

Explaining relationships between local dose and rectal toxicity in prostate cancer radiotherapy with voxel-based population analysis

Oscar Acosta^{1,2}, Gaël Dréan^{1,2}, Juan David Ospina^{1,2,4}, Antoine Simon^{1,2}, Pascal Haigron^{1,2}, and Renaud de Crevoisier^{1,2,3}

¹ INSERM, U 1099, Rennes, F-35000, France

² Université de Rennes 1, LTSI, F-35000, France

Oscar.Acosta@univ.rennes1.fr

³ Département de Radiothérapie, Centre Eugène Marquis, Rennes, F-35000, France

⁴ School of Statistics, Universidad Nacional de Colombia, Campus Medellín, Colombia

Abstract. Intensity Modulated Radiotherapy (IMRT) allows delivering of highly conformal dose to complex targets, implying nevertheless the choice of optimal constraints for the organs at risk (OAR) with the aim of reducing toxicity. To estimate the risk of toxicity, current predictive models stand on the dose-volume histograms (DVH) whose main drawback is the lack of spatial accuracy as they consider the organs as a whole volume and thus ignore the heterogeneous intra-organ radio-sensitivity. A framework for finding relationships between local dose and toxicity is proposed here. In this approach, the planned dose distributions are registered together on a common coordinate system and compared across a population at a voxel level, thereby allowing the highlighting of 3D anatomical patterns which may be in part responsible of toxicity. We demonstrated here the value of the approach by explaining rectal toxicity in prostate cancer radiotherapy (PCRT). 116 patients with 31 month median follow-up were considered. They received a total dose of 80 Gy in the prostate by IMRT. When analyzing rectal toxicity, significant difference of dose was found in large regions within the anterior wall close to the prostate (1cm). This promising voxel-wise approach allowed the highlighting of regions that may be involved in rectal toxicity.

1 Introduction

Radiation therapy (RT) is a commonly prescribed treatment for people diagnosed with prostate cancer which has proven to be efficient for tumor control. Several strategies have been recently developed to increase local control, particularly by increasing the dose of radiation demonstrating a close dose-effect relationship [1,2]. However, in prostate cancer radiotherapy (PCRT), rectal and urinary toxicity occurrences, that are frequent with standard prescribed doses (70 Gy), may increase for higher doses. With the precision of the accelerators steadily growing (ARC-Therapy, cyberknife), the possibilities for achieving better control by increasing the dose are available but at the expense of the risk of toxicity if efficient adaptive plannings allowing the inclusion of accurate predictive models are not devised.

The prediction of complications as a consequence of the irradiation has been largely treated in the literature [3] [4]. These predictions are commonly based on the planned

dose distribution using the dose-volume histograms (DVH) [5] within radiobiological Normal Tissue Complication Probability (NTCP) models [6,7,8]. NTCP models were proposed in the early 1980s to estimate the risk of toxicity, based on the dose distribution and the irradiated volume of the structures at risk. Different studies have shown a correlation between dose, volume and rectal toxicity [9,10,11,12,13,14]. However, current DVH-based models for prediction of toxicity exhibit many limitations. Firstly, they do not implicitly integrate individual's specificities (such as the medical history, ...) and concomitant treatments (chemotherapy, androgen deprivation), which may differ across a population. Secondly, they lack spatial accuracy since they are not able to correlate the treatment outcome with spatial patterns of dose thereby considering homogeneous radiosensitive organs. Indeed, the subtle correlation that may exist between local dose and toxicity may not be detected if the rich three-dimensional dose distribution is reduced and represented as a DVH. The waste may be even worse when the DVH is reduced to a single value such as the effective dose (D_{eff}) or the Equivalent Uniform Dose (EUD), which has also proved to be correlated with the risk of toxicity [15,14]. A tri-dimensional cartography depicting sub-regions presenting higher risk of damage will help to define more accurate organ constraints in terms of local dose.

The notion of spatiality and local dose related with toxicity has been raised in previous works [16] either with a parametric description of the dose distribution [17] [18] or within a voxel-based approach [19] however very approximative in terms of both anatomical matching and therefore dose mapping. In this particular work we are addressing the question of producing a 3D cartography (a set of parameters $\Phi(x)$, $x \in 3D$), which may explain the local dose-toxicity relationships from a voxel-based population analysis. The framework as depicted in fig 1 lies on non-rigid registration.

The particularity here is to take full advantage of the 3D dose distributions thereby explaining toxicity at a local level through voxel-wise comparisons. We use a non-rigid registration strategy which allows the inter-individual mapping of doses in a single coordinate system. This approach advantageously exploits information available at the planning, namely the 3D anatomical data, 3D organ delineations and TPS planned doses. It stands on a non-rigid registration scheme which combines organs delineations with CT scans in order to achieve a better organ matching across all the individuals.

