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Paper Summary
Group 5

Voxel-based analysis unveils regional dose differences associated with radiation-induced morbidity in head and neck cancer patients

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<u>Introduction:</u>

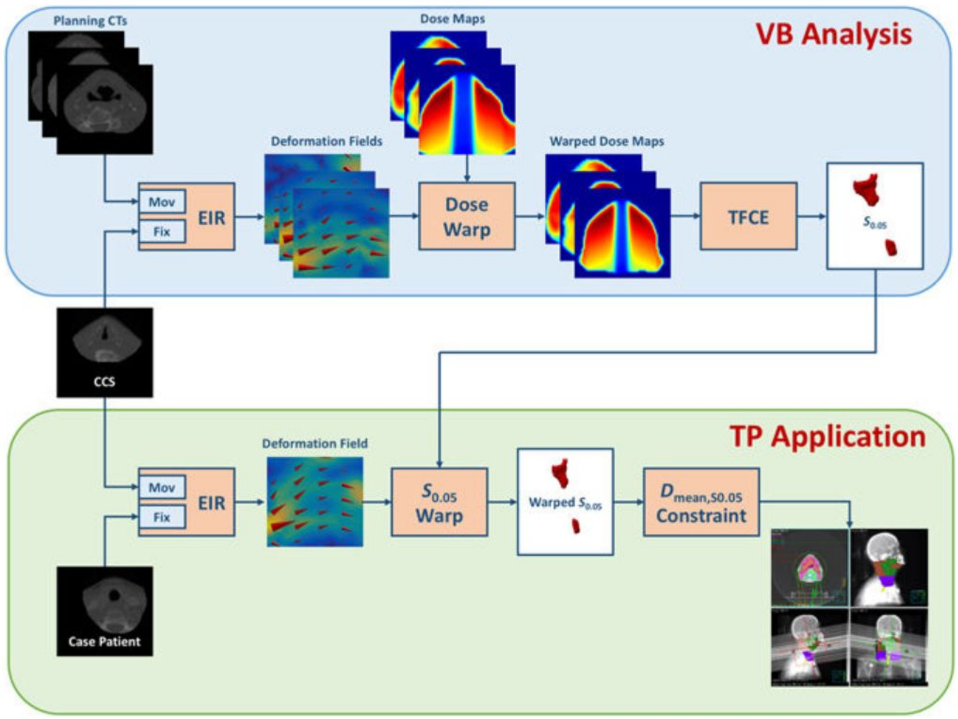
Our project is the development of a UI for dose toxicity analysis. The final UI will serve two primary functionalities: 3D segmentation and dose toxicity analysis. Currently, physicians and researchers without familiarity in command line lack a simple method of visualizing, segmenting, and analyzing 3D objects. Furthermore, dose toxicity analysis since the 1970s has predominantly been reliant upon dose value histogram (DVH) curves. Although DVH curves have utility, studies have shown that finer, more localized dose toxicity analysis provides more insights and can improve treatment planning [1] [2] [3] [4]. One of the motivations for our project is to allow physicians and researchers to segment 3D objects into smaller regions for dose toxicity analysis. This paper details the use of a more localized approach (voxel based) for dose toxicity analysis of head and neck structures. The authors demonstrate that using a voxel based method uncovers clinical insights that were not visible using traditional whole organ based methods, and they show that this approach can be applied to other head and neck structures.

<u>Summary:</u>

Whole organ based dose toxicity analysis has been the primary method of analyzing radiation therapy treatments for the past few decades. Applying traditional whole organ based analyses to head and neck structures is difficult and inconsistent because these structures are small and easily misidentified or overlooked in analysis. This motivated the authors to apply the voxel based method. The more localized, voxel-based approach has been shown to provide clinical insights in radiation therapy of the bladder, prostate, and gastrointestinal tract. Monti et al showed that a voxel-based approach could be applied to the intricate and complex structures of the head and neck. Furthermore, this paper demonstrated that a voxel-based approach to dose toxicity analysis can shed light upon the mechanisms underlying a specific complication following radiation therapy: radiation-induced acute dysphagia (RIAD).

