PhD RESEARCH REPORT

From global to local spatial models for improving prediction of urinary toxicity following prostate cancer radiotherapy

Abstract

External beam radiotherapy (EBRT) is a clinical standard for treating prostate cancer that aims to deliver a high radiation dose to the tumour to maximise the local control probability while sparing the neighbouring organs (mainly the rectum and the bladder). Radiation-induced damage to healthy tissues may lead to significant adverse events of urinary, rectal or sexual natures.

Urinary toxicity prediction is particularly challenging. Several studies have used the whole bladder's dose-volume histogram (DVH) in an attempt to explain radiation-induced toxicities but without any clear consensus. Predictive models of toxicity based on DVH reduce the 3D dose distribution within the whole organ to a unidimensional representation of the dose-volume relationship. The spatial information is, therefore, lost, ignoring the local variability of the 3D dose distribution. Analysis of the local dose distribution to the bladder and the urethra at fine spatial scales may improve our understanding of urinary toxicity and even be translated into recommendations for treatment planning in clinical practice. Going beyond the global, whole-organ-based models towards more local, sub-organ approaches, this thesis aimed to improve our understanding of radiation-induced urinary side effects and ameliorate the prediction of urinary toxicity following prostate cancer radiotherapy.

First, we sought to assess the contribution of urethra damage to urinary toxicity. In this regard, we devised a multi-atlas segmentation approach to accurately identify and segment the otherwise undetectable urethra on computed tomography (CT) images. The atlas consisted of a set of CT images of patients treated by brachytherapy, where the urethra was visible. For a new patient, geometric features were extracted from the image to be segmented and compared with the features from the atlas database. The urethra for this new patient was then defined by combining the urethras of the most similar atlases in a weighed-fusion process.

Different approaches were used to evaluate the dose-toxicity relationship with the objective of identifying subregions predictive of urinary toxicity. First, a dose-surface map (DSM) analysis of the dose to the surface of the bladder was performed to explore the local dose-response relationship for different urinary symptoms. Although three regions on the bladder surface were found to be predictive of urinary side-effects, a comparison with previous DSM analyses suggested that subregion identification might be strongly influenced by specific cohort characteristics, as only one of the subregions was confirmed.

Given that pixel-based approaches are inherently limited to the organ surface, another more sophisticated method was implemented in order to explore the entire 3D dose distribution in the bladder and the urethra without making any prior assumptions regarding the location of potentially sensitive subregions. This voxel-wise method, based on 3D dose-volume map (DVM) analysis, comprised different pre-processing steps, including: i) an accurate spatial normalisation to a single coordinate system; ii) the mapping of the doses to be analysed; and iii) a reliable methodology to perform local voxel-wise statistical analysis. In total, five subregions were found in the bladder and the urethra that were predictive of five urinary symptoms. Following an external validation on a large independent population, we confirmed that three out of five subregions remained predictive, highlighting the role of urethra and posterior bladder region in urinary toxicity.

Finally, a comparative study between different machine learning techniques was performed to provide insights on the advantages and disadvantages of different classifiers in urinary toxicity prediction. Our observations suggest that discriminant analysis algorithms, such as regularised discriminant analysis (RDA) and partial least square discriminant analysis (PLS-DA), may be suitable for analysing highly correlated, structured data, such as DVH bins. Additionally, in the case of class imbalance, synthetic oversampling (such as SMOTE) can effectively improve prediction capabilities of machine-learning algorithms.

Interview with author

What was the motivation for the topic of your PhD work?

Recent technological advances in prostate cancer radiotherapy have dramatically improved local control, at the expense, however, of increased radiation-induced toxicity. In an attempt to explain the relationship between dose and urinary toxicity, previous studies analysed the dose to the whole bladder, but without clear consensus. In my PhD, we tackled this problem from the sub-organ perspective, through pixel- and voxel-based approaches. Analysis of the local dose distribution to the bladder and the urethra at fine spatial scales may improve our understanding of urinary toxicity, ameliorate the prediction of urinary toxicity following prostate cancer radiotherapy and even be translated into recommendations for treatment planning in clinical practice.

