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State-of-the-Art Report
Visual Computing in Radiation Therapy Planning

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Abstract

Radiation therapy (RT) is one of the major curative approaches for cancer. It is a complex and risky treatment approach, which requires precise planning, prior to the administration of the treatment. Visual Computing (VC) is a fundamental component of RT planning, providing solutions in all parts of the process—from imaging to delivery. Despite the significant technological advancements of RT over the last decades, there are still many challenges to address. This survey provides an overview of the compound planning process of RT, and of the ways that VC has supported RT in all its facets. The RT planning process is described to enable a basic understanding in the involved data, users and workflow steps. A systematic categorization and an extensive analysis of existing literature in the joint VC/RT research is presented, covering the entire planning process. The survey concludes with a discussion on lessons learnt, current status, open challenges, and future directions in VC/RT research.

Categories and Subject Descriptors (according to ACM CCS): J.3 [Computer Graphics]: Life and Medical Sciences—Health, Medical information systems

1. Introduction

According to the World Health Organization (WHO), cancer is the second leading cause of death worldwide [Wor18]. In 2018, 18.1 million people were globally diagnosed with cancer, while 9.6 million deaths have been attributed to malignancies. For most cancer types, radiation therapy (RT) and surgery are widely used for curative purposes [DJFB05, ZM16]. RT has been used as cancer treatment for more than a century [Sla12], and has undergone steady development in the past decade [THM*13]. It is used as *therapeutic treatment* to cure the disease, as *adjuvant therapy* to prevent tumor recurrence, or as *palliative treatment* to relieve patients of symptoms. Often, RT complements surgery, chemotherapy, hormonotherapy, immunotherapy, or a combination of those [Was15]. The risky and complex nature of RT treatment make it a special field of application within VC, as it requires rather sophisticated combinations of a wide range of VC techniques.

RT is based on the use of ionizing rays, such as photon, electron or proton radiation, to destroy malignant cells. Tumors are treated with higher radiation doses, while adjacent healthy organ tissues must receive lower doses, to minimize the side effects of radiation [Was15]. The administered radiation dose used in RT is measured in Grays (Gy), and varies depending on the type and stage of the cancer, as well as the intent of treatment.

RT involves much higher dose of radiation than diagnostic modalities, such as CT and X-ray. Thus, there is a high risk of tissue damage leading eventually to secondary cancer, and planning is more important than in any other kind of medical treatment. Prior to dose administration, the treatment must be carefully planned to ensure adequate irradiation of the tumor target and to spare the surrounding healthy tissues, as much as possible. To this end, precise delineation of the target tumor and all adjacent organs at risk (OARs) is necessary. Dose calculation through simulation is then carried out for each individual patient, in order to assess whether a sufficient dose to destroy the tumor is achieved, while maintaining tolerable doses to the OARs.

The treatment process can be *internal* (e.g., Brachytherapy treatment) or *external* (e.g., External Beam Radiation Therapy or EBRT) [Was15]. In the former, radioactive sources are positioned precisely inside the area to be treated, affecting only a very localized region [GPM*02]. In the latter, the radiation source is a linear accelerator (LINAC), and is located outside of the patient. The LINAC accelerates electrons, allowing them to collide with a heavy metal target to produce high-energy x-rays, shaped to *conform* to the shape of the target volume covering the tumor. The beam is shaped by a multileaf collimator and is directed to the tumor by a gantry rotating around the patient, who lies on a movable treatment couch. A schematic depiction of a LINAC is presented in Figure 1. In this survey, we focus on EBRT, as it is the most widespread treatment in current clinical practice—hence, visual computing (VC) solutions have mostly addressed this.

The complex data, the compound processes and the multitude of user groups involved in RT make it particularly interesting for several fields of research [PB13]. These include image processing, visualization, VC and machine learning. Currently, there are several reasons which bring RT into the spotlight of clinical and technological research, leading also to new challenging research questions for

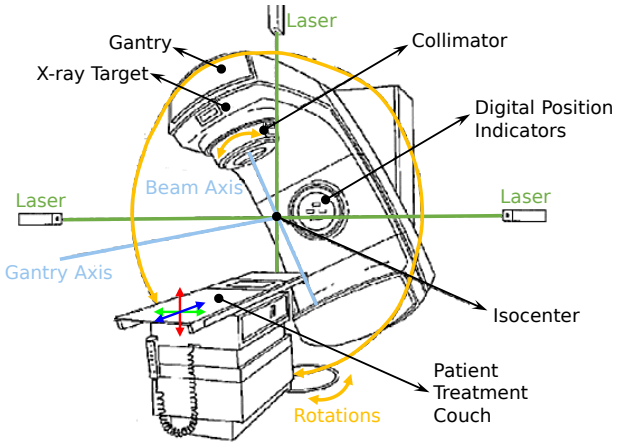

Figure 1: *Schematic depiction of a linear accelerator (LINAC) used in External Beam Radiation Therapy (EBRT) treatment, with its major components and employed axes. Rotational and translational movements of several parts are depicted with arrows.*

VC. Recently, there is an increasing demand for more personalized therapy, which will maximize tumor treatment and minimize side effects [THM*13, TOG06]. This trend requires the development of new means within the VC domain, while targeted patient treatment includes more and more often additional patient- and tumor-specific information [TOG06]. All this information is complex and heterogeneous, and new strategies for its visualization, exploration and analysis need to be designed [Rai17].

There is a significant amount of work applied in the various steps of the RT workflow, covering a wide range of VC research. Developing novel VC methods to support RT research and RT planning requires interdisciplinary strategies—integrating the whole VC portfolio from data, image and information fusion [NRS*14, SFA*17], to interaction [AvHL*17], exploration and visual analytics [Rai17, RBV17, RMB*16, RvD*15, RvdHvH*14]. The topic is also manifold, involving different sources of data and uncertainty, several specialist users, and a variety of applications and challenges—many of which are also applicable to other medical and non-medical domains.

As we will illustrate in the upcoming sections, RT planning involves multi-modal and multi-valued data [Was15]. Also, each step of the RT workflow involves heterogeneous sources of information. These might relate, for example, to multi-modal registration [SFJ*16] and segmentation data [RMB*16], to ensemble data from the optimization phase of the dose planning [SRV16], or to modeling data from tumor control probability (TCP) [RCM*16] and normal tissue complication probability (NTCP) [RBGR18, RCA*18]. Understanding, exploring and analyzing all these data channels can be a demanding and time-consuming task.

Additionally, uncertainty [Rai18, RPHL14] is present at all steps of the workflow, affecting the accuracy and precision of the final outcome [BCTT08, KMB*06, vRL02]. Uncertainties, which cannot be corrected or minimized, need to be addressed and their impact has to be predicted. For example, motion management in RT can be challenging for tumors and organs affected by breathing, e.g., the lung [BCTT08, KMB*06]. In particular, for treatment methods which involve critically high doses, such as Stereotactic Body RT (SBRT) for lung cancer, even slight movements cannot be ignored. 4D imaging and deformable registration can be used to model breathing motion [WSVHD08], but these introduce uncertainty [SFJ*16]. Uncertainties are also present in segmentation [RBGR18, RMB*16] and (radiobiological) modeling [RCA*18, RCM*16], to name a few. In particular, within radiobiological modeling, the careful quantitative reasoning about the probability of tumor control is unique for medical treatment. Thus, uncertainty qualification related to predictions and uncertainty visualization fit in the workflow of RT planning, as opposed to other types of medical treatment.

Another important aspect is the variety of specialists involved in the different steps of the RT workflow, such as radiologists, radiation oncologists, medical physicists and dosimetrists. While patient treatment is the primary goal, users have different benefits from the use of VC [PB13]. These may include, e.g., diagnosis, data exploration, verification or decision making. Therefore, the needs of different users need to be addressed individually, increasing the complexity of the visual design process [DNT09].

Despite the importance of VC in RT, the last surveys have been published over a decade ago [Eva08, PC00, Pel98, PGC*96, Rob99]. They address only imaging and volume rendering within the application domain of RT, and do not cover the latest advancements. There has not been any previous effort in systematizing existing literature in the field and in providing recommendations for future directions for VC in RT. With this survey, we expect to trigger interesting new directions for future work, both in RT applications and in other domains. Apart from the need for VC strategies to tackle challenges in RT planning, we foresee that existing ones for the RT workflow can be reusable, generalizable or applicable to other fields—also non-clinical ones.

Contributions—The contributions of this survey are:

- A comprehensive and comprehensible *taxonomy* of published work in the field of VC, applied to the domain of RT.
- A discussion, underlining the *achievements* of VC in RT so far, highlighting the main *challenges and limitations*, and envisioning *applicability for future work*.
- The identification of *key research directions* for the future based on the taxonomy and discussion.

Scope of this work—For the collection of previous work included in the taxonomy, we used an extensive search of literature databases. Results of the literature search were required to cover or to be related to visual computing, radiotherapy and its planning. After the initial literature search, results were removed if they were not within the scope. We consider within scope all applications from the field of VC (visualization, visual analytics and VR/AR applications) that are related to one or more steps of RT planning. We consider out of scope previous work that was not within the VC and RT planning interface. Details about the literature search and sources are explained in Section 3 and summarized in Table 1.

Outline—The remainder of this survey is structured as follows. In Section 2, we discuss necessary background notions of the RT do-

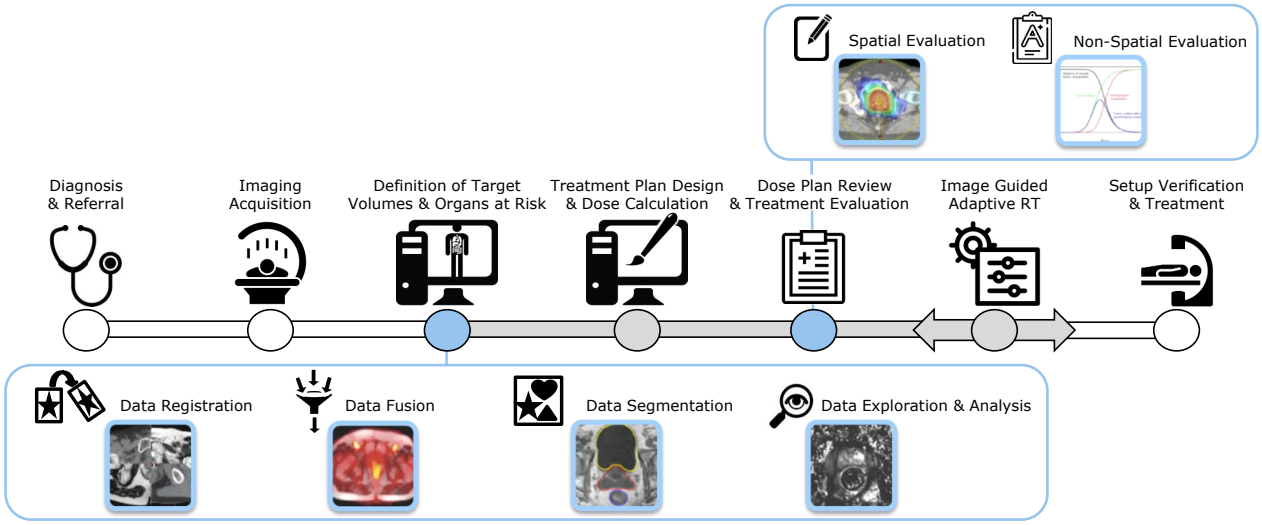

Figure 2: *The steps of the workflow of RT planning, as adapted from the book of Washington and Leaver [Was15]. Within this survey, we are concerned with the workflow parts, within the gray margins. Note that most of workflow steps comprise sub-steps, some of which are denoted in the blue pop-ups.*

main. In Section 3, we present the taxonomy scheme and a detailed description of previous work falling within each of the taxonomy categories. Furthermore, we discuss evaluation methods and areas of main concentration of the literature. Section 4 presents an outlook from the RT domain. Section 5 discusses so-far achievements of VC in RT, as well as present challenges or limitations, and directions for future work from a joint VC/RT perspective. Section 6 concludes the survey with a summary of this work.

2. Radiation Therapy Planning: Workflow, Data and Users

In the past decade, RT has undergone a steady evolution (see Section 4), offering flexibility in radiation dose delivery. The advent of new delivery techniques has improved treatment, such as Intensity-Modulated Radiation Therapy (IMRT) and more recently Volumetric Arc Therapy (VMAT)—both subsets of EBRT. These techniques can precisely address tumors, by modulating the intensity of the radiation beam around the tumor volume, while decreasing or avoiding radiation among the surrounding healthy tissues [Web01]. This modulation, i.e., shaping and aiming of radiation beams from several angles of exposure to cumulatively target the tumor, happens in the LINAC by the multileaf collimator, as shown in Figure 1.

Still, RT may result in a number of potential side effects depending on the dose, fractionation and location. These can range from acute skin irritation [Was15] to secondary cancer decades later [HW03]. To maximize the effectiveness of tumor treatment, while minimizing the damage to surrounding tissues, the radiation dose administration must be carefully planned in dedicated software [Was15]. RT planning follows a workflow, which can be outlined by a series of steps depicted in Figure 2. The time required for the planning procedure differs for each individual patient and is specific to the characteristics of the case and the tumor. An in-depth workflow analysis has been previously presented by Aselmaa et al. [AGL*13].

