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Building tools for image-guided adaptive radiotherapy of bladder cancer

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Chapter 1

General introduction and outline

1.1 Bladder cancer

In the Western world, bladder cancer is the fourth most common malignancy in men and the eighth most common in women [1]. In Europe and the United States, bladder cancer accounts for 5% to 10% of all malignancies in men [1]. The risk of developing bladder cancer at <75 years of age is 2% to 4% for men and 0.5% to 1% for women [1]. Bladder cancer is generally considered as a disease of older age, reaching a peak incidence in the sixth and seventh decades. In the Netherlands, bladder cancer is the 6th most common cancer type [2]. In the year 2002, the yearly incidence rate in the Netherlands was 21.7 per 100, 000 for males and 4.9 per 100, 000 for females and the incidence rate is rising at about 1.2 % per year [2]. Tobacco smoking is the main known contributor to bladder cancer. Cigarette smokers are two to six times more prone to develop bladder cancer than those who do not smoke [3]. In general, smoking is associated with men more than women, which can partially explain the higher incidence rate in men. Employees who work with dyes, metals, paints, leathers, textiles and organic chemicals have also been suggested to be at higher risk [1;4].

The bladder is a hollow muscular and elastic organ, located on the pelvic floor, which collects urine excreted by the kidneys before disposal through urination. In males, the base of the bladder lies between the rectum and the pubic symphysis. It is superior to the prostate and anterior to the rectum (figure 1.1 (a)). In females, the bladder is located inferior to the uterus and anterior to the vagina, thus leading to a lower maximum capacity than in males (figure 1.1 (b)).

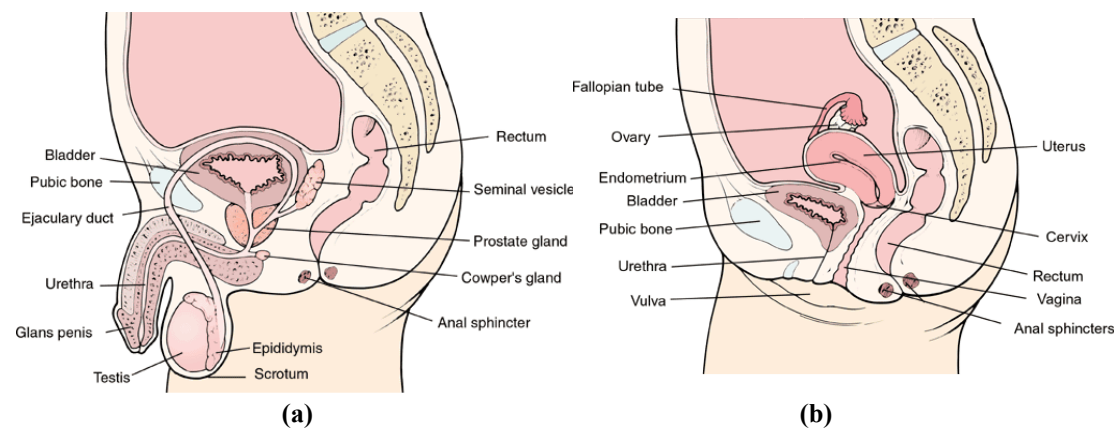


Figure 1.1: Sagittal view of male bladder (a) and female bladder (b).

1.2 Bladder cancer staging and treatment options

The gold standard for diagnosing and determining the stage of bladder cancer is biopsy obtained during cystoscopy [5]. Accurate staging is critical for patient management. The TNM (tumor, lymph node and metastasis) staging system defines T1 tumors as invading lamina propria but not muscularis propria; T2 tumors as invading muscularis propria; T3 tumors as invading perivesical tissue and T4 tumors as invading other organ structures (prostate, uterus, vagina, pelvic wall or abdominal wall) [1].

Radical cystectomy with pelvic lymph node dissection represents the gold standard for the treatment of muscle invasive bladder cancer (T2-T4). The survival rates after cystectomy are relatively high, with 5-year survival rates approaching 75% for T2 tumors and 55% for T3 tumors [6]. However, cystectomy itself may adversely affect quality of life. During and after procedure, patients may also be at risk for general operative complications.

Radiotherapy plays an important role in the management of muscle invasive bladder cancer. Radiotherapy was initially used in about 50% patients who were not candidates for cystectomy. In this selected population, the 5 year local control rate ranges between 35% and 45%, with a 5 year overall survival rate of 25%-40%. Those results were considered to be inferior to the results for cystectomy [7].

