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Building tools for image-guided adaptive radiotherapy of bladder cancer

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Chapter 7

General discussion and conclusion

7.1 General objective and achievements

The objective of this thesis was to study the feasibility of marker based image-guided radiotherapy (IGRT) of partial bladder cancer and to develop the plan generation and selection techniques for image-guided adaptive radiotherapy (IGART) of the whole bladder.

In Chapter 2, lipiodol markers were proven to be a feasible method to track bladder tumor for IGRT of partial bladder. However, a significant residual error after marker based position correction was observed by measuring the differential marker movements. In Chapter 3 and 4, a biomechanical finite element (FE) model was developed to simulate bladder deformation caused by bladder filling changes. This FE bladder model shows promise for the prediction of the bladder shape change using only one pelvic scan and the volume change of bladder as the input. It can potentially be used to generate multiple plans with different volumes for the IGART of bladder cancer. In Chapter 5 and 6, automatic and semiautomatic bladder segmentation methods were developed. These segmentation methods were shown to be suitable for selecting the optimal plan for IGART of the whole bladder. These segmentation methods using statistical shape model were robust to handle the relatively poor cone-beam CT (CBCT) image quality and allowed for fast and reliable segmentation of the bladder on online CBCT.

In this chapter, we will discuss the results and achievements along with possible applications and future research direction.

7.2 Marker injection techniques

The Netherlands Cancer Institute and Academic Medical Center were the first to use lipiodol markers in the bladder wall for tumor delineation and radiotherapy guidance. This liquid marker injection technique has been adopted by several groups [136;137].

The data from Chapter 2 was taken from 2006 to 2008, when we were still on a learning curve for lipiodol contrast injection. From 2006 to 2008, 50% of the patients who received lipiodol injections had a merged lipiodol bulk, which only allowed for registration based on the entire tumor region. After that, we have replaced the injection needle with a thinner needle used for Botox therapy to better control injection quantity. We introduced the c-arm x-ray fluoroscopy into the lipiodol injection room so that the lipiodol contrast markers could be immediately checked by fluoroscopy after injection. Failed injections could be detected and re-injection performed until the required number of markers stayed within the bladder wall. As a result, recent patients generally have more distinguishable small lipiodol spots.

7.3 Clinical treatment protocols

In the Netherlands Cancer Institute, there are already more than four years of experience in performing online position correction for partial bladder radiation in the

clinic. Online position correction is performed by automatically registering all lipiodol markers together between online CBCT and planning CT and then shifting the treatment table to correct mismatches. With this online position correction procedure, the PTV margin used in clinic was reduced from 20 mm to 12 mm. In Chapter 2, significant differential movements of markers were found especially for tumors with an elongated shape. Such residual registration error is one of the reasons why even with the online position correction method, a 12 mm PTV margin is still used for partial bladder radiation.

In the Academic Medical Center, lipiodol marker injection has also become a clinical routine for whole bladder with partial boost radiation for more than four years. Lipiodol markers are used for both tumor delineation and image guidance. Currently, a 10 mm margin is applied to the whole bladder PTV except for a 15 mm margin in the cranial direction, and a 10 mm margin is applied to the tumor boost PTV. During treatment, the patient position is corrected (for translation) by automatic registration of the lipiodol markers around the boost field between online CBCT and planning CT.

In the both centers, the patients receiving whole bladder radiation are still treated in a traditional way with 15 mm uniform PTV margin using only bone registration to correct setup errors.

7.4 IGART of bladder cancer

IGRT with rigid position correction cannot compensate for the bladder deformation associated with volume differences. Therefore, IGART is required for a more precise radiation of the whole bladder with or without a partial boost. Since bladder motion is rather predictable during the course of treatment, and is found to be highly associated with bladder and rectal filling changes [15;17;82], predictive modeling of individual bladder motion patterns at the planning or early treatment stages is very useful. Several cancer centers have been investigating different strategies for multiple-plan IGART.

7.4.1 Literature review

Christie Hospital NHS Trust in UK was the first institute to introduce a multiple-plan adaptive strategy [55]. Besides the standard PTV with a 15 mm margin, two other PTVs with 10 mm and 5 mm margins were created from the planning CT. On each treatment day, the smallest PTV to cover the bladder on CBCT with a 2 mm margin was selected as the plan of the day. It was found that this procedure allows the 15 mm margins used in some cases to be safely reduced to 10 mm on average.

