Towards image-guided radiotherapy of prostate cancer
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INTRODUCTION
CANCER TREATMENT IN ANCIENT HISTORY

Cancer has afflicted humans throughout recorded history. Some of the earliest evidence of cancer is found among fossilized bone tumors, human mummies in ancient Egypt, and hieroglyphic inscriptions. The earliest known descriptions of cancer (although the term cancer was not used) appear in seven papyri. Two of them, known as the ‘Edwin Smith’ and ‘George Ebers’ papyri, contain descriptions of cancer written around 1600 B.C., and are believed to date from sources as early as 2500 B.C.\(^{1-2}\)

The Greek doctor Hippocrates (460-370 B.C., \textbf{Figure 1}\(^{3}\)), considered as the ‘Father of Medicine’, is credited with being the first physician to reject superstitions and beliefs that ascribed supernatural or divine forces with causing illness\(^{1,3-4}\). He separated the discipline of medicine from religion, believing and arguing that disease was not a punishment inflicted by the gods but rather the product of environmental factors, diet and living habits. However, Hippocrates did work with many convictions that were based on what is now known to be incorrect anatomy and physiology, such as Humoral Theory\(^{5-6}\). He believed that the body contained 4 humors (body fluids) - blood, phlegm, yellow bile, and black bile. An excess of black bile collecting in various body sites was thought to cause cancer. According to the patient’s humor, treatment consisted of diet, blood-letting and/or laxatives next to hygiene and sleep.

Although Humoral Theory and treatment remained popular for many centuries, thoughts and treatment about cancer began to change since the Renaissance period. With the discovery of the blood system, the lymphatic system, the discovery of cells, and the discovery of radiation in 1895 by Wilhelm Röntgen and the discovery of radium in 1898 by Marie (\textbf{Figure 2}\(^{3}\)) and Pièrre Curie, a new era of cancer research and treatment began\(^{3}\).
PROSTATE CANCER

In The Netherlands, prostate cancer is diagnosed in about 8,000 men each year\(^7\text{-}^9\). About 75\% is at the age of 65 or older, although recently the illness is diagnosed at an earlier age (40-45 years) as a result of increased screening\(^10\). Prostate cancer occurs more often in men in Western countries and is largest in the United States, with a striking difference in incidence between black and white people: 30\% more in black than in white people\(^11\). The incidence of prostate cancer in China and Japan is much lower, probably as a result of differences in diet\(^12\), or by the difference in diagnostic strategies\(^13\). The influence of food types on prostate cancer is still uncertain\(^14\). And, probably, male hormones and environmental factors are of influence\(^15\text{-}16\). In about 5-10\% of all men prostate cancer is caused by hereditary factors\(^17\text{-}18\). The 5-year relative survival rate for prostate cancer in The Netherlands is high and increased from 74\% in the period 1992-1996 to 84\% in the period 2002-2006\(^9\).

The prostate lies at the base of the bladder (\textbf{Figure 3}\(^19\)). The anterior part of the prostate surrounds the urethra and the posterior part presses against the rectum. A prostate tumor is a lump created by an abnormal and uncontrolled growth of cells. It can either be malignant (cancerous) or benign. Cancerous tumors can grow through the prostate and spread to other parts of the body where they may grow and form secondary tumors. This process is called metastasis. The outer part of the prostate is most likely to develop cancer.
DIAGNOSIS AND STAGING

Prostate cancer is diagnosed\(^{(7-8)}\) through digital rectal examination of the prostate and a raised level of prostate-specific antigen (PSA) in the blood. In spite of the lack of a clear threshold value providing an optimal balance between sensitivity and specificity, the PSA blood test remains the best validated and most widely implemented screening tool for prostate cancer\(^{(20-21)}\). With a transrectal ultrasound (TRUS) device, prostate and irregularities can be visualized. With a prostate biopsy, small pieces of tissue are removed and examined in a laboratory by a pathologist to find out if it is a tumor and to determine its aggressiveness. A biopsy is the only way to confirm the presence of cancer. Additional tests may be performed like computed tomography (CT), magnetic resonance imaging (MRI) and/or bone scans to see how far the cancer has spread, if at all. CT scans can indicate whether the cancer has spread to the lymphatic system. CT finding can be confirmed by an operation through small incisions where suspect lymph nodes are removed and the tissue is examined by a pathologist. A MRI scan gives information about the size of the tumor and whether it has grown outside the prostatic capsule. A bone scan involves injecting a small amount of radioactive fluid into the vein. A bone scan of this can show if the cancer has spread to the bone.