What were the main findings of your PhD?

Our findings highlight the role of the dose to the urethra and the posterior bladder region in specific urinary toxicities, with this outcome potentially supplanting previous hypotheses of homogeneous bladder radiosensitivity. Specifically, through voxel-based analysis we were able to identify five urethro-vesical subregions that were predictive of specific urinary symptoms. Three of these subregions, located in the urethra and the posterior bladder region, were successfully validated in a large independent population as more predictive than the whole bladder for urinary incontinence, retention and dysuria (Figure 1).

We also demonstrated that voxel-based methods are suitable not only for single-organ analyses but also can be extended to multiple organs, as long as a robust multi-organ registration strategy is devised to cope with the high inter-individual anatomical variations (Figure 2). Comparing voxel-based (VB) methods with previous pixel-based approaches, we found that subregions identified through VB approaches might be superior both in terms of reproducibility, prediction capabilities and clinical transferability.

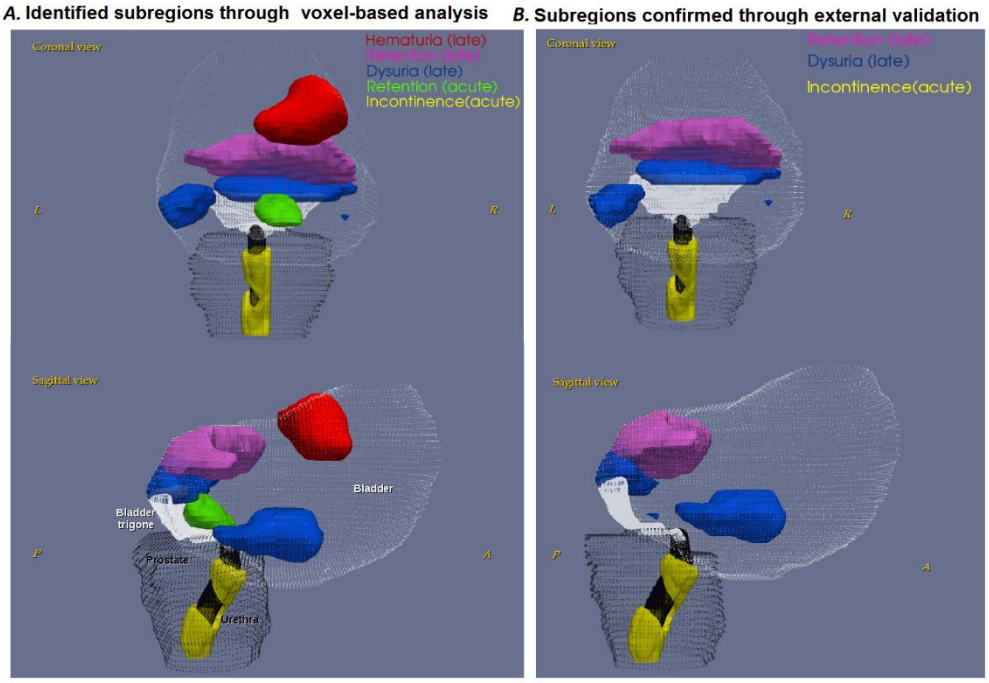

Figure 1 A) The five subregions that were identified after voxel-based analysis in the bladder and the urethra as predictive of urinary toxicities: late haematuria, retention and dysuria; acute retention; and acute incontinence. B) Three subregions were confirmed through external validation on a large independent population: late retention, late dysuria and acute incontinence.