After diagnosis and referral, patient images are acquired [TAKC09]. *Multiple imaging modalities* are often employed, as studies have demonstrated that the combination of different acquisitions can improve detection, diagnosis and staging [BJE*11, BRC*12, CKK*07, HCE*07]. Clinical imaging techniques can be classified into anatomic methods, which measure physical properties of tissue, such as tissue density acquired from Computed Tomography (CT), and functional imaging techniques, which measure functional characteristics, such as metabolism acquired from Positron Emission Tomography (PET) [Eva08]. In a prostate cancer case, multi-modal imaging can include CT Imaging, T2-Weighted Magnetic Resonance Imaging (MRI), Diffusion-Weighted Imaging (DWI), Dynamic-Contrast Enhanced MR Imaging (DCE-MRI) and MR Spectroscopy Imaging (MRSI) [BJE*11, BRC*12, CKK*07, HCE*07].

A crucial step of treatment planning is the *definition of target volumes*, i.e., the tumor tissue, and *organs at risk (OARs)*, i.e., volumes representing whole organs or parts which have to be spared during treatment [Nje08]. The delineation (or *segmentation*) of targets and OARs often employs more than one imaging source, which has proven to be advantageous with regards to specificity and sensitivity [LKCG12]. *Data fusion* for the integration and combination of various information channels is also part of this process, while interactive approaches for the *exploration and analysis* of the data are also employed. All aforementioned images need to be *registered* [ZF03], to be transformed into the same coordinate system as the planning CT.

After the localization of the tumor and adjacent organs, one (or more) *initial treatment plan(s)* is (are) designed, using treatment planning software (TPS). Complex constraints and guidelines are

employed to determine the geometric, radiobiological and dosimetric aspects of the treatment—taking into account the OARs, and optimizing for tumor treatment and for healthy tissue preservation [Was15]. For target volumes, a required minimum dose is prescribed, whereas OARs should receive doses as low as possible [BRC*12, HMP*18]. The tolerance for radiation differs between organs and depends on their tissue properties. This information is also incorporated to prescribe a level of radiation so that no damage is induced to them.

The calculated treatment plan(s) will undergo further *review and approval*. Dose volume histograms (DVH) [DMB*91] are often used to summarize the distribution of doses to the target and OARs. Also, the final prescribed radiation dose will not be administered all at once. Fractionation [THM*13, Was15] is used in most treatments, where the total dose is spread out in adequate amounts over time, to allow the recovery of normal cells and to prevent the repair of tumor cells between fractions. The step of radiobiological modeling is conducted for the effectiveness assessment of the selected RT strategy, involving Tumor Control Probability (TCP) modeling [WN93] and Normal Tissue Complication Probability (NTCP) modeling [MYJ*10]. TCP models are statistical models that quantify the probability that a tumor is effectively controlled, i.e. treated, given a specific radiation dose, and respectively NTCP models, that normal tissue around the tumor is harmed.

Image-Guided Adaptive RT (IGART) requires to further verify whether the initial plan is still applicable. Sometimes, changes in the tumor location and shape or anatomical changes of the patient, e.g. due to weight loss or due to rectal and urinary filling, require further plan modifications between treatment fractions. At the point of treatment delivery, a prior *verification* step ensures that the patient is correctly positioned.

2.1. Users Involved in RT Planning

Several clinical experts are involved in the steps of the RT workflow [AGL*13]. Each specialist has a different role—implying that VC has also different benefits for them. The most relevant specialist groups are:

1. Radiation oncologists (main responsibles for the prescription, approval and supervision of the treatment—involved in *all steps* of the RT workflow).
2. Medical physicists (scientists who advise on the best treatment strategy—involved in *Definition of Target Tumor(s) & Organs at Risk*, *Treatment Plan Design & Dose Calculation*, *Dose Plan Review & Treatment Evaluation*, *Image Guided Adaptive RT*).
3. Radiologists (doctors who specialize in medical imaging acquisition and interpretation—involved in *Diagnosis & Referral*, *Imaging Acquisition*, *Definition of Target Tumor(s) & Organs at Risk*).
4. Radiotherapists (or therapy radiographers, specialists who operate the treatment machines—involved in *Setup Verification & Treatment*).
5. Dosimetrists (main responsible for the careful calculation of the dose in the specialized equipment—involved in *Treatment Plan Design & Dose Calculation*, *Dose Plan Review & Treatment Evaluation*, *Image Guided Adaptive RT*).

2.2. Data Involved in RT Planning

The entire workflow of RT planning is based on the imaging acquisitions of the anatomy and pathology of the patient. Yet, each step of the workflow incorporates additional information or data derived from the imaging acquisitions, as depicted in Figure 2. The final outcome of the workflow is a dose plan, which incorporates 2D or 3D radiation dose information. During this entire planning process several imaging and non-imaging data accumulates around the patient [PPB15].

2.2.1. Imaging Data

In the image acquisition step, the necessary images needed for radiotherapy planning are acquired from a multitude of sources [HCE*07]. These can be CT and MRI data, and data derived thereof, depending on the target anatomy. For example, DWI, DCE, MRSI are used for prostate and cervical tumor treatment planning [BRC*12, BJE*11, CKK*07]. For lung tumors, the use of functional imaging, such as (4D) PET/CT, can be advantageous for tumor definition [SKO06]. Brain tumors may additionally require Diffusion Tensor imaging (DTI) [MBC15]. Details on each modality can be found in recent surveys [LSBP18, PBC*16]. During this step, the planning CT is acquired, a high quality CT which plays an important role in the planning. It serves as the reference coordinate system for target definitions, as well as for other images acquired using different modalities (registration to the planning CT). Furthermore, the tissue densities are used for the dose calculation.

2.2.2. Target Volumes Concept

An important concept within RT is the use of *Target Volumes*, developed by the *International Commission on Radiation Units & Measurements (ICRU)* [Ber07, GLC*04]. Many treatment planning approaches are specifically targeting one (or more) of these volumes, which are explained below. A schematic overview can be found in Figure 3 and two examples are presented in Figure 4.

The volume that contains the visible, *macroscopic* part of the tumor (within the limits of the employed imaging technique) is called the *Gross Tumor Volume (GTV)*. The *Clinical Target Volume (CTV)* contains the GTV and encompasses *microscopic* extensions into healthy tissues, that are not visible [Ber07, GLC*04]. The *Internal Target Volume (ITV)* addresses uncertainties due to organ motion [JYW99, RSO*96], and is only an intermediate volume that has to be expanded by margins for setup errors [SH02]. The ITV concept is not always required, but is common for lung cancer, where breathing motion has to be considered [JHP*15]. The *Planning Target Volume (PTV)* is the volume encompassing the CTV (and the ITV if employed), which takes into account the fact that the CTV and the involved patient anatomy might vary in position, shape and size within or between fractions. It accounts specifically for uncertainties, such as patient setup errors [SH02] to ensure that the CTV will receive the prescribed and planned dose, by adding margins to the CTV (or ITV) [Ben08, JYW99, MvM02]. Based on the PTV, appropriate beam sizes and beam arrangements will be selected to ensure that the prescribed dose is actually delivered to the CTV [Ber07]. The *Treated Volume (TV)* is planned to receive at least a dose, appropriate for the purpose of the treatment. It is, thus,

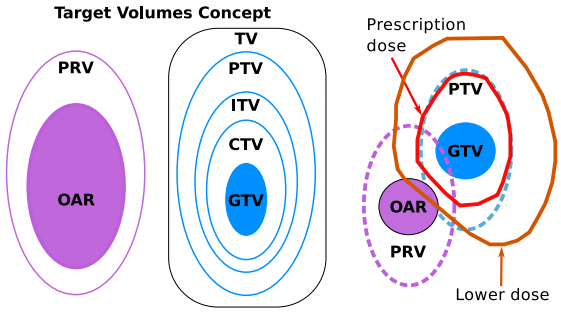

Figure 3: *Volume concepts used in RT planning. The Gross Tumor Volume (GTV), Clinical Target Volume (CTV), Internal Target Volume (ITV) and Planning Target Volume (PTV), as well as the organs at risk (OAR) are denoted. The Treated Volume (TV) is implicitly defined (by a dose value) after dose calculation. The PTV and ITV account for patient setup errors and other sources of inaccuracy, during the administration of the radiation dose. Planning Organs at Risk Volume (PRV) and Internal Target Volume (ITV) are not always defined. A possible configuration of a target close to an OAR is shown on the right. Overlapping volumes can have an impact on the dose calculation, and might lead to insufficient PTV coverage or undesired dose levels for the OAR.*

a volume enclosed by an isodose surface corresponding to that prescribed dose level [Ber07]. For example, if the prescribed dose is 40 Gy, and the minimum dose was 5% below, the TV is then enclosed by a 38 Gy isodose surface.

Organs at risk (OAR) are normal tissues whose radiation sensitivity may significantly limit the treatment. These can be the spinal cord in lung tumor treatment or pelvic organs in prostate tumor treatment. In analogy to the PTV, safety margins can be added around the OAR volumes [MvM02], leading to the concept of the *Planning Organ at Risk Volume (PRV)*.

In clinical reality, Target Volumes and OARs can overlap or even include each other. A patient with a brain tumor, for example, has the target inside the brain, which is an OAR itself. The same applies to a lung cancer patient, where the lung itself is an OAR. Some overlaps are more critical than others, such as the brainstem and PTV for brain cases, or trachea and ITV for lung cases. In Figure 4 the left image is on the lung border and the right image is central and is more critical. Furthermore, determining the margins is not straightforward and depends on a multitude of factors [vH04]. Overlaps of target volumes and OARs present a challenge as the shape of prescribed dose might not be achieved, and on the other side the OARs might receive too high doses in the overlapping regions as schematically depicted in Figure 3 (right). Including information about overlaps during treatment plan evaluation has the potential to improve the overall quality [WRS*09].

2.2.3. Uncertainty in RT Planning

RT planning is—among all therapy planning processes—the one where uncertainty, validation, and verification are considered essential by the involved physicians. In literature, there is no widely accepted definition of uncertainty. A definition is given by Griethe et al. [GS05], as *a composition of different concepts, such as error (outlier or deviation from a true value), imprecision (resolution of a value compared to the needed resolution), subjectivity (degree of subjective influence in the data) and non-specificity (lack of distinction for objects)*. In RT planning, we define uncertainty as any source which may cause variations in any step of the workflow and ultimately in the treatment outcome. Uncertainty is an additional data source, present at all steps of the planning workflow. The quantification and communication of uncertainty is essential for the accurate interpretation of the outcome, for reducing the existing uncertainties and risks, and potentially, for improving the outcome.

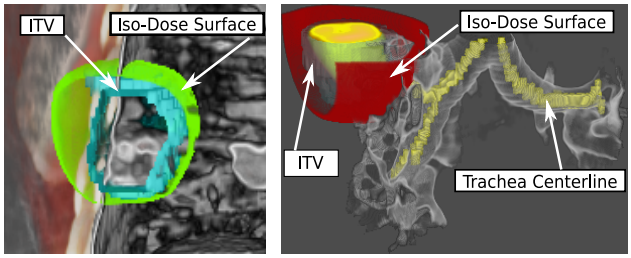

Figure 4: *Left: Isodose surface encompassing the ITV. This is a less critical example, due to the location of the tumor (at the lung border close to a rib), where the PTV (ITV with setup error margin) is not representing the TV well. Right: Example of a difficult case (central lung), where the tumor is close to an OAR. The PTV and PRV were overlapping in this case. Images adapted from [SFA*17].*

With regard to imaging modalities, both DWI and DCE imaging have highly varying sensitivity and specificity for tumor detection [KKP*08, KVCC08, TAKC09], depending on patient characteristics, on the tissue zone and on the scanning procedure itself. Poor spatial imaging resolution and image distortions, due to magnetic field inhomogeneities at the interfaces between different tissues are additional issues in DWI [BJE*11, CKK*07, SFA*05]. In addition to this, pharmacokinetic modeling, which is employed in clinical research for the derivation of additional tissue characteristics from DCE data, is also a source of uncertainty [BRP*04, TAKC09, TBB*99, VTM*12]. Often, to minimize uncertainty different imaging modalities are combined [BJE*11, BRC*12, CKK*07, HCE*07]. In the delineation of the target volumes and OARs, uncertainties due to patient motion, or due to changes in the anatomy and pathology of the patient are considered within the aforementioned target volume definitions (Section 2.2.2). In the other steps, uncertainty can be caused by an ad-hoc choice, assumptions, stochastic processes or inter-observer variability, as discussed in a recent work by Raidou et al. [Rai18]. A more detailed review on uncertainty visualization can be found in the survey by Ristovski et al. [RPHL14].

