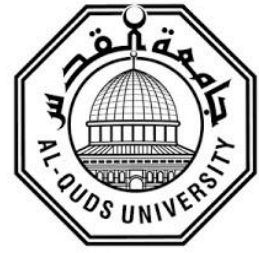


**Deanship of Graduate Studies
Al-Quds University**



**Effective Patient Preparation during Prostate
Radiotherapy Evaluations of Bladder and Rectum Doses**

Qusai Mohammad Mustafa Tamim Tamimi

M.Sc. Thesis

Jerusalem- Palestine

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Prepared By:

Qusai Mohammad Mustafa Tamim Tamimi

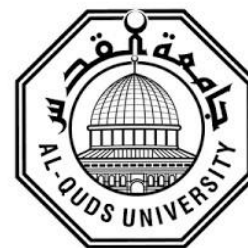
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**Thesis Approval Effective Patient Preparation during
Prostate Radiotherapy Evaluations of Bladder and
Rectum Dose**

Prepared by: Qusai Mohammad Mustafa Tamim Tamimi

Registration Number: 21712648

Supervisor: Dr. Mohammad Hjoui

Master thesis submitted and accepted, Date:

The names and signature of the examining committee members are as follows:

1- Head of committee: Dr. Mohammad Hjoui Signature: 

2- Internal Examiner: Dr. Sawsan Abusharkh Signature: 

3- External Examiner: Dr. Ahmad Abuarrah Signature: 

Jerusalem- Palestine

1441/2020

Dedication

I'd like to dedicate my work to:

- My parents and siblings for their support and encouragement.
- My lovely wife and my daughter for their endorsements and endless support during the challenging times of my study.

Quasi M. Tamimi

Declaration

I clarify that this thesis submitted for the degree of master, is the result of my own research, except where otherwise acknowledge, and that this study (or any part of the same) has not been submitted for a higher degree to any other university or institution.

Signature



Qusai Mohammad Mustafa Tamim Tamimi

Date: 22/8/2020

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Qusai M. Tamimi

Abstract

Prostate cancer is a form of cancer that affects the prostate gland, it is considered as the second most mortality rate cancer among men. In low and intermediate risk prostate cancer patients, radiotherapy is the choice of treatment. With the advent of the radiation therapy it is now possible to treat the cancerous tissue accurately by localizing the tumor and then providing the exact dosing without harming the surrounding normal tissues. Image-guided radiation therapy or IGRT can evaluate the dose of radiation therapy to the target and Organs at Risks OARs effectively. The dose-volume histograms obtained from IGRT can help in assessing the effective dose of radiation given to the prostate, rectum, and bladder.

This study was undertaken to assess the effect of bladder and rectum preparation protocol in dose-volume histograms (DVHs) in prostate cancer patients. The dosimetric changes resulted from the change in bladder and rectum volume with the bladder preparation and rectum clearance protocol were also evaluated in this study.

In this retrospective study total 15 patients were included and 396 Cone Beam Computed Tomography CBCT scanning data was evaluated to obtain information. The patients were subjected to a bladder and rectum preparation protocol and insuring that they followed the protocol strictly. After the irradiation process DVH was constructed. The maximum, minimum and average dose to Urinary Bladder and Rectum were checked and compared to the DVH at the original plan which was calculated on the CT simulation images for each patient. Statistical significance was set at a P value < 0.05 . Analyses were performed using R software and IBM SPSS version 23 for Windows.

The result indicated that there is a significant difference between the planned bladder volume and also the average volume. The bladder filling protocol used by this study was able to reach a mean bladder volume of 314 mL. During the treatment time, this value got reduced and a mean bladder volume of 207 mL was achieved at the time of the radiotherapy. Also a statistically significant differences was observed regarding the bladder and rectum doses between planning and daily treatment sessions. Statistically significant differences in Rectum volume in both planned volume and average volume were reported. These differences are in both real values (P -value=0.024) and proportions to planned values (P -value=0.007). The change in mean dose to the bladder would increase while the volume of the bladder shrinks (P -value=0.00).

The present study reported that rectum and bladder volume has a significant effect on the dosimetric parameters. The main contributing factor that can help in achieving the optimal plan is the bladder volume. Bigger bladder volume in the planning phase results in higher differences in volume and doses in the time of the treatment.