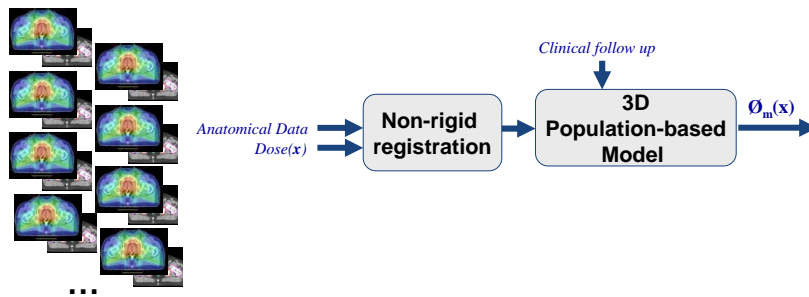


Fig. 1. 3D population-based approach. It includes inter-individual non-rigid registration for dose mapping before population comparisons.

2 Materials and Methods

The main steps of the method are depicted in figure 2. i) The inter-individual CT and contour delineations are non-rigidly registered towards a single template (common coordinate system), ii) the planned doses distributions are mapped towards the template by applying the computed transformations and iii) a voxel-wise comparison of the mapped doses is performed in the common coordinate system (in this work, two sampled t-tests). The output is a 3D map highlighting voxels where the differences are significant between two groups.

2.1 Data

116 individuals treated for prostate cancer with IMRT and a three-year follow-up were selected. The patients underwent a planning CT scan before the treatment. The size of the images in the axial plane was 512*512 pixels with 1 mm resolution 2-mm thick slices. For each patient, the bladder, rectum, prostate and seminal vesicles (SV) were manually contoured by the same expert. For each patient, the prescribed dose was computed in a standard Treatment Planning System (TPS) step and then resampled into the CT native space. The patients received a total dose of 80 Gy in the prostate. 2nd year-rectal toxicity was included in the analysis using the SOMALENT classification and bleeding scoring (at least 1 episode).

2.2 Registration

In order for the voxel-wise comparisons to be meaningful in terms of dose-effect relationships, anatomical correspondences across the population were previously computed through non-rigid registrations and dose mappings of all individuals towards a single template.

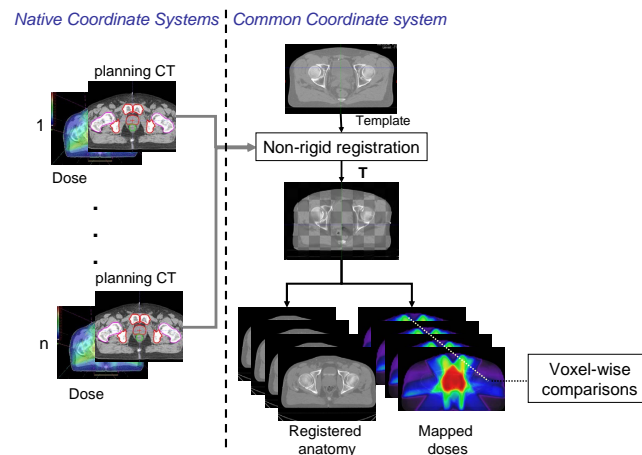


Fig. 2. Dose mapping using a non-rigid registration (NRR) approach.

Registering inter-individual CTs is particularly challenging because of the poor soft-tissue contrast, the large inter-individual variability and the filling differences of the bladder and the rectum [20]. In this context, it has been shown that a pure intensity-based registration is not accurate as required in population analysis and may lead to local errors [21]. If all the complementary knowledge about the individuals' anatomy is used, the performance of the registration would considerably improve. To this end, we developed an organ-driven non-rigid registration strategy which yields an accurate matching between organs in the common coordinate system (CS). In this study, the template was selected as a representative individual.

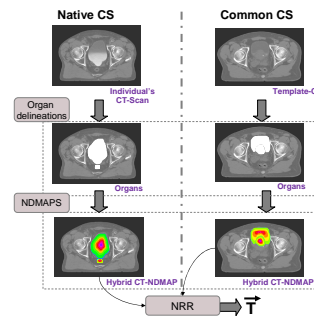


Fig. 3. Hybrid Non-rigid registration (NRR) approach bringing 3D doses from their native Co-ordinate System (CS) towards the Common CS. After organ delineation, Normalized Distance Maps (NDMAPS) are computed and combined with the CT scan to be registered. The result is the transformation used to fartherly map the dose.