2.2.4. Dose Plans and Dose Volume Histograms

Dose plans convey 2D or 3D radiation dose information (dose distribution), as generated from treatment planning systems based on a 3D reconstruction of a planning CT scan. Dose distributions are scalar data maps, where the values indicate in Gy the radiation dose

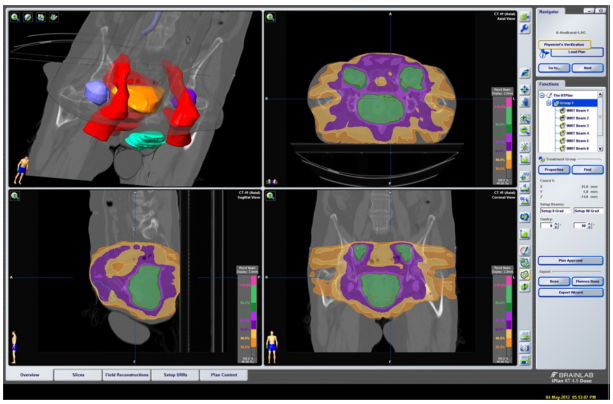

Figure 5: *The axial, sagittal and coronal slices together with a 3D overview to evaluate the simulated dose distribution used to treat prostate cancer. The 3D overview (upper left) shows the previously segmented anatomical structures along with the three orthogonal slices. The slice views employ isolines and colored regions to display the dose distribution as percentage of the target radiation in the tumor (Courtesy of Mathias Walke, Department of Radiation Treatment Planning, University of Magdeburg, taken from the book of Preim and Botha [PB13]).*

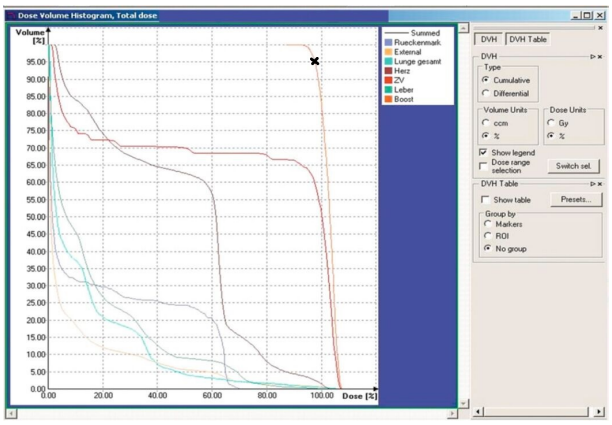

Figure 6: *The dose-volume histogram indicates which percentage of a structure volume receives a certain dose (x-axis) to treat an esophageal carcinoma. The orange curve relates to the tumor volume which indicates that 95% of its volume receive at least 95% of the target dose, as shown with the ✗-mark (Courtesy of Mathias Walke, Department of Radiation Treatment Planning, University of Magdeburg, taken from the book of Preim and Botha [PB13]).*

at each location of the patient—in reference to the space of the planning CT. An example of a dose plan is shown in Figure 5. Often, dose plans are regarded together with the so-called *dose volume histograms (DVH)* [DMB*91]. A DVH, as shown in Figure 6, summarizes the 3D dose in a 2D plot, relating radiation dose (horizontal axis) to tissue volume (vertical axis). This can be a tumor target or a healthy organ, and the plot can have a differential or cumulative form. A DVH often includes all targets and OARs involved in the radiotherapy plan, where each structure is represented by a color-encoded line.

3. Taxonomy and Presentation of Previous Work in VC for RT

In this section, previous joint research of VC and RT is discussed. First, we provide information about the selection of papers. To navigate the user through the existing literature, a taxonomy for the classification of the papers and the reasoning behind the selection of this taxonomy scheme is presented. Previous related work is, finally, discussed within the provided categorization.

3.1. Literature Search and Sources

We conducted an extensive search of literature databases. Titles and keywords used in the literature related to visual computing, radiotherapy and its planning. This led to the formulation of the following general search term: `("visualization" OR "visualisation" OR "visual computing" OR "visual analytics") AND ("radiotherapy" OR "RT" OR "radiation therapy" OR "radiation treatment") AND ("planning" OR "plan")`.

For the literature search, the sources reported in Table 1 were considered. When possible, logical search operators were used to directly apply the search term, for instance in Pubmed and IEEE Xplore. If this was not possible, multiple searches with potentially broader results were conducted. For instance, the Eurographics Digital Library search is very limited and three separate searches with the terms "`radiotherapy`", "`radiation therapy`" and "`radiation treatment`" were performed.

The query results were merged and duplicates were removed, e.g., Medline and IEEE Xplore both give results from TVCG. All results were considered potentially related, and were further reduced by removing unrelated or out of scope entries on a one-to-one basis. The initial search yielded 601 candidates: Medline (464), IEEE (71 additional to Medline), Eurographics Digital Library (33), CGF (19), Visual Computer (9) and ACM (5), which were reduced to 105 papers employed for building the taxonomy. Results were considered as unrelated or out of scope, if they were only matching the search term due to titles in the reference list or author biographies and if they were not within the joint VC and RT scope. Additionally, the papers were required to have a strong connection to visualization or visual analytics or visual computing within RT research. An example for a discarded paper would be a clinical study for an RT related topic where the tumor is "`visualized`" for demonstration purposes, or a pure imaging technique article using "`visualization`" in an imaging sense.

3.2. Taxonomy Description

As discussed in Section 2, RT has several particular characteristics with regard to the multitude of involved data, complex and risky processes and users. This requires the incorporation of many different strategies from the domain of VC. For example, registration or multi-modal visualization might be relevant for different steps of the workflow, but each step has specific clinical requirements and targets. Although previous work in the general domain of VC

Table 1: *Table representing the literature search and sources.*

Source	Index Multiple
Pubmed/Medline	Various including: – IEEE TVCG (since 2004) – IEEE TMI (since 1997) – IEEE CGA (since 2004) – Journal of CARS (since 2009) – CGF (PMC only)
IEEE Xplore	all IEEE
EG Digital Library	all EG
ACM Digital Library	all ACM
Computer Graphics Forum	-
The Visual Computer	-
Computer Methods in Biomechanics and Biomedical Engineering	-

might also be applicable for RT and is referenced in the upcoming sections whenever relevant, it is more appropriate and clinically significant to address each of the steps of the workflow separately. To this end, we do not focus on a method-based categorization, but on a taxonomy which reflects the steps of the clinical workflow. As the entire radiotherapy treatment process is based on this workflow, this division into the clinical steps is anticipated to be more natural for readers both from the VC and the RT domain. It is also more probable that readers of this article are more concerned with one specific part of the entire pipeline. Another important aspect is the adoption rates of the discussed approaches, in an attempt to identify significant trends and gaps within the current literature. Knowing whether previous work has been (partially) integrated in clinical routine is anticipated to give insights into unsolved issues, into challenging future pathways and into topics that upcoming joint VC/RT research could tackle. The taxonomy is built upon two dimensions:

1. **Steps** of the RT workflow addressed by the proposed methods—This dimension implies also a clinically-relevant categorization based on the available data, upon which the methods were built, as discussed in Section 2.2. It comprises the following categories:
   - Target and OAR Definition (Section 3.3)
     - Data Registration (Section 3.3.1)
     - Data Fusion (Section 3.3.2)
     - Data Segmentation (Section 3.3.3)
     - Multi-Parametric Data Exploration and Analysis (Section 3.3.4)
   - Treatment Plan Design and Dose Calculation (Section 3.4)
   - Dose Plan Review and Treatment Evaluation (Section 3.5)
     - Spatial Evaluation (Section 3.5.1)
     - Non-Spatial Evaluation (Section 3.5.2)
   - Planning Strategies for Image Guided Adaptive RT (Section 3.6)
2. **Adoption** of the proposed methods within clinical practice—This dimension implies also a categorization based on the users of the methods, as discussed in Section 2.1. It comprises the following categories:
   - *Integrable:*
     - Benefits for the practice have been proven.
     - Tackling issues of current clinical practice.
     - Routine implementation is possible today.
   - *Developmental*:
     - Benefits for the practice have not been proven yet.
     - Tackling less common issues of clinical practice.
     - Routine implementation might be possible in the future.

   This category does not imply a "hard" categorization, and some papers are categorized as *Integrable/Developmental* expressing an affinity to *Integrable*, and vice versa. The categorization was made at the (time) point of writing this survey. Thus, it may change in the upcoming years especially for the *Developmental* category, depending on whether approaches become accepted and widely used. Please note that this is based on the search results as well as the experiences and personal opinions of the authors. As it is not possible to discuss the adoption dimension separately for all the papers included below, we provide a summarization at the end of each major step-related subcategory, where we also comment on adoption. A detailed view on the adoption dimension is provided in Figures 7 and 8.

For the categorization of the existing literature based on the two aforementioned dimensions, the authors of this survey read all papers and decided on a one-to-one basis. This categorization has also been summarized in Figures 7 and 8. A particular aspect that was taken into account was whether an evaluation (and what kind of evaluation) of the presented methods had been conducted. This is documented separately in Section 3.7 and summarized in Table 2. The areas of main concentration of the literature are also identified and discussed in Section 3.8.

3.3. Target and OAR Definition

After all images are acquired, the tumor with its respective volume definitions and the adjacent OARs are delineated. Multiple subtasks are involved in this step, ranging from data exploration and analysis, data registration, data fusion to data segmentation (automatic or manual). These are crucial steps in the workflow, as the subsequent treatment design and dose calculation will be directly influenced by any inaccuracies.

3.3.1. Data Registration

Previous work related to data registration revolves around two major topics: *motion and accuracy assessment*, and *interactive approaches for registration*.

Approaches Related to Motion and Accuracy Assessment—As discussed previously, tumor motion represents a challenge in planning and delivery of radiotherapy [KMB*06]. In lung tumor treatment, 4D data for treatment planning in the presence of respiratory motion have been employed to several case studies. Deformable image registration (DIR) is an important component [RCCW05].

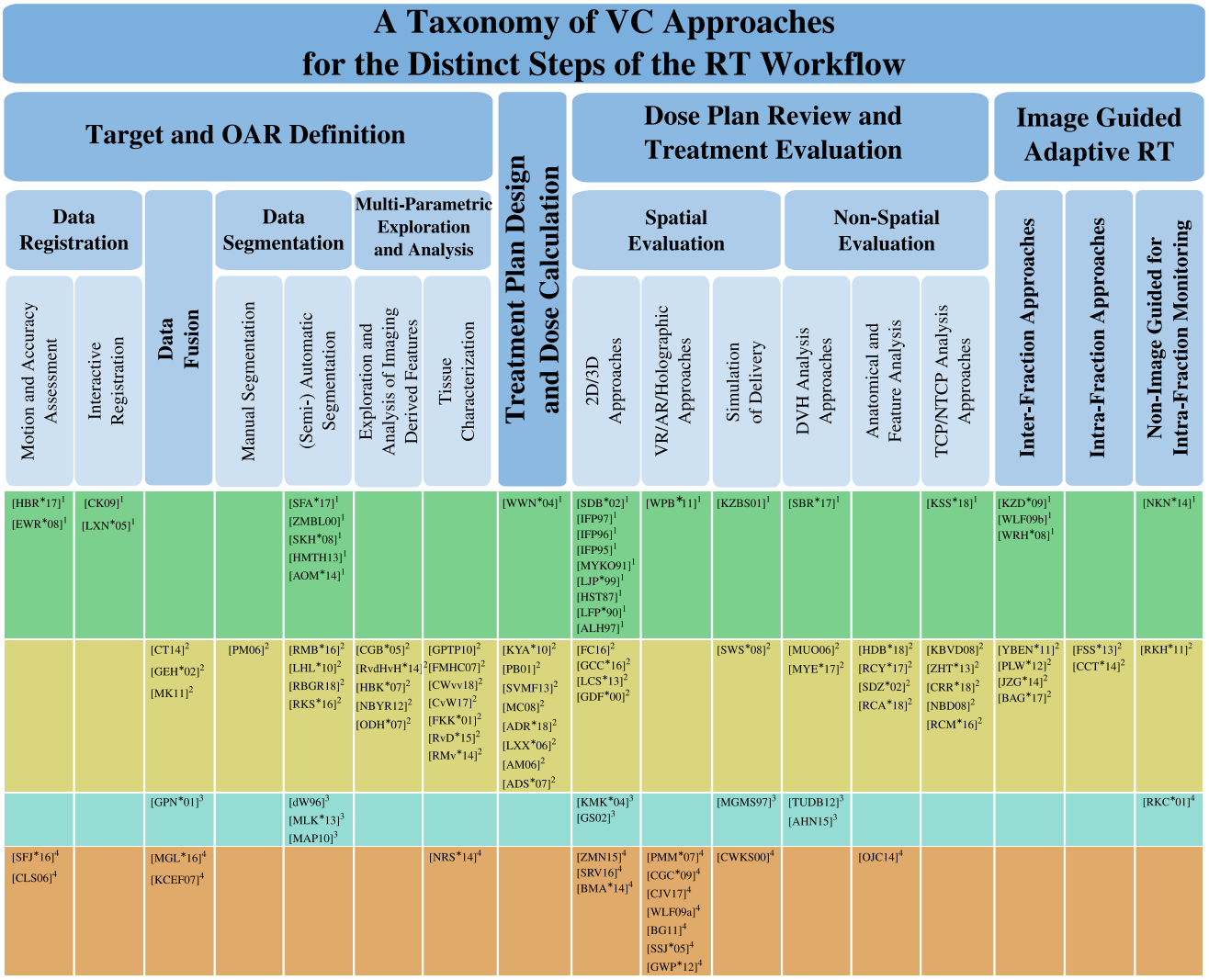

Figure 7: *Treemap representation of the first dimension of the taxonomy, related to the* **Steps** *of the RT workflow addressed in VC literature and the* **Adoption** *dimension of the taxonomy. Each reference is marked with* [1] *(first row, green) to indicate* Integrable *approaches, and with* [2] *(second row, yellow)* Developmental *approaches. We denote by* [3] *(third row, cyan)* Developmental/Integrable *and by* [4] *(fourth row, orange)* Integrable/Developmental *approaches.*

The amount of data generated with 4D imaging significantly increases the time needed for image review and target volume delineation, and DIR can be used for contour propagation [OJB*07] to reduce the workload of manual delineations.