Keywords: Prostate Cancer, Radiotherapy, Patient Preparation, Intensity Modulated Radiotherapy.

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List of Abbreviations:

ADT: Androgen Deprivation Therapy
AUA: American Urology Association
BDFS: Biochemical disease Free Survival
CBCT: Cone Beam Computed Tomography
CT: Computed Tomography
CRT: Conformal Radiation Therapy
CTV: Clinical Tumor Volume
DRE: Digital Rectal Examination
DVH: Dose Volume Histogram
EBRT: External Beam Radiotherapy
EPID: Electronic Portal Imaging Device
GI: Gastrointestinal
GTV: Gross Tumor Volume
GU: Genitourinary
GY: Gray
ICRU: International commission on Radiation Units and measurements
IGRT: Image Guided Radiotherapy
IMRT: Intensity Modulated Radiotherapy
KV: Kilo-Volt
MRI: Magnetic Resonance Imaging
MV: Mega-Volt
NCCN: National Comprehensive Cancer network
NTCP: Normal Tissue Complication Probability
OAR: Organs at Risk
PSA: Prostate specific Antigen
PTV: Planning Target Volume
RP: Radical Prostatectomy
SIB: Simultaneous Integrated Boost
TCP: Tumor Control Probability
TPS: Treatment Planning System
TRUS: Transrectal Ultrasound
VMAT: Volume Modulated Arch Therapy
WHO: World Health Organization

Chapter one:

Introduction

1.1 Background

Prostate cancer is the second most frequently diagnosed cancer in men (Ferlay *et al.*, 2015). Because of the unknown pathophysiology of prostate cancer, it becomes difficult to differentiate between the malignant and benign version of the disease (Shen and Abate-Shen, 2010). The prevalence of prostate cancer varies between different regions. Among all the cancers reported in men, approximately 7.1% of cancers were in the prostate. The number of prostate cancer incidence is maximum in North America and Oceania. In contrast to Asia and Africa where a lower incidence rate than the developed countries (Bray *et al.*, 2018).

The global burden of prostate cancer is expected to increase with approximately 1.7 million new cases along with 499,000 deaths predicted to happen by 2030. Although the exact cause of this prevalence remains unknown, the increase in life expectancy, increased exposure to the carcinogens and advanced diagnostic techniques are some of the probable factors that have been reported to cause this increased burden (Bashir, 2015).

The risk factors for prostate cancer are associated primarily with advancing age, ethnicity, a positive family history of prostate cancer, and a history of smoking. Prostate cancer is most prevalent in the African American population. However, this high prevalence could not be solely attributable to the race, and the influence of the socio-economic situation and the limited access to advanced medical technology also acts as a predisposing factor (Tao *et al.*, 2015).

Studies have identified several gene mutations that confer high risk for the disease. Moreover, nutritional factors such as lack of enough Vitamin D, high-fat diets, obesity and high intake of calcium have been reported as risk factors for prostate cancer (Tao *et al.*, 2015).

The main diagnostic modalities involved in the diagnosis of prostate cancer include digital rectal examination (DRE), determination of serum concentration of prostate-specific antigens (PSA), and transrectal ultrasound (TRUS) - guided biopsy (Heidenreich *et al.*, 2014).

Prostate cancer can be treated using various management techniques. External beam radiotherapy, prostatectomy, and brachytherapy are some of the methods that are used globally for the management of prostate cancer. Among all these modalities prostatectomy has the greatest negative influence on sexual functioning. Moreover, it was shown that patients undergoing prostatectomy also complain of urinary continence. Therefore, radiotherapy is recommended for patients where there is low or intermediate risk is associated with cancer (Gay and Michalski, 2018).

In the past decade, radiation therapy has improved tremendously to address the tumor volume better without causing any harm to the adjacent normal tissues. The recent modulation in the radiotherapy procedure namely “Intensity Modulated Radiotherapy” (IMRT) is an advanced technique that provides higher conformity of radiation dose. This technique guides the beam of radiation using 3D imaging techniques to tumor (Fischer-Valuck, Rao and Michalski, 2018).