Physicians at the Royal Marsden NHS Foundation Trust in UK acquired two extra follow-up CT scans at 15 min and 30 min after scanning the planning CT for each patient [23]. Three plans were created from these three CT scans with a 5 mm margin. The plan for smallest PTV safely covering the bladder on online CBCT was then selected to treat the patient.

Besides creating multiple plans in the planning stage, several institutes created multiple plans based on bladder shapes observed during the early treatment stage. Researchers at the Peter MacCallum Cancer Center in Australia generated three plans with different bladder volume from the planning CT and the first five CBCT images [58]. Small, medium and large plans are created by Boolean operations on the first six bladder contours with an extra margin of 5 mm. Similarly, Aarhus University Hospital in Denmark reported three different methods to generate small, medium and large plans from the first six bladder contours [22]. Researchers at the Princess Margaret Hospital in Canada generated four plans with different sizes from the first 15 CBCT images of each patient [57]. These three studies all concluded that a multiple plan adaptive strategy is feasible and results in a significant reduction in volume of irradiated normal tissue without reducing bladder coverage.

Several groups also investigated multiple plan image-guided adaptive strategies for the whole bladder irradiation combined with a partial boost. In the Tata Memorial Center in India, six plans were created from the planning CT with a uniform margin of 5 mm to 30 mm in 5 mm increments combined with a tumor boost volume with a 10 mm margin [56]. For each treatment fraction, after automatic bone registration, the table correction was manually adjusted to fit the bladder on CBCT into the smallest of the six PTVs. At the Helsinki University Central Hospital in Finland, 3-4 planning CT scans were acquired with different bladder volume to create 3-4 whole bladder PTVs and 2-4 tumor boost PTVs with 10-15 mm anisotropic margins. On the treatment day, the plan with the smallest PTV to cover the bladder volume in CBCT with a 3 mm margin was selected as the plan of the day [29]. Also these multiple plan adaptive strategies resulted in a remarkable reduction of irradiated small bowel volume while maintaining the dose coverage of CTV at a similar level as with conventional treatment techniques.

7.4.2 Plan generation methods

As described above, there are different ways to model individual bladder motion patterns to predict the bladder shape on treatment day, e.g. using different margin sizes from the bladder in planning CT, acquiring multiple planning CT scans with different bladder volumes, or predicting bladder shapes with different volumes by doing Boolean operations of bladder shapes observed in the early treatment stage. Reports indicate that in the last method, generating multiple plans from the bladder shapes observed in the early treatment stage, yields better sparing organs at risk than other methods. However, a drawback of this method is that it can only work in later treatment stages and patients have to receive conventional irradiation during early treatment stages. The optimal number of images to use to generate the library of plans is still an open question.

In chapters 3 and 4, a biomechanical finite element bladder model was developed to model the patient-specific geometry and simulate the bladder deformation caused by bladder volume changes. This model can predict the bladder shapes using only one planning image and the bladder volume as input. It provides another option to generate the library of plans with different bladder volumes and can do without the extra CT and CBCT images needed by other methods. However, a comparison of the

library of plans created by the finite element simulation method and other image based methods has yet to be done.

7.4.3 Plan selection methods

In the multiple-plan IGART, a fast and robust plan selection methodology is an important component. Due to the complexity of the patient anatomy and low contrast of the CBCT, computer aided plan selection methods are preferred. In Chapter 5 and 6, bladder segmentation methods using patient-specific and population based statistical shape models are proposed for plan selection. The segmentation method using a patient-specific model requires the planning CT and first five CBCT images as prior information for each patient, while the segmentation method using population based model just requires a generic model and planning CT as inputs. Therefore, we suggest choosing the segmentation method using a patient-specific model for multiple-plan adaptive strategies, that start after the early treatment stage, since the CBCT images needed for model building are required to generate the library of plans. For multiple-plan strategies starting from the first treatment day, the segmentation method using a population based bladder model combined with manual correction is recommended to segment the bladder and select the optimal plan. More discussion about the bladder segmentation methods can be found in section 7.8.

In Chapter 5 and 6, the plan selection decision is made based on volume coverage of the bladder by different PTVs. Lu et al. developed an integrated segmentation and deformable registration framework to simultaneously segment multiple pelvic organs [121]. A similar multiple pelvic organs segmentation strategy could be investigated in the future such that plan selection would not only be done based on target coverage but to also take dose constraints on the organs at risk into consideration.

