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Building tools for image-guided adaptive radiotherapy of bladder cancer

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Chapter 2

Behavior of lipiodol markers during image-guided radiotherapy of bladder cancer

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Abstract

Purpose: To investigate the stability of a novel type of markers used in partial bladder tumor irradiation and tumor deformation as indicated by the markers.

Materials and Methods: In fifteen patients with solitary bladder cancer, lipiodol was injected in the bladder wall during flexible cystoscopy to identify the tumor. A planning CT scan was made, followed by daily cone beam CT (CBCT) scans during treatment. To study the accuracy of using these markers for image guidance, uncertainties U1 and U2 were calculated, which were defined as the difference between sub-mask registration (covering single marker) and the average of all sub-mask registrations and the difference between the sub-mask registration and the general mask registration (including all markers), respectively. Finally, to study tumor deformation, the relative movement of each marker pair was correlated with the relative bladder volume (RBV).

Results: The analyzed patients had 2.3 marker injections on average. The lipiodol spot size was $0.72 \pm 1.1 \text{ cm}^3$. The intensity of spots in both CT and CBCT was significantly higher than the surrounding bladder tissue. The uncertainties U1 and U2 were comparable, and the uncertainties in L-R direction (0.14-0.19 cm) were smaller than those in C-C and A-P directions (0.19-0.32 cm). The relative marker movement of within-zone marker pairs was much smaller (and has less dependence on the RBV) than across-zones marker pairs.

Conclusions: Lipiodol markers are a feasible method to track bladder tumor by using online CBCT. Tumor deformation is observed, especially for tumors that cross the defined bladder zones.

2.1 Introduction

Radiotherapy (RT) is an important treatment option for patients with muscle-invasive urinary bladder cancer. It is currently used as the definitive treatment for patients unsuitable for radical cystectomy and has potential to play a key role in an organ-sparing combined-modality treatment [59].

The standard technique for radical radiotherapy of bladder is the treatment of the whole bladder [39]. However the dose is limited due to the presence of organs at risk. Therefore, up to 95% of tumors recur at their original site within the bladder [60] and failure to control the primary tumor is present in 90% of patients who die of bladder cancer [61]. Recently, several institutions [8;25-28;62] have reported the treatments of partial bladder irradiation with increased dose or boosting the primary tumor site after conventional treatment to the whole bladder. Cowan et al. [25] showed that reduction in treatment volume allowed delivery of an increased radiation dose without increased toxicity and online verification techniques could potentially improve local control and survival for bladder cancer.

Due to changes in volume of bladder and adjacent organs, uncertainty in the location of bladder tumors can be as much as 3 cm [18]. This uncertainty represents a major challenge in the irradiation of bladder cancer. Because of the large geometric uncertainty, a large safety margin around the clinical target volume (CTV) is required, leading to significant irradiation of healthy parts of the bladder, rectum and small bowel [15]. A previous study [36] found that bladder tumor tissue can be regarded as being rigid, and that variations in tumor shape are small compared to variations in tumor position. This means that for partial bladder treatment online adaptation or image-guided radiotherapy (IGRT) is feasible and has great potential to reduce the geometric uncertainty.

With the recent availability of in-room volumetric CT imaging techniques, it is possible to acquire 3D CT scans just before treatment with the patient in treatment position to implement IGRT. However, soft-tissue contrast in cone beam CT (CBCT) is relatively poor and the bladder tumor is barely visible. Therefore, fiducial markers have been used as surrogate of the tumor position. Finding feasible markers is a challenging task for IGRT of bladder cancer. Hulshof et al. [32] inserted surgical clips through a rigid scope at the borders of the visible tumor. This procedure was feasible and of clear help in tumor delineation on the planning CT scan. Mangar et al. [48] developed a technique of gold seed implantation through a rigid cystoscope. The gold seeds are visible on both CT and electronic portal images (EPI). Both these techniques have some limitations. First there is a problem of marker loss during treatment, making online positional verification unreliable. In addition, the use of the rigid cystoscope is considered less patient-friendly, and some sites in the bladder are not easily reached.