<u>Technical Approach:</u>

This paper can be divided into 3 stages: 1) mapping patient HN structures and dose distributions to a common coordinate system (CCS), 2) performing voxel-based statistical analysis to assess regional dose differences between patients with and without RIAD, 3) demonstrating how to adjust a treatment plan to minimize applied dose to critical regions. The workflow is demonstrated in figure 1 of the paper, copied below.



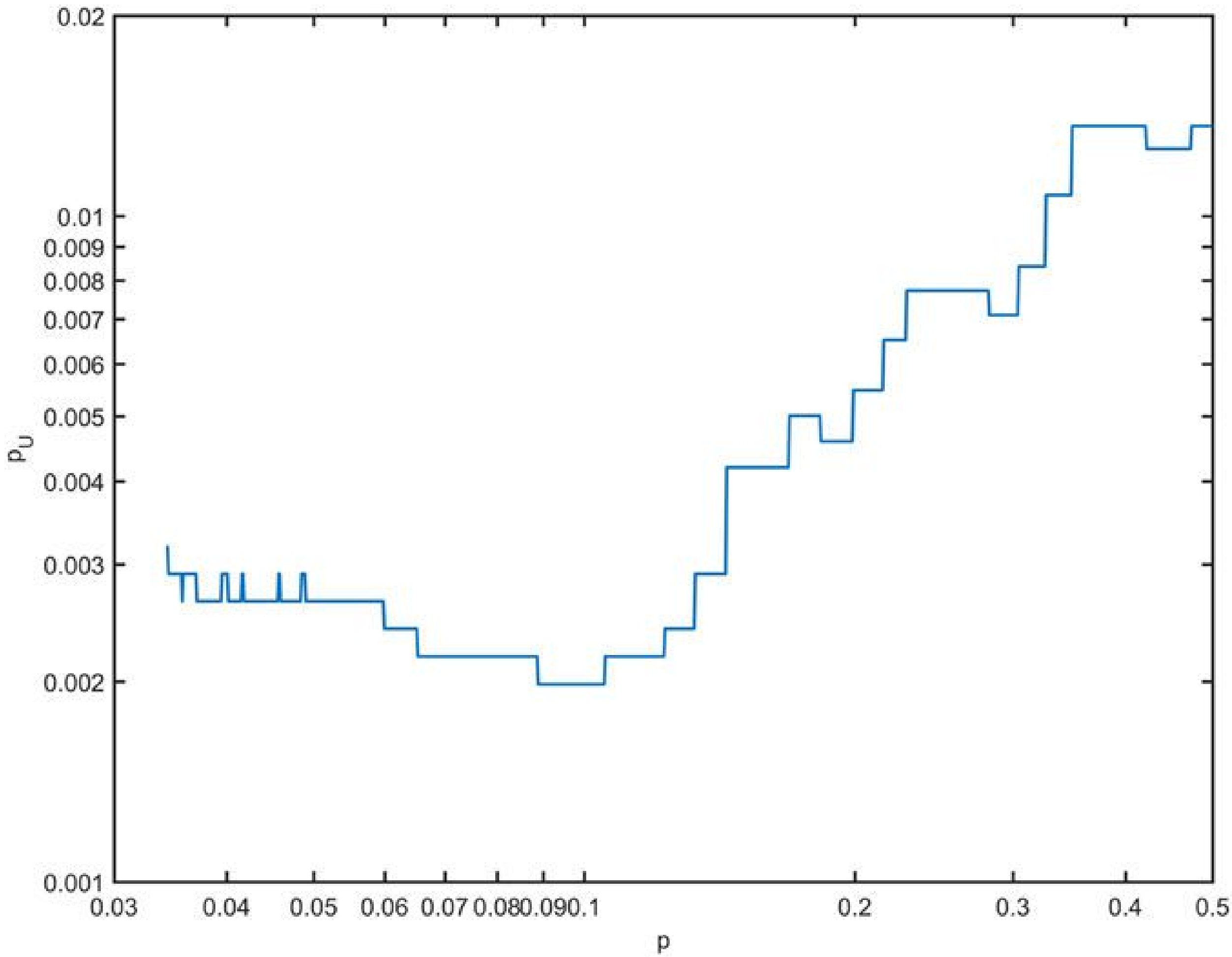
First, the authors performed an inter-patient elastic image registration (EIR) to map head and neck (HN) structures and warp dosages to a CCS using a log-diffeomorphic demons approach [5]. The EIR was verified visually and using Dice, modified Hausdorff distance, and dose-organ overlap scores.

