Visual Analytics for Digital Radiotherapy: Towards a Comprehensible Pipeline

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Abstract

Prostate cancer is one of the most frequently occurring types of cancer in males. It is often treated with radiation therapy, which aims at irradiating tumors with a high dose, while sparing the surrounding healthy tissues. In the course of the years, radiotherapy technology has undergone great advancements. However, tumors are not only different from each other, they are also highly heterogeneous within, consisting of regions with distinct tissue characteristics, which should be treated with different radiation doses. Tailoring radiotherapy planning to the specific needs and intra-tumor tissue characteristics of each patient is expected to lead to more effective treatment strategies. Currently, clinical research is moving towards this direction, but an understanding of the specific tumor characteristics of each patient, and the integration of all available knowledge into a personalizable radiotherapy planning pipeline are still required. The present work describes solutions from the field of Visual Analytics, which aim at incorporating the information from the distinct steps of the personalizable radiotherapy planning pipeline, along with eventual sources of uncertainty, into comprehensible visualizations. All proposed solutions are meant to increase the – up to now, limited – understanding and exploratory capabilities of clinical researchers. These approaches contribute towards the interactive exploration, visual analysis and understanding of the involved data and processes at different steps of the radiotherapy planning pipeline, creating a fertile ground for future research in radiotherapy planning.

Categories and Subject Descriptors (according to ACM CCS): I.3.8 [Computer Graphics]: Applications—Applications; J.3 [Computer Applications]: Life and Medical Sciences—Life and Medical Sciences

1. Introduction

Cancer involves a group of diseases, which are characterized by the uncontrollable and abnormal division of cells. Prostate cancer affects the prostate gland and is one of the most common malignancies in males [Was15]. However, this type of cancer can be successfully treated, usually through radical prostatectomy, chemotherapy or radiotherapy. Among these, the latter is the most common, with 60% of all prostate cancer patients being referred to radiotherapy at some stage of their treatment [DJFB05].

In the past decade, radiotherapy technology has undergone a big revolution, offering exceptional flexibility in dose delivery. It has managed to improve treatment by irradiating tumors with a high dose, while minimizing the side effects of radiation on the adjacent healthy organ tissues [Was15]. Despite the significant achievements of radiotherapy, there is still room for further improvement.

Tumors are heterogeneous tissues, consisting of distinct regions with different characteristics. Understanding better the specific anatomical and intra-tumor characteristics of each patient and incorporating these into treatment planning, by selecting the most adequate radiation strategy for each tumor region, can lead to the design of more effective treatments [TOG06]. Currently, clinical research is moving towards this direction, but the incorporation of the specific tumor characteristics of each patient, and the integration of all available knowledge into a new, more accurate radiotherapy planning pipeline are still required.

The patient- and tumor-specific radiotherapy planning pipeline involves complex multi-modal and multi-valued data. Understanding and analyzing this data can be a demanding and time-consuming task. In particular, the exact relation between the information from different imaging modalities and the specific intra-tumor tissue characteristics is still unknown. Additionally, all implicated data include sources of uncertainty, which can affect the accuracy and/or precision of the final planning outcome. Some of these uncertainties can be minimized. The rest, which cannot be avoided, need to be studied and their effect on radiation therapy planning needs to be predicted. As a consequence, there is an emerging need for solutions and tools, which can help clinical researchers explore, understand and analyze all the available patient- and tumor-specific information.

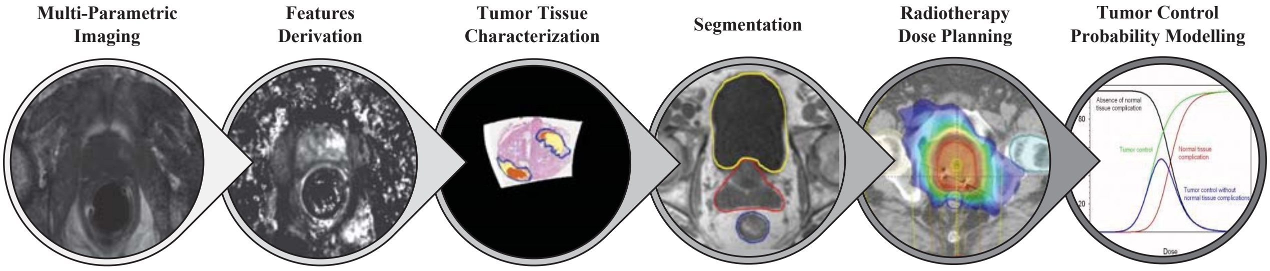

Figure 1: *Schematic depiction of the steps of the patient-specific radiotherapy planning pipeline, employed in clinical research to create personalized, tumor-tailored radiotherapy plans.*