From the diagnostic data, the clinical stage according to the TNM standard of the American Joint Committee on Cancer, is determined\(^{(22)}\). The T-stage expresses whether the tumor (T) is not palpable or visible (T1), the cancer is confined to the prostate lobes (T2), the tumor has been grown beyond the prostatic capsule and/or has spread into the seminal vesicles (SV) (T3), or if the tumor invades adjacent structures (T4). The N-staging expresses whether regional nodes (N) in the lymphatic system are positive and the M-staging expresses whether there is metastatic (M) spread to the bone. Together with the PSA level, size of the tumor and the pathological Gleason score (grading between 2 and 10)\(^{(22)}\), which determines the aggressiveness of the tumor cells, these data are used to determine the prognosis and treatment options for the patient.
Treatment for prostate cancer depends on a number of factors such as staging and grading of the tumor, age and whether the cancer has spread and if so, how far\(^7\). Among them, radical prostatectomy (removal of prostate and SV), radiotherapy with inserted radioactive sources (brachytherapy) and external beam radiotherapy (See next paragraph) are the most common treatment options\(^8\). Radical prostatectomy and brachytherapy are mainly used for patients whose tumor is small and not spread beyond the prostate. However, recent studies state that radical prostatectomy is also feasible for locally advanced disease\(^{23}\). A new surgical development is (robotic-assisted) prostatectomy, where the prostate is removed through small incisions\(^{24}\). With high dose-rate (HDR) brachytherapy, also in combination with external beam radiation therapy, treatment of intermediate to high-risk prostate cancer is also possible. It was found that the combination of external beam radiotherapy and HDR brachytherapy results in a good biochemical control and overall survival\(^{25}\). Sometimes, particularly for slow-growing tumors or for patients with a life-expectancy of <10 years, no treatment is the best course of action\(^8\). This is called active monitoring or watchful waiting. It has been shown that prostate cancer mortality did not differ between patients with deferred or active treatment\(^{26}\). Counterindications for deferred treatment included younger age, higher clinical stage, higher Gleason score, and higher PSA at diagnosis.

**EXTERNAL BEAM RADIOTHERAPY**

Curative treatment of prostate cancer by means of external beam radiotherapy is the main treatment option for patients with a locally advanced tumor and a life expectancy ≥ 10 years\(^8\). External beam radiotherapy is also used as palliative treatment, e.g., to relief pain, and is effective in almost 70% of all patients\(^{27.28}\). Sometimes, external beam radiotherapy is used solely, but very often it is used as a concomitant treatment with surgical eradication of the prostate, hormonal therapy or both.
The aim of curative external beam radiotherapy is to achieve local tumor control, i.e., to destroy all primary tumor cells and spare the surrounding healthy tissue. Patients generally receive a total dose of 66-80 Gy which is fractionated in a daily dose of about 1.8-2.0 Gy during 6-7 weeks, 5 days a week. Patients often receive a drinking protocol and, in some institutes a dietary protocol, to achieve a full bladder and empty rectum before the planning CT scan and during treatment, as it has been shown that the prostate moves due to variation in rectal filling\(^{(29)}\). Strategies to improve local control and to reduce the radiation received by healthy tissue, such as the bladder and the rectum, include three-dimensional conformal radiotherapy technique (3D-CRT), intensity-modulated radiotherapy (IMRT), dose escalation, and hypofractionation. 3D-CRT and IMRT provide opportunities to escalate the prostate dose and has been proven to be more effective\(^{(30)}\). With IMRT, acute toxicity was significantly lower than with 3D-CRT\(^{(31)}\). Hypofractionation appears to be promising, although longer-term follow-up is necessary to fully define the toxicity after hypofractionated treatment\(^{(32)}\).

Fractionated external beam radiotherapy requires that localization of the prostate before each treatment fraction is accurate. Geometrical uncertainties in positioning of the tumor will be outlined in the next paragraph. In general, the (visual) tumor volume (gross tumor volume, GTV) is delineated and should, according to the ICRU 62 report\(^{(33)}\), be expanded into the clinical target volume (CTV) to account for microscopic tumor extensions (i.e., a small region around the visual tumor volume). As for prostate, the GTV is not visible on CT scans, the prostate gland is defined as the CTV. In the past, uniform treatment planning target volume (PTV) margins of 1 cm around the CTV used to guarantee that the tumor receives the required daily dose. More accurate localization would allow for reduction of the treatment margins around the prostate, which in turn will provide opportunities for dose escalation.

**GEOMETRICAL UNCERTAINTIES**

To treat the tumor of the patient as accurate as possible, the position of the patient and tumor for each fraction has to be determined as accurate as possible. The geometrical uncertainties in positioning the tumor can be attributed to treatment setup variation, including the accuracy of the used
registration technique, delineation variation and organ motion, i.e., tumor position uncertainty within the patient.

**TREATMENT SETUP VARIATION**

In the past decades, treatment setup has been performed by using skin markers, lasers, immobilization devices, portal imaging and online or offline setup protocols. It has been shown that treatment setup variation is relatively small in advanced institutes\(^{(34)}\).

**DELINEATION VARIATION**

The delineation determines which target area will receive the required dose and, in addition, the delineations of critical organs that are used for treatment planning. Delineation variation is significant, and influenced by image quality and inter/intra observer variation as has been shown by Steenbakkers et al.\(^{(35)}\) for delineation of lung tumors. Rasch et al.\(^{(36)}\) showed that delineation variation and also the delineated volume on MRI images was smaller compared to delineations on CT scans and that the largest delineation variation is found at the apex, the prostate-bladder border and the base of the seminal vesicles due to poor visibility at these regions on CT. Modern radiotherapy using IMRT and/or image-guided radiotherapy (IGRT) aims at reducing margins and therefore it is essential that delineation variation is minimized. For accurate delineation in general of target volumes and organs at risk it is advised to use other imaging modalities, like MRI, positron emission tomography (PET), single photon emission computer tomography (SPECT) or ultrasound (US), typically in combination with CT\(^{(37-40)}\). This topic is, however, beyond the scope of this thesis.