Therefore, the Netherlands Cancer Institute (NKI) started a pilot study of injection of liquid markers (lipiodol) through a flexible scope. Lipiodol, an iodized oil, is a well-known contrast medium, presently used mainly for lymphography and hysterosalpingography [63]. Local lipiodol demarcation has been used for localization of tumors in the lung and prostate visualized on fluoroscopy, CT and ultrasonography [64;65]. Lipiodol can be used for tumor demarcation and image guidance on the

treatment machine as was shown by Remeijer et al. [66]. After the demonstrated feasibility, this technique was also implemented at the Academic Medical Center (AMC), University of Amsterdam.

Lipiodol exhibits advantages over clips and gold seeds, in particular in terms of access to all bladder tumor sites (because a flexible scope can be used) and no problems of marker loss. However, limited quantitative information on lipiodol marker diffusion and washout is available. Furthermore, geometrical uncertainties caused by tumor deformation could hamper tumor tracking. Therefore, the aim of this study is to investigate the behavior of lipiodol markers during IGRT of bladder cancer, including evaluation of the quality of marker matching and quantifying the differential marker movement caused by tumor deformation.

2.2 Materials and Methods

2.2.1 Patients and CT data

Fifteen patients with unifocal T2-T3N0M0 solitary bladder cancer, 11 males and 4 females, with a mean age of 78 years (range 66 to 88) were included. Nine patients were treated at the NKI and six were treated at the AMC between March 2006 and January 2008. Patients were selected according to the following criteria: lipiodol markers were successfully injected, more than one lipiodol spot is available and every lipiodol spot in planning CT and CBCT is visually distinguishable from others. All patients had a transurethral resection of their bladder tumors before radiotherapy, and no patients received neoadjuvant, concurrent or adjuvant chemotherapy.

In each patient, the lipiodol marker was injected around the visible tumor during a cystoscopy session using a flexible scope. Through the working channel of the flexible scope, a flexible needle with needle length of 6.0 mm is inserted. Under cystoscopic guidance, the needle is inserted at the site of the macroscopical tumor border and a small deposit of approximate 0.25 ml lipiodol is placed under the urothelium in the bladder wall. The injections were done at the locations around the primary tumor. This procedure was simple and no complication was encountered. One day after the lipiodol injection, a planning CT was made, with a resolution of $1 \times 1 \times 3 \text{ mm}^3$. All patients were treated with an adaptive radiotherapy (ART) technique [26] in combination with partial bladder irradiation. For the 6 patients in AMC, oral contrast was administrated before the acquisition of the planning CT, to visualize the small bowel. The patients in AMC were treated with an elective field to the small pelvic combined with a concomitant partial bladder boost. In the other 9 patients in NKI, no oral contrast was taken and treatment was given with partial bladder irradiation only. All the patients were instructed to void, drink 250 ml of water and refrain from urination at least one and half hour before simulation and treatment. No specific instructions were given regarding the bowel habit. In the first week of the 4-6 weeks treatment period, daily CBCT scans were acquired and in the later three weeks CBCT was performed once a week. The CBCT scans were acquired using an Elekta Synergy system prior to treatment with the following acquisition parameters: 120 kV, 32 mA and 40 ms and a two minute scan time (medium field of view, about 600 projection

images). Fourteen patients were treated in supine position, and one in prone position on a belly board.

The GTV and bladder contours were delineated on the planning CT by an experienced radiation oncologist. Consecutively, the bladder contours were delineated on the CBCT scans. This bladder contour was only used to determine the effect of bladder volume changes on tumor deformation.

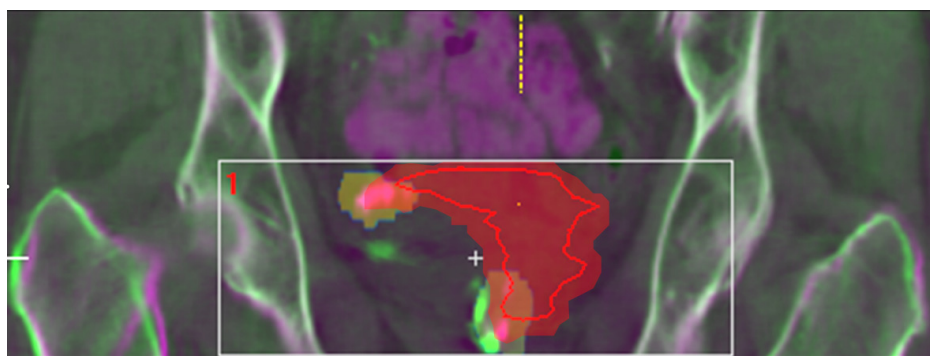


Figure 2.1: Illustration of daily CBCT image (green) acquired during the course of treatment superimposed on the reference CT data (purple). Two lipiodol spots are visible around the GTV (red contour). Furthermore this image shows the alignment clipbox for bone registration (rectangle), the general mask based on the shape of GTV (red) and sub-masks covering individual lipiodol spots (yellow).

