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WITHDRAWN: VAPOR: Visual Analytics for the Exploration of Pelvic Organ Variability in Radiotherapy

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## VAPOR: Visual Analytics for the Exploration of Pelvic Organ Variability in Radiotherapy

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### ABSTRACT

In radiation therapy (RT) for prostate cancer, changes in patient anatomy during treatment might lead to inadequate tumor coverage and unplanned radiation of healthy tissues in the involved pelvic organs. Exploring and analyzing anatomical variability throughout the course of RT can help clinical researchers to design more robust treatment strategies while identifying patients that are more prone to radiation-induced toxicity. We present *VAPOR*, a novel application for the exploration of pelvic organ variability across the entire treatment process, in a cohort of patients. Our application addresses (i) the global exploration and analysis of anatomical variability in an abstracted tabular view, (ii) the local exploration and analysis thereof in anatomical 2D/3D views, where comparative and ensemble visualizations are integrated, and (iii) the correlation of anatomical variability with radiation doses and potential toxicity. The workflow is based on available retrospective cohort data, which include segmentations of the bladder, the prostate, and the rectum through the entire treatment period. *VAPOR* is applied to four usage scenarios, which were conducted with two medical physicists. Our application provides clinical researchers with promising support in demonstrating the significance of treatment adaptation to anatomical changes.

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### 1. Introduction

Prostate cancer is the most frequent malignancy in the male population [1]. Radiation therapy (RT) is a common therapeutic approach for prostate cancer patients, requiring detailed treatment planning to identify where the tumor is located and how to treat the disease effectively [2, 3]. In RT, high radiation doses are administered to treat the tumor. Although current dose administration techniques allow for precise treatment, the surrounding healthy tissues may still be affected by radiation [4, 5, 6]. This can lead to potentially severe side effects—commonly known as *toxicity*.

Recent clinical research suggests that the healthy tissues of the bladder or the rectum of certain patients might be receiving increased radiation doses, due to high anatomical variability [4, 5, 6]. The RT dose is not delivered all at once but is split into multiple sessions over a period of weeks [3]. During this time, anatomical variations of the organs occur naturally. As it is not practically feasible to recalculate the entire treatment plan before each session, only alignment corrections are made before dose administration [2]. During these corrections, the main goal is to prioritize the irradiation of the tumor location. Thus, discrepancies between planned and administered doses occur. In *adaptive RT*, adapting the workflow to encompass changes in organ shape is anticipated to enable higher precision with less damage to healthy tissues [7], but this is not widely incorporated into clinical practice.

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The overall robustness of specific treatment options is currently evaluated by means of retrospective cohort studies, while individual patient exploration accounts for particular cases. To achieve this, clinical researchers and medical physicists working on the design of robust treatment strategies require a better understanding of the anatomical, i.e., shape and positional, variability of all pelvic organs in a cohort of patients, and an indication of the correlations between anatomical variability and toxicity manifestation [8, 9, 10, 11]. In the past, visual analytics approaches for treatment strategy evaluation have been proposed for the bladder [4, 12, 13], without considering other pelvic organs. Other previous work [14] does not support the correlation of anatomical variability to RT doses and toxicity. By incorporating the relation between anatomical variability, dose variability and toxicity effects in the pelvic region, we aim to support clinical researchers in demonstrating the significance of dose plan adaptation to anatomical changes.

Our contribution is the design and development of *VAPOR*. This is a novel visual analytics application for the exploration of pelvic organ variability during RT treatment. We focus on:

- the *global* exploration and analysis of the *positional and shape variability* of all pelvic organs in a cohort of patients (T1)
- the *local* exploration and analysis of all pelvic organs in individual patients or cohort partitions (T2), and
- the *correlation* of anatomical variability to RT dose variability and potential toxicity effects (T3).

For *VAPOR*, we retrospectively employ pelvic organ data from a cohort of 24 prostate cancer patients, for whom detailed Cone-Beam Computed Tomography (CBCT) and dose plan data are available for 13 treatment sessions. The application allows clinical researchers to explore the entire pelvis anatomy of a cohort of patients in a quick and easy way, and also enables in-depth exploration of particular patients or cohort partitions, with regard to the administered dose and potentially induced toxicity.

## 2. Clinical Background

For patients diagnosed with prostate cancer, a common treatment method is external beam radiotherapy (EBRT) [3]. EBRT follows a complex workflow, which involves an interdisciplinary team and incorporates several processes from imaging to pre-processing, and from treatment plan simulation to evaluation [2]. Radiation doses are delivered using multiple beams, aimed at the tumor location. When superimposed, these beams sum up to a high dose applied to the targeted tumor area and a lower dose to the surrounding tissue. The planned dose is not administered at once but is instead split up over several weeks, to allow the recovery of healthy tissue, while minimizing tumor growth [3]. This process is called *fractionation*, and its distinct sessions are called *fractions*. Recent techniques allow us to effectively spare normal tissue while delivering the desired high dose to the tumor volume [15]. However, parts of healthy organs of the pelvis are still unavoidably irradiated and this can lead to side-effects affecting the quality of life of the patient.

The anatomy of the male pelvis is depicted in Figure 1. In every human, it presents unique variations, which can be either occurring naturally across individuals, or due to pathological factors, or due to day-to-day changes in the same person. The latter occurs because the pelvic organs are soft deformable tissues, which are flexible and their shapes are affected by filling changes [8, 9, 10, 11, 16]. Organs, such as the bladder and the rectum are especially prone to this effect and their positions and shape vary significantly on a daily basis [6]. Recent studies suggest a link between pelvic organ motion/deformation, and increased toxicity risks [4]. This is due to the inherent complexity of the RT workflow, which does not make it possible to adapt the treatment plan before every fraction. Usually, tumor location is prioritized.

The standard treatment procedure is to generate one initial treatment plan and to use it as a basis for all subsequent sessions. To facilitate this, the setting of the initial planning is reproduced during the treatment. For example, prostate treatment commonly requires a full bladder regime [3], while positioning inaccuracies are addressed with simple translational adaptations. As there are many different factors that lead to shape deformations and position variations over the course of the treatment, these cannot be entirely covered by small adaptations to the initial plan [4]. Actual adjustment of the target volume in prostate cancer therapy on a per-treatment basis needs to be considered in the future [6, 8, 9, 10, 11]. Prostate cancer research starts looking into adaptive treatment approaches—similarly to lung cancer treatment, where breathing motion is considered [17]. These adaptive approaches take into account the shape variability and movement of all pelvic organs through treatment [7].

## 3. User Task Analysis

### 3.1. Intended Users

In the course of RT treatment, several clinical experts are involved [18, 2]. The present work is targeting clinical researchers and medical physicists, i.e., scientists who evaluate the robustness of different treatment regimes, advise on the best

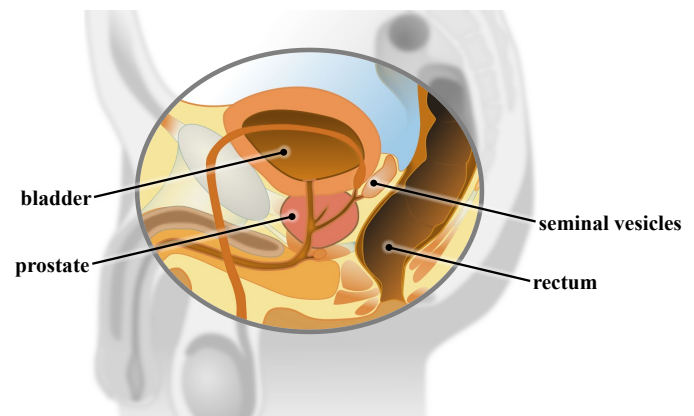


Fig. 1. Pelvis anatomy of the male body. We depict the main organs targeted in this work.

1 treatment strategy to follow, and research new, more effective  
2 ways of treatment.

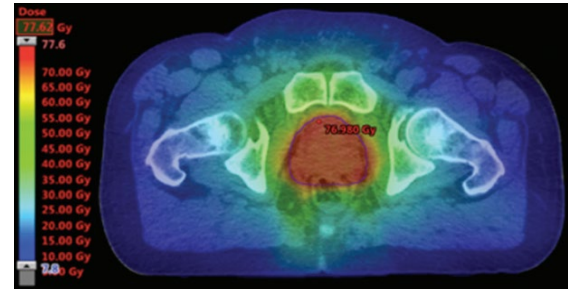
### 3 3.2. Current Workflow

4 In clinical practice, the evaluation of a treatment plan is cur-  
5 rently done in two ways [2]. Both are shown in Figure 2. First,  
6 *spatial 2D/3D views* (Figure 2 (a)) allow the experts to see how  
7 the dose affects the tumor and its surrounding organs for a given  
8 point in the treatment period [19]. This approach does not sup-  
9 port an easy exploration of multiple patients or multiple frac-  
10 tions at the same time—an important aspect for judging the  
11 robustness of treatment strategies. Second, *dose volume his-*  
12 *tograms (DVHs)* (Figure 2 (b)) show how much radiation is re-  
13 ceived by the volume of each organ and allow the experts to  
14 quickly identify organs at risk of toxicity [3]. Although DVHs  
15 scale well for a large number of patients, they do not allow for  
16 an easy link to patient anatomy.

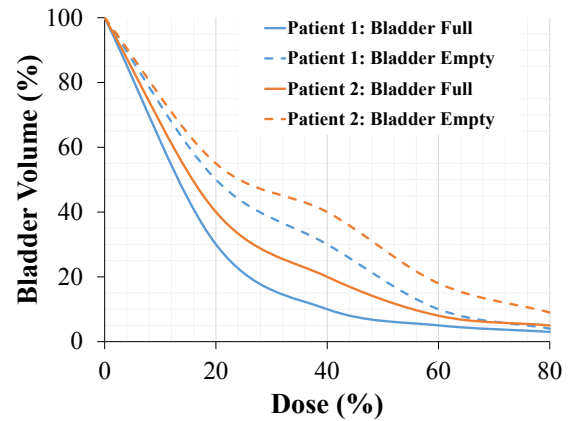
17 Adequate tools for the inspection and analysis of pelvic organ  
18 variability within the content of RT do not exist—with the ex-  
19 ception of the *Bladder Runner* [12] and the *Pelvis Runner* [14].  
20 The former application has demonstrated its clinical usefulness  
21 in a retrospective clinical study with a single focus on bladder  
22 toxicity in cohorts of patients [13]. However, the *Bladder Run-*  
23 *ner* does not support the exploration of anatomical variability of  
24 *all pelvic organs* during the entire RT treatment period. It also  
25 does not support the exploration of *motion* of the pelvic organs.  
26 The *Pelvis Runner* supports the exploration of the anatomical  
27 variability of all pelvic organs, but it does not provide func-  
28 tionality for the correlation of the anatomical variability to *dose*  
29 *administration and potential RT-induced toxicity*. As we will  
30 demonstrate in the upcoming sections, *VAPOR* builds upon our  
31 previous work on the *Bladder Runner* [12] and the *Pelvis Run-*  
32 *ner* [14], to support the exploration of the entire pelvis anatomy  
33 of a large cohort of patients in a quick and easy way, with regard  
34 to the administered dose and potentially induced toxicity.