**ORGAN MOTION**

A major source of uncertainty in radiotherapy of prostate cancer is organ motion. Organ motion can be divided into interfraction and intrafraction motion. Prostate motion is mostly affected by rectal filling changes which leads to relatively large interfraction motion, especially rotation around the LR axis of the prostate\(^{(41)}\). Intrafraction prostate motion occurs, for example,
when large gas pockets move in the rectum. Some institutes use defecation protocols, laxatives or rectal balloons to minimize prostate motion\(^\text{[42]}\). Verification of organ motion can be done offline and online. The use of implanted markers, which can be detected by, for example, an electronic portal imaging device (EPID), the use of US, in-room CT or cone-beam CT (CBCT) mounted on the accelerator are means to determine prostate position at the time of treatment. The development of online and offline protocols for IGRT of the prostate is the topic of this thesis.

**MAGE-GUIDED RADIOTHERAPY**

IGRT is defined as ‘use of any kind of imaging device during radiotherapy to correct for setup error and organ motion’. Knowledge of the precise position of the target would improve the accuracy of treatment. This may in turn provide opportunities to reduce the margins around the target volume that are used to guarantee that the moving target receives the required dose. Margin reduction will reduce the amount of dose given to the surrounding structures which in turn will provide an opportunity to escalate the dose, which has been proven to increase the probability of disease control\(^{[43-45]}\).

The use of implanted markers to correct for setup error and organ motion is very common. Although markers are invasive for the patient and might be subject to migration, marker based correction strategies are considered to be very accurate. The markers can be easily detected on megavolt (MV) or kilovolt (kV) planar imaging devices just before treatment. Markers can also be used in combination with e.g., fluoroscopy or CBCT. The use of US imaging for prostate localization and setup correction is less popular nowadays, as studies have shown that there are large differences in accuracy and systematic errors between US and marker based correction strategies. Some of the errors might be due to the pressure of the probe on the abdominal wall.

Many different setup protocols are used to correct for interfraction prostate motion\(^{[42]}\). Adaptive radiotherapy (ART) was one of the first methods to correct for systematic interfraction motion by means of constructing a patient specific planning target volume\(^{[46]}\). Methods to correct online for prostate interfraction motion are currently also widely available. For example, a CBCT
device that is mounted on the treatment machine (Figure 4) provides the opportunity to visualize the prostate in 3D and to localize the prostate just before treatment\(^\text{47-48}\). This information could be used to correct online or offline for the daily changing prostate position.

One of the differences between a CBCT imaging device and a conventional CT scanner is the difference in image quality. Instead of slice by slice scanning to acquire the conventional CT scan, a CBCT scan is acquired by rotating the gantry once around the patient while acquiring the kV EPID images, which, after collecting all the images, are reconstructed to a CBCT scan. This is the reason for a CBCT device being more vulnerable to motion of the target and surrounding tissues to be imaged. The difference in scatter, scanning and reconstruction technique of the images are reasons for the difference in image quality.

The availability of 3D information of the target and surrounding tissues prior to each treatment fraction by means of CBCT has lead to a new era of research in IGRT, of which this thesis is part.

**Figure 4.** Linear accelerator (with retracted electronic portal imaging device, EPID) and a cone-beam computed tomography device (extended), consisting of a kilovolt (kV) source and EPID that are mounted perpendicular to the radiation beam direction.
OBJECTIVES OF THIS THESIS

The introduction of a CBCT device in the clinic will make it possible to retrieve 3D information of the prostate and SV at the time of treatment.

Therefore, the main objective of this thesis was to develop a method for reliable and accurate prostate localization for online or offline IGRT using a CBCT device (CHAPTERS 2-4). With regard to online purposes and short-term organ motion, the method to be developed should be fast. For that reason, the technique used for prostate localization described in this thesis is by means of an automatic 3D grey-value registration method.

The registration method was first tested on conventional CT scans (CHAPTER 2) and subsequently tested and adapted for CBCT scans (CHAPTER 3).

The influence of a dietary protocol on the performance of the registration algorithm for CBCT scans was next evaluated (CHAPTER 4). In addition, the influence of the dietary protocol on interfraction prostate motion for patients subject to the dietary protocol and those who were not was investigated.

Other objectives of this thesis were to investigate marker-based and US-guided prostate localization strategies (CHAPTERS 5 AND 6). The residual error of seminal vesicles with respect to the prostate gland was quantified for marker-based correction strategies (CHAPTER 5). And, the amount of prostate displacement during transabdominal US imaging for prostate localization was investigated and quantified (CHAPTER 6).
REFERENCES


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Introduction


