Moving organ toxicity management in radiation therapy with simple fuzzy logic

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Abstract. The aim of present work is to estimate and manage real time toxicity of moving organ bladder in deciding level of damage using a simple fuzzy logic method. The target and bladder inter-treatment motions are considered in radiation therapy of prostate cancer in the present study. Materials and methods: The prostate target and nearby critical structures like bladder varies due to physiological behaviour during the course of radiation therapy treatment. The total displacement errors of prostate target shift ranging from 0-5 mm s.d. was considered in this study while maintain tumor dose conformity. The Mamdani-type Fuzzy Inference System (FIS) was applied for determine biological acceptable margin using TCP and NTCP parameters. The bladder volume variations with weekly analysis of cone beam CT (CBCT) were considered. Using irradiated volume-risk relationship in planning, the overlapped risk volumes were estimated. Fuzzy rules and membership function were used basis on setup errors, asymmetrical nature of organ motion and limitations of normal tissue toxicity in margin formulations. Results and discussion: The prostate target motion management was in a good consistent with conventional margin formulations at 5 mm s.d. displacement error range to maintain conformity index (CI) of target. With application of conventional margins of target volume, the sub-volumes of critical organs such as bladder and corresponding its NTCP values were fuzzified using inter treatment volume variations of critical organs. The risk factor (RF) of critical organs were qualitatively assessed with for each fractional volume of irradiated to total volume and relevant NTCP values. Conclusion: A simple fuzzy logic may be suitable to estimate critical moving organs toxicity like bladder biologically. Using proposed simple and fast method, there is interplay between volume-risk relationship and NTCP of OARs to management of normal-tissue risk level of radiation therapy.

1. Introduction
The treatment of cancer using radiation therapy is the process of optimization of maximizing radiation dose to tumour cells whilst sparing healthy tissues and critical organs. In course of treatment, target volumes and critical organs should be outlined clearly. Otherwise inductions of adverse side effects on the normal tissues and critical organs may develop sever complications. There is always trade-off between complications and cure depends on best possible margins to achieve favorable treatment outcomes. The margin formulations...
were studied based on probabilistic dose distributions by considering a linear relationship between planning target volume (PTV) margin and radiotherapy errors [1]. Currently the PTV margins are symmetric or linear nature for all treatment strategies today. But due to presence of organ motion and other radiotherapy setup errors encountered in actual fractionated radiotherapy treatment phase, delivered dose may differs from planned dose. Further the main disadvantage of currently used margin formulations is that they do not consider the effects of organ motion and surrounding organ at risk when deriving PTV margins. It was found that fuzzy region of PTV to derive exact margin in prostate cancer (PC) radiation therapy from the clinical observations as prostate gland position is likely to change between treatment fractions also critical organs will affect anatomically, adjacent to prostate target. Therefore PTV margins should be precisely defined as well as account for radiobiological effects of tumour and surrounding normal structure at planning level [2] in the treatment of moving organ like prostate. A study was done by Yartsev S et al [3] which illustrate fuzziness of PTV margins of moving targets and may effect on nearby normal overlapped volumes. Also critical organs such as bladder volumes change during the prostate cancer radiotherapy [4]. This has an impact on thus, further radiation induced toxicities [5]. Hence the rigidity of currently using conventional formulation may be limited to adapt for many treatment scenarios such as prostate like dynamic tumour volumes. Introducing fuzzy logic has a distinct advantage as it allows linkage of geometrical and radiobiological parameters of radiotherapy planning through using fuzzy rules and membership functions (MFs). The relationship is difficult between these parameters to quantify mathematically or may have a large degree of variability. Recently, Patnaikuni et al. [6] studied asymmetric 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. The present study is based on earlier work by Patnaikuni et al [6].

The objective of present work is to estimate bladder toxicity biologically using a simple novel two-level fuzzy logic method. The VMAT was choice for prostate cancer radiation therapy. To estimate real time bladder toxicities, both prostate target and bladder internal motions are considered in the present study at low displacement error range of organ motion based on earlier work by Patnaikuni et al [6]. The first level fuzzy logic is adopted [6] to apply biological acceptable target margin using TCP and NTCP parameters. In second level fuzzy, bladder volume variation with weekly analysis of cone beam CT (CBCT) was considered here. Fuzzy rules and membership function were used basis on setup errors, asymmetrical nature of organ motion and limitations of normal tissue toxicity in margin formulations. The final risk factor (RF) of critical organs was qualitatively assessed with for each fractional volume of irradiated to total volume and relevant NTCP values.