Motion-encompassing methods use DIR to derive a single scan out of a 4D-CT scan for target delineation, which represents the tumor in its time-averaged mid-position [WSVHD08]. Furthermore DIR can be used to model breathing motion. Ehrhardt et al. [EWR*08] use DIR for the generation of a mean motion model of the lung, to predict the breathing motion of a patient without the knowledge of 4D information by matching the model. The motion is visualized by color encoding the displacement field magnitudes. Cover et al. [CLS06] demonstrate the standard approach employed for the visualization of motion in 4D-CT lung data, which comprises simple color intensity projections. Although very simplistic, this kind of images are common for the representation of motion or deformation during registration and fusion.

Registration is accompanied by uncertainty, primarily related to the inherent characteristics of the different imaging modalities that are co-registered. In addition to this, different registration algorithms may bring different types of uncertainty, related to localization accuracy or robustness [KBP*07]. This might be an important aspect to consider, for instance when used for dose warping [VLM*15]. The literature on registration methods is vast [FVW*11,KBD16,MV98,SDP13,VMK*16,ZF03] and different algorithms can be employed, each with different strengths and

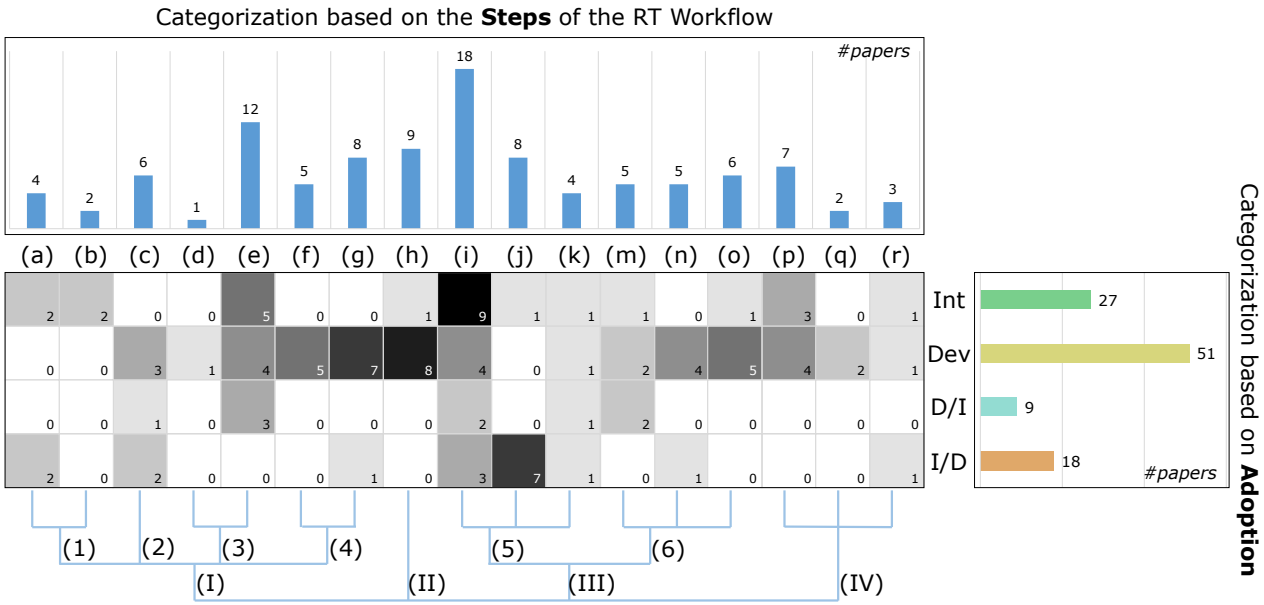

Figure 8: *Heatmap and histogram representations to depict the distribution of previous literature within the two dimensions of the taxonomy. Horizontal axis: Categorization according to the addressed* **Steps** *of the RT workflow. Vertical axis: Categorization according to the* **Adoption** *of the methods within clinical practice. We also show the hierarchy within the taxonomy. The grayscale color encoding denotes the increasing number of papers, going from white (0) to black (max). Annotations: (a) Motion and Accuracy Assessment, (b) Interactive Registration, (c) Data Fusion, (d) Manual Segmentation, (e) (Semi-) Automatic Segmentation, (f) Exploration and Analysis of Imaging-Derived Features, (g) Tissue Characterization, (h) Treatment Plan Design and Dose Calculation, (i) 2D/3D, (j) VR/AR/Holographic, (k) Simulation of Delivery, (m) DVH Analysis, (n) Anatomical and Feature Analysis, (o) TCP/NTCP Analysis, (p) Inter-Fraction, (q) Intra-Fraction, (r) Non-Image Guided for Intra-Fraction Monitoring. (1) Data Registration, (2) Data Fusion, (3) Data Segmentation, (4) Multi-Parametric Data Exploration and Analysis, (5) Spatial Evaluation, (6) Non-Spatial Evaluation. (I) Target and OAR Definition, (II) Treatment Plan Design and Dose Calculation, (III) Dose Plan Review and Treatment Evaluation, (IV) Image Guided Adaptive RT.*

implications. In particular, the use of non-rigid registration requires the selection of parameters, which can yield results with large variability [ESS12, RPSWI10]. In other cases, the lack of objective ground truth in the validation of registration creates the need for manual registrations by experts, which introduces uncertainty that is related to inter-observer variability.

The accuracy of the registration method needs to be analyzed and validated. Visual assessment is one way to verify that the accuracy is sufficient enough for the use in planning. In the study of Hamdan et al. [HBR*17] checkerboard visualizations are used to verify the alignment of the registration of MRI and CT images for prostate images together with contours. Visualization of DIR quality using local image dissimilarity has been proposed by Schlachter et al. [SFJ*16], where the verification is based on voxel-wise calculated dissimilarity value to indicate the match or mismatch. Furthermore, it includes different interaction and visualization features for exploration of candidate regions to simplify the process of visual assessment. This approach is presented in Figure 9.

Interactive Registration Approaches—Interactive rigid image registration of multiple imaging modalities using a volume-view-guided system has been developed by Li et al. [LXN*05]. To distinguish each individual volume in the registration process, monochrome visual representations are used for each image modality, such as red, green, or blue. The color distribution on the voxel volume or a sub-volume can be used as registration criterion, where the homogeneity of the color distribution is used as an indicator for an optimal match. Interactive DIR using landmarks to steer the algorithm has been presented by Cheung et al. [CK09]. Landmarks can be added, removed, and adjusted between repeated registrations. In their approach, landmark pairs were based on visual correspondences, identified by the user on the images to be registered. The visualization methods used for showing the quality include checkerboard display of the fixed and moving images, 3D visualization of the deformation field using glyphs overlaid on a slice of the target image, and a warped grid to show the transformation warping.

3.3.2. Data Fusion

Single modality may not provide enough information with respect to tumor tissues, as well as the tissues that surround target organs. Combining different modality images can be a necessary tool in cancer treatment [LSBP18, PBC*16]. The specifics of the integration and combination of various channels of data information is done through multi-modality image fusion. Lawonn et al. [LSBP18] recently authored a survey on the visualization of multi-modal medical data. Furthermore, an overview on volume vi-

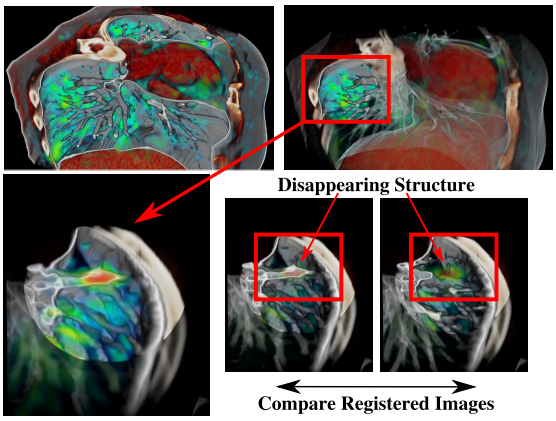

Figure 9: *Assessment of deformable image registration quality, measured by local image dissimilarity, and visualized together with the original images. Different interaction and rendering modes allow for a detailed inspection in areas, where dissimilarity indicates errors due to the underlying registration algorithm [SFJ*16].*

sualization with a focus on medical applications can be found by Zhang et al. [ZEP10]. Therefore, we focus on data fusion restricted to radiation treatment planning. Image fusion, i.e., the combination of various images into a single image, is required for an integrated interpretation of the complementary information in the underlying imaged structures. For example, PET/CT or PET/MRI data can be fused to combine functional and anatomical information [LSBP18]. Often, the different modalities are overlaid and presented with a color-encoded scheme. An overview on medical image fusion in general is given by James and Dasarathy [JD14].

An approach that goes beyond the mere color-encoded, overlaid representation of fusion is proposed by Kim et al. [KCEF07]. The authors propose an entire workflow for interactive multi-volume visualization and the fusion of PET/CT images of lung and brain. The images are initially segmented using a fuzzy c-means cluster analysis. Subsequently, the resulting segmentation map, together with the initial PET and CT data are rendered, fused and interchanged. In the work of Chavan et al. [CT14], an approach for multi-modality image fusion is employed with the purpose of providing better visualization (i.e., representation), accurate diagnosis and appropriate treatment planning. In this work, different *fusion rules* are employed and evaluated against each other in order to determine which are the ones that carries less uncertainty, i.e., noise or visual artifacts, with a focus on uncertainty minimization. Illustrative rendering which combines anatomical information from CT scans with functional information from PET are found in the work of Merten et al. [MGLS*16]. Illustrative rendering techniques, combining order-independent transparencies with boundary enhancements and silhouettes are proved to provide an excellent spatial perception and evaluation of tumor position, metabolic and therapeutic agent activity.

Additional information has been incorporated with the inclusion of MRSI data in the fusion process [NLK*14]. Graves et al. [GPN*01] present an initial attempt to include 3D MRSI information in the planning process with basic viewing of MRSI data as fixed contours embedded within MRI and CT data. The fusion of multiple MR images (T1, T2 and MRSI) is proposed by Marino et al. [MK11] using a score volume which takes into account each of the three acquisition types. The MRSI score is based on detecting areas of increased chemical ratios indicating the possibility of cancer.

3.3.3. Data Segmentation

For the definition of the tumor target and the surrounding organs at risk, conventional approaches involve *manual segmentation* through expert delineation and *(semi-)automatic segmentation* methods. An overview on medical image segmentation can be found in Pham et al. [PXP00] or the book of Birkfellner [Bir14], and—with a focus on interaction—by Olabarriaga and Smeulders [OS01]. A review on deep learning in medical imaging segmentation, focusing on MRI data was recently given by Lundervold and Lundervold [LL18].

Approaches Related to Manual Segmentation—Manual delineations, although conducted by expert radiologists, might result in errors due to inter-observer variability [PM06]. This well-known problem affects the entire RT workflow [GEH*02].

Approaches Related to (Semi-)Automatic Segmentation—Automated segmentation algorithms can greatly reduce the delineation time and the efforts of a human expert. For example, automatic segmentation based on statistical shape modeling has been proposed by Seim et al. [SKH*08] for the segmentation of pelvic bones, or by Vik et al. [VBS*12] for the segmentation of pelvic organs. However, when automatic segmentation is employed, the resulting segmentation needs to be verified, before used for dose calculation. Three main sub-topics can be regarded within this category: approaches *aiding* the segmentation of relevant structures, approaches *enhancing* the segmentation outcome by post-processing and approaches *assessing* the outcome of the segmentation. All three subcategories incorporate user interaction with the segmentations, which has been discussed by Ramkumar et al. [RDK*16].

Within the *aiding* category, de Geus et al. [dW96] propose an approach for the detection, modeling and visual stylization of structures of interest from CT images. Stylization, within the work of de Geus, is defined as a combination of segmentation and 3D visualization, where the resulting segmentation of the critical structures conforms to the bounding volume of the real shape. Moreover, assisted contouring can be employed to reduce some of the manual workload, or adjust the result of automatic segmentations. Zindy et al. [ZMBL00] propose assisted contouring based on scattered data interpolation methods. Instead of warping individual contours, a surface is interpolated through any data point that has already been placed on contour boundaries. This surface can be iteratively refined by adding points on the CT slices. Additionally, sketch-based editing tools for segmentation have been proposed by Heckel et al. [HMTH13], considering image information for extrapolation, as well as previous and contradictory inputs. Other, more complex approaches, involve the work of Akino et al. [AOM*14] for the automatic estimation of tumor motion using segmentation of cine-MRI, with the detection of feature points. Motion vectors are calculated and applied to contours, while a potential ITV is calcu-

lated from the accumulation of GTVs. This involves the incorporation of motion information from cine-MRI and 4DCT data. Raidou et al. [RKS*16] employ a visual analytics approach to improve classifier design for brain lesion detection using features derived from diffusion imaging. This semi-automatic approach integrates the knowledge and skills of specialist users with automatic methods for smart feature selection and for the evaluation of the classification outcome.

Within the *enhancement category*, smoothing algorithms can be considered. Smoothing algorithms allow to reduce artifacts from mesh generation, but often degrade accuracy. Relevant features may be removed and distances between adjacent structures get changed. Li et al. [LHL*10] present fast 3D-reconstruction and visualization of tumor target and organs at risk from a series of cross-sectioned contour points. In this approach, after the pre-processing of the contour points dataset, an iso-surface is extracted and simplified. Then, the surface model undergoes a linear transformation and smoothing. The proposed approach, despite being simple, is accurate and fast and the visualization part consists of simple iso-surface renderings of the involved organ structures. Moench et al. [MAP10] present a modification to common mesh smoothing algorithms to preserve non-artifact features by focusing on previously identified staircase artifacts. To further improve the handling of mesh smoothing filters, Moench et al. [MLK*13] introduce model quality graphs and model quality bars which are evaluated in real-time and presented to the user to perform parameter adjustments and to provide immediate visual feedback on accuracy and smoothness.