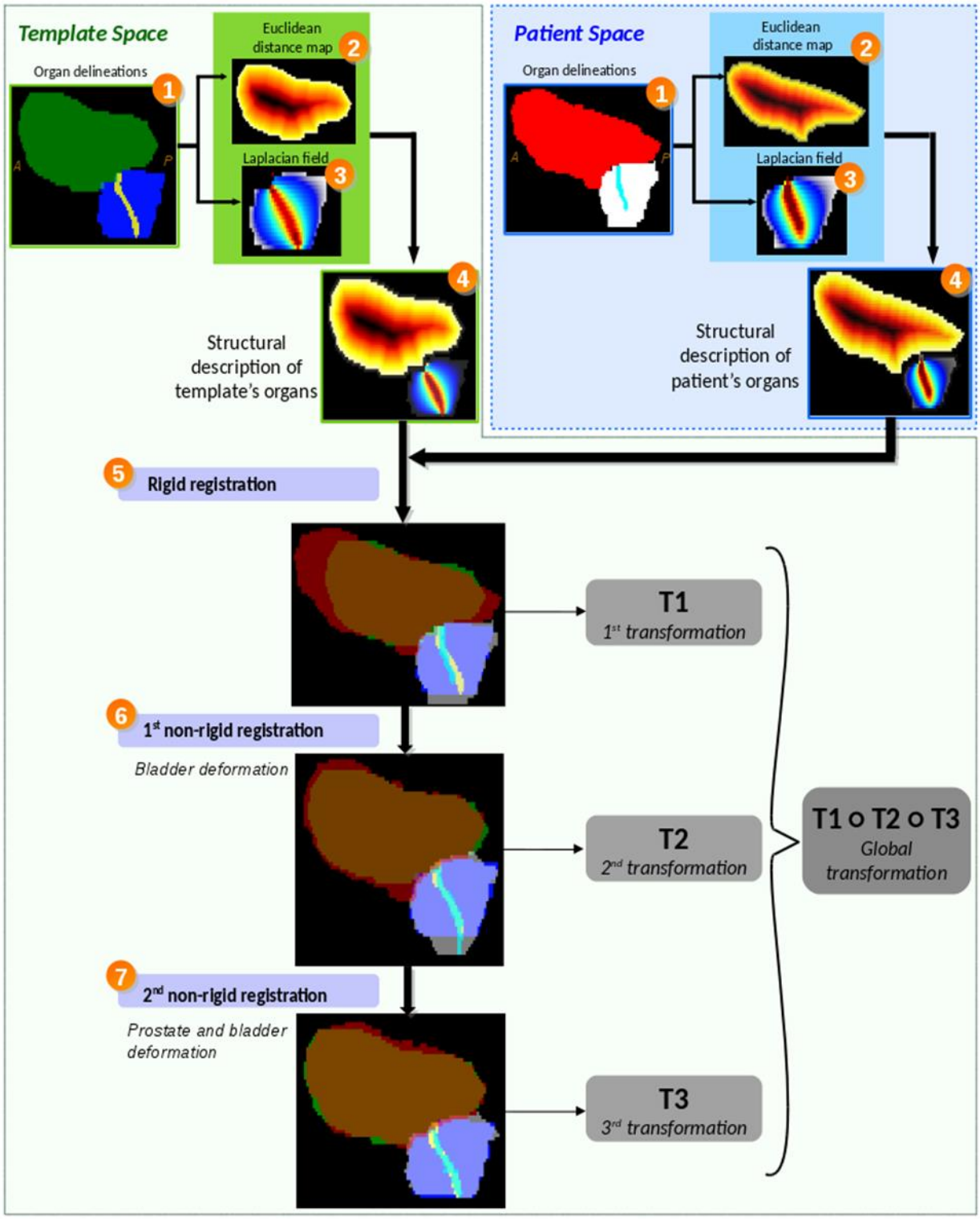

Figure 2 Workflow for inter-individual registration to a common template via structural description of the bladder, prostate and urethra. This step is required to perform voxel-wise analysis of 3D dose distributions.

Can you comment on the impact of your work to the field?