### 35 3.3. Available Dataset

36 For this work, we had access to data from a cohort of 24  
37 patients undergoing RT for prostate cancer. The provided data  
38 includes 13 treatment sessions for each patient. The first five  
39 are from the five daily sessions of the first week, while the sub-  
40 sequent datasets were evenly sampled from the following treat-  
41 ment weeks [4]. The initial treatment plan was calculated for  
42 patients with an empty rectum and full bladder. At each session  
43 of their treatment, the patients were instructed to have roughly  
44 the same organ fillings. Before each treatment, a Cone Beam  
45 Computed Tomography (CBCT) acquisition was done for pa-  
46 tient alignment using rigid translations. For each of these ses-  
47 sions, pelvic organ delineations in the form of contour lines are  
48 available. For all patients, the bladder and rectum delineations  
49 are included. Additionally, delineations of either the prostate,  
50 or the prostate and seminal vesicles, or the prostate, seminal  
51 vesicles, and lymph nodes might also be included. Within the  
52 context of this work, we use for simplicity the term “prostate”  
53 for the first category (prostate only) and “clinical target volume  
54 or CTV” for the other two. The dataset is depicted schemati-  
55 cally in Figure 3.



(a)



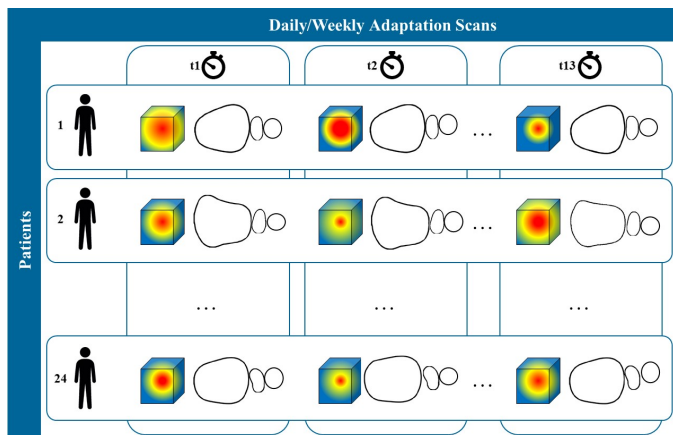
(b)

Fig. 2. (a) Spatial 2D view on the RT plan of one patient. The employed rainbow colormap represents the dose distribution, and it is used commonly in the clinical practice of RT. (b) Dose Volume Histogram (DVH) of two patients for two treatment regimes (empty and full bladder).

### 3.4. Requirements and Tasks

56 Clinical researchers and medical physicists working on the  
57 design of robust treatment strategies require functionality that  
58 can provide them with a better understanding of the general  
59 shape and positional variability of all pelvic organs within the  
60 cohort, as well as the anatomical variability of subgroups of pa-  
61 tients. Correlating anatomical variability with administered vs.  
62 planned RT doses and the resulting toxicity is also a required  
63 functionality. These functionalities, combined in one compre-  
64 hensive tool, are not available within other applications, as we  
65 will discuss in Section 4. Another requirement is to aim for  
66 general setup and interface that would be easily understandable  
67 for a user from the medical community, with representations  
68 that are not unnecessarily complex [2]. Although the clinical  
69 experts, for whom the application is designed, are visualization-  
70 literate, they still prefer representations that are common prac-  
71 tice in the domain. Finally, common interaction schemes, such  
72 as selection and filtering, as well as zooming, panning, rotation,  
73 and *F+C* are welcome. To ensure that all these requirements are  
74 met, one of our domain experts has been involved in the early  
75 design phases of *VAPOR*.  
76

77 With regard to the tasks, the clinical co-authors of this paper  
78 are initially interested in extracting the *amount of variability* of  
79 the available pelvic organs among all patients and across time  
80 (T1). Therefore, for each organ class, we need to quantify or-  
81 gan similarity and estimate the variability of each organ. Subse-  
82 quently, we need to visualize the variability of the organ classes



**Fig. 3.** Schematic depiction of the cohort data used in this work. The delineations of pelvic organs (bladder, prostate, and rectum) of 24 patients are available. Each of them has 13 sessions throughout his treatment.

within the *whole cohort*. This provides a quick overview of the entire cohort, as well as capabilities to identify patients or organs with high variability, i.e., outliers. At this point, patient and time correspondences should not be lost.

When interesting parts of the cohort are identified, a more *detailed exploration* needs to be conducted (T2). Drilling down to individual objects should be possible, i.e., exploring individual patients and/or organs, to understand which regions of certain organs are prone to variations and how large these differences are. Changes in position and shape should be displayed.

Finally, the anatomical variability needs to be explored in relation to the *administered RT dose*, and its *variability throughout the treatment period* (T3). This exploration, *steered by the domain experts*, is anticipated to provide useful insights about why and when potential toxicity may occur.

#### 4. Related Work

To facilitate understanding of the daily occurring shape variations in pelvic organs and especially their correlation to toxicity, some studies are already available [4, 19]. These are, however, limited to the exploration of spatial 2D/3D views or DVH analysis, as discussed in the previous section. These studies give insight into what kind of visualizations are commonly used in the domain of RT, and also show that looking at more than one patient or more than one time point of treatment simultaneously is a tedious process that does not scale well. Wentzel et al. [20] presented a visual computing approach for the estimation of RT plans in head and neck cancer patients, where anatomical similarity based on topology and measures of image fidelity were considered. With this approach, it is still not possible to derive any information with regard to potential RT-induced toxicity. Solutions for the visualization of many pelvic organs in an entire cohort of patients through the entire treatment period can be provided by the domains of *shape space* and *cohort analysis*, and with *comparative and ensemble visualization*.

VAPOR is building upon the previous work of the *Bladder Runner* [12] and the *Pelvis Runner* [14]. The *Bladder Runner* aimed at providing information about the amount of radiation

applied to the bladder across the treatment for a cohort of patients. The entire approach is based on a 14-D shape descriptor vector for the cohort of bladders [21]. The 14-D shape descriptors are given as input to a t-Distributed Stochastic Neighbor Embedding (t-SNE) [22] followed by clustering [23] to detect cohort partitions with similar bladder shapes and evolutions through the treatment period. Using multiple coordinated views, the users analyze the cohort of bladders through the RT treatment sessions, while the dose distributions and toxicity information are also incorporated in the views.

Extending the *Bladder Runner* to include multiple organs resulted into the *Pelvis Runner*, where different subsets of organs in the data (e.g., for one patient we have the delineations of the bladder, rectum and prostate and for another one we have additionally the seminal vesicles) are supported. Here, changes in the shape descriptor were made, as the 14-D vector of the *Bladder Runner* is not adequate for describing other than spherical shapes, e.g., it is not suitable for the rectum. However, the *Pelvis Runner* still does not support the correlation to dose administration, the analysis of its variability and the investigation of potential RT-induced toxicity. This functionality is the main addition, which resulted into VAPOR.

Other previously proposed frameworks include the work of Reiter et al. [24] to explore and analyze the variability in multiple pelvic organs. For this, they use an approach based on spherical harmonics [25]. To distinguish clusters across organ classes, they employ t-SNE [22], while to distinguish clusters within organ classes (and more importantly, outliers) they use Principal Component Analysis (PCA) [26]. Their data is derived from automatic segmentation algorithms where a triangle-to-triangle correspondence can be ensured across the individual structures. Yet, this approach does not support multi-timestep analysis. Also, the 8-D descriptor from the spherical harmonics frequencies that was employed in this work is not sufficient to describe non-spherical organs, such as the rectum. Generally, the use of descriptors, as presented in the former works, supports the efficient differentiation between different shapes, but it lacks the ability to synthesize arbitrary elements in their shapes.

In *shape space analysis*, Hermann et al. [27, 28, 29] investigate anatomic covariances in ensembles of data, providing also a state of the art report with prospects on the visual analysis of shapes [30]. Busking et al. [31] propose to use a 2D scatter plot to represent the distribution of elements inside a cohort and to synthesize additional arbitrary objects in the shape space. For comparing objects, they later deal with visualizing intersecting 3D surface meshes [32]. Landesberger et al. [33] extend the scatter plot concept for parameter sensitivity analysis in segmentation and the link to the segmentation outcomes. Considering the high learning curve for many complex visualizations of high dimensional data, such as cohort data, Blumenschein et al. [34] propose concepts aimed at people who are not from the visualization domain.

More specifically for *cohort analysis*, Klemm et al. [35] focus on the extraction of spine canal variability and the exploration of clusters of similarly shaped spines. This work has been extended to incorporate additional patient informa-

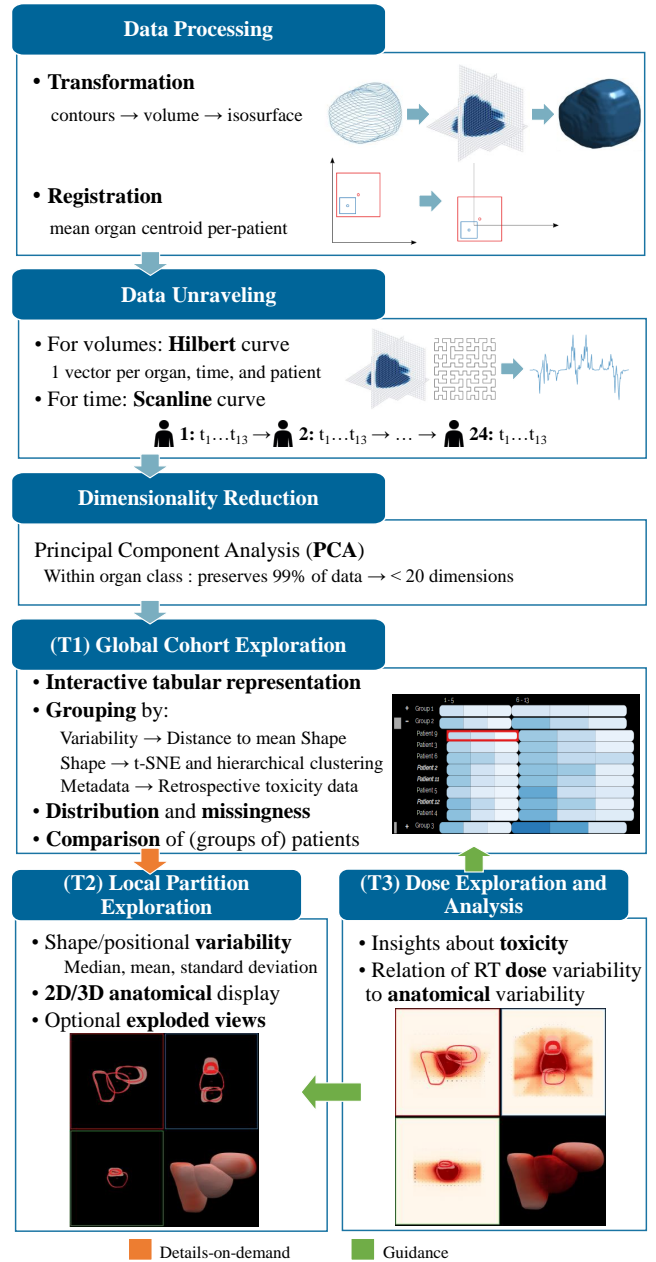
**Table 1. Schematic comparison of VAPOR and the most relevant previous work, with regard to the task analysis of Section 3.**

	Multiple Organs	Possibly Different Organs	Multiple Patients	Multiple Time Points	Relation to Dose & Toxicity
VAPOR	✓	✓	✓	✓	✓
[12]	✗	✗	✓	✓	✗
[14]	✓	✓	✓	✓	✗
[20]	✓	✓	✓	✗	✗
[24]	✓	✗	✓	✗	✗
[27, 28, 30]	✗	✗	✓	✗	✗
[31]	✗	✗	✓	✗	✗
[33]	✗	✗	✓	✗	✗
[34]	✗	✓	✓	✗	✗
[35, 36]	✗	✗	✓	✗	✗
[37]	✗	✗	✓	✗	✗
[43]	✗	✗	✓	✗	✗
[44, 45, 46]	✗	✗	✓	✓ (in [46])	✗
[48]	✗	✗	✓	✓	✗
[49]	✗	✗	✗	✓	✗
[50]	✗	✗	✓	✗	✗

tion [36], demonstrating how to effectively reduce and visualize image cohort data and to facilitate their understanding on a broader basis. Steenwijk et al. [37] also go beyond shape analysis by proposing a framework for the interactive and structured visual analysis of cohort data. Cohort analysis has also been tackled by Preim et al. [38], Bernard et al. [39] and Alemzadeh et al. [40], for various purposes.