Within the *assessment category*, Raidou et al. [RMB*16] propose a visual tool to facilitate the exploration and analysis of the outcomes and errors of automatic segmentation methods, supporting cohort and individual patient investigation for the detailed assessment of their pelvic organ segmentations. This work has been extended later on by Reiter et al. [RBGR18], in a web-based visual analytics approach to facilitate understanding how the shape and size of pelvic organs affect the accuracy of automatic segmentation methods and to enable quick identification of segmentation errors and their correlation to anatomical features. Schlachter et al. [SFA*17] develop a visualization framework for rapid quality assessment of segmentation targeting temporal data. The framework allows for fusion of 4D multi-modal data sets and joint visualization of segmentation data. The focus of the approach was to allow exploration of the full 4D imaging information, and to offer interaction and navigation features for a simplification of this process. This approach is presented in Figure 10.

3.3.4. Multi-Parametric Data Exploration and Analysis

Often, the acquired multi-parametric, multi-modal medical imaging data need to be explored and analyzed, in order to derive additional (biological) information. Two major trends were observed in the previous work of this topic. The first relates to the *exploration and analysis of imaging-derived features* and the second to *tissue characterization or classification*.

Exploration and Analysis of Imaging-Derived Features—Two early works, with a particular focus on the segmentation and visualization of MRI perfusion data, have been proposed by Coto et al. [CGB*05] and Hennemuth [HBK*07]. Coto et al. propose an application that combines advanced interaction, segmentation and visualization techniques to explore breast Dynamic Contrast Enhanced (DCE)-MRI data, using well-established interaction and rendering techniques. The second work tackles myocardial data, and, thus, also motion correction. A comprehensive workflow of registration, segmentation and visualization for the exploration of enhancement curves and parameter distributions in automatically segmented or user-selected areas is discussed.

Oeltze et al. [ODH*07] propose a visual analysis tool that enables the exploration of the correlations and relations between several features and parameters of perfusion data. From contrast-agent enhancement time-intensity curves (TICs), they derive per-voxel parameters that can be used as indicators in the diagnosis of breast tumors. They employ Principle Component Analysis (PCA) to reduce the dimensionality of their parameter space, and they use multiple linked views to enable exploration and analysis. This work facilitates the localization of specific characteristics of the parameter space in the anatomic and temporal domain. It also enables a multi-variate analysis of the parameter space and facilitates the local exploration of the data. A survey of perfusion data analysis approaches has been published by Preim et al. [POM*09]. This survey includes applications on breast tumor analysis, and also on the analysis of myocardial, and ischemic data.

An additional layer of complexity to the exploration and analysis of perfusion data has been added by Nguyen et al. [NBYR12] and Raidou et al. [RvdHvH*14]. For the exploration, analysis and minimization of uncertainty, in the form of intra- and inter-modeling-induced variability, Nguyen et al. propose an approach that works with kinetic PET modeling parameters. To show additional relations between DCE-MRI kinetic modeling-derived parameters and the effect of variability on these, Raidou et al. propose iCoCooN. It is a Visual Analytics tool based on the design of a visual representation that integrates perpendicularly Parallel Coordinate Plots (PCPs) with Cobweb Charts (CCs or star plots). PCPs display the variations in all parameters among modeling choices, while CCs present the relations in a whole parameter set for each modeling choice. The tool is equipped with interactive features to support the exploration of all data aspects in a single combined view. Additionally, interactive brushing facilitates to link the observations bi-directionally to the anatomy.

Tissue Characterization—Beyond the exploration and analysis of the data, there is a significant amount of work on linking the analyzed data to tissue characteristics and other information, such as Gleason or PI-RADS scores [Was15]. For many years, tumors have been considered homogeneous masses. In reality, tumors are heterogeneous tissues, enclosing multiple regions with distinct characteristics, e.g., necrotic portions without perfusion and highly vascularized regions. Incorporating patient-specific intra-tumor tissue information into radiotherapy planning is potentially important in tumor diagnosis and in designing more effective treatment strategies, where distinct intra-tumor tissues are irradiated with adequately selected radiation doses [GBM*12,GMK*10]. Investigation of tumor heterogeneity at micro-scale supports the general understanding of the distribution and type of tumor cells in tissue, and is today done using data acquired from invasive procedures, including biopsies and post-operative inspection of histopathological slices. These are

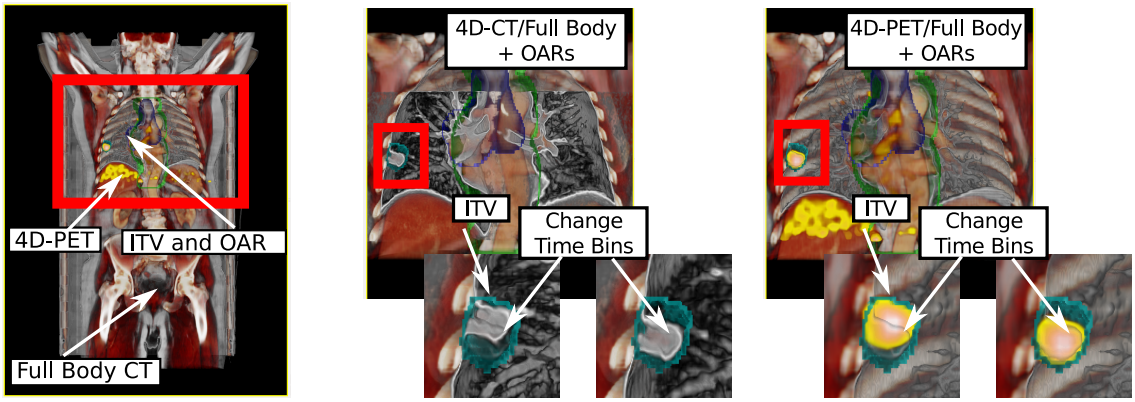

Figure 10: *Example visualizations of 4D multi-modal data sets and segmentation data for quality assessment of ITVs in lung cancer treatment planning. The focus of the approach was to allow exploration of the full 4D imaging information, and to offer interaction and navigation features for a simplification of this process. Figure adapted from Schlachter et al. [SFA*17]).*

tumor or tissue sections, which have been frozen or fixated chemically. The slides are stained with pigments in order to reveal cellular consistency and to increase contrast, and are observed under the microscope. Motivated by the currently tedious process of discovery and interpretation of findings in histopathological slides, Corvo et al. [CvW17, CWvv18] proposed recently two approaches for the support and improvement of the diagnostic procedure and reporting. These approaches are quite distinct from the others in the remainder of this subsection, as they analyze high-resolution histopathological images.

For a non-invasive in-vivo identification and exploration of intra-tumor tissues, clinical researchers need to associate histopathological findings, such as Gleason scores [EEA*16] or PI-RADS scores [Was15] with features derived from co-registered imaging data. The exploration and analysis of the characteristics of distinct intra-tumor regions is a challenging subject, relating to new research directions for treatment planning [TOG06]. Within this topic, researchers evaluate and assess supplementary clinical data that are often used as reference or as a means of diagnosis and outcome prediction [GMK*10]. These clinical reference data may be, for instance, data from risk prediction models [GBM*12]. Furthermore, the exploration of tumor tissue characterization could be of particular interest for researchers developing classification algorithms, to aid the design of classifiers that can differentiate between distinct tissue types, as well as to understand the behavior of such classifiers.

In vivo, intra-tumor tissue heterogeneity can be visualized only at mesoscale employing molecular and functional imaging. For RT planning these imaging data can be used to aid the definition of the *Biological Target Volume (BTV)* [LHL*00] aiming at integrating tumor heterogeneity as an additional factor for biologically targeted dose distributions [Ben08]. Nunes et al. [NRS*14] describe an integrated, flexible visual analytics framework for BTV definition enabling multi-modal fusion of MRSI data with PET and MRI data to gain insight into patient specific tumor heterogeneity. With the proposed system, the user can interactively fuse, analyze, visualize and explore high dimensional patient specific metabolic tissue signatures from MRSI data in the spatial context of other available imaging modalities to refine BTV contours in a fast and efficient way.

Feleppa et al. [FKK*01] propose an approach for conducting tissue characterization, i.e., pixel-wise likelihood, for prostate cancer based on spectrum analysis of ultrasound B-mode data. Fang et al. [FMHC07], instead, build upon the concept of time activity curves to propose three methods to analyze and visualize time-varying data through the creation of adequate transfer functions. In these three methods, the user can build a 1D or 2D histogram, or a 2D scatter-plot with integrated multi-dimensional scaling to create transfer functions that reflect different tissue activities, i.e., distinct tissue characteristics in PET, SPECT and fMRI data. Intra-tumor classification has been discussed by Glasser et al. [GPTP10] for the division of a tumor into regions with distinct DCE-MRI perfusion characteristics, by employing a region merging method, which is summarized in a glyph-based representation for a fast overview of the whole breast tumor.

The work of Raidou et al. [RMvE*14, RvD*15] enables not only the identification of intra-tumor regions, but also the additional exploration and analysis of large multi-parametric cancer imaging data. The identification of anatomically significant intra-tumor regions with distinct tissue characteristics is supported by the use of a dimensionality reduction technique (t-distributed Stochastic Neighborhood Embedding [VH08]). Moreover, these regions can be individually and comparatively analyzed, to gain further insight into tumor heterogeneity [TOG06], at both tumor and voxel level in lung, prostate, and cervix tumors. The particular characteristic is that the analysis can be done with respect to reference data used in clinical research, e.g., features derived from histopathological data or modeled data, while uncertainty (in the form of accuracy or variability) is also incorporated in the analysis [RvD*15]. The approach is presented in Figure 11.

⇒*With regard to the approaches related to target and OAR definition, there are several interesting trends. Most of the work has been conducted in the domain of data segmentation and of multi-*

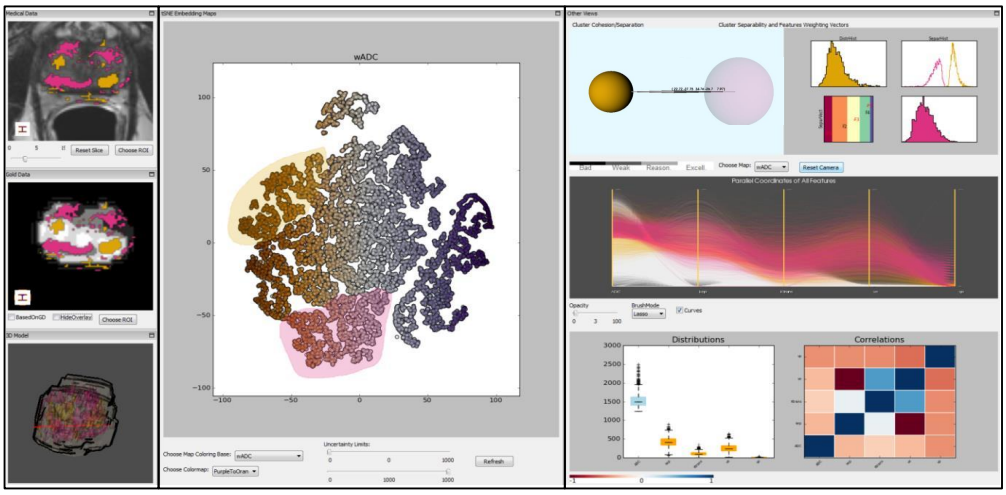

Figure 11: *A visual analytics approach to study tumor tissue characteristics. It comprises three main parts: (a) views for the anatomical analysis of tumor tissue characteristics, (b) a t-SNE embedding view, abstracting the high dimensional space of tissue features in a simple 2D scatterplot and (c) a cluster analysis view for the analysis of the high dimensional space of tissue features of user-selected visual clusters in the t-SNE representation [RvD*15].*

parametric data exploration and analysis. However, both domains have mainly investigated approaches which did not manage to be fully integrated into the clinical routine, and remain developmental. This could be because still clinical routine heavily relies on manual delineations of the target volumes and OARs, despite the significant advancements of (semi-)automatic segmentation methods. Also, multi-parametric data exploration and analysis, in particular tumor tissue characterization, has only recently started being incorporated in clinical setups. Given the attention that such approaches have recently received both within RT and VC research, we anticipate more work in this domain in the future.

3.4. Treatment Plan Design and Dose Calculation

The design of the treatment plan and the dose calculation are performed in dedicated treatment planning software. This software optimizes for an accurate assessment of the dose distribution. To this end, they are often based on Monte Carlo simulations. The input to these simulations is patient-specific information, such as CT images of the patient, and structure definitions (targets and OARs), as well as (device dependent) beam geometry properties. The output of such simulations is the dose plan, as discussed in Section 2.2. An overview of dose calculation for EBRT can be found by Ahnesjö and Aspradakis [AA99].

A proposed multi-modal radiation treatment system is MINERVA by Wemple et al. [WWN*04]. This system can be used for analyzing several imaging modalities, accommodating multi-modal treatment planning. Liu et al. [LXX*06] incorporate a neural network algorithm for tissue density calibration used in the calculation. For the visualization, simple 2D or 3D contour map views are employed. Other automatized approaches for the optimization of the dose distribution have been proposed, for example by Alber and Meedt [AM06], where an assessment of optimal dose distributions generated by different beam arrangements is performed in a visualization tool. A combined Monte Carlo-based dose calculation and visualization system has been developed Kimura et al. [KYA*10] in order to make a validation or a comparison of results between a Monte Carlo simulation and an analytical simulation such as radiotherapy treatment planning system. The visualization system deals with displaying detector geometry, particle trajectories to simultaneously display the patient data and dose distributions calculated by the simulation.