The methodology exploits both the CT scans and the organ delineations as depicted in fig. 3. Thus, normalized Distance Maps (NDMAPS) for each of manually-segmented organs (prostate, bladder and rectum) were obtained as follows: For each individual's organ, i) an euclidean distance map was computed, ii) the distance maps of both the individual and the template were multiplied by the maximum distance of the template's and the individual's maps, respectively. Those maps replaced the corresponding individual's organs within the CT scan yielding a new hybrid image where the organs appear clearly defined. Finally, the diffeomorphic demons algorithm [22] was applied to register those images towards the template.

2.3 Voxel-based Analysis

According to predefined inclusion criteria, comparisons between non-toxic individuals and individuals with different toxicity scores were performed. For each comparison, two-sampled t-tests at a voxel-basis, produced 3D maps for both the dose differences and the p-values. Voxels where the differences were significant between the groups (p-values < 0.01) were characterized in terms of: absolute volume, mean dose difference and their localization in the rectum, namely the distance of the region to the prostate and the seminal vesicles surfaces as shown in Fig 3.

3 Validation and Results

3.1 Registration

To assess the quality of the registration, the Dice Similarity Coefficient defined as $DSC = 2 \left(\frac{S_C \cap S_R}{|S_C| + |S_R|} \right)$ was computed between each individual's registered rectum and the corresponding organ in the common coordinate system. 30 individuals were randomly selected from the data base and leave-one-out cross validation was performed thereby obtaining averaged DSC. Results were compared with different intensity registration strategies [23,24,22] as illustrated in Fig. 4 illustrates the results.

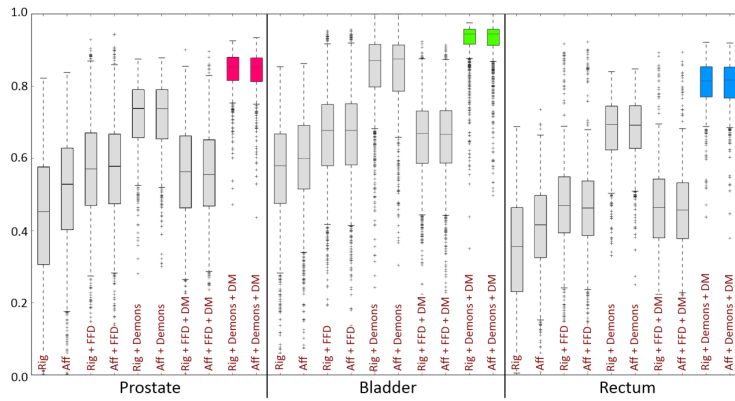


Fig. 4. Dice score comparisons between different intensity-based registration strategies and the hybrid approach used in this paper. The different strategies result from a combination of Rigid, Affine [23], Free Form Deformation (FFD) [24] and Demons [22] non-rigid registration.

Considering the whole population (116 patients), the median dice score was 0.75 ± 0.12 for the rectum and 0.92 ± 0.13 for the bladder. Fig. 5 depicts an example of the dose mapping from the native coordinate system to the common coordinate system (template) through the different steps of this method. (fig. 5(a)), individual's CT, (fig. 5(b)) manual segmentations on the template (fig. 5(c)) individual's planned dose distribution and (fig. 5(d)) mapped dose distributions in the template CS.

3.2 Voxel-based comparisons

The statistical analysis was conducted only on the properly registered patients (Dice score ≥ 0.7), leading to the inclusion of 74 patients for the rectal toxicity analysis. Median follow-up was 31 months (6 to 64). Grade 1 and 2 rectal acute toxicity rates were 26% and 4% respectively. Two year rectal toxicity (> grade 2) and bleeding rates were: 9% (95% CI: 3-14) and 20% (95% CI: 12-27). As shown in table 1 significant differences of dose were found in large regions. More than 90% of them were within the first 1cm (anterior wall). These results suggest that rectal bleeding is more related with higher dose in regions close to the prostate. The more sensitive area seems to be between 10 and 15mm. fig. 6

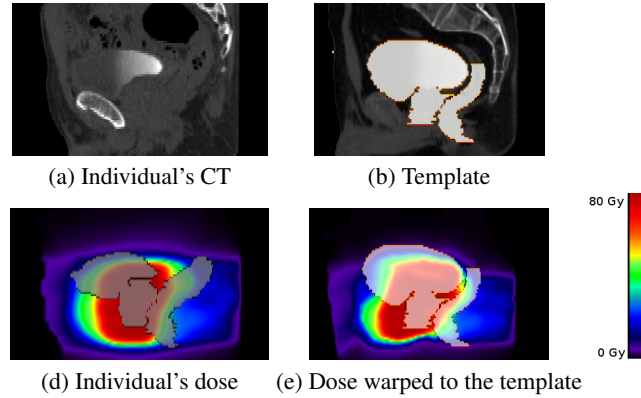


Fig. 5. 3D Dose mapping through an organ-driven non-rigid registration methodology. (a) A typical individual's CT; (b) Manually Segmented organs on the template; (c) Individual's TPS planned dose in the native CS; (d) Dose mapped to the template CS.