Given the available data, which are contour delineations of the pelvic organs, we cannot overlook the previous work in *ensemble visualization* [41]. Our work relates to contour boxplots by Whitaker et al. [42], their extension for streamline ensemble data by Mirzargar et al. [43], and the recent techniques of Ferstl et al. [44, 45, 46]. The latter are applied on weather simulation ensemble data, covering 2D lines, 3D volumes and also the time evolution thereof. In *comparative visualization* [47], for the investigation of jaw movement, Keefe et al. [48] introduce small juxtaposed representations, where the movement is explicitly encoded giving a good overview of all the data, while parallel coordinates allow for an in-depth search. Tory et al. [49] investigate a superposition approach for the development of brain lesions extracted at different time points from MRI images. The use of explicit encoding to highlight structural differences is used by Schmidt et al. [50], where they compare a large number of similar meshes and can quickly identify regions of differences in multiple linked views.

To sum up, previous literature includes approaches that tackle a multitude of individual objects (in our case, either multiple patients or multiple organs). In some cases, different object sets, i.e., sets missing some instances (in our case, organs), are also tackled. Also, previous work proposes approaches that visualize the development of structures through time (in our case, multiple timesteps). The most relevant works and their characteristics are summarized in Table 1. However, there is no approach with comprehensive functionality that covers all aspects of the problem, as described in Section 3—spanning from the quantification and visualization of multiple organs in a cohort of patients throughout the treatment time, to the correlation of anatomical variability and toxicity manifestation. We aim to cover this literature gap with VAPOR.

**Fig. 4. Schematic depiction of the workflow, the main components of VAPOR and their in-between links.**

## 5. Methods within VAPOR

As discussed in Section 3, VAPOR focuses on three main objectives: the *global* exploration and analysis of pelvic anatomy variability across the treatment period and across a cohort of patients (T1), the *local* exploration and analysis of pelvic anatomy variability across the treatment period for individual patients or cohort partitions (T2) and the *correlation* of anatomical variability to radiation dose and toxicity (T3).

Our general workflow is presented in Figure 4. Our approach starts with data processing, and with quantifying the similarity of the organ shapes in order to estimate their anatomical variability. For visualizing the variability in the organ shapes, an aggregation approach based on Ferstl et al. [44] is employed.

For (T1), a low dimensional embedding of each organ is used to calculate the variability on a per-patient basis and to visualize the whole cohort. After grouping, a tabular plot is employed to explore the cohort partitioning in a flexible and intuitive manner. For (T2), information on the anatomical space is shown on demand. We enable the user to drill down to selected groups or patients from the cohort and to perform a detailed inspection of the organ variations. This is achieved by reconstructing the initial 3D objects from their low dimensional embeddings. By sampling the embedding space for the median and the standard deviation of the organs, we reconstruct the shape variations and we show them in a representation similar to contour boxplots [42]. For (T3), we compute and visualize the distribution of the administered RT dose, i.e., the average and standard deviation, for selected groups of patients. As the clinical co-authors of this work are interested mainly in pelvic organ regions with high anatomical variability and high radiation dose, they have the option to guide and restrict the anatomical variability computation to regions with doses that exceed a user-selected threshold.

### 5.1. Data Processing, Unraveling and Reduction

The first step in the organ shape analysis is to *transform* the organ data into a format that is easier to handle and to visualize. The organs in the cohort are delineated by medical experts in a form of contours at individual slices of patients' cone-beam CT scans. We first convert the contours to volumetric coverage masks (i.e., volumes). The resolution of our volumes is given by the resolution of the cone-beam CT scans. In our data, it is 2.5 x 2.5 x 2.5 mm per voxel. Each organ for each patient and timestep is stored in a separate volume, which initially covers the entire pelvic region (the entire volume captured in the CT scans) to preserve the original position with respect to other organs. We have chosen to store each organ in a separate volume for convenience, as the shape analysis is performed separately for each organ class. Additionally, with storing all organs in one volume there is a risk of overlaps at the neighboring voxels of different organs.

Next, we need to *register* the volumes. For each patient, the individual timesteps are already aligned manually by medical experts. Therefore we want to preserve the persisting positional variations between individual timesteps of a single patient as they indicate how the organs moved during the treatment. However, we still need to align different patients to each other. To do this, we compute the mean centroid across all timesteps separately for each organ and patient (e.g., if we have 24 patients and 3 organs, we compute 72 mean centers). We then align the organs so that the mean centroid for a given organ and patient is translated to the center of the coordinate system. Although this approach adds small translational variations, it preserves the volume changes and their main growth directions. Therefore the shape analysis is performed on data aligned in this way. After registration, the volumes are cropped to the uniform size based on the bounding box containing all of the volumes. However, we store the translation vectors for all organs in order to be able to retrieve their original positions and compute new mean positions for subgroups of the cohort—while for the computa-

tion of shape and positional changes the organs are aligned individually, for rendering we align the groups based on the mean centroid of all organs.

As we mentioned above, our per-patient data are already pre-aligned by medical experts who used the prostate as a reference organ (although some per-patient positional variations of the prostate can still be observed). This is a common approach in prostate cancer treatment, as the radiation dose is also centered around the prostate. However, this approach also has some limitations. It only allows us to analyze the average between-timestep (inter-fraction) organ motion of the groups of patients with respect to the prostate, which is a mobile organ itself. For a more robust analysis of positional changes, registration based on the position of pelvic bones or femoral heads would be necessary, as bones are the most rigid structures in the human body. This approach would preserve the positional variations of all pelvic organs. Unfortunately, this approach was not feasible for us, as segmentation of the bones would require additional contouring from medical experts (or, at the very least, corrections if automatized segmentation was used) which is a very time-consuming process.

Our 3D volumetric patient data need to be *unraveled* before we can employ dimensionality reduction step. At the same time, we need to map the two dimensions of our cohort, i.e., patients and timesteps, into a single one without losing correspondences within the data. For this, we employ linearization strategies along two curve types: Scanline Curve and Hilbert Curve [51]. The volumes, which initially correspond to binary coverage masks, are converted to signed distance maps representing the distance to the organ's surface. The distance volumes are then unraveled into 1D vectors using the 3D space-filling Hilbert Curve that allows us to analyze how the shape differentiation capabilities of our method changes if the sampling density is reduced. This has also been employed by Weissenböck et al. [52] and by Demir et al. [53] for volume data comparison. After unfolding, there is a unique vector for each organ, patient, and timestep. The vectors representing organs from the same class are then organized following the Scanline principle, as we are interested in preserving the temporal order within the data. We create a data structure where all timesteps of the first patient are followed by the timesteps of the second patient, and so forth. This allows us to easily select patients and their timesteps, while we can also efficiently add new patients in the analysis. Each organ class is stored and processed separately.

After the volumetric data have been transformed into vectors without losing patient and timestep correspondence within the cohort, they are *reduced* into a low dimensional vector representation that allows us to create a computationally efficient way to store and process large cohorts of patient data. The dimensionality reduction step creates a low dimensional embedding of the structure of the high dimensional space where each cohort data point, i.e., an individual patient's organ at a specific timestep, is represented by one position in space, where similar shapes are placed nearby. As we have already discussed in Section 4, the approaches used in our previous works (e.g., 14-D space based on shape descriptors from Bladder Runner [12])

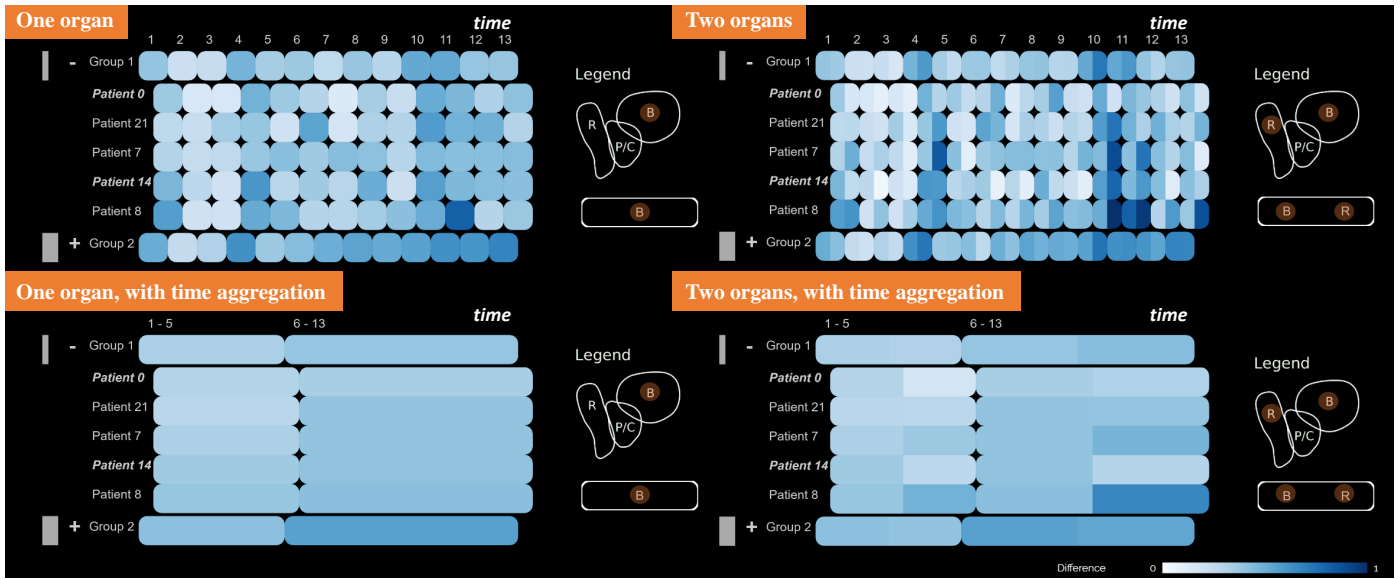


Fig. 5. Some of the possible configurations of the tabular view—with one or multiple organs, and with or without time aggregation.

are not easily generalize to other pelvic organs, which can have vastly varying shapes, e.g., rectum, seminal vesicles, or bowel loops. This led us to a selection of a different approach. We employ Principal Component Analysis (PCA) [26] to create low dimensional embedding of the data and use only as many components as are needed to ensure the preservation of 99% of the original data. In our case we needed up to 20 dimensions, depending on the organ class.