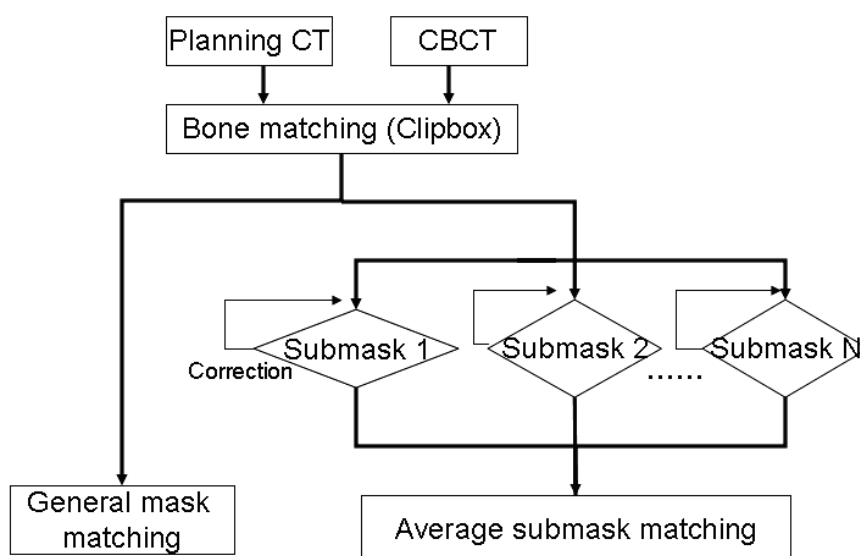


Figure 2.2: Flow chart of the registration procedure.

2.2.2 Lipiodol marker registration procedure

Lipiodol marker registration was performed using in-house developed image guidance software. On each planning CT, we defined a general mask that covers all lipiodol spots together, and multiple sub-masks for each individual lipiodol spot (figure 2.1). Using these masks, general mask registration (including all lipiodol markers) and sub-

mask registrations (covering individual marker) were next performed starting from the pelvic bone registration (figure 2.2). The residual cost function after registration is a measure of deformation of the lipiodol spots. A more detailed description of the procedure is given in the Appendix.

2.2.3 Statistical analysis

Some basic features of lipiodol markers were recorded, such as their number, and their volume and intensity. The success rate of automatic registration was also determined.

The cost function value of sub-mask registration was used to estimate the deformation of the lipiodol spots. For each patient, the observed cost function values were correlated with elapsed time, to detect possible washout of diffusion of the lipiodol.

Because mask definition is somewhat subjective, and failed automatic registrations incur manually registration steps, the reproducibility of the entire procedure was tested. Another observer (an experienced radiographer) repeated the registration procedure (including mask definition) on 5 randomly selected patients. Differences between the results of two observers were computed.

To quantify relative marker movement caused by tumor/bladder deformation, uncertainties U_1 and U_2 were defined as follows:

U_1 = sub-mask registration - average of all sub-mask registration

U_2 = sub-mask registration - general mask registration.

The systematic and random components of U_1 and U_2 were calculated. The systematic error was defined as the standard deviation (SD) of the average individual errors in same sub-mask group. The random error was defined as root mean square (RMS) of the SD of the day-to-day errors [67].

Relative movement of each marker pair was next correlated with the relative bladder volume (RBV) which is the CBCT bladder volume divided by the planning CT bladder volume, to investigate tumor deformation. For the 15 patients, we studied relative movement of 24 marker pairs, including 12 pairs from 12 patients with two lipiodol markers, 6 pairs from 2 patients with three lipiodol markers and 6 pairs from 1 patient with four lipiodol markers.