2. Methods and materials

In the present study Mamdani-type fuzzy inference system (FIS) was applied in possible OAR risk management procedure. Because Mamdani-type FIS is expected output suited to human thinking and so widely accepted for capturing expert knowledge which is very significant particularly in real time organ toxicity assessment of radiation therapy treatment. The localized prostate radiotherapy patients (n=08) were selected for study with dose prescription of 73.5 Gy. The preferred planning method was volumetric modulated arc therapy (VMAT). Planning Objectives and Dose Constraints were mentioned using Eclipse 15.6 Treatment planning system (TPS), Varian Medical Systems (VMS) with gEUD based parameters setting. The radiobiological parameters TCP and NTCP were calculated in Matlab R2018a based simulation tool [7] using the equivalent uniform dose (EUD) modelling with required statistical values from all plans. The framework of our study involves two levels along with standard setup errors were incorporated in each level. In the first level, possible PTV margin was estimated based on target motion displacement error s.d < 5 mm. In the second level, the possible OAR toxicity was estimated in the same error range on employing fuzzy PTV margin from first level.
2.1. Fuzzy logic framework based on organ motion

In the first level fuzzy framework, target margin derivation procedure was started with statistical analysis of target motion using in-house using tracking methods such as image guidance analysis [8-9]. All asymmetric margins were generated for target PTV from minimal to maximum motion limits based on nature of displacement of target which was observed statistically. Here 1mm stepped size margin was manually added using TPS to subsequent asymmetric PTV margin up to maximum limit. All VMAT plans were performed from minimum acceptable value of PTV margin to maximum. Biological parameters TCP and NTCP were calculated for each plan. After each stepped increment margin of PTV, recalculation of new TCP and NTCP values were done and compared with base value which is corresponding plan with minimal PTV margin. Subsequent changes in TCP and NTCP due to target volume displacements were used these initial TCP and NTCP values to estimate subsequent loss in TCP (i.e., ΔTCP) and increase in NTCP (i.e, ΔNTCP). The FIS consisted of two inputs as ΔTCP and ΔNTCP while one output as PTV margin. The fuzzification of inputs (TCP and NTCP) and defuzzification of output (PTV margin) were done in Mamdani-type FIS with adopted rules and membership functions. 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. The 3D output surface [6] represents combination of ΔTCP, ΔNTCP and PTV margin values that indicates 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. All results were studied below 5 mm s.d. of target displacement errors which was considering as lower error region. Finally the margin obtained from fuzzy model was applied in actual VMAT treatment planning for bladder toxicity estimation and management.

The second level fuzzy framework was started with VMAT plans generation using fuzzy PTV margin. The overlapped bladder volumes and corresponding NTCP values were fuzzified in second level fuzzy using bladder volume variations. The final risk factor (RF) [10] of OARs was qualitatively assessed with for each fractional volume of irradiated to total volume and relevant NTCP values. The risk or toxicity estimation of any critical organ around the tumour depends upon its volume gets irradiated during irradiation. Sub-volume of volume of interest (V_{VOI}) based NTCP was calculated for each CBCT. It is directly proportional to the fragment or sub-volumes of OAR which gets irradiated by its tolerance dose. Also toxicity or risk depends on its entire volume (V_{TVO}) of OAR. If the total volume of OAR is more, then its risk of damage or risk factor (RF) is less during irradiation and vice versa. RF is inversely proportional to the total volume of the organ. Bladder volume varies significantly on a daily basis, so the actual radiation prescribed dose received by the bladder may be expected different in comparison to the planned radiation dose. To assess the volumetric variation of bladder, cone beam computed tomography (CBCT) was used for each patient on weekly basis. In each patient, five CBCT-scans obtained in 5 day interval each through the treatment course. The bladder volume was manually outlined on CBCTs along with actual planning CT (CTp) so resulting in 6 bladder contours for each patient. All bladder contours obtained from each patient were imported and merged with CTp as reference. Recalculation of bladder volume and dose was done for each CBCT using CTp with same set up beams. Fuzzy rules were framed according to OAR bladder toxicity limits so that each CBCT vs. CTp was assessed to estimate real-time sub-volume related NTCP. For assessing the risk of damage rationally, MFs were selected for inputs (i.e; fractional volume and its NTCP) and output (i.e; RF). MFs of input NTCP were selected as Medium, High, vary high risk regions while MFs of input V_{VOI}/V_{TVO} were selected 0-25%, 25-50%, 50-75%, 75-100% respectively. The MFs of output RF were defined as medium, high and very high.

2.2. OAR bladder toxicity estimation and clinical assessment

The risk or toxicity estimation of any critical organ around the tumor depends upon its volume gets irradiated
during irradiation. The MFs of output RF were defined as medium, high and very high. Near to 0% then the OAR is completely safe which was impractical for moving organs. So MFs for RF were practically considered on clinical situations. Medium RF: If the numerical value of RF is 50% or less, then the OAR will get partially damaged during the course of irradiation. High RF: If the numerical value of RF is 75% or higher which means OAR will get completely damaged during the course of irradiation. In our study MFs for bladder risk (RF) were defined by risk factor scale by Ansari et al. For MFs of NTCP as medium (0-2%), high (2-4%) and very high (above 4%). The acceptance of bladder toxicity limits may vary patient to patient and existing co-morbidities. If toxicity limits exceeds based on intended NTCP, target volume or normal structure contours will be altered for re-optimization and planning. The selection of MFs and rules were mainly based on high displacement error s.d., organ type such as serial organ or parallel organ or serial–parallel organ. The NTCP values were based on quantitative analysis of normal tissue effects in the clinic (QUANTEC) dose constraints.