The *contribution* of the present work is the investigation and design of Visual Analytics strategies for the interactive exploration and analysis of the complex radiotherapy planning data and processes, enabling the integration of the knowledge and cognitive skills of the intended clinical users. Up to now, this was not possible with the current means of exploration. Our proposed solutions and tools have been extensively evaluated in different clinical research settings and are being used in several institutions.

2. Clinical Background: The Pipeline of Digital Radiotherapy

Current clinical research is moving towards the direction of understanding the specific tumor characteristics of each patient and integrating all available knowledge into a more accurate radiotherapy planning pipeline. Developing a pipeline tailored to the specific anatomical and intra-tumor characteristics of each patient was the main goal of the *FP7 European Project DR THERAPAT – Digital Radiation Therapy Patient*, part of which is this work. The pipeline is depicted in Figure 1.

Initially, *imaging data* of the prostate of the patient from several modalities are acquired. From this, *additional features* indicative of tissue characteristics may be computed, using different methods. Subsequently, *tumor tissue characterization* takes place to enable the identification of distinct intra-tumor regions. At this point, the specific characteristics of each region, such as aggressiveness or resistance to treatment, are derived. The structures surrounding the prostate, which need to be spared during treatment, must be identified as well. This is performed during the *segmentation step*. Based on all this information, radiation doses can be selected adequately, to more effectively treat the different tumor parts, without harming the adjacent healthy organs, during the *planning phase*. After the radiotherapy plan is designed, the eventual *response of the tumor* to the employed radiotherapy treatment strategy is modeled. From that, clinical researchers can predict the outcome of the treatment.

This tumor-specific radiotherapy planning pipeline involves data, which are constantly growing in complexity. Moreover, this data might include noise, inaccuracies, errors and uncertainties, which also need to be considered, studied, or predicted. Therefore, identifying – for example – which imaging modalities are more adequate for intra-tumor tissue characteristization, or identifying the best planning strategy, or studying its effect on the outcome of the patient can be a tedious task, even for experienced clinical researchers. Our designed and implemented visual tools and solutions, to help clinical researchers explore, understand and analyze the complex data of the tumor-tailored radiotherapy planning pipeline, are described in the following section.

3. Visual Analytics for Digital Radiotherapy

Visual Analytics is particularly suitable for facilitating interactive data exploration and analysis, and for providing a deeper cognitive insight [KAF*08]. In the present context, Visual Analytics has the potential to provide a direct means of feedback on imaging data, tumor tissue characterization, segmentation and modeling of the tumor response to treatment for clinical researchers.

To the best of our knowledge, involving clinical experts through visual analysis and interaction in the workflow of the entire radiotherapy pipeline has not been addressed before. In addition to that, despite the broadness of applications that the field of Visual Analytics has tackled, the exploration and analysis of the data involved in the radiotherapy planning pipeline has also not been addressed. Although there are numerous ways of visualizing multi-dimensional and complex data [Kei02], the most relevant previous approaches [JZF*09, CLKP10, BBP07, SMB*10, HPvU*16] are not fully compatible with our specific field of application, nor with the involved data and requirements of clinical researchers. To this end, we propose new visualization strategies in the form of novel application prototypes, which advance the state-of-art in visualization. Our proposed solutions are structured following the radiotherapy pipeline, as shown in Figure 2. In the remainder of this section, we will present our solutions for the different steps of the pipeline.