Due to the shortcomings of both cystectomy and radiotherapy when used alone, a multi-modality conservative treatment consisting of a complete transurethral resection (TUR) of the bladder tumor followed by radiotherapy with or without concomitant chemotherapy has been introduced [8-12]. The modern bladder preservation series have reported an improvement in survival. The 5-year overall survival rates range from 40% - 67% [11-13], similar to those achieved in modern cystectomy series. At 10 years, overall survival rate is 31% - 36% [11;12]. Such a bladder preservation approach provides patients the opportunity to maintain an intact and functional bladder with a survival rate similar to that of radical cystectomy [7].

1.3 Challenges of external beam radiotherapy

The general challenge in radiotherapy is to deliver a high radiation dose to the target while sparing the surrounding organs at risk (OARs). For radiotherapy of bladder cancer, the first major challenge is definition of the radiation target for treatment planning. The introduction of modern radiotherapy techniques, e.g. conformal radiotherapy (CRT), intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), allows for the planning and delivery of highly conformal dose distributions. These techniques enable an increase in the dose to target volumes and a better sparing of normal tissue in general and for the bladder [14] as well. However, large anatomical changes in bladder patients significantly limit the benefits of these techniques. Hence, the second major challenge of bladder cancer radiotherapy is the localization of the target during treatment.

Taking the inaccuracy of tumor delineation and large mobility of bladder wall into consideration, very large safety margins (2-3 cm) have to be used, leading to irradiation of large parts of the healthy bladder, rectum and small bowel [15]. Because of the toxicity to OARs, the total dose generally applied for bladder tumors (55-60 Gy) is relatively low compared to other solid tumors, which might be a cause for the relatively poor outcome in bladder cancer radiotherapy. There are several retrospective analyses suggesting a significant improvement in outcome with dose escalation [13;16]. Pos et al. found that based on biological modeling an increment in dose of 10 Gy would yield an expected 1.44-1.47 increase in the odds for local control [16]. Majewski et al. reported a 5-year local control rate of 47% after 60 Gy while it was more than 60% for a dose of 70 Gy [13]. These data suggest that bladder cancer

is a good candidate for dose escalation. However, dose escalation is only feasible if precision of the entire radiotherapy chain (target definition and dose delivery) is improved [17;18].

1.3.1 Target definition for treatment planning

Traditionally, the planning target volume (PTV) in bladder RT consists of the whole bladder including the tumor with a 2-3 cm safety margin [19-23]. A possible strategy to reduce treatment volumes in radiotherapy for bladder cancer is partial bladder radiation [24-26], in which only the bladder tumor is irradiated, leaving the healthy part of bladder out of high dose region (figure 1.2). Several groups, including the Academic Medical Center (AMC) and the Netherlands Cancer Institute (NKI), have reported on whole bladder radiation in combination with partial boost [8;11;27-30], in which 40-50.4 Gy was given to whole bladder including bladder tumor and a concomitant boost of 10-22.5 Gy was given to the bladder tumor only.

Due to the risk of micrometastases to locoregional lymph nodes, some institutes include these nodes in the clinical treatment volume (CTV) [27;28;30]. The question of the necessity of lymph node irradiation has, however, never been the issue of any randomized trial.

For target definition, delineating the bladder volume on planning CT is quite accurate. Meijer et al. quantified the geometric uncertainties of bladder delineation and found that generally very small delineation variations (1.5-3 mm, 1SD) occurred between observers, although larger discrepancies were observed in discerning the bladder from the base of the prostate [31]. Delineating the bladder *tumor* on planning CT is much more difficult. Several causes can lead to inadequacies of bladder tumor delineation on CT. There is often no visible tumor on CT due to previous TUR or neoadjuvant chemotherapy. Alternatively, TUR causes bladder wall edema that is hard to distinguish from tumor. Hence, inaccurate delineation of bladder tumors is one of the major problems for partial bladder radiation and whole bladder radiation with a partial boost.

Cystoscopy is at present still the most accurate diagnostic tool for determining tumor location and size. Demarcation of the tumor borders during cystoscopy in such a way that can be seen on a CT scan will help to delineate the tumor more accurately on the planning CT scan. Hulshof et al. inserted surgical clips through a rigid cystoscope at the borders of the visible tumor [32]. This procedure was feasible and of clear help in tumor delineation on the planning CT. Drawbacks of this technique are that the procedure is not patient-friendly, that some areas in the bladder are not easily reached and in particular that markers are often lost during radiotherapy.