The low dimensional embedding allows us to efficiently store the data and to perform further calculations and analysis, but accurate representation of the patients' anatomy is also a vital part of any medical visualization software. We can always reconstruct the volumetric data from the low dimensional space, however, the visualization of volumetric data is very computationally expensive. Thus, for the visualization components, we employ the triangular meshes that are generated on-demand from reconstructed volumes as iso-surfaces.

### 5.2. (T1) Global Exploration of Anatomy within a Cohort

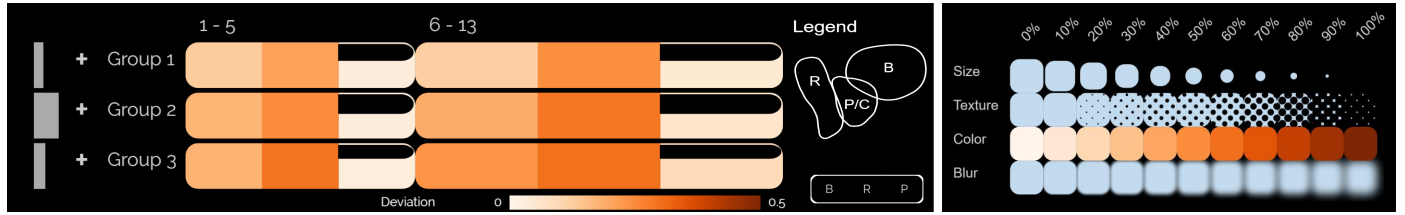
For (T1), we need to enable clinical researchers to manage the comparison of the *different pelvic organs in multiple patients* throughout *several timesteps*. In some cases, the patient data also incorporate *different sets of organs*, as the delineations include either the prostate, or the prostate and seminal vesicles, or the prostate, vesicles, and lymph nodes.

We first provide users with an *overview of the whole cohort data*. The main idea behind this is to generate a high-level representation that conveys the general patterns present in the data before the user starts a detailed investigation of individual interesting cases. This is based on the low dimensional outcome of the previously discussed dimensionality reduction step and we offer two possibilities here. The first option is based on the distance of each organ to the mean per-patient organ shape in low dimensional space. The distance calculation between data points enables the explicit estimation of outliers on a per-patient basis. It also indicates how much the shape varies across the

treatment time points for each patient. For this, we calculate the *Euclidean distance*, similar to Klemm et al. [35]. Alternatively, clustering can be used for the extraction of the main shape groups within patients. The drawback of clustering is that subtle differences between shapes are obscured as clustering only offers a binary variability option—either the shape belongs to a cluster or not. However, analysis and comparison of the clusters can offer an understanding of what shape types are to be expected in patients and how prominent they are. To get better separation between the shapes we first perform t-Distributed Stochastic Neighborhood Embedding (t-SNE) [22] on the low dimensional data from PCA. We then employ a *hierarchical clustering with complete linkage* [54] similarly to Klemm et al. [35], as our clustering task is very similar. We chose this method, as hierarchical clustering is more flexible, gives more intuitive results, and has fewer assumptions about the distribution of the underlying data than other clustering techniques, e.g., k-means, which is an essential requirement for a generally applicable system. However, a limitation of this method is that we need to decide in advance how many clusters we allow. From our experience in working within clinical applications, an approach that would give more than 3-4 clusters would be considered too confusing and suboptimal, therefore we limited the number of clusters to four.

From the previous calculations, we receive a single distance metric and/or cluster value per combination of patient, timestep and organ. To represent this, we employ a *tabular representation* similar to the contingency matrix of the *Bladder Runner* [12] or the representation in the work of Blumenschein et al. [34]. This representation (Figure 5) has been chosen to show the shape change information, while at the same time preserving information about time and patient correspondences. We also want to ensure that the visualization itself is readily understandable by users who do not employ visual analytics tools on a regular basis. In the tabular view, patients are denoted on the vertical axis and timesteps on the horizontal one, to enable com-





**Fig. 6. Left: Encodings for the standard deviation from the mean shape (orange colormap) and for data missingness (emptiness of cells). Right: Alternative encodings considered for the standard deviation of each organ from the mean value (size, texture, color, and blur).**

1 parison across both timesteps and patients. The encoded val- 48  
 2 ues represent the similarity distance encoded with a sequen- 49  
 3 tial white(low)-to-blue(high) colormap (Figure 5), or cluster 50  
 4 membership denoted with a qualitative colormap (Figure 9 (a)). Both 51  
 5 of these maps have been taken from Colorbrewer [55]. To extend 52  
 6 this approach for multiple organs, we split each cell of the 53  
 7 tabular view into equally sized parts—one for each organ (Fig-  
 8 ure 5, right). With this encoding, the users can directly compare  
 9 the values of multiple organs and detect patterns and correla-  
 10 tions, similar to a glyph-based representation, as also demon-  
 11 strated by Blumenschein et al. [34]. The users manually filter  
 12 which organs are shown every time, as well as whether they  
 13 want to show the Euclidean distance or the clustering. Labels  
 14 and legends accompany the representation.

15 The tabular representation can accommodate additional in-  
 16 formation with regard to the *underlying data distribution* and  
 17 to the amount of *missing data*, i.e., missing organ delineations,  
 18 as both of these indicate trustworthiness. The former is rep-  
 19 resented with additional distribution histograms accompanying  
 20 the groups and positioned to the left-hand side of the tabular  
 21 plots, as shown with the gray bars in Figure 5. The latter is  
 22 represented with an “empty glass” metaphor on each cell in the  
 23 tabular plot. As shown in Figure 6 (left), the emptier the cell,  
 24 the less data it contains and this partition is less trustworthy.  
 25 For example, in Figure 6 (left), Groups 1 and 2 have less avail-  
 26 able data for the prostate (the third component of the glyph,  
 27 see also the legend) than Group 3. Going one step further, the  
 28 user might also be interested in finding out how different *shape*  
 29 *group types compare* to each other. For this, several encod-  
 30 ings, i.e., size, texture, color, and blur, have been investigated,  
 31 as shown in Figure 6 (right), for the encoding of the standard  
 32 deviation of each observation from the mean value.

33 While the initial layout of the overview visualization pro-  
 34 vides the option to see the whole cohort at once, the analysis  
 35 process would require the user to scan row-by-row the repre-  
 36 sentation to detect similarities or outliers. This can be time-  
 37 consuming even for a small cohort of patients. To this end, we  
 38 enable Focus+Context (F+C) [56], sorting and grouping [57],  
 39 and visual aggregations for patients and timesteps as shown in  
 40 the bottom row of Figure 5. Patients can be split into groups  
 41 based on organ shape clustering, organ variability, or categori-  
 42 cal patient metadata (e.g., available retrospective toxicity data).  
 43 With the clustering option, the patients are split into groups  
 44 based on their prevalent organ shape type identified by the clus-  
 45 tering algorithm. For organ variability-based grouping, we esti-  
 46 mate the variability as the average Euclidean distance of organ  
 47 shapes over time to the patient’s mean organ shape (in the low

dimensional PCA embedding). The patients are then grouped 48  
 based on their average shape distance. Four different groups are 49  
 automatically generated, i.e. low < 25%, medium 25% – 75%, 50  
 and high > 75% average distance values based on the interquar- 51  
 tile range, as well as one group for patients with missing values 52  
 in case no data for the given organ are present. 53

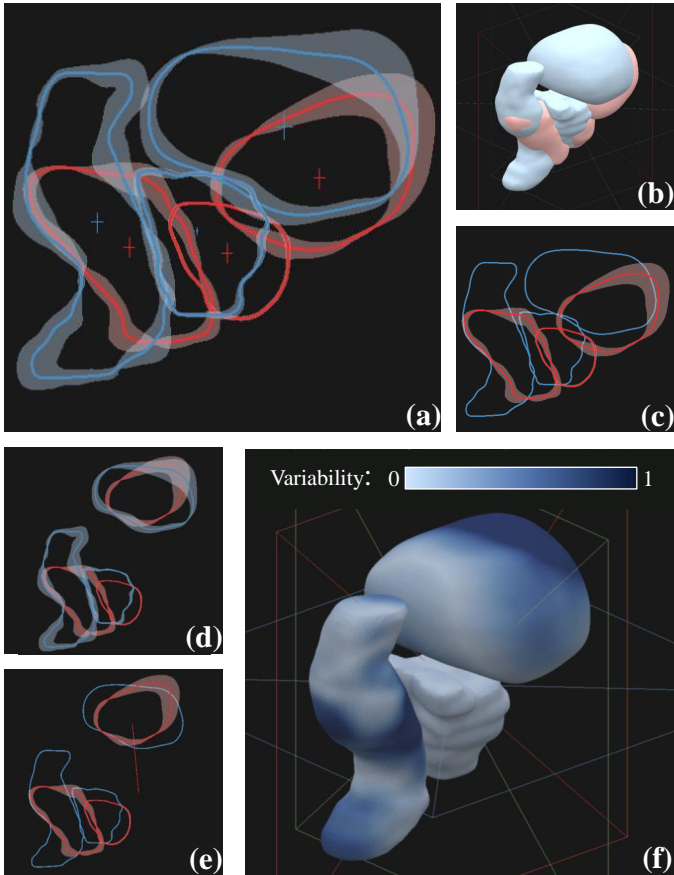
### 5.3. (T2) Local Exploration of Anatomy in Cohort Partitions 54

55 During the exploration and analysis of the entire cohort, the  
 56 users identify specific interesting cases, i.e., individual patients  
 57 or partitions of the cohort, which require further investigation.  
 58 We enable the users to drill down to individual patients or part-  
 59 titions, for local exploration. Up to this point, only abstract key  
 60 figures with regard to the cohort and its shape properties have  
 61 been displayed in the tabular view. We provide an additional  
 62 view of the anatomical shape of selected patients or partitions.  
 63 Multiple patients or subgroups within the cohort are selected  
 64 respectively by clicking on a cell or a row label in the cohort vi-  
 65 sualization. Each selection is assigned with a unique color from  
 66 a qualitative scheme by Colorbrewer [55].

67 For the *summarization of shape variations*, we first extract  
 68 the geometric median element inside the low dimensional em-  
 69 bedding of the shape space as a general representative of the  
 70 group. In this way, we retrieve a representative shape that ex-  
 71 ists in our cohort—as opposed to the mean shape. We then  
 72 employ the approach proposed by Ferstl et al. [45] for the ana-  
 73 lytical transformation of confidence intervals in the low dimen-  
 74 sional PCA embedding to the spatial domain. This way we re-  
 75 trieve representatives of the shape distribution. We are using  
 76 this method with the interval  $(\mu - \sigma, \mu + \sigma)$ , where  $\mu$  is the  
 77 mean shape and  $\sigma$  is the standard deviation. However, this can  
 78 be adjusted to show 90% confidence intervals or interquartile  
 79 ranges.

80 The analysis of the center point variations is indicative of  
 81 the organ movement. For this, we also use the mean and stan-  
 82 dard deviation of the center point of each organ to calculate the  
 83 main variation directions for groups of organs. This is also in  
 84 accordance with our registration method, where we also took  
 85 the average center point for each patient to align its organs be-  
 86 fore the analysis. Before this step, we have already performed  
 87 a Kolmogorov-Smirnoff test to confirm that the distribution of  
 88 the shapes within the cohort is indeed close to a normal dis-  
 89 tribution. This combined approach has also been employed by  
 90 Ferstl et al. [44, 45].

