostate cancer. Med Dosim 2005; 30 (3): 155–161.
2. Van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. Int J Radiat Oncol Biol Phys 2000; 47 (4): 1121–1135.
3. Alasti H, Petric MP, Catton CN, Warde PR. Portal imaging for evaluation of daily on-line setup errors and off-line organ motion during conformal irradiation of carcinoma of the prostate. Int J Radiat Oncol 2001; 49 (3): 869–884.

https://doi.org/10.1017/S1460396920000904 Published online by Cambridge University Press

4. Deasy JO, Charles SM, Colin GO. Treatment optimization and evaluation should be biologically and not physical dose/volume based. Med Phys 2015; 42 (6): 2753–2756.
5. Yartsev S, Bauman G. Target margins in radiotherapy of prostate cancer. Br J Radiol 2016; 89: 20160312.
6. Chen Z, Yang Z, Wang J, Weigang H. Dosimetric impact of different bladder and rectum filling during prostate cancer radiotherapy. Radiat Oncol 2016; 11: 103–110.
7. Patnaikuni SK, Saini SM, Chandola RM, Chandrakar P, Chaudhary V. Study of asymmetric margins in prostate cancer radiation therapy using fuzzy logic. J Med Phys 2020; 45: 88–97.
8. Nuyttens JJ, Milito S, Rust PF, Turrisi AT. Dose volume relationship for acute side effects during high dose conformal radiotherapy for prostate cancer. Radiother Oncol 2002; 64: 209–214.
9. Ling CC, Liu M, Berthelet E, Patterson K, Dick K, Kwan W. Various techniques of contouring the rectum and their impact on rectal dose volume histograms. Med Dosim 2003; 28: 189–192.
10. NCCN. Prostate cancer. NCCN Practice. https://www.nccn.org/. 2016. Accessed on 05th August 2018.
11. Niemierko A. Reporting and analyzing dose distributions: a concept of equivalent uniform dose. Med Phys 1997; 24 (1): 103–110.
12. Mzenda B, Hosseini-Ashrafi ME, Palmer A, Hodgson DF, Liu H, Brown DJ. Determination of target volumes in radiotherapy and the implications of technological advances: a literature review. J Radiother Pract 2009; 8 (1): 41–51.
13. Benk VA, Adams JA, Shipley WU et al. Late rectal bleeding following combined X-ray and proton high dose irradiation for patients with stages T3–T4 prostate carcinoma. Int J Radiat Oncol Biol Phys 1993; 26 (3): 551–557.
14. Combs WE, Andrews JE. Combinatorial rule explosion eliminated by a fuzzy rule configuration. IEEE Trans fuzzy Syst 1998; 6 (1): 1–11.
15. Mzenda B, Hosseini-Ashrafi M, Gegov A, Brown DJ. Implementation of a fuzzy model for computation of margins in cancer treatment. International Conference on Fuzzy Systems IEEE 2010, ISBN 978-1-4244-6919-2. 2010: 1931–1938.
16. Lee TF, Fang FM, Chao PJ, Su TJ, Leung SW. Dosimetric comparisons of helical tomotherapy and step and shoot intensity modulated radiotherapy in nasopharyngeal carcinoma. Radiother Oncol 2008; 89 (1): 89–96.

https://doi.org/10.1017/S1460396920000904 Published online by Cambridge University Press