Pos et al. developed a liquid marker injection technique [33]. Lipiodol, an iodized oil and well known contrast medium, was injected around the visible tumor during a cystoscopy session using a flexible scope (figure 1.3 (a)). The lipiodol injections, apart from mild pain during injection and mild transient haematuria, were not associated with additional toxicity. Compared with the clip mark, lipiodol can be easily injected to all locations of the bladder including the bladder neck. After

injection, the lipiodol markers are clearly visible on CT and cone beam CT (CBCT) scans, and they can be used both for tumor demarcation and image guidance (figure 1.3 (b) and (c)).

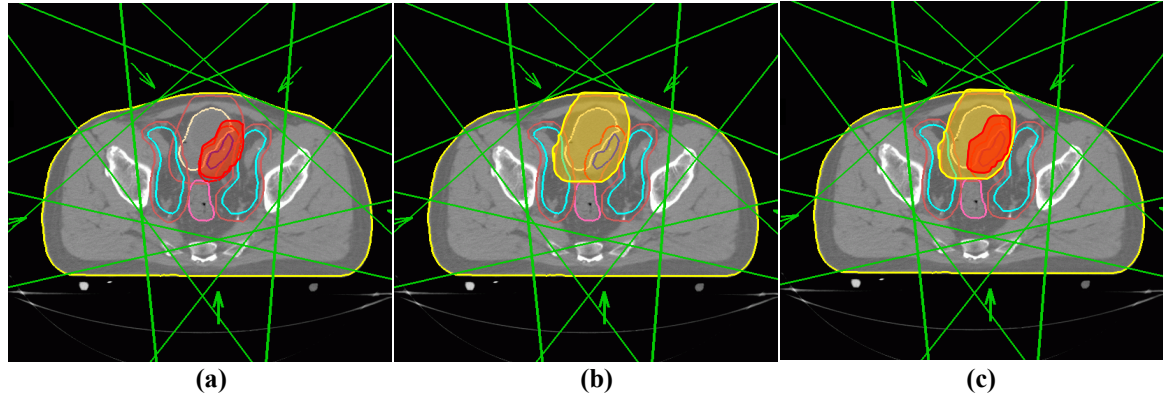


Figure 1.2: Three different radiation techniques for bladder cancer: partial bladder radiation (a), whole bladder radiation (b) and whole bladder with partial boost radiation (c). The red region in (a) is the radiation target surrounding the bladder tumor. The yellow region in (b) is the radiation target surrounding the whole bladder including tumor. The yellow region in (c) is the elective field that will be given a low dose and the red region in (c) is the boost field which will be given a high dose.

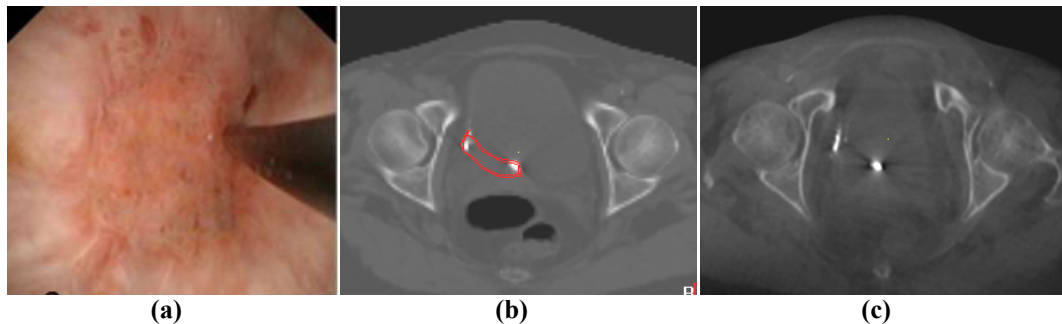


Figure 1.3: (a) A lipiodol marker is injected into the bladder wall around the tumor under guidance of cystoscopy. After this injection, the lipiodol markers show as high intensity spots in both CT (b) and CBCT (c). These markers can be used for tumor demarcation (b) and image guidance (c).