Pfeiffer et al. have implemented real-time dose calculation and visualization for ocular tumors [PB01], which resolves the common separation between parameter definition, dose calculation and evaluation. It allows a direct examination of the expected dose distribution while adjusting the treatment parameters. The resulting dose distribution is visualized as a 3D surface model on any 2D slice or on the surface of specified ocular structures. Flexible and patient-specific treatment planning software with Monte Carlo dose calculations suitable for large-scale prospective and retrospective treatment planning studies has been designed by Alexander et al. [ADS*07]. Treatment planning information, such as patient images, structures, beam geometry properties and dose distributions, are used as inputs to the software, while 2D and 3D visualization views for images, structure contours, and dose distributions are provided. Other standard tools, such as for contouring tools, for DVH analysis, or for dose matrix comparison tools are incorporated. An interaction-driven approach is presented by Schlaefer et al. [SVMF13], where basic primitive elements are employed to introduce new user-determined constraints for the recalculation of the dose in 3D.

Mori et al. [MC08] present a quantification and visualization tool

to permit the identification of beam angles that show range uncertainties quantitatively during respiration. It is useful for a quick assessment of uncertainties in lung cancer patients. For the evaluation of the impact of metal artifacts on dose calculation accuracy, Andersson et al. [ADR*18] compare two commercial CT metal artifact reduction algorithms for use in treatment planning in head and neck patients. A human-like phantom with removable metallic implants was employed to evaluate two algorithms used in treatment planning, showing that the two algorithms improve image quality in dose calculation.

⇒*Treatment plan design and dose calculation approaches have not been intensively investigated in the joint VC/RT research. At the same time, the only approach that has been integrated into clinical practice is MINERVA by Wemple et al. [WWN*04], which incorporates a simple—yet, robust—2D-based strategy, as discussed before. A potential reason for that could be that the plan design and dose calculation is more often posed as an optimization problem and rarely as a VC-related topic. However, the increasing complexity and granularity of current dose planning outcomes is expected to trigger changes within this domain.*

3.5. Dose Plan Review and Treatment Evaluation

In this category, we focus first on the *spatial* evaluation of the dose plan, i.e., the assessment of the planned dose distribution for eventual changes, and then, on the *non-spatial* evaluation of the treatment with respect to actual tumor control and potential complications, which involves topics such as DVH analysis, interfractional changes and radiobiological (TCP and NTCP) modeling. Quality assurance today still lacks of formalized standards and may vary from institution to institution. A survey analyzing the institutional differences for planar IMRT quality assurance is presented by Nelms and Simon [NS07].

3.5.1. Spatial Evaluation

The previously proposed approaches for the visual representation of planning results and for the facilitation of plan reviewing are classified into three main categories. Conventionally, *2D visual representations* of the planned dose distributions have been used, which evolved into or are combined with *3D volume renderings*. Additionally, *VR/AR and holographic approaches* have been proposed. Finally, we discuss *simulation approaches* of the delivery step, which can complement the plan evaluation.

2D/3D Approaches—Hahn et al. [HST87] first proposed 2D color encoded visualization as an aid to the comparison of treatment plans, taking advantage of the conventional cross-sectional representations of the patient contour and selected anatomical features. For the interpretation of the correlation between dose, target and OARs, and the comparison of several plans, the authors propose the so-called images of regret, where color is employed to denote limits of acceptability, i.e., areas in which the required dose levels are not satisfied.

Initial approaches on volume rendering in radiation treatment planning have been proposed already in the 90s, with the work of Levoy et al. [LFP*90], Miyazawa et al. [MYKO91] and Interrante et al. [IFP95, IFP96, IFP97]. Levoy et al. discuss approaches that employ region boundary surfaces for the anatomy, polygonal meshes for the treatment beams, and isovalue contour surfaces for the dose distribution, enhanced by shading, texturing, fogging and shadowing. Miyazawa et al. propose a 3D visualization system for use in radiotherapy planning simultaneously visualizing original 3D image data, segmentation, and isodose surfaces. Later, Interrante et al. tackled the issue of showing isodose surfaces and anatomical surfaces together—a typical multi-modal visualization problem. Semi-transparent isodose surfaces were the baseline method. They later enhance transparency with ridge and valley lines for better perception of the shape and depth of structures, such as the skin [IFP95], employ artist-inspired curvature-directed strokes, for the same purpose [IFP96], and investigate texturing of layered surfaces [IFP97]. Alakuijala et al. [ALH97] present the Beam's light view, a texture mapping method to be used together with traditional 3D radiotherapy renderings from the beam's eye view and room's eye view. The utility of volume rendering as an alternative visualization technique to surface rendering for head and neck radiotherapy planning has also been discussed by Lee et al. [LJP*99]

Gambarini et al. [GDF*00] present a new toolkit for full volumetric shape and shape-transforming information from multi image sequences of absorbed dose, measured in tissue-equivalent phantoms. The visualization of the different isodose levels on the phantom data are rendered in 3D using a standard marching cubes algorithm. Multi-modal volume visualization is also described by Sibomana et al. [SDB*02], where Volumes of Interest (VoIs) are extracted, registered, resliced and visualized for a head and neck application. The method of Kaiser et al. [KMK*04] targets the virtual simulation of a boost field in adjuvant radiotherapy of the breast and the visualization of dose distributions thereof, while Lam et al. [LCS*13] conduct an evaluation of a multi-scale texture analytic procedure for the detection of abnormalities and lesions in CT images of the pelvis, which is based on a visualization platform for the representation of treatment planning, CT image-guided positioning and treatment delivery.

Recently, Fonseca et al. [FC16] propose SOFT-RT, a Software for IMRT simulations, which produces a 3D rendering of a set of patient images, including the tumor target definitions and the OARs, as well as the features and orientation of the radiation beams. The rendered outcomes represent the tissues exposed to radiation, as well as the amount of absorbed dose in the tumors and the healthy tissues. Abdo-Man [GCC*16] involves a pipeline (imaging, organ definition, 3D mesh generation, 3D printing) for the production of a 3D printed anthropomorphic phantom that can be used as a validation tool for dosimetry.

For *risk and/or uncertainty assessment*, several methods have also been presented. Brodin et al. [BMA*14] discuss an interactive decision-support tool for individualized risk-based radiation therapy plan comparison. The tool displays dose-response relationships and other features related to normal tissue side effects, and it is meant for facilitating the optimization of a treatment plan, based on the aforementioned information, using a combination of dose-response curves and 2D views of the dose distribution on the patient anatomy. Zhang et al. [ZMN15] introduce a risk visualization method, based on clinical risk guidelines. The risk distribu-

tions are summarized in 2D visual representations on the patient anatomy, and provide a means for the visualization and assessment of the risks of secondary cancer in tissues of the human body. For the comparison and decision-making about an optimal plan among several alternatives, Gopal et al. [GS02] and Silva et al. [SRV16] discuss different approaches. In the work of Gopal et al., treatment plans are represented as points in a multidimensional space called *plan space*, where given specific selection criteria and clinical considerations, the user can obtain the best plan available tailored to the unique anatomy of each patient. Silva et al. propose an approach for the visualization of variability in treatment plans, in order to interactively explore and analyze an ensemble of possible dose plans. This work allows to analyze the dose plan at two different levels: first, based on the isodoses, i.e., the radiotherapy dose iso-contours, across the alternative dose plans, and, secondly, directly at a voxel level. The visualization is based on the concept of contour boxplots [WMK13] and on multiple, interactive linked views.

VR / AR / Holographic Approaches—*Virtual Reality (VR)* approaches for RT include the work of Su et al. [SSJ*05], which proposes the use of VR in RT treatment planning, integrated with computer graphics techniques for the reconstruction of the treatment room and the collimator, and image reconstruction techniques from CT for the patient body. The authors discuss how the system can be expected to reduce preparation time and can be employed in RT training, paving the way for other works, such as the work of Patel et al. [PMM*07] and Boejen et al. [BG11]. Patel et al. present a VR solution for the evaluation of radiotherapy plans, with a focus on understanding spatial relationships in the patient anatomy and on illustrating the calculated dose distribution. Similarly, Boejen et al. propose an immersive visualization in a 3D perspective system for planning and delivery of external radiotherapy, targeting in particular the understanding of spatial relationships in the patient anatomy. Boejen et al. focus more on the training purposes of such a VR system. A comparison between VR and conventional systems for RT dose planning has been conducted by Glaser et al. [GWP*12], showing that the VR system requires more time, but yields higher accuracy, while potentially increasing clinical efficiency. Also, Ward et al. [WPB*11] proposed an immersive virtual environment—VERT—that simulates a radiotherapy treatment room to provide staff and students with training aids for treatment of virtual patients.

Augmented Reality (AR) approaches in RT include applications for the evaluation of the plans and also for patient education. In the former category, the work of Wang et al. [WLF09a] targets the evaluation of radiotherapy plans, by displaying CT images, dose distribution, and mesh models of radiotherapy targets and by providing calculated feedback on acceptance or rejection of the plan on an individual patient basis. Also, Chu et al. [CGC*09] propose a comparable approach, but on a holographic display. This approach targets the comparison of multiple plans for each patient based on a hologram and was evaluated in a multi-institutional study, showing that a holographic display is preferred for treatment planning than 2D displays. In the second category, RAD-AR [CJV17] is an AR tool for radiotherapy, in order to present the real RT world scene and to demonstrate the RT procedure to patients, i.e., serving as a patient education means.

Simulation of Delivery—The delivery itself is considered out of the scope of this review. Yet, certain aspects which are important for plan adaptation will be discussed in Section 3.6. Simulation of the delivery, though, can be part of the planning and might be of interest for VC. An attempt to unify the simulation, planning, treatment and verification phases has been proposed by Moore et al. [MGMS97], which gives clinicians access to a single, animated environment, designed to objectively model the complex 3D irradiation of cancer patients. Cai et al. [CWKS00] propose a similar system with an additional collaborative component so that physicians distributed at different locations can work together via network to plan or to validate the plan. A 3D Simulator for EBRT has been developed by Karangelis et al. [KZBS01] with volume visualization of patient images, beam geometry visualization and room view, where the model of the simulator room is reconstructed using surface rendering techniques. A real-time simulation and visualization framework that models a deformable surface lung model with tumor has been presented by Santhanam et al. [SWS*08]. They simulate the tumor motion and predict the amount of radiation doses that would be deposited in the moving lung tumor during delivery.

3.5.2. Non-Spatial Evaluation

With regard to non-spatial evaluation, three major topics have been discussed in previous work. First of all, there are *DVH-related approaches*. Then, there are approaches that discuss the *analysis of shape and features* of tumors, or of affected organs. Finally, other approaches discuss *radiobiological modeling*, i.e., are related to the analysis of TCP and NTCP modeling, as discussed in Section 2.

Approaches Related to DVH Analysis—DVHs can be explored as a supplementary and summarized source of information, where no spatial inferences can be made due to the aggregation and representation of the dose against the volume in a graphical 2D plot. However, DVHs are good for the comparison of multiple cases, either alternatives for one patient or for cohort exploration. Maleike et al. [MUO06] propose the simulation and visualization of dose uncertainties due to interfractional organ motion. They simulate stochastic properties of the dose distribution to display probabilities of individual voxels which receive doses above critical levels, as well as a diagram that shows the variability of the DVH.

For the visualization of setup errors, i.e., errors with respect to the patient position during treatment, Samanta et al. [SBR*17] propose DVH bands. The impact of setup errors onto the DVH is visualized by introducing random errors and calculate a series of DVHs for each structure, which may help to select the plan with lower influence of setup errors over another. A similar approach for the visualization of a variety of possible dosimetric outcomes using DVH bands is proposed by Trofimov et al. [TUDB12]. Here, the intensity of the shading in the bands reflects the relative probability of the outcome.

Mayo et al. [MYE*17] follow an approach to develop statistical DVH metrics of previous plans. The current DVH gets visualized on top of the statistical DVHs to quantify the comparison of treatment plans with historical experience and across institutions. Alfonso et al. [AHN15] propose a method for assessment and decision making in dose calculation. In this work, a dose-volume histogram approach is followed. In particular, data from dose-volume

histograms provided by treatment planning systems with respect to target coverage and organ sparing are combined into a dose distribution index (DDI), i.e., an individual score for the comparison of radiotherapy planning variants.

Approaches Related to Anatomical and Feature Analysis—Among the *anatomical analysis approaches*, Oh et al. [OJC14] propose GLOBE (Geometric reLocation for analyzing anatomical OBjects Evolution), a technique to quantify and compare anatomical shape, with a proof-of-concept application on cervical cancer. This work comprises of a number of steps: first, the contour surface is triangulated to form a mesh, which is subsequently deformed to a sphere using parametric active contours (PAC). Then, the magnitude of the deformation is sampled on the geodesic dome and, finally, it is unfolded on a plane. These unfolded planes can be subsequently color-coded to show various parameters, such as the magnitude of the surface normal vector from planning CTV to PTV, systematic and random variations, or other distributions. In this way, they allow for easy juxtaposed comparison, either across time or across patients. Hargrave et al. [HDB*18] propose an image-guided decision support framework incorporating a Bayesian network and visualization tool for online cone-beam computed tomography (CBCT)-based image-guided radiotherapy for prostate cancer patients. The Bayesian network represents the relationships between pelvic organ volume variations, an image feature alignment score, delivered dose, treatment plan compliance, intra-fraction motion, contouring and couch shift errors. The visualization component presents a global summary of residual errors after online CBCT-planning CT registration with Mollweide projections.