Significant ($p < 0.01$) voxel characteristics	Rectal Bleeding (2 years)	Grade 2 rectal toxicity (2years)	
Absolute Volume(mm ³)	1555.07 (4.45%)	2913.02 (8.33%)	
Dose Difference	8.06	10.16	
Distribution (%) of the voxels by the distance of the voxel from the prostate and the seminal vesicles	5mm	16.02 6.35Gy	48.87 10.33Gy
	10mm	96.65 7.98Gy	94.27 10.21Gy
	15mm	99.65 8.05Gy	94.64 10.22Gy
	20mm	100 8.06Gy	94.64 10.22Gy
	30mm	100 8.06Gy	94.64 10.22Gy

Table 1. voxel-wise comparison: characterization in terms of absolute volume, mean dose difference and localization in the rectum, defined as the distance to the prostate and the seminal vesicles surfaces.

4 Discussion and conclusion

We proposed in this paper a methodological framework based on non-rigid registration aimed at determining the local dose-effect relationship in PCRT, thereby helping to unravel the heterogeneous intra-organ radio-sensitivity to predict toxicity. Further work considers the inclusion of individuals clinical variables that may also be involved in toxicity (age, concomitant treatments, etc). Another issue to take into account is the differences between the planned and delivered doses, as during the treatment the organs at risk may deform or displace with respect to the initial conditions at the planning step.

To a large extent, determining the heterogeneous intra-organ sensitivity across a population, combined with patient-specific information in an inverse IMRT planning will allow to produce a personalized treatment with high local control and reduced toxicity. This general framework may be extended in order to adapt the ongoing treatment and thereby take into account not only data from a model but also integrate the dynamic individual's specificities (i.e. tumour response, anatomical modifications) as depicted

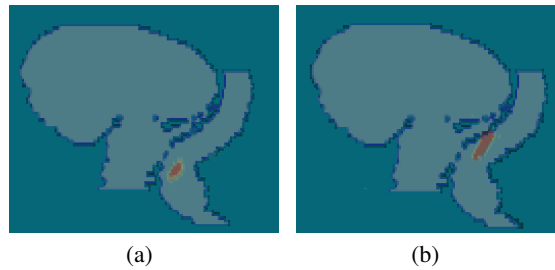


Fig. 6. Results of voxel-wise analysis in the template: regions where the difference in dose are significant (p -values < 0.01) for rectal bleeding at 2 years (a) and rectal toxicity at 2 years (b).

in fig. 7. In this framework for adaptive radiotherapy, the set of parameters Φ extracted from population data may be then combined with the individual's parameters $\phi_p(t)$, which may change during the treatment (t) in order to adapt the therapy.

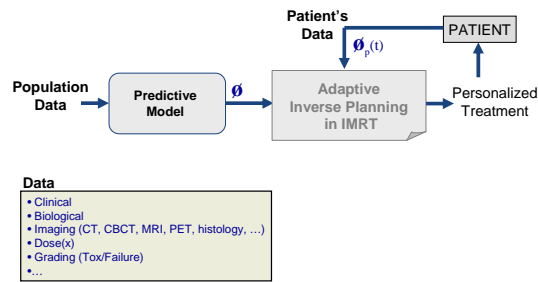


Fig. 7. General Adaptive Inverse Planning considering population data and dynamic individual's specificities ($\phi_p(t)$ =anatomical modifications, tumor response).