Besides bladder volume variation, the tumor size, tumor position and special material properties of tumor could also influence the tumor deformation. All patients had solitary T2-3N0M0 tumors and had similar pre-treatment, so we assume that the material properties of the tumor are the same for all patients. According to different stiffness properties of surrounding organs, the bladder was separated into 3 zones, which are shown in figure 2.3. Zone1 is in contact with small bowel and uterus (for female), zone 2 is close to rectum and other pelvic structures and zone 3 is connected with prostate (for male) and close to pelvic bone. Corresponding to bladder wall definition in standard bladder map, zone 1 is the dome and part of ventral wall, zone 2 is the left-right lateral wall and dorsal wall and zone 3 is the bladder neck and part of ventral wall. Lotz et al. [36] showed that zone 1 was most mobile, zone 2 had

intermediate mobility and zone 3 had least motion with changing of bladder volume. The zone of every lipiodol spot was noted. Marker pairs were next separated into 6 groups: group 1, 2 and 3: pair lies within zone 1, 2, 3; group 4 and 5: pair lies between zones 1-2 or 2-3; group 6: pair lies between zones 1-3. This categorization also implies different tumor sizes and shapes: small and round tumors are found in group 1, 2 and 3 (within the same zone), intermediate tumor sizes and elongated shapes are found in groups 4 and 5 (across adjacent zones) and large tumor sizes for group 6 (across non-adjacent zones).

Correlation coefficients were calculated and linear regression analysis was performed between marker pair distance and bladder volumes for these 6 groups. Because having a fuller and emptier bladder compared with the planning CT has a similar effect on marker distance, the reciprocal of relative bladder volumes smaller than one was taken in the correlation calculation.

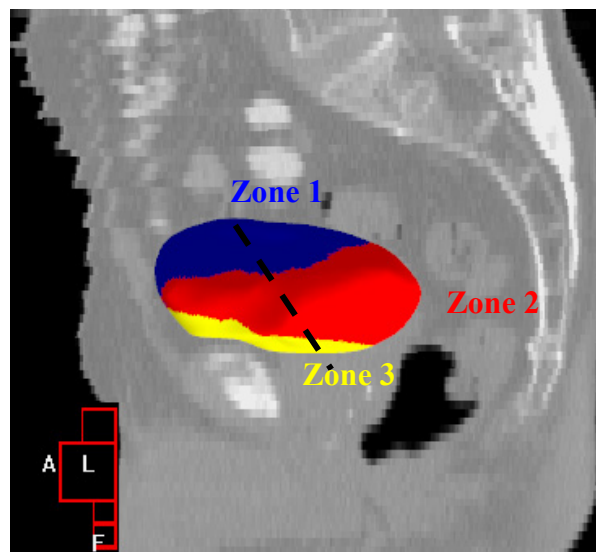


Figure 2.3: Sagittal view of the three zones used to separate the location of lipiodol spots. Zone1 is the dome and partial ventral bladder wall in contact with small bowel and uterus (for female), zone2 is the lateral and dorsal bladder walls close to rectum and other pelvic structures and zone3 is the bladder neck and partial ventral wall close to pelvic bone and in contact with prostate (for male).

2.3 Results

2.3.1 Basic features of lipiodol markers

There were 2.3 (2 to 4) lipiodol marker injections on average for patients enrolled in this study. The average of the lipiodol spots size in CT scans was $0.72 \pm 1.1 \text{ cm}^3$ (1 SD). In both CT and CBCT, the lipiodol spots could easily be visually discerned. However, the intensity of lipiodol had a wide range: between 15% and 150% higher than the bladder wall. Thirty-four out of 37 (92%) lipiodol spots were still present on the last CBCT, 5 weeks after the injection. Two lipiodol markers washed out

gradually and disappeared in the second treatment week. One lipiodol marker was not visible due to image artifacts caused by femoral head prosthesis.

The average cost function after successful sub-mask registration was 1.8 ± 0.9 mm. This value represents the average shape difference caused by segmentation differences, differences in image resolution, and marker diffusion. Note that this cost function is the average distance over all contour points and was therefore not direction specific [68]. To estimate diffusion, we performed linear regression of the cost function versus elapsed days. A statistically significant time trend of the residual cost function was found in 5 of the 37 lipiodol markers. For these 5 lipiodol markers, the average cost function increase was 0.65 mm after 4 weeks, indicating that lipiodol marker washout was limited.