Second, statistical analysis of dose differences was performed on the warped dose maps of patients with RIAD and compared to the dose maps of patients without RIAD. Two, statistical analysis methods were employed. The first method confirmed that there exists a significant dose difference between patient with and without RIAD. This method solves the multiple comparison problem, and outputs a single test statistic to signify a significant difference between categories of images [7]. The second method, the threshold-free cluster enhancement (TFCE), identified clusters of voxels with the highest dose difference between dose maps for patients with and without RIAD [8]. These clusters were combined into a single region, $S_{0.05}$.

Finally, the first quartile of the mean dose of the $S_{0.05}$ region for all patients with RIAD was computed. A new treatment plan was devised that identified $S_{0.05}$ as an avoidance region by adding the constraint that the mean dose applied to the $S_{0.05}$ region, $D_{mean,S0.05}$, not exceed the first quartile calculated above.

Results:

The $S_{0.05}$ region identified via TFCE was analyzed with a Mann-Whitney U test. Figure 5 from the paper is copied below. The p value threshold input for TFCE is on the x axis. The output p value of the Mann-Whitney U test on the $S_{0.05}$ region is on the y axis. This figure shows dosage applied to the $S_{0.05}$ region has statistically significant correlation with the presence of RIAD, as patients with higher dose to the $S_{0.05}$ region were more likely to have RIAD.



Using an altered treatment plan as described above, the authors showed that an equally effective treatment plan can be devised that also reduces radiation dose to the $S_{0.05}$ region without significantly increasing dosage to other regions.

Assessment:

This paper demonstrates the efficacy of using voxel-based analysis in radiation treatment plans. There are two primary contributions of this paper: 1) the authors overcame the difficulties associated with the small, variable, and complex HN structures to successfully applied the voxel-based dose toxicity analysis to a new set of cancers in the HN, 2) for a specific consequence of radiation therapy to the HN, RIAD, the authors were able to demonstrate that voxel-based analysis can shed insight into certain structures involved with RIAD that are especially sensitive to radiation therapy.

The positive aspects of this paper included the reliance on validation methods and validated algorithms for the application of the voxel-based method. In addition, the adjusted treatment plan showed a significant reduction in dose to the sensitive regions in just one iteration on analysis. This simplicity and efficacy lends credence to the ultimate integration of voxel-based analysis into clinical treatment planning. Finally, this paper was well written and easy to understand, even for a reader with minimal radiology knowledge.

Negative aspects of this paper include the limited scope of the application of the voxel-based method. The authors investigated a single side effect of radiation therapy to the HN structures, but they also assert that this study shows that voxel-based analysis is applicable to other side effects of radiation therapy to the HN structures. If the authors had applied the voxel-based method to a different side effect and demonstrated similar correlations, their assertion of generalizability would hold more credence. Also, the use of the 1st quartile as the upper constraint for treatment planning was never justified. It remains unknown if this constraint is unnecessarily too low, or to high for clinically significant changes in outcome.

This paper impacts our project by validating the need for dose toxicity analysis of smaller regions segmented from larger organs.One the the major features of the UI will be integration with segmentation tools for more refined dose-toxicity analysis. This paper demonstrated that regional dose differences between patients can lead to different side effects of radiation therapy. This validates the ultimate inclusion of segmentation tools in our UI. In addition, this voxel-based approach is worth investigating for potential incorporation into the UI. Our UI would not incorporate the entire pipeline demonstrated in the paper, but certain aspects such as regional dose comparisons to a reference dose distribution may become modules in the maximum deliverable.

<u>References</u>

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