References

1. Beckendorf, *et al.*: multicenter study on dose escalation with conformal and conventional radiotherapy for the treatment of localized prostatic cancer. preliminary results of tolerance and quality of life. *Prog Urol* **11**(2) (Apr 2001) 264–276
2. Zietman, *et al.*: Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. *J Clin Oncol* **28**(7) (Mar 2010) 1106–1111
3. Fiorino, C., Rancati, T., Valdagni, R.: Predictive models of toxicity in external radiotherapy: dosimetric issues. *Cancer* **115**(13 Suppl) (Jul 2009) 3135–3140
4. de Crevoisier, R., Fiorino, C., Dubray, B.: Dosimetric factors predictive of late toxicity in prostate cancer radiotherapy. *Cancer Radiother* **14**(6-7) (Oct 2010) 460–468
5. Ting, J.Y., *et al.*: Dose-volume histograms for bladder and rectum. *Int J Radiat Oncol Biol Phys* **38**(5) (Jul 1997) 1105–1111
6. Jensen, I., *et al.*: Radiobiological impact of reduced margins and treatment technique for prostate cancer in terms of tumor control probability (TCP) and normal tissue complication probability (NTCP). *Med Dosim* (May 2010)

7. Cambria, R., *et al.*: Evaluation of late rectal toxicity after conformal radiotherapy for prostate cancer: a comparison between dose-volume constraints and NTCP use. *Strahlenther Onkol* **185**(6) (Jun 2009) 384–389
8. Grigorov, G.N., *et al.*: IMRT: improvement in treatment planning efficiency using NTCP calculation independent of the dose-volume-histogram. *Med Phys* **33**(5) (May 2006) 1250–1258
9. Sohn, M., Alber, M., Yan, D.: Principal component analysis-based pattern analysis of dose-volume histograms and influence on rectal toxicity. *Int J Radiat Oncol Biol Phys* **69**(1) (Sep 2007) 230–239
10. Fiorino, C., *et al.*: Rectum contouring variability in patients treated for prostate cancer: impact on rectum dose-volume histograms and normal tissue complication probability. *Radiother Oncol* **63**(3) (Jun 2002) 249–255
11. Fiorino, C., *et al.*: Relationships between dvhs and late rectal bleeding after radiotherapy for prostate cancer: analysis of a large group of patients pooled from three institutions. *Radiother Oncol* **64**(1) (Jul 2002) 1–12
12. Marzi, S., *et al.*: Relationships between rectal wall dose-volume constraints and radiobiologic indices of toxicity for patients with prostate cancer. *Int J Radiat Oncol Biol Phys* **68**(1) (May 2007) 41–49
13. Benk, V.A., *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* **26**(3) (Jun 1993) 551–557
14. Rancati, T., *et al.*: Fitting late rectal bleeding data using different NTCP models: results from an italian multi-centric study (airopros0101). *Radiother Oncol* **73**(1) (Oct 2004) 21–32
15. Schwarz, M., Lebesque, *et al.*: Sensitivity of treatment plan optimisation for prostate cancer using the equivalent uniform dose (eud) with respect to the rectal wall volume parameter. *Radiother Oncol* **73**(2) (Nov 2004) 209–218
16. Kupchak, C., Battista, J., Dyk, J.V.: Experience-driven dose-volume histogram maps of NTCP risk as an aid for radiation treatment plan selection and optimization. *Med Phys* **35**(1) (Jan 2008) 333–343
17. Buettner, F., *et al.*: Assessing correlations between the spatial distribution of the dose to the rectal wall and late rectal toxicity after prostate radiotherapy: an analysis of data from the mrc rt01 trial (isrctn 47772397). *Physics in Medicine and Biology* **54**(21) (2009) 6535
18. Buettner, F., Gulliford, *et al.*: Modeling late rectal toxicities based on a parameterized representation of the 3d dose distribution. *Physics in Medicine and Biology* **56**(7) (2011) 2103
19. Heemsbergen, W.D., *et al.*: Urinary obstruction in prostate cancer patients from the dutch trial (68 gy vs. 78 gy): Relationships with local dose, acute effects, and baseline characteristics. *Int J Radiat Oncol Biol Phys* (Jan 2010)
20. Acosta, O., *et al.*: Evaluation of multi-atlas-based segmentation of ct scans in prostate cancer radiotherapy. In: *Biomedical Imaging: From Nano to Macro, 2011 IEEE International Symposium on.* (30 2011-april 2 2011) 1966–1969
21. Dréan, G., Acosta, *et al.*: Evaluation of inter-individual pelvic ct-scans registration. *IRBM* **32** (2011) 288–92 –
22. Vercauteren, T., Pennec, *et al.*: Non-parametric diffeomorphic image registration with the demons algorithm. *Med Image Comput Comput Assist Interv* **10**(Pt 2) (2007) 319–326
23. Ourselin, S., Roche, *et al.*: Reconstructing a 3d structure from serial histological sections. *Image and Vision Computing* **19**(1-2) (2001) 25 – 31
24. Rueckert, D., Sonoda, *et al.*: Nonrigid registration using free-form deformations: Application to breast MR images. *IEEE Transactions on Medical Imaging* **18** (1999) 712–721