2.3.2 Reproducibility of registration procedure

The mean and standard deviation of the difference between twice general mask registrations is 0.01 mm and 0.05 mm, respectively. The mean and standard deviation of the difference between twice average sub-mask registrations are 0.06 mm and 0.18 mm. This implies that the general mask and sub-mask registration methods are highly reproducible.

2.3.3 Uncertainties of marker based registration

The systematic and random components of the marker based matching of uncertainties U1 and U2 are listed in table 2.1. The two different alignment methods gave very similar results. U2, the discrepancy between each sub-mask registration and general mask registration, was always slightly larger than U1, the discrepancy between each sub-mask registration relative to average sub-mask registration. The uncertainties in the left-right direction were smaller than in other directions. The highest uncertainty occurred in the cranial-caudal direction of U2, with Σ and σ both 0.32 cm, i.e., the largest deformation occurs in that direction.

Table 2.1: Systematic and random components of lipiodol marker based matching uncertainties U1 and U2 in three orthogonal directions. U1 and U2 are difference between sub-mask registration and average of all sub-mask registrations and difference between sub-mask registration and general mask registration, respectively.

Uncertainty	U1			U2		
	R-L (cm)	C-C (cm)	A-P (cm)	R-L (cm)	C-C (cm)	A-P (cm)
Σ	0.14	0.25	0.19	0.16	0.32	0.20
σ	0.17	0.19	0.20	0.19	0.32	0.26

2.3.4 Relative movement of lipiodol markers as function of bladder volume

Despite the application of a drinking protocol, there was a large variation in planning bladder volume for different patients, ranging from 108 cm³ to 445 cm³. The bladder volumes of all planning and follow up scans ranged from 72 cm³ to 632 cm³ (mean 190 cm³). The RBV during treatment had a range of 0.35 - 2.33.

The correlation between RBV and marker pair distance is illustrated in figure 2.4. The color of each symbol in figure 2.4 represents one marker pair group. Group 6 (with markers in zone 1 and 3) was not found in our patients. We observed that group 4 and group 5 were much more affected by RBV than group 1, group 2 and group 3.

To quantify the relation between RBV and relative movement of marker pair, the reciprocal of RBV values smaller than 1 was taken and the 6 groups were combined to just two groups: within-zone and across-zone (figure 2.5). Both curves have a slope that differs from zero ($p < 0.001$) and start around 3 mm distance for RBV=1. The slope of the within-zone group was 6 times smaller than the slope of the across-zone group. The latter slope was 1.21 cm for a doubling of the bladder volume, with a correlation coefficient R of 0.86. This difference could only partly be explained by differences in marker pair distance (see discussion).

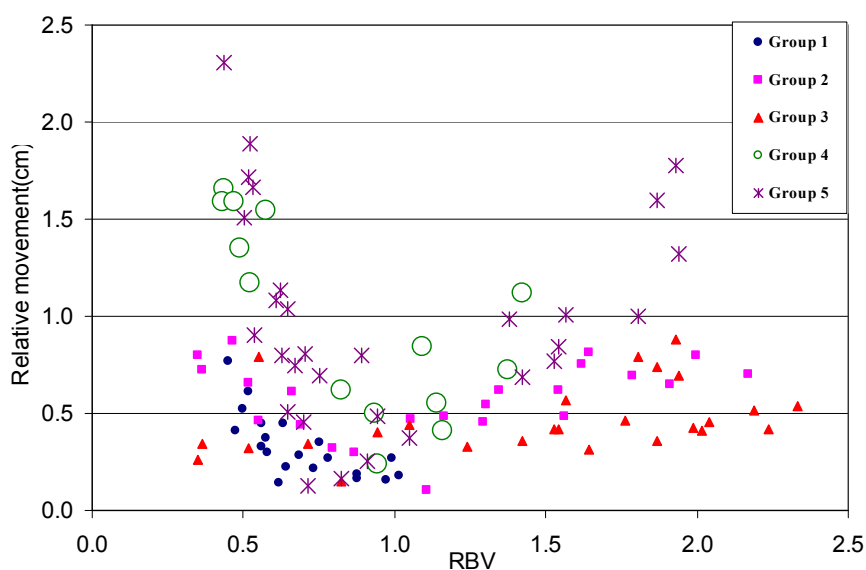


Figure 2.4: Correlation between relative movement of marker pairs and RBV for the 5 groups.