91 To *display the above-summarized shape and positional vari-*  
 92 *ability*, we employ the common combination of three anatom-  
 93 ical 2D planes (sagittal, coronal and axial) with a 3D view, as



**Fig. 7.** Comparison of two cohort partitions (red and blue) in the anatomical view. (a) Shape (contour boxplots) and positional (cross glyphs) variability are visible in 2D. (b) Superposed 3D view. (c) F+C for shape variability on the red partition. Positional variability has been hidden. (d) Exploded view for the extrusion of bladders in 2D. (e) F+C on the exploded bladder view with an indication of the extent of the extrusion to see the red partition. (f) Explicit encoding of variability in the 3D view for the blue group.

of surface variation, using a sequential colormap based on the organs' group color. With this view, we aim at supporting users trying to find regions with interesting shape changes. As the adjacency of the organs may cause overplotting and difficulties in judging the shape variations, we provide also an optional *exploded view* [58], where the user can extrude the organs in the display (Figure 7 (d,e)). In this exploded view, the same organ of all groups is taken and placed in such a way that it does not overlap with any other shape, while at the same time being centered at a common point. To preserve parts of the initial context, a line glyph connects the center of the extruded organ to its original position (Figure 7 (e)).

#### 5.4. (T3) Dose Exploration and Analysis

In RT, it is important to administer a high enough dose to the target volume, i.e., the volume that covers the tumor area, while at the same time minimizing the dose to the healthy tissues. Regions close to the target volume are particularly prone to toxicity risk, due to their high anatomical variability. The clinical co-authors of this work need a functionality that supports dose exploration and analysis, i.e., functionality for relating dose administration, anatomical variability and toxicity effects, in a global and a local way—accompanying the previous tasks (T1) and (T2).

Not all regions of the pelvic organs are equally important. The most critical regions are those where anatomical variability, as resulting from (T1), is high and the radiation dose is also high. To set this constraint, the domain experts can guide the global anatomical variability exploration and analysis of (T1) by restricting the RT dose, with the use of a *user-selected threshold*, e.g., by determining that the “maximum acceptable dose is 67 Gy”. This is linked to the methods used for (T1). The data, as they result from the low dimensional embedding described in Section 5.1, are reconstructed back to the 3D space. A mask containing the thresholded RT dose, e.g., all voxels receiving a dose above 67 Gy, removes the organ regions where the dose is below the user-defined threshold. This is performed for each patient and each treatment session. The data are subsequently linearized using the Hilbert Curve and then processed in the same way as the low dimensional embedding described in Sections 5.2 and 5.3. The *updated tabular representation* depicts now the anatomical variability information, but only in regions where the RT dose exceeds the user-determined threshold. As the tabular representation also supports the incorporation of retrospective toxicity information, it is possible to *relate toxicity with the anatomical variability and the locations of high dose administration*.

In addition to knowing the locations of high radiation dose and high anatomical variability, it is necessary to have a more localized view on these regions of interest. In (T2), when a group of patients is selected, the anatomical views show the local organ variability within the selected group. To link this to the RT dose and its variability, we compute the distribution of the administered RT dose, i.e., the average dose and the standard deviation. We subsequently show the average dose as a *background colormap* in the 2D anatomical planes, as shown in Figure 8 (a-b). This follows a sequential white (low dose)-to-red (high dose) color scale [55], but can be changed by the

seen in Figure 13 (c). Standard interaction, e.g., zooming, panning, and slicing through the volume, is possible. For the comparative visualization of the pelvic organs of multiple patients within a 2D view, two alternatives are possible [47]: (i) superposition of stacked contours, where each patient instance is denoted with a distinct color, (ii) superposition of contour boxplots [42], where each patient or cohort partition is denoted with a distinct color. The latter is shown in Figure 7 (a). A combination of the two is also possible, e.g., when comparing one patient instance to a specific partition. We additionally display the center point variation for each organ. This is explicitly encoded by drawing a cross, the bars of which extend to indicate the main directions of organ motion, as shown in Figure 7 (a).

In the 3D views, we show the median shapes of all selected groups superimposed (Figure 7 (b)). The lighting in the scene and the surface material aim at highlighting the organ structure, while transparency is not employed. Instead, if a specific group is selected, it is brought forward with a F+C strategy in the 2D (Figure 7 (c)) and the 3D views. On demand, the 3D view can show the explicit encoding of the surface variations (Figure 7 (f)). In this case, the surface color is used to encode the amount

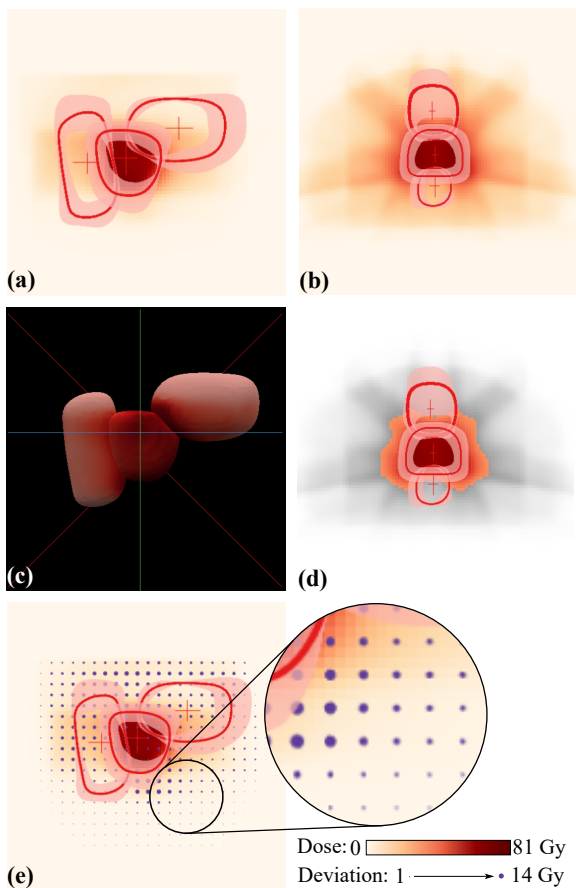


Fig. 8. Anatomical views incorporating the RT dose mapping (a) in the sagittal plane, (b) in the coronal plane, and (c) in 3D. (d) F+C employed to gray out the RT dose below a user-defined threshold. (e) Dose deviation mapped on the area of the superimposed circular glyphs.

1 user to match domain conventions [2]. In the 3D view, we  
 2 encode the average dose on the mean organ shape using the same  
 3 color scheme (Figure 8 (c)). The standard deviation is mapped  
 4 on the area of *superimposed circular glyphs* [59], similarly to  
 5 Raidou et al. [60] (Figure 8 (e)). We considered, as an alterna-  
 6 tive encoding, the approach of Ristovski et al. [61], but we  
 7 decided not to use it, due to two reasons. First, our clinical  
 8 experts were already familiar with the superimposed circular  
 9 glyphs [62] and, second, the approach of Ristovski et al. would  
 10 require from the user to zoom into the treatment plan to obtain  
 11 details on the variability, which is more intensive in interac-  
 12 tion than our approach. To preserve anatomical context, F+C  
 13 is employed [56] and regions that have been discarded by the  
 14 previously described dose thresholding are kept in the view, but  
 15 grayed out, as shown in Figure 8 (d).

## 16 5.5. Implementation

17 VAPOR is designed as a server-client application. A web  
 18 server in conjunction with MATLAB performs the computa-  
 19 tionally expensive operations, including data processing, un-  
 20 raveling, and dimensionality reduction. A client-side browser  
 21 application written in JavaScript receives the shape information  
 22 and creates the visualizations using three.js and D3.js.

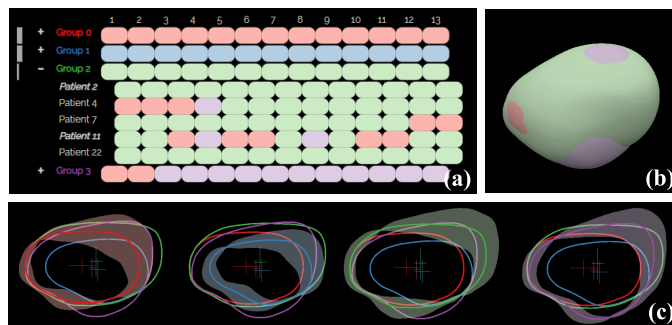


Fig. 9. Scenario for shape type identification, applied to bladder analysis for the completion of (T1). Four clusters are identified and denoted with the four distinct colors, representing bladder groups with different shape characteristics and different kinds of anatomical variability.

## 23 6. Results

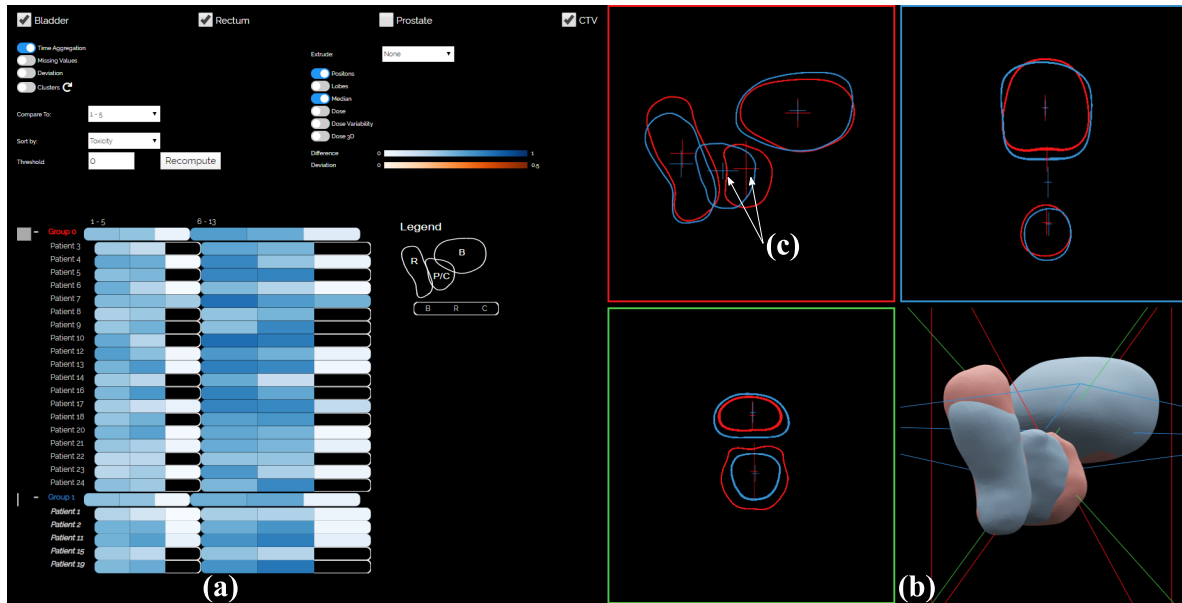
24 In this section, we present four scenarios of increasing com-  
 25 plexity, as conducted together with two medical physicists to as-  
 26 sess how well tasks (T1), (T2), and (T3) are fulfilled with VA-  
 27 POR. We further document the feedback of the domain experts  
 28 giving an initial indication of the strengths and weaknesses of  
 29 VAPOR, and directions for future improvements.