Exploration of the anatomical variability of OARs, together with analysis of potential toxicity risk has been researched by Raidou et al. [RCA*18], within the Bladder Runner framework. The work uses the example of bladder toxicity in prostate cancer analysis, to present a novel tool for the detailed visual exploration and analysis of the impact of bladder shape variation on the accuracy of dose delivery. The Bladder Runner enables the investigation of individual patients and cohorts through the entire treatment process, and it can give indications of RT-induced complications for the patient, allowing clinical researchers to correlate bladder shape variations to dose deviations and toxicity risk through cohort studies. The Bladder Runner is presented in Figure 12-(a). *Feature-related approaches* include the work of Roy et al. [RCY*17], who investigate the use of hybrid 18-Flurodeoxyglucose PET/MR imaging for early visualization of tumor changes during treatment, which can be employed for adaptation of the treatment. The authors investigate changes in anatomical and functional (DWI and PET) parameters of head and neck tumors, during the initial stages of treatment, and visualize them in juxtaposed comparison for further analysis. Stamatakos et al. [SDZ*02] propose novel Monte Carlo simulation algorithms that describe tumor growth and response to irradiation, in combination with 3D visualizations of the predicted outcome. These algorithms incorporate information of cell division and interaction, cell response to irradiation, tumor expansion and shrinkage, which are visualized in 3D renderings that reflect the response of the tumor to radiation schemes.

Approaches Related to Radiobiological (TCP/NTCP) Analysis—Conventional TCP models are visualized in simple diagrammatic plots, depicting curves which quantify the probability that a tumor is effectively controlled, i.e., treated, given a specific radiation dose. Recently, new TCP models incorporating functional imaging have been built, improving radiobiological accuracy [CvR*16]. However, showing the uncertainties propagated from the respective imaging modality, or illustrating the sensitivity of the models to a number of parameter assumptions, has also become important. Raidou et al. [RCM*16] propose a visual tool that enables clinical researchers to explore their TCP models, by supporting uncertainty and parameter sensitivity exploration, while enabling inter-patient response variability analysis. This visual analysis tool has been later used in a clinical study, to quantify dose and TCP uncertainty bands when initial cell density is estimated from MRI-based apparent diffusion coefficient maps of the patients [CRR*18]. This approach is presented in Figure 12-(b).

NTCP models are regarded either in the same way of TCP models, within curve diagrams or in renderings of the affected organs. Kraeima et al. [KSS*18] explore the second direction and propose a method for planning a 3D virtual guided resection and reconstruction of the mandible in osteoradionecrosis. The method enables a 3D rendering of all isodose fields in relation to the model of the mandibular bone. Other approaches include the work of El Naqa et al. [ENBD08], on methods for the visualization of the high-dimensional space composed of the interaction between toxicities and treatment, anatomical, and patient-related variables of NTCP in head and neck patients. To this end, they employ an approach based on PCA and support vector machine (SVM), where prediction can be performed based on resampling within logistic regression to find the balance between dosimetric indicators and other patient variables. The visualization consists of a combination of static plots, such as surface plots and histograms, to aid decision making. Kupchak et al. [KBVD08] present a novel method for mapping NTCPs onto dose-volumetric regions that incorporate statistical information of risk. The method is based on a Monte Carlo algorithm that creates a large set of DVH curves by simulating random walks through the dose-volume space, guided by a base set of clinical DVHs. A scoring of the dose-volume points is performed, where an NTCP tolerance value is selected and the risk of complications is visualized in a gray-scale map in regions of dose-volume space.

A comprehensive method to visualize the uncertainty in predicted TCP and NTCP models has been proposed by Zhang et al. [ZHT*13]. Inter-individual variation of the underlying radiosensitivity is simulated and visualized as a scatter-plot superimposed to the population-based dose response curves. Additionally, probability histograms quantifying the probability of specific TCP or NTCP values are derived for individual patients from the underlying population.

⇒ *Dose plan review and treatment evaluation approaches comprise the most populated category within the taxonomy. This does not come as a surprise, as RT is heavily concerned with security aspects throughout the pipeline, as well as the verification and evaluation of the plan prior to administration. Within this category, we encounter also most of the integrable applications—in particular, within the spatial evaluation subgroup. It is of particular interest that chronologically older works [HST87, LFP*90, MYKO91, IFP95, IFP96, IFP97] that were mainly concerned with 2D repre-*

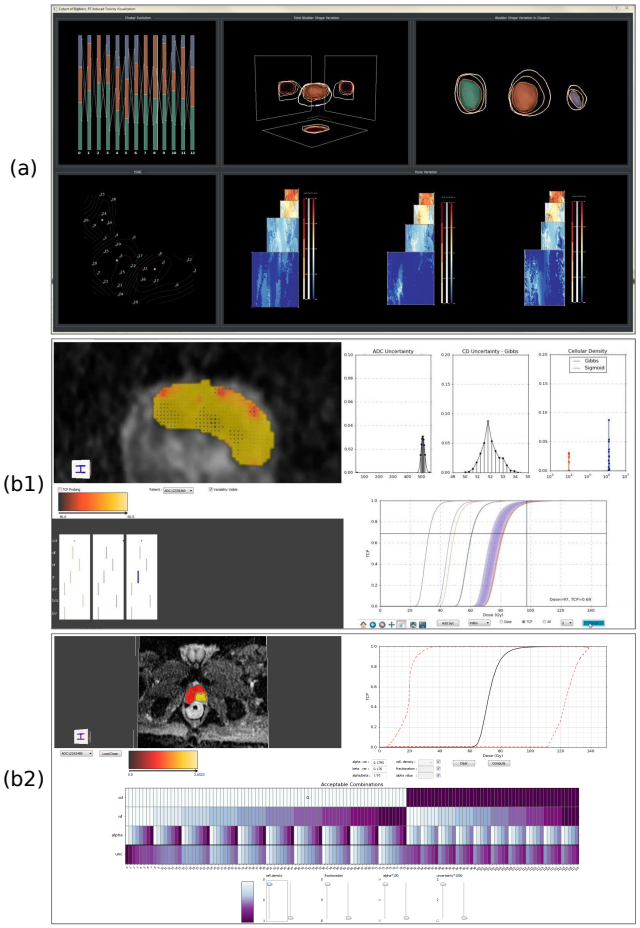

Figure 12: *(a) The Bladder Runner [RCA*18], proposed for the analysis of potential RT-induced genito-urinary toxicity risk, with respect to day-to-day exploration of bladder shape variations in a cohort of prostate cancer patients. (b) The approach proposed by Raidou et al. [RCM*16] for the exploration and analysis of Tumor Control Probability (TCP) modeling in prostate cancer patients. (b1) shows the incorporation of ADC-induced uncertainty and parameter sensitivity into the analysis and (b2) shows an inverse approach used for retrospective evaluation.*

*sentations are well-established in clinical routine, while newer 3D approaches [GDF*00, LCS*13, FC16, GCC*16] have remained at a developmental stage. A lot of VR/AR approaches are also, at least partially, integrable—the most important example being the work of Ward et al. [WPB*11]. Approaches incorporating anatomical feature analysis and work in regard to radiobiological modeling is also at a developmental stage, as anatomical feature analysis and radiobiological modeling are still under clinical evaluation in RT research.*

3.6. Planning Strategies for Image-Guided Adaptive RT

In this category, we introduce adaptive approaches which try to optimize the treatment either by re-planning or by modification during the delivery. During the course of radiotherapy, both the tumor and the healthy surrounding organs are variable in size and position. This can be attributed to anatomical changes between fractions (inter-fraction) or to changes during beam delivery within one treatment fraction (intra-fraction). The former can happen, e.g., in patients with a tumor in the pelvic area, where the position is dependent on bladder and bowel filling, but changes can also occur due to weight loss and tumor shrinkage [KWCM13]. The latter can happen, e.g., in patients with lung cancer where the tumor moves with breathing. As the anatomy and geometry of a patient is based on medical images acquired at previous stages of the planning workflow, it might not be anymore well-reflected at the time of delivery. More details about IGART in general can be found in Yan [Yan06]. One way to compensate for these uncertainties is by including them into the PTV (or ITV) with appropriate safety margins as explained in the previous sections. Otherwise, Image-Guided Adaptive RT (IGART) tries to optimize dose delivery by taking into account intra- and inter-fractional image data. Current LINACs are equipped with on onboard imaging which can be used for IGART. For instance, CBCT imaging has become an integral part of radiation therapy, with images typically used for offline or online patient setup corrections based on bony anatomy co-registration with the planning CT. For some purposes, the image quality of CBCTs can be insufficient, and the use of contrast-enhanced CBCT imaging for adaptive radiotherapy has been proposed by Soevik et al. [SRS*10].

Approaches Related to Inter-Fraction— To change the plan or to re-plan according to the recent state of anatomy every time, would be too time-consuming. An alternative is to keep the original plan, but recompute the accumulated dose based on the current state of anatomy. If the deviation between the accumulated dose deviates too much compared to the planned dose, re-planning might be a better option. The calculation of the true dose distribution for a patient requires accurate DIR to reduce dose warping uncertainties due to the registration algorithm [VLM*15]. Registration for IGART has different problems as there are regions within the images to be registered, where explicit correspondences cannot be established [KZD*09] for the reasons mentioned above. The work of Song et al. [SSB*05] evaluates the efficacy of various image-guided adaptive radiation therapy techniques to deliver and escalate dose to the prostate. Furthermore, the normal tissue sparing potential of adaptive strategies in radiotherapy of bladder cancer has been shown by Wright et al. [WRH*08]. Open source software suites, such as DIRART [YBEN*11] or SlicerRT [PLW*12] targeting multiple aspects of IGART including registration and visualization, are freely available. A multi-modality image registration and visualization framework, which is addressing the transfer of structures of RT plans onto follow-up images for re-planning, has been presented by Wang et al. [WLF09b]. An alternative to dose warping is Cherenkov imaging, which can estimate the dose in real time 2D [JZG*14] and 3D [BAG*17].

Approaches Related to Intra-Fraction—For lung cancer patients, it is more important to monitor the tumor position during the fraction, ensuring a good setup, as well as monitoring of the breathing motion range. Tumor tracking algorithms that are able to follow the lung tumor based on a combination of in-beam imaging and kilovoltage (kV) imaging have been developed. Furtado et al. [FSS*13] implement a real-time tumor motion tracking by 2D/3D registra-

tion using on-board kV imaging which allows for a reduction of the PTV and therefore healthy tissue sparing. Chang et al. [CCT*14] propose an approach that integrates real-time ultrasound (US) for the visualization of the target, which is registered to CT images.

Non-Image-Guided Approaches for Intra-Fraction Monitoring—Alternative non-image-guided tracking approaches exist for monitoring of the position of the patient during treatment in RT. Depth sensor-based real-time tumor tracking by Nutti et al. [NKN*14], or tracking with an implantable wired electromagnetic transponder by Ravkilde et al. [RKH*11] are examples of such approaches. A combination of 2D electronic portal images and 3D optical surface sensors is also possible and can be found in the work of Riefenstahl et al. [RKC*01].

⇒ *Image-guided adaptive RT is a relatively new concept which has not yet been fully established in clinical practice. Therefore, most of the approaches in joint VC/RT research are also still under investigation. However, some approaches are already integrated into the routine—especially, those related to inter-fraction [KZD*09, WRH*08, WLF09b].*

3.7. Evaluation of VC Applications in RT

All reviewed papers conducted some form of evaluation. Table 2 summarizes the evaluation alternatives followed in the reviewed papers. For the evaluation of the previously discussed VC approaches, we noticed three main trends. Half of the previous work provides quantitative results to back their statements (Quantitative Results: 55/105 papers, 52%), followed by papers which reported only qualitative results, by either presenting visualization examples, case and use studies, usage scenarios, or summarized expert feedback (Qualitative Results: 43/105 papers, 41%). The remainder of the papers falls in between categories, where combinations of the above have been employed, together with quantitative user evaluations. No particular trends or correlations have been detected with respect to the taxonomy categories and the form of evaluation that has been performed. Also, we did not notice any trend with regard to the time of publication.