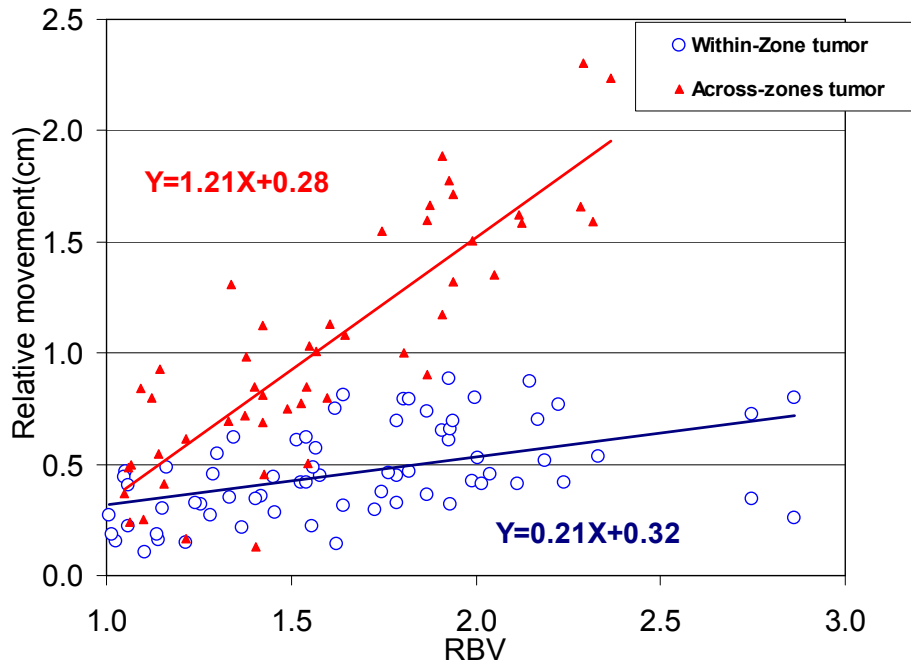


Figure 2.5: Correlation between relative movement of marker pair and RBV for across-zones and within-zone groups.

2.4 Discussion

This study investigated the behavior of lipiodol markers during IGRT. These markers were well visible in CT and CBCT, and can be successfully registered by chamfer matching algorithm. Therefore, lipiodol markers offer a reliable method to track bladder tumors.

Automatic registration of the markers is an essential component of IGRT. In this study, two methods were tested. The simplest method is to register all lipiodol spots together. This method is easy to implement and will work even if lipiodol spots are connected or lost, and has a high success rate. However, the disadvantage of this “general mask registration” is that larger lipiodol spots will dominate the registration. Thus, diffusion or deformation of a single large lipiodol spot could lead to a bias. The sub-mask registration procedure is more complex, and will not work if lipiodol spots are connected or lost. We therefore propose to implement both procedures and use the difference between general mask registration and sub-mask registration to detect tumor deformation.

In this study, for the purpose of investigating tumor deformation, we selected 15 patients with clear distinguished lipiodol spots to allow measuring relative markers movement. In the same period, another 17 bladder patients were also injected with lipiodol markers. In 16 out of these patients, the lipiodol markers were split or joined. This will not hamper general mask registration as IGRT technique. In one out of the 17 patients, no contrast in the bladder wall was observed. Pooling this material we find that 47% patients are eligible for both the general mask and sub-mask registration

methods, 50% patients are only suitable for general mask registration and 3% patients are ineligible for IGRT. The single observed lipiodol injection failure is not yet understood. It may be related to specific infiltration properties of bladder wall or just due to a poor injection technique. We are still in learning curve, and methods for more automatic injection need to be developed.

We analyzed the relative marker movement and found that it is strongly correlated with bladder volume variation. For patients with a small tumor, the deformation is small. For the patients with across-zone tumors deformation is more important. In this group, online ultrasound could be a feasible way to measure the relative bladder volume and predict the marker uncertainty [69]. A simple way to correct for systematic errors in tumor location and deformation is to repeat the planning CT when extreme bladder volumes are observed. According to the average bladder volume (190 cm^3) of all patients, $150\text{-}250 \text{ cm}^3$ is recommended as the volume range of planning scan.