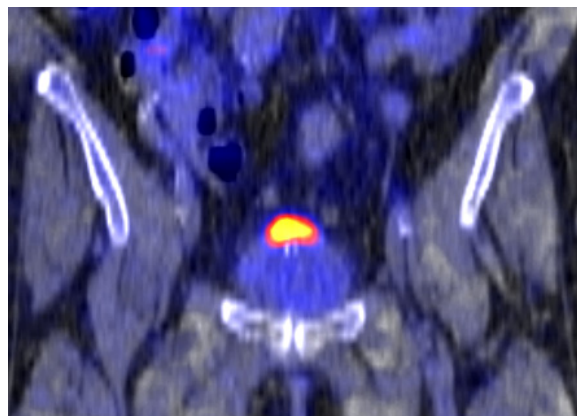


Figure 1.4: Fused FDG-PET image with CT image in coronal view. There is a hot spot at the upper bladder wall, which indicates the possible location of the primary tumor.

Positron emission tomography (PET)/CT is another modality for detecting and staging tumor, as well as monitoring response to treatment [34]. ^{18}F -Fluoro-2-deoxy-D-glucose (FDG) -PET/CT provides additional information on the metabolic activity, i.e., glucose utilization of the tumor. Bruin et al. have developed a catheter assisted FDG-PET/CT protocol for bladder cancer and to image the primary bladder tumor (figure 1.4) [35]. Such additional functional information from PET/CT can potentially improve the accuracy of bladder tumor definition.

1.3.2 Target localization during treatment

1.3.2.1 Organ motion

Due to changes in volume of the bladder and adjacent organs, such as rectum and small bowel, movement of the bladder wall between different treatment days could be as much as 3 cm [15;18]. Contrary to the elastic bladder wall, the bladder tumor is known to be stiffer and deform much less than the healthy part of bladder wall [36]. Besides the day-to-day bladder wall movement, significant intra-fractional bladder wall displacement may occur during bladder radiotherapy delivery [37;38]. As a consequence, a wide range of PTV safety margins is used in practice [18;39].

For partial bladder radiation, the radiation target is only the bladder tumor. Lotz et al. reported that the deformation of bladder tumor was small compared to its translational motion [36]. Hence, with lipiodol markers placed on the border of the bladder tumor, image guidance devices have a great potential to compensate for this geometrical uncertainty and considerably reduce the safety margin.

In contrast to the mostly rigid tumor motion, the motion of the whole bladder is mainly associated with bladder volume changes. When the bladder volume changes, the cranial and anterior parts of the bladder have larger movements than other parts of the bladder [40]. In general, the bladder shows anisotropic deformation as bladder volume changes and the volume of radiation target therefore changes between different treatment days and during treatment. Hence, the rigid position correction strategy in image guided radiotherapy cannot compensate for bladder deformation, which is a problem for whole bladder irradiation.

For whole bladder irradiation combined with partial boost, both the relatively rigid motion of the boost target (tumor) and the deformable motion in the elective target (healthy part of bladder wall) have to be taken into account. A simple table shift cannot fully compensate for such differential motion.

1.3.2.2 Image-guided radiotherapy

Image-guided radiotherapy (IGRT) is the use of frequent imaging during a course of radiotherapy to improve the precision and accuracy of the delivery of treatment. In IGRT, the linear accelerator is equipped with an imaging system so that the patient can be imaged immediately before or even during radiation delivery. Using specialized computer software, these images are then compared to the planning CT

taken during simulation. Any necessary adjustments of patient position are then made to compensate for the observed geometrical error. IGRT provides opportunities to reduce the safety margins around the target that are used to guarantee that the moving target receives the prescribed dose. Margin reduction will reduce the dose given to the surrounding structures, which will in turn provide opportunities to escalate dosage and increase the probability of disease control [41;42].

In the past decades, treatment setup has been performed by using skin markers, lasers, immobilization devices, and portal imaging with online or offline setup protocols. It has been shown that treatment setup variation is relatively small in institutes using consistent portal imaging based verification [43].

For the two most commonly used image guidance modalities, portal imaging and CBCT, the contrast of some tumor types from the surrounding soft tissue is not strong enough for image guidance. Therefore, fiducial markers are often implanted into the tumor volume to be used as surrogate. Although marker placement is invasive for the patient and markers might migrate, fiducial markers can be accurately localized before and even during each treatment fraction, which allows for daily inter- and intra- fraction position correction. Marker-based position verification has become standard clinical practice for prostate cancer patients at many institutes [44-46]. Fiducial markers are also increasingly used for IGRT of cervix cancer [47], bladder cancer [48], liver cancer [49], lung cancer [50] and breast cancer [51]. As mentioned in section 1.3.1, Hulshof et al. and Pos et al. investigated clips and lipiodol injection as fiducial markers for both tumor delineation and image guidance of bladder cancer [32;33]. Pos et al. reported that lipiodol markers are clearly visible on CBCT scans and the registration accuracy of lipiodol markers is within 2 mm (SD), which is considerably smaller than the original tumor motion [33].