Table 2: *Summary of whether and how authors of the papers included in this survey evaluated their approaches. We make a distinction among quantitative results, quantitative user evaluations or qualitative results (use cases, case studies, example images).*

Quantit. Results	Quantit. User Eval.	Qualit. Results	
✓	✗	✓	[AOM*14] [ADS*07] [AHN15] [ADR*18] [BMA*14] [BAG*17] [CWKS00] [CRR*18] [CCT*14] [CT14] [CGC*09] [CJV17] [CLS06] [EWR*08] [FKK*01] [FSS*13] [GDF*00] [GCC*16] [GEH*02] [GWP*12] [GS02] [GPN*01] [HBR*17] [HDB*18] [HBK*07] [IFP95] [IFP96] [IFP97] [KMK*04] [KZBS01] [KZD*09] [KCEF07] [KBVD08] [LCS*13] [LXN*05] [LHL*10] [MK11] [MYE*17] [MAP10] [MGMS97] [ENBD08] [NKN*14] [OJC14] [PM06] [RKS*16] [RKH*11] [RCY*17] [SBR*17] [SVMF13] [SKH*08] [SDZ*02] [TUDB12] [WLF09a] [WRH*08] [ZHT*13]
✓	✓	✓	[SFJ*16] [SFA*17]
✗	✓	✓	[MGLS*16] [RvD*15] [WPB*11]
✓	✗	✓	[GPTP10][HMTH13]
✗	✗	✓	[ALH97] [AM06] [BG11] [CK09] [CvW17] [CWvv18] [CGB*05] [FMHC07] [FC16] [dW96] [HST87] [JZG*14] [KYA*10] [KSS*18] [LJP*99] [LFP*90] [LXX*06] [MUO06] [MYKO91] [MLK*13] [MC08] [NBYR12] [NRS*14] [ODH*07] [PMM*07] [PB01] [PLW*12] [RMvE*14] [RvdHvH*14] [RCM*16] [RMB*16] [RCA*18] [RBGR18] [RKC*01] [SWS*08] [SDB*02] [SRV16] [SSJ*05] [WLF09b] [WWN*04] [YBEN*11] [ZMN15] [ZMBL00]

3.8. Identification of Literature Concentration

Figure 8 summarizes the categories, where most of the previous work in VC for RT is concentrated. The majority has been conducted for developmental purposes (51/105 papers, 49%), i.e., most of the approaches have not been integrated into clinical practice. This can be either because they tackle new experimental directions of clinical research, or because they are proof of concept approaches whose benefits have not been proven yet for clinical practice. Previous work falling into the purely *integrable* categorization are only one fourth of the reviewed papers (27/105, 26%). The remainder of the work is neither purely *integrable* nor purely *developmental*. Please note that the categorization is based on the experiences and personal opinions of the authors.

With respect to the workflow steps, most work has been conducted within the field of *Dose Plan Review and Treatment Evaluation* (46/105 papers, 44%), followed by *Target and OAR Definition* (38/105 papers, 36%). Not a lot of work has been conducted in the *Treatment Plan Design and Dose Calculation* (9/105 papers, 9%) and in *Image Guided Adaptive RT* (12/105 papers, 11%).

Within the respective subcategories of the two previously mentioned categories, previous work has mainly focused on *Data Segmentation* (13/105, 12%), *Multi-Parametric Data Exploration and Analysis* (13/105, 12%), *Spatial Evaluation* (30/105, 29%) and *Non-Spatial Evaluation* (16/105, 15%). Among these, *2D/3D Dose Plan Review Approaches* (18/105, 17%) and *(Semi-)Automatic Segmentation Solutions* (12/105, 11%) are the most commonly encountered in previous literature. In *Target and OAR Definition* literature, most previous work is developmental, while in *Dose Plan Review and Treatment Evaluation*, it is integrable. For the other two main steps, i.e., for *Treatment Plan Design and Dose Calculation* and *Image Guided Adaptive RT*, most work is developmental. Very little work has been done in sub-domains, such as integrable work for *Data Registration*, *Data Fusion* and new research fields involving developmental approaches for *Anatomical and Feature Analysis* and *Radiobiological (TCP/NTCP) Analysis*. Also, purely experimental fields of clinical research, such as *Multi-Parametric Data Exploration and Analysis* have proposed so far only developmental approaches.

4. Outlook from the RT Domain

In this section, we present the clinical outlook from the RT domain with regard to past lessons, present status and future directions for VC research in RT treatment. This section underlines the achievements so far, as well as main challenges and limitations of VC in RT, as obtained from an informal interview with two clinical specialists—a medical physicist and a radiation oncologist.

Past Lessons—In the 80s, the use of imaging and VC in RT changed treatment planning and delivery, tremendously. There has

been an *evolution from 2D treatment to 3D approaches*, incorporating densities of tissues and yielding more granular and more complex treatment plans. RT is now able to visualize patients in the 3D space, enabling to know where we are irradiating. Before that, only a rough, single slice-based way was possible [LFP*90, IFP95, IFP96, IFP97] . Additionally, different *anatomical densities* are incorporated, and the radiation dose is calculated in a few seconds within the 3D model of a patient [GDF*00, FC16, GCC*16]. Finally, RT is efficiently informed about the *dose interaction* with distinct tissues. All this had an enormous influence on treatment planning. Given this evolution, it is difficult to detach VC and, especially visualization, from RT.

The contribution of VC in the field of RT has allowed the *development of new, fast and accurate treatment* planning calculation algorithms, and the *computerized control* of the treatment. This has brought new possibilities into the treatment, and the ability to modulate the beam intensity and direction, in order to avoid certain critical organ tissues [WSVHD08, CLS06, VLM*15]. Both aspects are very important to achieve conformal dose distributions with improved target control and sparing of normal tissues, through efficient and optimized inverse planning. Moreover, VC has enabled the *integration of multiple modalities* [LSBP18, CT14, NRS*14, RvD*15] . This has facilitated the integration of all different imaging information, increasing precision and insight in what would not be otherwise seen. Nowadays, 4D conformal and intensive tumor treatment is possible, while sparing the OARs. Different visualizations have provided an *intuitive understanding* of the 3D patient anatomy, and made patient motion manageable, e.g., due to breathing [EWR*08].

Experience with joint VC/RT research showed that it is *not easy to introduce new approaches in the clinic* [PMM*07], with the exception of applications for training and education [WPB*11, BG11] . New developmental solutions are often too costly in time, resources and money—this being the main reason for not having a clinical impact. All major algorithms that are actually adopted by clinical practice, need to be supported by large companies—also, due to certification issues. Therefore, interaction and collaboration between the clinic, academia and industry is necessary. Additionally, VC researchers should always be aware of the specialist needs, and aim for a *reduction of complexity* and *improvement of usability*. The majority of applications that are actually used to treat patients are simple solutions, and those are the ones that should be improved. Additionally, VC researchers should always keep in mind the basic processes of the workflow and aim for *patient-driven solutions*.

Present Status—In clinical practice, most efforts and adopted applications within RT planning focus on *simpler solutions*. For example, in treatment planning, the most commonly encountered visualizations are 2D/3D approaches, where the different planes of the patient are shown, different tissue intensities are visible, additional information (e.g., from DWI or DCE) are color-coded and sometimes overlaid, together with dose distributions and contours of the involved anatomical structures.

On the one hand, more intuitive, and easy to understand representations, with a *less complex* interface design are needed. Human perception and cognition is currently under-addressed, and a lot of solutions do not necessarily meet the needs of clinical routine. On the other hand, current applications are able to tackle individual patients, focusing only on the visualization of a small number of images—often, just two. Still, to compare patient cohorts, e.g., in retrospective or prospective Radiomics studies, where a multitude of information from all modalities should be analyzed and learned from, current options are limited. In this case, tools that allow a *comprehensive inspection and exploration* of all available patient data—going beyond single-patient statistical analysis are required [RvD*15, RKS*16, RCA*18, RBGR18]. Therefore, ways to reduce the complexity of the data, while also being able to have a "digestible" overview of all of it, are essential.

Future Directions—Future VC-related developments should focus more on approaches that provide *better insight and understanding* of the data, and that can be *used clinically* without adding unnecessary complexity or risks. Additionally, VC/RT research should strive for a better and seamless *integration* of systems, focusing on processes and on patients. Currently, processes within the workflow of radiotherapy are regarded as detached parts, supported by the respective visualizations. Instead, we should aim to obtain an integration based on patient and process information, where everyone has access to relevant information supporting the treatment. To this end, visualizations—and also the components of user interface and cognition—should be *standardized*.

Future directions should also revolve around the topic of *intuitiveness*. There are a lot of processes that are not intuitively obvious, especially with the incorporation of concepts from Artificial Intelligence (AI), such as Deep Learning algorithms [SPG14, CGM*17, PHG*18] . A vast majority of these processes are tackled with automatic methods—the results of which, are better or, at least, not anymore differentiable from a human recommendation. With increasing complexity, we will soon not be able to *understand the outcome* of automatized approaches, and it is of major importance to have control over this outcome. Yet, tools for assessment of the automatic algorithms should still be simple and intuitive.

Last but not least, VC/RT research should keep in mind that RT is a *patient-oriented process*, and aim to turn developmental solutions into products that can reach many institutions. VC and RT people need to *collaborate* more, to see what is possible, to invest time in new developmental settings and aim for VC/RT collaborations, where we can *learn from each other*—possibly, at the interface between hospitals, universities and companies. Since patients and society are the most important stakeholders, the most relevant aspect of our work is what benefits them: patient-oriented, more effective treatment.

5. Discussion and Conclusion

Despite the significant achievements of joint VC/RT research, there are still many issues covering all areas of the workflow, which can be improved. We found that most of the previous work has been concentrated in the reviewing phase of the workflow, followed by the definition of tumors and healthy organs, as discussed in Sections 3.3 and 3.5.2. This does not come as a surprise, given the inherent characteristics of RT treatment: it is based on an optimization approach, which tries to maximize treatment of tumors, while

minimizing toxicity on the healthy organs [Was15]. Image-Guided Adaptive RT is, also as expected, not very prominent yet in VC, as discussed in Section 3.6. It is quite surprising that from domains, such as registration, fusion, and multi-parametric imaging, mainly developmental approaches, e.g., [RvD*15, SFA*17, SFJ*16] have emerged, as demonstrated in Section 3.8 and in Figure 8. This may be due to the fact that either these components are not widely employed in current clinical practice, e.g., multi-parametric imaging, or that they are complex, not mature enough, or less cost-efficient to enter clinical practice. As proposed in Section 4, future approaches should focus on addressing adequately the maturity, complexity and efficiency of these methods, and assess later whether they can be beneficial—if integrated into the RT workflow.

Several interesting aspects have been raised and presented in Section 4. Despite the interesting outcomes of many research projects, these are not easy to introduce in the clinic [PMM*07]. Still, for training and education of new specialists, experimental approaches are more often included and well-accepted [BG11, WPB*11].

Moreover, a close collaboration between the clinic, academia and industry is necessary, to ensure that the newly developed approaches can be picked up and adopted, later on. The community should focus even more on simpler—yet, creative—solutions, and more intuitive, easier to understand and to use approaches. To this end, the needs of the specialists and of the patients, as well as the basic processes of the workflow, should always be considered when developing new VC strategies. Easy, fast, standardized, and cost-efficient approaches are expected to be the ones that will stay in clinical practice. Interaction is an important aspect within these approaches [AvHL*17].

Another important topic that emerged from the outlook in Section 4 is that the two domains of RT and VC still "speak in different languages". To address this issue, there should be more generalized efforts for collaboration between VC and RT, where both domains can learn from each other. This is expected to yield more developmental settings, which could be further turned into products that would serve many institutions and that would be integrated into the workflow. Two examples of such projects are two past FP7 European Projects: DR THERAPAT–Digital Radiation Therapy Patient [DR 13] and SUMMER–Software for the Use of Multi-Modality images in External Radiotherapy [SUM12].

From the current trends in RT research, we foresee that future directions will target topics within the domains of *personalization*. 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]. However, in this case, two main issues can emerge. The first one is the selection of adequate AI methods to deal with an increasing number of data-derived features. The second one is maintaining the ability to understand, assess and reason with respect to the outcome of such methods. The former topic is being addressed in current VC research, but in most of the cases, results cannot be achieved interactively, which is not always optimal and time-efficient. To this end, the field of *Progressive Visual Analytics* [SPG14], where partial results of an algorithm can be produced and interactively analyzed, may be beneficial. Additionally, as Visual Analytics solutions tend to be complex, target users are not able to fully exploit their potential. Guided Visual Analytics is a concept that puts emphasis on the effective use of such systems by domain experts the domain of *Guided Visual Analytics* [CGM*17]. Future research towards these directions would be an interesting enhancement to current work.

Designing and employing Progressive and Guided Visual Analytics solutions can additionally facilitate understanding and deliberating about the results of the employed AI-supported methods [PHG*18]. With increasing complexity, it will become of major importance to gain understanding, as well as control over automatized outcomes. From a visualization point-of-view, follow-up and inter-patient analysis would be challenging, due to the implicated dimensionality and complexity of the data, and because anatomic correspondences are not ensured [RBV17]. Smart strategies to address these two key-points need to be devised.

Another topic of major importance is the incorporation and exploration of *uncertainties* of RT. Although extensive studies have been conducted with regard to uncertainties, such as errors or inaccuracies of the imaging acquisition step, other sources of uncertainties remain challenges and open directions for the future. One of the most important parts of uncertainty in RT is related to the propagation of uncertainty and its accumulation through the different steps, e.g., from imaging to registration, segmentation and to the final outcome of the worfklow. Uncertainty propagation and accumulation has only been partially addressed [Rai18]. Additionally, investigating delivery-related uncertainties in the future is anticipated to improve significantly the efficiency of the treatment and the minimization of side-effects.

6. Summary

In this survey, we reviewed the role of VC in the development of the RT treatment planning domain. We conducted an extensive literature search, which has built the basis for the taxonomy that we presented in Section 3. The presented taxonomy systematically categorizes the previous literature work into approaches that address a specific step (or sub-step) of the RT treatment workflow, together with their adoption status (possible to integrate vs. developmental). For each of the categories that have been determined within the taxonomy, we discussed previous joint VC/RT work, with a focus on the advancement that they offer to the RT field. We discussed also drawbacks and evaluated them comparatively, within each subcategory. Additionally, the taxonomy facilitated the identification of topics concentration within existing literature—in particular, subfields that have not been deeply investigated, in the past. We considered the evaluation to be an integral component of the previous work, so we comment on whether the discussed approaches have been evaluated and with which methods. Finally, we gave insight in the past developments, present status and future directions within the joint research area of VC/RT, in an outlook from the RT domain. We expect that the field of VC/RT joint research will become even more widespread in the upcoming years, and that closer collaborations between researchers, both in academia and industry, and clinical experts will become more and more imminent.

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