In figure 2.5, the linear fits do not go through the origin even for an RBV of one there is still on average a 3 mm difference between the marker pair distances. This residual error is probably related to other causes of bladder deformation such as changes in rectum and small bowel volume. The largest relative movement of marker pairs is observed in the C-C and A-P directions, in accordance with Meijer et al. [31].

Our observed tumor deformations contradict the study of Lotz et al. [36], who found limited tumor deformation. A possible explanation for this contradiction is that the markers may be injected away from the border of the tumor, which indeed occurred for one patient. However, we believe that the main reason for the difference is that our detection method is more sensitive.

Lotz et al. [36] also found that bladder wall deformation depends on the location in the bladder: the largest deformation occurs in the cranial and anterior parts. These observed differences in (healthy) bladder wall deformations are not reflected in tumor deformations: group 1, 2 and 3 behave the same in figure 2.4. Only the tumors crossing different zones (group 4 and 5) bend when bladder filling changes. Since couch shifts cannot correct such tumor deformations, IGRT should be used with care for patients with across-zone tumors.

The bladder wall was separated into 3 zones that border different anatomical structures and physically represents the deformation ability of bladder. Since the bladder shape differs largely among different patients, the bladder zone definition is somewhat arbitrary and can bring some uncertainty to tumor deformation prediction. The difference between across-zone and within-zone tumors could also reflect the influence of tumor size.

The observed slopes of tumor deformation as function of RBV were compared with estimated deformation of the healthy bladder wall. The result is that within-zone tumors are about twice as rigid as the normal bladder wall, while the across-zones tumors show a similar deformation as the normal bladder wall.

It is not simple to estimate the safety margin required when dealing with the observed deformations: classical margin recipes [67] assume that the target is a single rigid

object. Online re-planning and subsequent adaptation of the patient's position and/or the treatment plan is perhaps the ultimate solution to correct for all shifts and deformations. However, continuous bladder filling during the IGRT procedure means that even in such a case margins cannot be zero.

2.5 Conclusion

Lipiodol markers are a feasible method to track bladder tumor position changes during treatment and have a large clinical potential to replace IGRT based on bony anatomy for partial bladder treatment. Even though lipiodol marker diffusion is negligible, significant tumor deformation was found, in particular for tumors with an elongated shape (across-zones). The deformation is strongly correlated with bladder filling. Even with online position correction, a generous margin is still necessary to account for these deformations, and a larger margin is needed for across-zones tumors than within-zone tumors.

2.6 Appendix: Lipiodol marker registration procedure

For this study modifications were made to in-house developed image guidance software (XVI) that is similar to the Elekta Synergy system and has a shared code base. The proposed marker registration procedure consists of two parts: pre-processing and registration. During pre-processing, the planning CT and associated contours are loaded into the XVI software. First, a box-shaped region of interest (ROI) for pelvic bone registration was defined. Second, the GTV was expanded by 5 mm to create a shaped ROI for registration of all markers at once (general mask). It was manually edited to ensure it included all lipiodol spots and excluded any contrast or bone. Finally, each lipiodol marker was delineated as a separate ROI (sub-mask).

In the registration procedure, planning CT and CBCT were displayed in a purple/green overlay (figure 2.1). First, the pelvic bone was registered. Then, the general mask was projected onto the CBCT and edited to contain all lipiodol markers and exclude bone in CBCT. General mask registration and sub-mask registrations for each lipiodol spot were next performed starting from the bone registration (figure 2.2). All registrations were visually checked. In case of a visual mismatch, the selected ROI was manually aligned between the CT and the CBCT and automatic registration was restarted. If automatic registration was still not successful, the manual registration was taken as result.

The chamfer matching algorithm [68] is used for bone, general mask and sub-mask registration. In this algorithm, first the selected feature (bone or lipiodol spots) is segmented using an intensity threshold that is 20% higher than the intensity of muscle. The segmented CBCT volume was next processed by a distance transform, and the segmented planning CT was converted to a set of contour points. The registration cost function, measuring the goodness of fit between the distance transform and the contour points, is the average pixel value in the distance transform map at the location of the contour points. Registration was performed by iteratively minimizing the cost function.

Because small lipiodol spot shape changes can easily be interpreted as a rotation, general mask and sub-mask registrations were restricted to translations only, while pelvic bone matching included translations and rotations.