Traditionally, IGRT is used to detect tumor motion and compensate it by moving the patient using translations and sometimes (limited) rotations. However, for whole bladder radiation, the major variation is volume related deformation, which can hardly be compensated by translations and/or rotations. For such large deformations, adaptation of the plan is required.

1.3.2.3 Adaptive radiotherapy

Adaptive radiation therapy (ART) is a strategy first introduced by Yan et al. [52]. ART involves a closed-loop radiation treatment process, where the treatment plan is modified based on measurements during treatment.

ART is becoming an important option for bladder cancer treatment as it enables correction of deformation errors in the target by changing the plan during the course of treatment [53]. Up until now ART is mostly an offline strategy, where after reviewing serial repeat scans, a new plan is made to correct for systematic errors [26;54]. However, offline ART does not account for random daily bladder filling variations [15]. The ideal approach to deal with bladder deformation is online ART with daily plan re-optimization. Such online ART is, however, not yet feasible in clinical application due to technical limitations.

Recently, various groups have developed multiple plan image-guided adaptive radiotherapy (IGART) strategies for bladder cancer [22;23;29;55-58]. In such treatment strategies, multiple plans with different bladder volumes are created based on images acquired before or early during treatment. Subsequently, the plan for smallest PTV safely covering the bladder as seen on CBCT is selected online as the plan of the day. All reported that multiple plan IGART improved coverage of the bladder CTV and/or reduced the amount of small bowel irradiated compared to the offline adaptive plan or traditional planning [22;23;29;54-57].

1.4 Thesis objectives and outline

To meet the two challenges mentioned above, a Dutch Cancer Foundation (KWF) project was started in collaboration between the NKI and the AMC. My thesis work, performed at the AMC, focuses on the question of “target localization during treatment”. CBCT devices integrated with the linear accelerators and lipiodol markers provide the enabling technology to perform IGRT and IGART for bladder cancer.

Therefore, the main objectives of this thesis are to study the feasibility of lipiodol markers to enable image-guidance of focal radiotherapy of bladder cancer (**Chapter 2**) and to develop tools for computer-aided generation of multiple-plans and plan selection for IGART of the whole bladder (**Chapters 3-6**).

Injecting multiple lipiodol markers around the tumor allows for accurate measurement of residual tumor deformation apart from rigid motion. However, limited quantitative information on tumor deformation and marker diffusion and washout is available. Therefore, in **Chapter 2**, we investigate the behavior of lipiodol markers during IGRT of bladder cancer, including an evaluation of the quality of marker matching and a quantification of residual registration errors indicated by differential movements of the markers.

In **Chapter 3**, a biomechanical bladder model is constructed to simulate the interaction between bladder and surrounding pelvic organs. This biomechanical model uses a finite element (FE) method to model patient-specific pelvic geometries and simulate deformation of pelvic organs solely caused by bladder volume changes. Such FE bladder model can predict bladder deformation using just one image data set and bladder volume changes as input, and can potentially be used for generating multiple plans with different bladder volumes for IGART of the whole bladder.

In practice, two factors prevent the clinical application of the FE bladder model described in Chapter 3. First, quite a bit of manual labor is required to construct the FE model with high mesh quality. Second, the computation time needed to construct the FE model and solve the FE equations is very long. In **Chapter 4**, we address these issues by constructing a low-resolution voxel-based model directly from a binary segmentation images. The voxel-based mesh generation allows for automatic and robust creation of FE bladder model without user intervention and speeds up simulation time.

Multiple-plan IGART of bladder cancer is difficult to implement because complex decision making for plan selection must take place immediately before treatment. In **Chapter 5**, to achieve a robust computer aided plan selection, we develop an automatic bladder segmentation method on CBCT using patient-specific bladder shape information.

A drawback of the segmentation method presented in Chapter 5 is that it can only work after collecting and segmenting several CBCT images for each patient. This step still imposes quite some workload and is not applicable from the first treatment day. In **Chapter 6**, we further improve the segmentation method by using a population based bladder model combined with spherical harmonic expansion and manual correction. This method requires only one planning CT as input and saves the delineation and model building required for each patient in Chapter 5.

The thesis ends with a general discussion and a summary.