### 30 6.1. Shape Type Identification in a Cohort

31 This scenario is depicted in Figure 9, and it investigates pos-  
 32 sible organ shape types resulting from the clustering. There-  
 33 fore, it focuses only on the first task, i.e., (T1) for the explo-  
 34 ration of the anatomical variability of organs within a cohort.  
 35 In the case of the bladder, four groups (Figure 9 (a): red, green,  
 36 blue, and purple) are obtained. Each group is selected to in-  
 37 spect their median shapes, confidence bands, and positions, as  
 38 shown in Figure 9 (c). The green and purple groups contain  
 39 bladders with bigger sizes. Bladders from the green group are  
 40 more convex, while purple bladders protrude further in the di-  
 41 rection of the prostate (bottom left side of the shapes in Fig-  
 42 ure 9 (c)). This is not only visible in the 2D views but also  
 43 in the superimposed 3D view (Figure 9 (b)). The red and blue  
 44 groups contain smaller bladders, which are again split into con-  
 45 vex bladders (red) with a flatter interface towards the prostate  
 46 (bottom left side of the shapes in Figure 9 (c)) and bladders  
 47 with more concave shape (blue). In general, all bladders tend  
 48 to present the largest growth on their upper side, as there the  
 49 bladder has the fewest constraints by other internal organs and  
 50 can freely extend. Most of the bladders move predominantly  
 51 along the vertical axis, with the red group also demonstrating  
 52 large positional variability along the sagittal axis, i.e., left-to-  
 53 right in Figure 9 (c). This verifies findings of previous clinical  
 54 work [4, 63].

### 55 6.2. Retrospective Toxicity Analysis

56 This scenario is depicted in Figure 10, and investigates possi-  
 57 ble correlations of organ shapes to toxicity manifestation, i.e.,  
 58 addresses tasks (T1) and (T2) of Section 3. Figure 10 also  
 59 showcases the comprehensive interface of VAPOR. For the tox-  
 60 icity, retrospective data of all patients are available. The ele-  
 61 ments are sorted based on this attribute, as seen in Figure 10 (a).

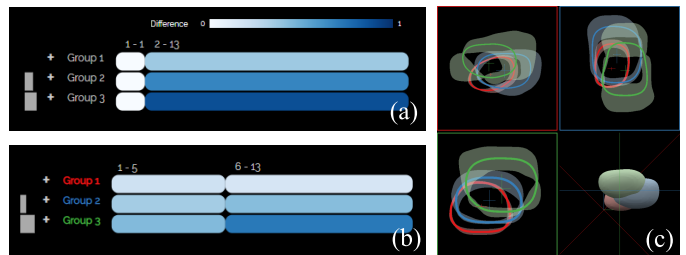


**Fig. 10.** Scenario for retrospective toxicity analysis, to compare patients with toxicity (blue) against patients without (red). This scenario addresses all three tasks. A preliminary analysis indicates that the shape variability does not vary significantly between the two groups, but the positional variability of CTV looks vastly different among the two groups.

1 The red group presents no toxicity and the blue group presents  
 2 toxicity (T1). In the toxicity group, there are patients with high  
 3 (2, 11, and 19) and low (1, 15) shape changes (T2). Also, there  
 4 are patients whose average shape of the first five days is similar  
 5 to the rest of the treatment (1, 2, and 15), and those whose average  
 6 shape is not (11 and 19), leading to higher variations. Both  
 7 of these findings do not indicate a connection between shape  
 8 variability and induced toxicity, but the number of patients is  
 9 too small for a conclusive statement. When looking at the  
 10 anatomical views, there are no large differences in the shapes  
 11 themselves, although the group with toxicity (blue) seems to  
 12 have slightly bigger organ shapes (Figure 10 (b)) (T1). However,  
 13 the positional changes of the CTV look vastly different for  
 14 the two groups of patients. Looking at the sagittal view (Figure  
 15 10 (c)) indicates that the group with toxicity (blue) seems to  
 16 move more in the sagittal direction than the one without (red),  
 17 as shown by the cross glyphs. Increasing the number of patients  
 18 might provide in the future more information about these  
 19 preliminary findings.

### 20 6.3. Single Organ Exploration in a Cohort

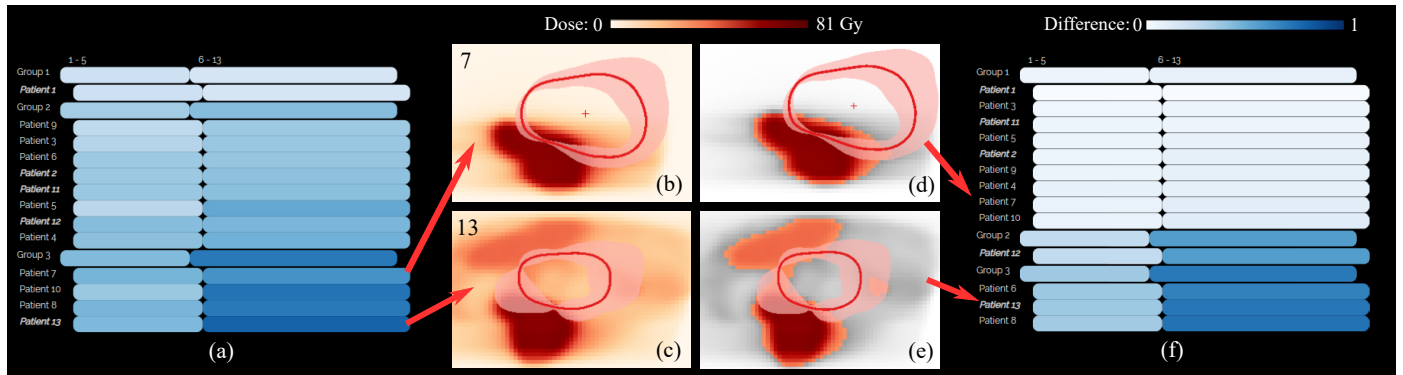
21 This scenario is depicted in Figures 11 and 12, and addresses  
 22 all three tasks of Section 3. The exploration starts with group-  
 23 ing patients based on their average bladder shape changes (T1).  
 24 When comparing each shape to the first treatment day (Figure  
 25 11 (a)), all bladders change significantly through the treat-  
 26 ment period, as seen by the different shades of blue for all  
 27 groups in the tabular representation. This is an important  
 28 argument in favor of adaptive RT. The current clinical practice  
 29 uses only the first timestep for treatment planning, and our find-  
 30 ing confirms that simple translational adaptations of the initial  
 31 treatment plan will not suffice. When comparing each shape  
 32 to the mean of the first five treatment days (Figure 11 (b)), the  
 33 variability is lower. This is an indication that performing the



**Fig. 11.** Scenario for single organ cohort exploration, showing the shape and positional variability of bladders. This scenario addresses the first two tasks, showing preliminary indications that performing the planning based on the first five timesteps (instead of only the first one) may more precisely model the bladder shape over time. VAPOR may allow to identify early patients with high organ shape variability in critical regions (group 3, green), and account for this information in treatment planning.

34 planning based on the first five timesteps instead of only the  
 35 first one may more precisely model the bladder shape over time.  
 36 The anatomy of the respective shape variations can also be seen  
 37 in the contour boxplots of Figure 11 (c). All groups have similar  
 38 shapes, which can be due to the fact that patients with high  
 39 average variability are found all over the shape space and have  
 40 no individually distinctive shape. The group with low shape  
 41 variability (group 1, red) has also small local shape variations,  
 42 i.e., smaller bands, and the group with high shape variability  
 43 (group 2, green) has also large local shape variations, i.e., larger  
 44 bands. With regard to positional variations, higher shape vari-  
 45 ability correlates with larger positional variations, as denoted  
 46 by the cross glyphs in Figure 11 (c). The positions largely vary  
 47 along the sagittal axis (top-down in the figure), which corre-  
 48 sponds to previous findings [4].

49 The contour boxplots of the sagittal view of Figure 11 (in  
 50 (c), red square) indicate that groups 1 and 2 present the lowest  
 51 shape variability in the area of the prostate. In group 3, this



**Fig. 12.** Scenario for single organ cohort exploration along with the radiation, showing the variability before (left) and after dose masking (right). Patients from group 3 are particularly interesting, as high shape variability in combination with high RT dose administration can potentially lead to complications.

1 is not the case. Expanding the tabular representation helps inspecting individual patients (Figure 12 (a)) (T2). Patients from group 3 are particularly interesting, as high shape variability can potentially lead to complications. When looking at the individual patients from this group, some patients, e.g., patient 7 (Figure 12 (b)), exhibit a similar variability pattern to patients from groups 1 and 2, i.e., the shape changes mostly outside of the high dose region. However, some patients, e.g., patient 13 (Figure 12 (c)), exhibit high shape variability also in the area of high dose. For such cases, the dose masking feature of our tool can be used to recompute the shape variability only based on the regions, where the RT dose exceeds the user-determined threshold (T3). Figures 12 (d) and (e) show patients 7 and 13, respectively, after dose masking. After the recalculation, the tabular representation shows that the order and grouping of patients has changed (Figure 12 (f)). Patient 7 was moved from group 3 to group 1, as he exhibits low organ shape variability in the masked area. Patient 13 stayed in group 3. This indicates that our tool can be used to separate patients with high organ variability in high dose regions from patients with low overall shape variability or low variability in high dose regions. Also, there is a clearer separation between groups 1 and 2. This is visible already in the first five timesteps of the treatment and is even more apparent in the remaining timesteps. This is in line with the hypothesis that a few initial plans obtained over the first few days of treatment (e.g., 5) may allow to identify early patients with high organ shape variability in critical regions, and account for this information in treatment planning.

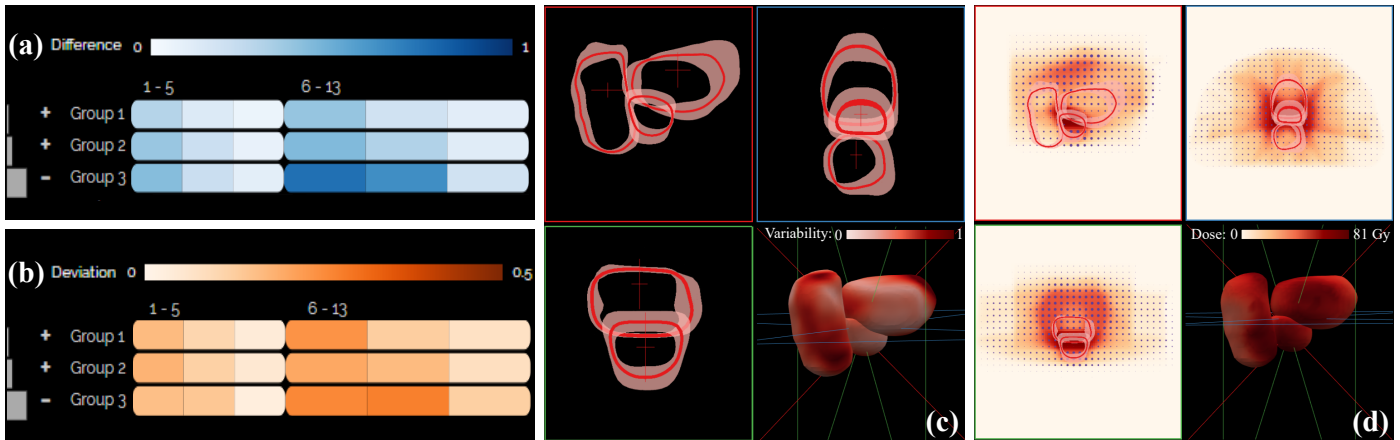
#### 29 6.4. Multi-Organ Exploration in a Cohort