From a methodological point of view, the work undertaken in this thesis paves the way for future studies to investigate the local dose-volume effect relationship on different populations and with respect to different treatment techniques. Through better understanding of urinary symptom manifestation, we might be able to improve urinary toxicity prediction following prostate cancer radiotherapy. Apart from prostate cancer radiotherapy, the proposed voxel-based pipeline can be extended to other anatomical sites in order to assess the implications of multiple structures on radiation-induced side effects.

From a clinical point of view, the outcomes of this work may be translated into recommendations for treatment planning in clinical practice. A potential benefit is the possibility of performing personalised treatment planning by identifying the radiosensitive subregions in the specific anatomy of the patient and adding specific dosimetric constraints. The sparing of subregions during the treatment may prevent specific side effects but this has yet to be demonstrated in future clinical trials.

What was the most challenging part during your PhD?

The primary technique implemented in my thesis for identification of predictive subregions was the voxel-based method which relies on voxel-based analyses of 3D dose-volume maps (DVMs). This technique offers the advantage of considering the entire dose distribution without making a priori assumptions regarding the location of potentially sensitive regions. However, it requires reliable multi-organ deformable image registration to enable meaningful voxel-wise analyses. In our case, it was particularly challenging to register multiple organs, and particularly the bladder, which exhibits tremendous variability across the population. To cope with this, a structural description of the organs was obtained by combining different scalar maps into the 3D image to be registered using a customised algorithm (Figure 2).

Who or what inspired you most during your studies?

I was certainly inspired by the interdisciplinary environment of my department, which comprised physicians, engineers, biologists, mathematicians and medical physicists. The high level of professionalism of the people I had the chance to work with, in-depth discussions and fruitful collaborations laid the foundations for my research focus. Outside my department, my sources of inspiration have been leaders in the field of radiotherapy predictive modelling, in particular Tiziana Rancati and Martin Ebert, with whom I had the honour to collaborate thanks to mobility grants such as the European SocieTy for Radiotherapy and Oncology (ESTRO) mobility grant (Technology Transfer Grant).

Will you stay in the field? What are your plans for the future?

Yes, as a medical physicist I am passionate about applying cutting-edge technology in the service of cancer research. I am currently working at the Signal and Image Processing Laboratory (LTSI) of Research Unit INSERM 1099 at the University of Rennes 1, France, as a post-doctoral researcher. I aim to combine machine learning methods with the 3D voxel-wise models developed during my PhD and transfer them to clinical routine practice through participation in an industrial transfer project.

Which institution were you affiliated to during your PhD?

The same institution at which I now work: LTSI-INSERM 1099, University of Rennes, France.

When did you defend your thesis and who was your supervisor?

I defended my thesis on 2 December 2019.

Professors Renaud de Crevoisier and Oscar Acosta were my PhD supervisors. I especially valued their expert advice on theoretical and practical aspects of my thesis and the unlimited hours of scientific discussion that we had.

Eugenia Mylona
Signal and Image Processing Laboratory (LTSI)
Research Unit INSERM
University of Rennes
Rennes, France

About the author

Eugenia Mylona received her Bachelor of Science degree in physics in 2013 and a Master of Science degree in medical physics in 2015, at the University of Patras in Greece. In 2019 she received her PhD in electronics and telecommunications from LTSI and the University of Rennes 1 in France.

Her research interests are focused on the design of predictive models for radiotherapy outcomes based on the integration of a large number of multimodal data and the use of original image and data processing methods. During her PhD her research activity was focused on the development and application of statistical analyses and machine learning methods for large datasets to build and optimise predictive models for radiation-induced side effects. She is currently employed as a post-doctoral fellow

on the validation and transfer of predictive models to clinical routine practice through participation in an industrial transfer project (EXPECT).

The results of her work have been published in high-impact journals in the field of radiation oncology and presented through oral communications in leading conferences. She has been awarded international mobility grants through which she has established international collaborations with leaders in the domain of radiotherapy predictive modelling.
www.linkedin.com/in/eugenia-mylona-26b25819b

https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=%22Mylona+Eugenia%22&btnG=