There are some alternative ways for multiple-plan selection that do not use ionizing radiation. Ultrasound was reported to provide a quick and reliable measurement of bladder volume [37;79]. The bladder volume measurement is considered as a surrogate measure of bladder motion during radiotherapy and could be used as an alternative tool to select the optimal plan from the library of plans. Li et al. from Karlsruhe Institute of Technology in Germany developed an impulse radio ultra wideband radar for detecting water accumulation in the human body [138]. It provides a cost efficient way to measure the water volume in the bladder in real time [139], and can also be used potentially for online plan selection.

For the IGART of whole bladder with a partial boost, a major difficulty is that there is differential motion between the tumor and healthy part of bladder. The tumor boost region mostly shows rigid motion (and some bending in elongated tumors), while the healthy part of the bladder mainly shows volume associated anisotropic deformations. The boost field is usually prescribed at a 50% higher dose than the elective field. Hence, the position correction of the boost field is more important than the elective field. To further improve the precision of the elective radiation field, we propose to use a marker-based image guidance combined with a multiple-plan adaptive strategy for the whole bladder irradiation combined with partial boost. The bladder tumor should be included into the finite element model to simulate the differential

deformation of tumor and healthy bladder caused by bladder filling. After finite element simulation, multiple artificial CT images with different bladder volumes would be created. Multiple plans containing integrated elective and boost fields would then be generated based on the created artificial CT images. During treatment, the patient position should first be corrected by the registration of lipiodol markers to guarantee that the boost field will receive a high dose. From the position with marker registration, the optimal plan would be selected as the plan of the day such that the healthy part of bladder on online CBCT is safely covered by the elective PTV.

7.5 Intra- fractional motion correction

Intra-fractional motion associated with continuous bladder filling is a unique problem in radiotherapy of bladder cancer. So far, most radiotherapy delivery systems cannot compensate for intra-fractional motion of the bladder other than by adding safety margins.

At the Netherlands Cancer Institute, two CBCT scans were performed before and after treatment delivery. It was found that the mean, systematic error Σ and random error σ of intra-fractional bladder motion were 0.16 mm/min, 0.16 mm/min and 0.23 mm/min respectively for patients with empty bladder protocol, and 0.12 mm/min, 0.13 mm/min and 0.18 mm/min respectively for patients with full bladder protocol. According to the van Herk margin recipe for a one dimensional case, the margin is given by: $\text{mean} + 1.64\Sigma + 0.6 \sigma$ [67]. The margin needed for intra-fractional motion during an 8 min long treatment is 4.4 mm for patients treated according to an empty bladder protocol and 3.5 mm for patients with a full bladder protocol. Note that the size of the margin is highly correlated with the overall treatment time. Fast radiation delivery techniques like volumetric-modulated arc therapy can significantly reduce the treatment time and therefore reduce the required intra-fractional safety margin.

The CyberKnife system (Accuray, CA, USA) is a possible option to track and correct intra-fractional bladder tumor motion in real time. Using an integrated tracking system designed for real-time guidance through a robotic arm, CyberKnife allows for real-time organ position and motion correction during radiotherapy. Therefore, for the partial bladder radiation with lipiodol fiducial markers, CyberKnife might correct the intra-fractional bladder tumor motion during radiation treatment. A disadvantage of the CyberKnife is that treatment times are quite long. That is possibly the reason why bladder cancer treatment has rarely been attempted on CyberKnife device [140]

7.6 Margins

For the IGRT of the partial bladder, setup error and translational tumor motion error can be corrected by shifting the treatment table using marker registration. However, after such position correction, there are still residual errors indicated by the differential motion of markers found in Chapter 2. The marker registration in Chapter 2 only includes translation. Hence the differential movements of markers could contain both rotation and deformation. The van Herk margin recipe [67] is not

applicable to rotational and deformational motions. Remeijer et al. [141] and van Kranen et al. [142] investigated the margin recipe for rotational and deformable targets, respectively. The margin recipe for rotational uncertainties requires the measurement of rotation deviations in three directions and is only able to estimate the margin for systematic rotational uncertainties [141]. In the future, we plan to convert the differential marker movements to the rotational deviations relative to the isocenter for the purpose of margin calculation. However, the margin for random rotational uncertainties is still an unsolved question. The margin recipe for a deformable target requires the correlation of surface points as input to calculate the margin [142]. In Chapter 2, only 5 patients have more than two markers that allow extracting of some statistics on deformation besides translation and rotation. More patients with several markers should be collected in the future to obtain the input data to calculate the margin for deformation uncertainties.