30 This scenario is depicted in Figure 13, and targets all three  
 31 tasks of Section 3. The explorative tasks of the scenario presented  
 32 in Section 6.1 can be repeated for all the available organs (T1).  
 33 In Figure 13 (a), the tabular representation encodes the average  
 34 variability values of the three organs side-by-side. In Figure 13  
 35 (b), it presents their deviations. The prostate volumes (in the  
 36 rightmost cells) do not undergo any large shape variations. These  
 37 low values are encoded with almost white color for the cells of all  
 38 groups. The anatomical view of group 3 (Figure 13 (c)), which is  
 39 the one with the highest shape variability, shows all shape and  
 40 positional changes of the organs (T2). While the prostate and the  
 41 bladder undergo positional changes

mostly along the vertical axis, as indicated by the cross glyphs, 42  
 the motion of the rectum is predominant along the sagittal axis, 43  
 i.e., the back-to-front axis of a patient. Overlaps between the 44  
 prostate shape and other organs can be due to the fact that the 45  
 CTV includes an additional safety margin [2]. Regarding the 46  
 shape changes, the bladder extends mostly towards the direction 47  
 away from the prostate, similar to the results of Section 6.1. For 48  
 the rectum, there is no predominant direction of change, which 49  
 might be due to the fact that the rectum is an organ with inherently 50  
 high anatomical variability. The dose distribution within the same 51  
 group (Figure 13 (d)) indicates that both bladder and rectum are 52  
 exposed to high RT dose, as seen in the 3D view (T3). The circular 53  
 glyphs superposed on the anatomical planes denote a high RT dose 54  
 variability and higher doses outside of the region of the prostate. 55  
 A possible explanation for this is that some patients in this group 56  
 received also lymph node irradiation to reduce recurrence, therefore 57  
 the irradiation field was much larger. 58  
 59

#### 60 6.5. Initial Feedback

61 We also address here the strengths, weaknesses, limitations, and  
 62 future improvements of our work. The involved domain experts  
 63 commented that the application provides a flexible and systematic  
 64 way to explore the data—allowing them to aggregate information  
 65 in different ways and inspecting the most interesting aspects of  
 66 these. The approach is “a promising and useful decision-making  
 67 tool for radiation oncologists”. As they stated, “there are many  
 68 possibilities, and many features” and this allows them to approach  
 69 their data in many different ways—depending on their specific  
 70 hypothesis or exploratory task. It allows them to see individual  
 71 organs, multiple organs, multiple patients, and also subgroups of  
 72 the cohort, at the same time. Although this was not intended  
 73 functionality, they commented that “the tool offers a way of  
 74 identifying the setup uncertainty of the entire treatment”, as it  
 75 allows an overview of the motion, i.e., uncertainty, of the prostate.  
 76 The exploded views have been created to allow the users to  
 77 “drag apart” the different organs so that the overlaps would not  
 78 interfere with their understanding of variability at organ interfaces.  
 79 The reaction of experts to this functionality was rather neutral. It  
 80 was seen as an additional (neutral) feature—neither absolutely  
 81 necessary nor useless. The 2D views seemed to be more useful  
 82 than the 3D views, which



**Fig. 13.** Scenario for multi-organ cohort exploration along with the radiation, showing (a) the average anatomical variability of the three involved organs and (b) their deviation, (c) the shape and positional variability of all pelvic organs, as well as (d) the dose variability in the most varying group. Group 3 manifests the highest shape and positional variability, and within this group, both bladders and rectums are exposed to high RT dose.

1 is a common observation in radiation therapy treatment [2]. 3D  
 2 views are, in general, not very common in clinical practice, and  
 3 all representations are mainly 2D-based. We included the 3D  
 4 view for a matter of completeness and context. The domain ex-  
 5 perts expressed that they would like to explore further the data  
 6 in the frame of their future clinical research. They expect that  
 7 working more with the application will bring forward interest-  
 8 ing aspects for improvements—but most importantly, for the  
 9 improvement of treatment planning. For example, the applica-  
 10 tion could give “indications of patients that will fail or that may  
 11 develop toxicity at the beginning of the treatment”, allowing  
 12 them to adapt the employed strategy. Potentially, it could help  
 13 “creating thresholds [i.e., guidelines] for patient treatment”. As  
 14 points for future work, the domain experts proposed the addi-  
 15 tion of functionality for conducting easy annotations and mea-  
 16 surements concerning, e.g., the confidence bands of the contour  
 17 boxplots. This would quantify the up-to-now qualitative inspec-  
 18 tion of the variability and could be done by, for example, prob-  
 19 ing along the median contour. This is considered to be initial  
 20 informal feedback, and in the future, we would like to conduct  
 21 an extensive evaluation, also within the scope of a retrospective  
 22 clinical study with a larger cohort.

## 23 7. Conclusions and Future Work

24 We present *VAPOR*, a visual analysis application for the ex-  
 25 ploration of pelvic organs in multiple patients, across the whole  
 26 RT treatment procedure. *VAPOR* focuses on the global explo-  
 27 ration and analysis of pelvic organ variability in an abstracted  
 28 tabular view and on the local exploration and analysis of shape  
 29 and positional variability in a combined 2D/3D anatomical  
 30 view. The application integrates functionality for the analysis  
 31 of the irradiated dose with regard to the anatomical variability  
 32 and the possibility to relate the analysis to retrospective toxic-  
 33 ity information within cohort studies. We showcased the func-  
 34 tionality of *VAPOR* with four usage scenarios conducted with  
 35 two domain experts. Directions for future work include a thor-  
 36 ough evaluation with the intended users, as well as a quantita-  
 37 tive evaluation to assess the robustness of the current partition-

ing approach. For this, a larger cohort would also be needed. 38  
 The registration part of the workflow could also be evaluated 39  
 and improved to yield more robust results. The capabilities of 40  
 hierarchical clustering could be harvested further in the future, 41  
 to enable a more thorough inspection and refinement of clusters 42  
 by the users. In its current state, *VAPOR* has been designed for 43  
 domain experts—namely, medical physicists—who are famil- 44  
 iar with the implemented analysis and are also (up to a certain 45  
 extent) visualization and machine learning literate. For clini- 46  
 cians, who are more involved in the design and administration 47  
 of treatment plans, the application is not yet suitable, and this 48  
 group might significantly benefit from a simplified version that 49  
 focuses more on describing the organ shape variations of indi- 50  
 vidual patients. While *VAPOR* supports, e.g., different possi- 51  
 bilities of grouping patients, organs or timesteps, each option 52  
 is suitable for different types of tasks. For each task, the ex- 53  
 ploration is quite straightforward—if the user has a specific hy- 54  
 pothesis or exploratory task in mind. Without a clear task in 55  
 mind, the number of options could be overwhelming. Guidance 56  
 concepts [64] and a higher degree of automatization should be 57  
 integrated, in this case. *VAPOR* is a first step towards the an- 58  
 alysis of variability in multi-organ patient cohorts, the investiga- 59  
 tion of the effects of anatomical variability on dose adminis- 60  
 tration and potential RT-induced toxicity, and its inclusion in 61  
 adaptive RT. 62

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## 69 References

- 70 [1] Delaney, G, Jacob, S, Featherstone, C, Barton, M. The role of radio-  
 71 therapy in cancer treatment. *Cancer* 2005;104(6):1129–1137.