First of all, after the images of the patient have been acquired, pharmacokinetic modeling is employed to derive a number of imaging features, which are indicative of tumor tissue characteristics. These are derived from Dynamic Contrast Enhanced (DCE) Magnetic Resonance Imaging (MRI), and many different pharmacokinetic modeling approaches can be followed. Each one of them produces imaging features with different distributions – even different features. Currently, knowing how different choices in modeling affect the resulting pharmacokinetic parameters and also where parameter variations appear is a tedious and time-consuming task for clinical researchers, as they do not have the means to perform their data analysis. To solve this, we propose a visualization application [RvdHvH*14] for the interactive exploration and analysis of

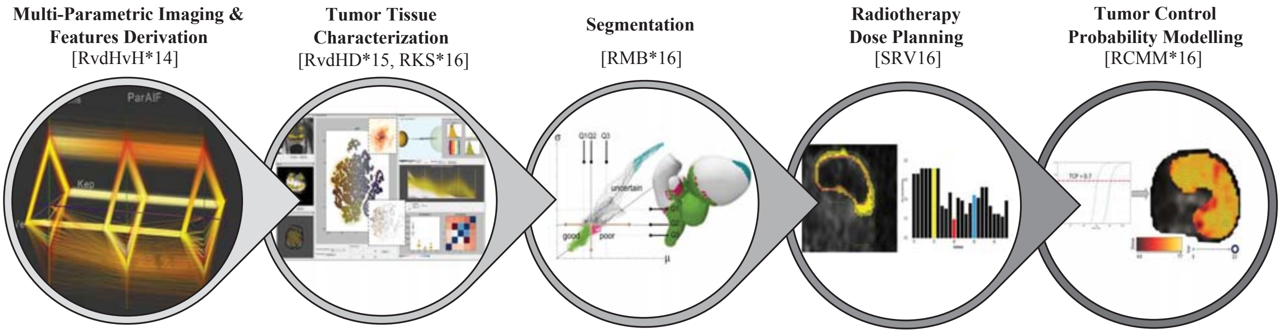

Figure 2: *Overview of the contributions of the visual tools and solutions, which are proposed in the current work. Each component addresses one or more steps of the tumor-tailored radiotherapy pipeline, as depicted in Figure 1.*

model-induced variations in pharmacokinetic parameters. For this reason, we combined in a single combined view Parallel Coordinate Plots with Star Plots to provide an overview on all aspects of the data and the potential variability in the imaging-derived features. In our application, particular attention is given to the interactive association of observations from the feature space to patient anatomy, with respect to the variability of the features.

After feature derivation, tumor tissue characterization needs to be performed. As mentioned before, characterization of distinct intra-tumor regions can improve patient diagnosis and enable a better targeted treatment. Several different features can be derived from imaging modalities, but their exact relation to tissue characteristics is not known, especially when it comes to linking imaging features to observations from histopathological data. Currently, the exploratory approach used in clinical research consists of juxtaposing these data, visually comparing them and mentally reconstructing their relationships. This approach – but even a fully automated approach – are not suitable for the exploration of the complex imaging-derived feature space. In our user-guided exploratory tool [RvdHD*15, RKS*16], we employ as central view, a 2D t-SNE [VdMH08] embedding of the imaging-derived features to reveal potential intra-tumor regions with consistent high-dimensional characteristics. Additional multiple linked interactive views provide functionality for the user-driven exploration and analysis of the local structure of the feature space, enabling linking to patient anatomy and clinical reference data, taking into consideration the knowledge of our intended users.

An additional crucial step in the radiotherapy pipeline requires the definition of the organs at risk, which are located around the tumor. However, the automatic model-based methods that are often employed may produce inaccurate segmentations. These, if used as input for diagnosis or treatment, can have detrimental effects for the patients. In our proposed approach [RMB*16], the focus is on the visual analysis of errors in the segmentation of the involved pelvic structures surrounding the prostate and on how Visual Analytics can supply insight into the prediction of the performance of the employed segmentation algorithms. These two key-points of the segmentation step of the radiotherapy pipeline have not been addressed before. Our approach supports the exploration of errors of pelvic organ segmentations in a cohort of patients, where the performance of an algorithm can be assessed. Also, it enables the detailed exploration and assessment of segmentation errors, in individual subjects. All this is achieved in a web-based Visual Analytics tool, with multiple linked views.