For traditional whole bladder irradiation, an anisotropic margin derived from the finite element simulation could be used to replace the isotropic margin, leading potentially to a better sparing of organs at risk. For multiple-plan IGART, the margin for each plan needs to be further investigated. We finally believe that the margin can be dramatically reduced, if online plan re-optimization is available.

7.7 Finite element model of bladder

7.7.1 Improvement in FE bladder model

The FE models in Chapter 3 and 4 only describe the bladder deformation caused by bladder filling changes in healthy volunteers with a constant rectal filling. It has, however, been reported that bladder shape also depends on the rectum volume [15;17;82]. Hence, rectal filling should be modeled in the future to better simulate possible bladder deformations for bladder cancer patients. The accuracy of FE models in this thesis is mainly limited by the poor definition of biomechanical material properties. A simple model with population based linear elastic material properties was used since patient-specific data is difficult to obtain for human tissues, whereas non-linear models significantly increase the computation time. However, in reality, biological material always shows non-linear and non-elastic behavior [96-98]. Veronda et al. presented a material law that expresses the feature of soft tissue through an exponential term [96]. The most common non-linear material models used to describe smooth muscle tissue are the Odgen, Mooney-Rivlin and Yeoh models, which are all available in the Abaqus FE software [97;98]. In the future, such non-linear properties will be added to our model, as well as a separate segmentation of bladder tumors, which is known to be stiffer than the healthy part of the bladder wall [36]. Another limitation to this study is that the sliding between tissues in the deformation process was not included in the FE model. That is because of the lacking knowledge of the friction factor in contact layers and the dramatic increase in computation time required for simulation of sliding tissues. In the future, a simulation of the effect of friction factor should be done for the FE bladder model.

7.7.2 Tetrahedral versus voxel-based hexahedral meshes

Tetrahedral and hexahedral meshes are the most common types of meshes utilized for three-dimensional finite element analysis. Hexahedral meshes are generally preferred over tetrahedral meshes because of their superior performance in terms of convergence rate and accuracy of the solution. However, hexahedral meshes are rarely used to model human structures. This is because tetrahedral volume meshing from the surface meshes of complex human structures is usually automatic, while hexahedral volume meshing commonly requires user intervention and is labor intensive. In medical imaging applications, however, the organ segmentation images are composed of solid discrete voxels, which can be directly converted to a regular hexahedral mesh. This approach eliminates the extra step of generating a 3D surface mesh (Chapter 4).

In general, the tetrahedral mesh and voxel-based regular hexahedral mesh do not show a significant difference in accuracy when simulating bladder deformation using a linear model. However, generating a voxel-based hexahedral mesh does not require any manual labor and such a model (a low resolution) dramatically speeds up the finite element equation solving time from 1 hour to 3 min without much loss in accuracy. Hence, voxel-based mesh generation approaches makes FE modeling more feasible to clinical implementations, e.g. for multiple-plan adaptive radiotherapy.

A limitation of the voxel-based mesh generation is that sliding cannot be included in the FE analysis due to the jagged interface between organs. As significant sliding occurs between the pelvic organs, we therefore recommend combining tetrahedral and hexahedral meshes for FE analysis.

7.8 Bladder segmentation

In Chapter 5 and 6, two bladder segmentation methods using patient-specific and population based statistical shape models were developed for different IGART strategies. Mostly, bladder shape variations and image artifacts occurring in CBCT images acquired during the early treatment stages are representative of those during later stages. Thus, the patient-specific model based approach in Chapter 5 allows for automatic and reliable segmentation of bladder on CBCT. However, one limitation of the patient-specific model is that the actual bladder deformation patterns shown on the online segmentation image may not occur in the patient-specific training set. Increasing the size of the patient-specific training data set could improve the representativeness of such a model. However, the price is that more manual labor will be needed and fewer fractions are available for the actual multiple-plan adaptive radiotherapy. The population based bladder model is more representative of any bladder shape and can segment bladder on CBCT using just the planning CT as input. However, the low similarity in bladder edge features between planning CT and CBCT often drives the optimization to undesirable segmentation results. Therefore, in Chapter 6, after automatic segmentation, a quick manual correction is performed to drive the optimization to the desired result. These two segmentation methods may be combined to further improve the robustness of bladder segmentation.

7.9 General conclusion

From this thesis, we can conclude that lipiodol markers are a feasible method to track bladder tumors for IGRT of partial bladder. We succeeded in developing a biomechanical bladder model and bladder segmentation methods for online CBCT, which are useful tools for computer-aided plan generation and selection techniques for IGART of bladder cancer. Clinical implementation of the IGART for bladder cancer is the next step to be taken.