- [2] Schlachter, M, Raidou, R, Muren, L, Preim, B, Putora, P, Bühler, K. State-of-the-art report: Visual computing in radiation therapy planning. In: Computer Graphics Forum; vol. 38. 2019, p. 753–779.
- [3] Washington, CM, Leaver, DT. Principles and practice of radiation therapy. Book. Elsevier Health Sciences; 2015.
- [4] Casares-Magaz, O, Moiseenko, V, Hopper, A, Pettersson, NJ, Thor, M, Knopp, R, et al. Associations between volume changes and spatial dose metrics for the urinary bladder during local versus pelvic irradiation for prostate cancer. *Acta Oncologica* 2017;56(6):884–890.
- [5] Moiseenko, V, Liu, M, Kristensen, S, Gelowitz, G, Berthelet, E. Effect of bladder filling on doses to prostate and organs at risk: a treatment planning study. *Journal of Applied Clinical Medical Physics* 2007;8(1):55–68.
- [6] Viswanathan, AN, Yorke, ED, Marks, LB, Eifel, PJ, Shipley, WU. Radiation dose–volume effects of the urinary bladder. *International Journal of Radiation Oncology\* Biology\* Physics* 2010;76(3):S116–S122.
- [7] Thariat, J, Hannoun-Levi, JM, Myint, AS, Vuong, T, Gérard, JP. Past, present, and future of radiotherapy for the benefit of patients. *Nature reviews Clinical oncology* 2013;10(1):52.
- [8] Chai, X, van Herk, M, van de Kamer, JB, Hulshof, MC, Remeijer, P, Lotz, HT, et al. Finite element based bladder modeling for image-guided radiotherapy of bladder cancer. *Medical physics* 2011;38(1):142–150.
- [9] Lotz, HT, van Herk, M, Betgen, A, Pos, F, Lebesque, JV, Remeijer, P. Reproducibility of the bladder shape and bladder shape changes during filling. *Medical physics* 2005;32(8):2590–2597.
- [10] Chai, X, van Herk, M, Hulshof, MC, Bel, A. A voxel-based finite element model for the prediction of bladder deformation. *Medical physics* 2012;39(1):55–65.
- [11] Rios, R, De Crevoisier, R, Ospina, JD, Commandeur, F, Lafond, C, Simon, A, et al. Population model of bladder motion and deformation based on dominant eigenmodes and mixed-effects models in prostate cancer radiotherapy. *Medical image analysis* 2017;38:133–149.
- [12] Raidou, RG, Casares-Magaz, O, Amirkhanov, A, Moiseenko, V, Muren, LP, Einck, JP, et al. Bladder runner: Visual analytics for the exploration of rt-induced bladder toxicity in a cohort study. In: Computer Graphics Forum; vol. 37. 2018, p. 205–216.
- [13] Casares-Magaz, O, Raidou, R, Pettersson, N, Moiseenko, V, Einck, J, Hopper, A, et al. Bladder changes during first week of RT for prostate cancer determine the risk of urinary toxicity. *European Society for Radiation & Oncology (ESTRO)* 38 2019;.
- [14] Grossmann, N, Casares-Magaz, O, Muren, LP, Moiseenko, V, Einck, JP, Gröller, E, et al. Pelvis Runner: Visualizing Pelvic Organ Variability in a Cohort of Radiotherapy Patients. In: Eurographics Workshop on Visual Computing for Biology and Medicine (VCBM 2019). The Eurographics Association; 2019, p. 69–78.
- [15] Quan, EM, Li, X, Li, Y, Wang, X, Kudchadker, RJ, Johnson, JL, et al. A comprehensive comparison of imrt and vmat plan quality for prostate cancer treatment. *International Journal of Radiation Oncology\* Biology\* Physics* 2012;83(4):1169–1178.
- [16] Muren, LP, Smaaland, R, Dahl, O. Organ motion, set-up variation and treatment margins in radical radiotherapy of urinary bladder cancer. *Radiotherapy and Oncology* 2003;69(3):291–304.
- [17] Schlachter, M, Fechter, T, Adebahr, S, Schimek-Jasch, T, Nestle, U, Bühler, K. Visualization of 4d multimodal imaging data and its applications in radiotherapy planning. *Journal of applied clinical medical physics* 2017;18(6):183–193.
- [18] Aselmaa, A, Goossens, R, Laprie, A, Ken, S, Fechter, T, Ramkumar, A, et al. Workflow analysis report. Delft University of Technology 2013;.
- [19] Nejad-Davarani, SP, Sevak, P, Moncion, M, Garbarino, K, Weiss, S, Kim, J, et al. Geometric and dosimetric impact of anatomical changes for MR-only radiation therapy for the prostate. *Journal of applied clinical medical physics* 2019;20(4):10–17.
- [20] Wentzel, AP, Hanula, P, Luciani, T, Elgohari, B, Elhalawani, H, Canahuate, G, et al. Cohort-based t-ssim visual computing for radiation therapy prediction and exploration. *IEEE Transactions on Visualization and Computer Graphics* 2019;26:949–959.
- [21] Peura, M, Iivarinen, J. Efficiency of simple shape descriptors. *Aspects of visual form* 1997;:443–451.
- [22] Maaten, Lvd, Hinton, G. Visualizing data using t-sne. *Journal of machine learning research* 2008;9(Nov):2579–2605.
- [23] Comaniciu, D, Meer, P. Mean shift: A robust approach toward feature space analysis. *IEEE Transactions on Pattern Analysis & Machine Intelligence* 2002;(5):603–619.
- [24] Reiter, O, Breeuwer, M, Gröller, ME, Raidou, RG. Comparative visual analysis of pelvic organ segmentations. In: Proceedings of the Eurographics/IEEE VGTC Conference on Visualization: Short Papers. Eurographics Association; 2018, p. 37–41.
- [25] Kazhdan, M, Funkhouser, T, Rusinkiewicz, S. Rotation invariant spherical harmonic representation of 3 d shape descriptors. In: Symposium on geometry processing; vol. 6. 2003, p. 156–164.
- [26] Shlens, J. A tutorial on principal component analysis. *arXiv preprint arXiv:1404.1100* 2014;.
- [27] Hermann, M, Schunke, AC, Klein, R. Semantically steered visual analysis of highly detailed morphometric shape spaces. In: 2011 IEEE Symposium on Biological Data Visualization (BioVis). IEEE; 2011, p. 151–158.
- [28] Hermann, M, Schunke, AC, Schultz, T, Klein, R. A visual analytics approach to study anatomic covariation. In: 2014 IEEE Pacific Visualization Symposium. IEEE; 2014, p. 161–168.
- [29] Hermann, M, Schunke, AC, Schultz, T, Klein, R. Accurate interactive visualization of large deformations and variability in biomedical image ensembles. *IEEE Transactions on Visualization and Computer Graphics* 2016;22(1):708–717.
- [30] Hermann, M, Klein, R. A visual analytics perspective on shape analysis: state of the art and future prospects. *Computers & Graphics* 2015;53:63–71.
- [31] Busking, S, Botha, CP, Post, FH. Dynamic multi-view exploration of shape spaces. In: Computer Graphics Forum; vol. 29. 2010, p. 973–982.
- [32] Busking, S, Botha, CP, Ferrarini, L, Milles, J, Post, FH. Image-based rendering of intersecting surfaces for dynamic comparative visualization. *The visual computer* 2011;27(5):347–363.
- [33] Von Landesberger, T, Bremm, S, Kirschner, M, Wesarg, S, Kuijper, A. Visual analytics for model-based medical image segmentation: Opportunities and challenges. *Expert Systems with Applications* 2013;40(12):4934–4943.
- [34] Blumenschein, M, Behrisch, M, Schmid, S, Butscher, S, Wahl, DR, Villinger, K, et al. Smartexplore: Simplifying high-dimensional data analysis through a table-based visual analytics approach. In: IEEE Conference on Visual Analytics Science and Technology (VAST) 2018. 2018;.
- [35] Klemm, P, Lawonn, K, Rak, M, Preim, B, Tönnies, KD, Hegenscheid, K, et al. Visualization and analysis of lumbar spine canal variability in cohort study data. In: *Vision, Modeling and Visualization*. 2013, p. 121–128.
- [36] Klemm, P, Oeltze-Jafra, S, Lawonn, K, Hegenscheid, K, Völzke, H, Preim, B. Interactive visual analysis of image-centric cohort study data. *IEEE Transactions on Visualization and Computer Graphics* 2014;20(12):1673–1682.
- [37] Steenwijk, MD, Milles, J, Buchem, M, Reiber, J, Botha, CP. Integrated visual analysis for heterogeneous datasets in cohort studies. In: IEEE VisWeek Workshop on Visual Analytics in Health Care; vol. 3. 2010, p. 3.
- [38] Preim, B, Klemm, P, Hauser, H, Hegenscheid, K, Oeltze, S, Toennies, K, et al. Visual analytics of image-centric cohort studies in epidemiology. In: *Visualization in Medicine and Life Sciences III*. Springer; 2016, p. 221–248.
- [39] Bernard, J, Sessler, D, May, T, Schlomm, T, Pehrke, D, Kohlhammer, J. A visual-interactive system for prostate cancer cohort analysis. *Computer Graphics and Applications (CG&A)*, IEEE 2015;35(3):44–55.
- [40] Alemzadeh, S, Hielscher, T, Niemann, U, Cibulski, L, Ittermann, T, Völzke, H, et al. Subpopulation Discovery and Validation in Epidemiological Data. In: EuroVis Workshop on Visual Analytics (EuroVA). The Eurographics Association; 2017;.
- [41] Wang, J, Hazarika, S, Li, C, Shen, HW. Visualization and visual analysis of ensemble data: A survey. *IEEE Transactions on Visualization and Computer Graphics* 2018;25(9):2853–2872.
- [42] Whitaker, RT, Mirzargar, M, Kirby, RM. Contour boxplots: A method for characterizing uncertainty in feature sets from simulation ensembles. *IEEE Transactions on Visualization and Computer Graphics* 2013;19(12):2713–2722.
- [43] Mirzargar, M, Whitaker, RT, Kirby, RM. Curve boxplot: Generalization of boxplot for ensembles of curves. *IEEE Transactions on Visualization and Computer Graphics* 2014;20(12):2654–2663.
- [44] Ferstl, F, Kanzler, M, Rautenhaus, M, Westermann, R. Visual analysis of spatial variability and global correlations in ensembles of iso-contours. In: Computer Graphics Forum; vol. 35. 2016, p. 221–230.
- [45] Ferstl, F, Bürger, K, Westermann, R. Streamline variability plots for

- 1 characterizing the uncertainty in vector field ensembles. *IEEE Transactions on Visualization and Computer Graphics* 2016;22(1):767–776.
- 2
- 3 [46] Ferstl, F, Kanzler, M, Rautenhaus, M, Westermann, R. Time-hierarchical clustering and visualization of weather forecast ensembles. *IEEE Transactions on Visualization and Computer Graphics* 2017;23(1):831–840.
- 4
- 5
- 6 [47] Kim, K, Carlis, JV, Keefe, DF. Comparison techniques utilized in spatial 3d and 4d data visualizations: A survey and future directions. *Computers & Graphics* 2017;67:138–147.
- 7
- 8
- 9 [48] Keefe, D, Ewert, M, Ribarsky, W, Chang, R. Interactive coordinated multiple-view visualization of biomechanical motion data. *IEEE Transactions on Visualization and Computer Graphics* 2009;15(6):1383–1390.
- 10
- 11
- 12 [49] Tory, MK, Möller, T, Atkins, MS. Visualization of time-varying mri data for ms lesion analysis. In: *Medical Imaging 2001: Visualization, Display, and Image-Guided Procedures*; vol. 4319. International Society for Optics and Photonics; 2001, p. 590–599.
- 13
- 14
- 15 [50] Schmidt, J, Preiner, R, Auzinger, T, Wimmer, M, Gröller, ME, Bruckner, S. YMCA—Your mesh comparison application. In: *2014 IEEE Conference on Visual Analytics Science and Technology (VAST)*. IEEE; 2014, p. 153–162.
- 16
- 17 [51] Hilbert, D. Über die stetige Abbildung einer Linie auf ein Flächenstück. In: *Dritter Band: Analysis·Grundlagen der Mathematik·Physik Verschiedenes*. Springer; 1935, p. 1–2.
- 18
- 19
- 20 [52] Weissenböck, J, Fröhler, B, Gröller, E, Kastner, J, Heinzl, C. Dynamic volume lines: Visual comparison of 3d volumes through space-filling curves. *IEEE Transactions on Visualization and Computer Graphics* 2019;25(1):1040–1049.
- 21
- 22
- 23 [53] Demir, I, Dick, C, Westermann, R. Multi-Charts for Comparative 3D Ensemble Visualization. *IEEE Transactions on Visualization and Computer Graphics* 2014;20(12):2694 – 2703.
- 24
- 25
- 26 [54] Everitt, B, Landau, S, Leese, M. *Cluster analysis*. A member of the Hodder Headline Group, London 2001;:429–438.
- 27
- 28 [55] Harrower, M, Brewer, CA. Colorbrewer.org: an online tool for selecting colour schemes for maps. *The Cartographic Journal* 2003;40(1):27–37.
- 29
- 30 [56] Buja, A, Cook, D, Swayne, DF. Interactive high-dimensional data visualization. *Journal of computational and graphical statistics* 1996;5(1):78–99.
- 31
- 32
- 33 [57] Furmanova, K, Gratzl, S, Stitz, H, Zichner, T, Jaresova, M, Ennemoser, M, et al. Taggle: Scalable visualization of tabular data through aggregation. *arXiv preprint arXiv:171205944* 2017;.
- 34
- 35 [58] Balabanian, JP, Viola, I, Gröller, ME. Interactive illustrative visualization of hierarchical volume data. *Proceedings of Graphics Interface 2010*;:137–144.
- 36
- 37
- 38 [59] Borgo, R, Kehrler, J, Chung, DH, Maguire, E, Laramée, RS, Hauser, H, et al. Glyph-based visualization: Foundations, design guidelines, techniques and applications. In: *Eurographics (STARs)*. 2013, p. 39–63.
- 39
- 40 [60] Raidou, RG, Casares-Magaz, O, Muren, LP, Heide, Uvd, Roervik, J, Breeuwer, M, et al. Visual analysis of tumor control models for prediction of radiotherapy response. *Computer Graphics Forum* 2016;35(3):231–240.
- 41
- 42 [61] Ristovski, G, Garbers, N, Hahn, HK, Preusser, T, Linsen, L. Uncertainty-aware visual analysis of radiofrequency ablation simulations. *Computers & Graphics* 2019;79:24–35.
- 43
- 44 [62] Casares-Magaz, O, Raidou, RG, Rørvik, J, Vilanova, A, Muren, LP. Uncertainty evaluation of image-based tumour control probability models in radiotherapy of prostate cancer using a visual analytic tool. *Physics and Imaging in Radiation Oncology* 2018;5:5–8.
- 45
- 46 [63] Pinkawa, M, Asadpour, B, Gagel, B, Piroth, MD, Holy, R, Eble, MJ. Prostate position variability and dose–volume histograms in radiotherapy for prostate cancer with full and empty bladder. *International Journal of Radiation Oncology\* Biology\* Physics* 2006;64(3):856–861.
- 47
- 48 [64] Ceneda, D, Gschwandtner, T, May, T, Miksch, S, Schulz, HJ, Streit, M, et al. Characterizing guidance in visual analytics. *IEEE Transactions on Visualization and Computer Graphics* 2016;23(1):111–120.
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
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