3. Results and discussion

The VMAT plans were performed with 6 mm fuzzy PTV margins corresponding to total displacement standard errors < 5 mm s.d. PTV dose distribution and dose-volume histogram (DVH) of fuzzy PTV-plan was compared to currently using Van-Herk margin models. All plans were clinically acceptable in the present study in view of target volume (PTV) dose conformity so there were no significant changes found in PTV objectives when compared with currently using margin models. This may be due to fuzzy margin was found to be more or less similar compared to currently using van-Herk margin methods in our radiotherapy centre. However taking the modelling uncertainty into account, results showed good match between fuzzy PTV margin calculated and currently using margin formulation in first-level fuzzy PTV margin derivation of moving target of up to displacement error 5 mm s.d. Figure 1 represents combination of \( \Delta TCP, \Delta NTCP \) and PTV margin values that indicates uneven changes in PTV margin with required TCP/NTCP relation. With application of fuzzy margin obtained from first level fuzzy, overlapped bladder volumes and corresponding NTCP values were fuzzified in second level fuzzy using bladder volume variations. The final risk factor (RF) of OARs was qualitatively assessed with for each fractional volume of irradiated to total volume and relevant NTCP values. Figure 2 represents risk factor estimation of with required NTCP and sub-volume relationship of OAR bladder using second level fuzzy logic. The bladder risk or toxicity (%) corresponding to NTCP values for one patient under low displacement errors s.d. was demonstrated for one patient as in Table-1. From the table it was observed all NTCP values were well within toxicity limits so that RF of bladder is acceptable. Hence no action was recommended for re-planning of treatment. Though all NTCP values and its associated RF values were well within limit but at CBCT3, RF is relatively higher than CTp. The reason may be depends on different bladder volumes due to organ motion related physiological behavior of OAR bladder at the time of acquiring CBCTs. The effect of real-time organ motion related RF was may not be feasible until there might be manual assessment approach which takes usually longer time in routine radiotherapy treatment. Because in the routine radiation therapy, the treatment plan is normally performed for one time at the beginning of treatment course. So with help of FIS tool in our study, it may be feasible to manage radiation induced risk of moving organ like bladder biologically.

The currently using standards of deriving margins in radiotherapy have their limitations, they have been used for many patients over the years and the survival rates are generally satisfactory. The early and or late effects on critical organs and normal tissues is however variable. These methods work but they can be clearly improved to get better outcomes. No ‘gold standard’ method currently exists in this field which addresses all the previously mentioned limitations to be used for comparing the models from this study. The novelty of the method proposed in this study lies more in that they allow for the calculation of individualised patient margins, which is currently very difficult to accomplish due to manual setup of current techniques. These
margins are expected to lead to better clinical outcomes. With help of simple fuzzy logic, it may be expected to assess the possible OAR toxicity on plan of the day or week basis. However clinical trials are required to fully validate this observation. It is concluded that the RF is a comprehensive evaluation tool for conformal radiotherapy plans which encompasses a wider range of clinically relevant parameters, isodose volumes and tolerance dose of OARs. It is expected as an advance tool to check the qualitative nature of a conformal plan including the assessment of degree of damage of the OARs. The major advantage of current study is that it gives information about the conformity of dose to tumor and severity level of damage of OARs at a glance in clinical application. The major limitation of our work was the estimation of toxicity level under small standard errors s.d only with small number in the sample over course of treatment.

Figure 1. Fuzzy output as 3D-surfaces in first-level fuzzy PTV margin derivation of moving target [6].

Figure 2. Fuzzy output as 3D-surfaces in second-level fuzzy for risk factor estimation of OAR bladder.

Table 1. The bladder risk or toxicity (%) corresponding to NTCP values for one patient under low displacement errors s.d, was demonstrated quantitatively for one patient case.

| Parameter       | CTp | CBCT1 | CBCT2 | CBCT3 | CBCT4 | CBCT5 |
|-----------------|-----|-------|-------|-------|-------|-------|
| Sub-volume(%)   | 20  | 15    | 14    | 30    | 18    | 10    |
| NTCP(%)         | 3.1 | 2.6   | 2.4   | 4.1   | 2.9   | 1.98  |
| Bladder RF      | 0.41| 0.344 | 0.342 | 0.49  | 0.491 | 0.2   |
4. Conclusions
The various limitations of current using margin recommendations can be addressed by the use of computational techniques to give margin models which include organ motion and other setup errors. The feasibility of the new models have been tested using clinical studies and the fuzzy models have been found to quality improvement method for better critical organ sparing and toxicity management while maintaining tumor control probability the in the presence of errors.

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