Another important aspect of the radiotherapy pipeline is the impact of choices or parametrizations occurring at several previous stages on the computed radiotherapy dose plan. At each step of the pipeline performed before planning, different assumptions and/or parameterizations can be made, which may result in several alternative dose plans. As it is not known a priori which of these assumptions or parameter settings lead to better results, it is valuable for clinical researchers to be aware of the produced variability and to evaluate whether different choices in the planning pipeline have an impact on the final treatment planning. Currently, variability assessment is not incorporated in the analysis, due to time and resource constraints. To facilitate this, we propose a new visualization design to address the exploration and analysis of variability in an ensemble of radiotherapy dose plans [SRV16] at two different levels: first, based on the radiotherapy dose iso-contours across different dose plans, and, secondly, directly at a voxel level.

Once the radiotherapy dose planning has been determined, clinical researchers want to predict whether the chosen radiotherapy strategy will treat effectively the tumor. To this end, Tumor Control Probability (TCP) modeling is performed to evaluate and predict the outcome of a radiotherapy treatment. Recently, TCP models started becoming more accurate by incorporating additional information from imaging modalities. However, the employed imaging modalities are subject to uncertainties with significant impact on the modeling outcome. Also the models are sensitive to a number of parameter assumptions. These two aspects are not being incorporated in the analysis, due to time and resource constraints. To address this, we establish a new Visual Analytics system [RCMM*16] for the exploration and analysis of tumor control probability modeling. With our introduced approach, the – up to now disregarded – imaging-induced uncertainty and parameter sensitivity analysis can be incorporated in the workflow of clinical researchers, providing new possibilities for the evaluation of the selected radiotherapy strategies, even in a larger cohort of patients. We also provide a new way of exploration, by allowing clinical researchers to start their analysis from the desired outcome and to determine whether there are feasible radiotherapy strategies to achieve it.

All proposed solutions have been thoroughly evaluated with their respective intended clinical users, in order to determine whether they fulfill their intended use and whether they provide the required insight. In most of the cases, the evaluations have been conducted with clinical researchers from multiple institutions. More details about all proposed tools, the achieved results and the conducted evaluations can be found in the respective references.

4. Discussion and Conclusions

As radiotherapy technology focuses on providing a more accurate treatment based on the specific intra-tumor tissue characteristics of each patient, the integration of all available patient- and tumor-specific knowledge from the distinct steps of the radiotherapy pipeline, is required. Current limitations in the exploration and analysis of the involved information can be overcome, by employing solutions from the field of Visual Analytics.

In radiotherapy research, we accomplished to provide solutions and tools for clinical researchers, which address their exploratory needs at all steps of the tumor-tailored radiotherapy planning pipeline. Involving clinical experts through visual analysis and interaction in the workflow of the entire radiotherapy pipeline had never been tackled before, and our proposed Visual Analytics solutions address specific tasks that could not be conducted with previously existing tools. The development of new interactive and investigative tools has now provided new exploratory possibilities, which have been thouroughly evaluated, appreciated and used by our clinical collaborators.

In visualization research, we managed to expand the field of Visual Analytics to support a new clinical domain. Although there are numerous ways of visualizing multi-dimensional and complex data, none of them was fully applicable to the data and processes of radiotherapy planning. Our contribution to the field of Visual Analytics is a compound of applications tailored to the specific steps of the pipeline, to the involved data and to the requirements of clinical researchers. All proposed approaches promote the integration and combination of the strengths of human perception for exploration and analysis, together with semi-automated methods, with the purpose to increase the understanding in complex data and processes.

Nevertheless, a multitude of topics for future research have also been revealed. For example, it would be interesting to allow the extension of a number of applications to enable meaningful follow-up or inter-patient analysis. In essence, we expect that this research direction can help clinical researchers to explore, analyze and deliberate, with respect to the progression of a disease, or to treatment response, also regarding different groups of individuals. From this, diagnosis, prognosis and treatment may significantly benefit. Also from a visualization point of view, follow-up and inter-patient analysis would be a very challenging topic, due to the implicated dimensionality and complexity of the data. Smart strategies to address these two key-points need to be devised.

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