The radiation intensity and also the shape of the beam are changed from different angles so that it can match the shape of the tumor correctly. In this process, the prescribed amount of radiation falls on every part of the tumor while the rest of the normal adjacent tissues remain unharmed. This technique minimizes the dose of radiation to the organ at risk. This allows the dose escalation to the prostate while bladder and rectum doses get reduced. Past studies have also shown that the IMRT technique has reduced toxicity (Michalski *et al.*, 2013).

Various studies in the past have shown that this dose-escalated therapy is quite helpful in prostate cancer patients (Zietman *et al.*, 2005). However, the effectiveness of the treatment planning in this procedure completely depends on the intra and inter-fraction motion of the normal tissue and the tumor during the treatment (Ping, 2014).

IMRT techniques use the computer-controlled algorithms that are commonly termed as the "inverse treatment planning and optimization" systems. This process helps the user to select the objectives, goals, and constraints. Further, a dose can be selected based on the target organ and organs at risk. Based on the objectives the penalties are selected (Cahlon, Hunt and Zelefsky, 2008).

From the initial days of implementation, several approaches are used for IMRT. Among them the most frequently used approach uses several coplanar fields usually 5 to 9 static fields are placed in almost equal places around the patient. The dose homogeneity can be

increased by increasing the number of treatment fields. Volumetric-modulated arc therapy (VMAT) is another variation that has been developed to further improve the dose distribution. In this technique, Non-coplanar beam arrangements are used (Fischer-Valuck, Rao and Michalski, 2018).

The main advantage of IMRT is to provide treatment for prostate cancer by accurately localizing the tumor and then providing the exact dosing. However, the volume and shape of the surrounding organs such as rectum and bladder affect the dose delivered to the prostate. Hence, the relative position and shape of the organ at risk (OAR) along with the target organ is an important parameter that dictates the dose delivery accuracy (Ping, 2014).

With further advancement in the technology presently cone-beam computed tomography (CBCT) technique is used attached to radiotherapy. Image-guided radiation therapy or IGRT can evaluate the dose of radiation therapy to the target and OARs effectively. Moreover, studies have also shown that the change in the bladder and rectum volumes can also be effectively traced using this modality (Varadhan *et al.*, 2009).

The dose-volume histograms obtained from IGRT can help in assessing the effective dose of radiation given to the prostate, rectum, and bladder. It was previously elucidated that variation in bladder volume can affect the planned dose distribution while changes in rectal volume have a significant effect on the after radiation effects. Hence, to control the risk of enhanced toxicity it was recommended to keep the bladder and rectum dose constant by maintaining a consistent planning protocol (O'Doherty *et al.*, 2006).

Till date very little information is available about the effect of bladder and rectum preparation protocol on the dosimetric changes. Therefore, this study was undertaken to assess the effect of bladder and rectum preparation protocol in dose-volume histograms (DVHs) in prostate cancer patients. The dosimetric changes resulted from the change in bladder and rectum volume with the bladder preparation and rectum clearance protocol were also evaluated in this study.

1.2 Problem Statement

Plenty of studies showed that dose escalation to prostate brings many benefits and rises the treatment efficiency. In same time, it is a challenging to protect the OAR to reduce the treatment side effects. Effective patient preparation plays a major role in a successful treatment.

1.3 Hypothesis

1. There are statistically significant differences at P value of 0.0009 and 0.043 in the means of bladder volume variations between daily treatment sessions and the CT planning.
2. There are statistically significant differences at P value of 0.024 and 0.007 in the means of rectum volume variations between daily treatment sessions and the CT planning.
3. There are no statistically significant differences at P value of 0.151 and 0.077 in the means of bladder doses received during daily treatment sessions form the doses at the planning phase.
4. There are statistically significant differences at P value of 0.032 and 0.018 in the means of rectum doses received during daily treatment sessions form the doses at the planning phase.

1.4 Objectives

This study was conducted to assess the following:

- The effectiveness of patient preparation protocol as an indicator of the effectiveness of the treatment.
- To assess the effect of day to day variation in bladder and rectum volume on the received doses to the organs.

Chapter Two:

Review of Literature

2.1. Prostate Cancer

The prostate gland is a male sexual gland. The anatomic location of the gland is in front of the rectum and between the bladder and the penis (Seisen *et al.*, 2012). The cancer of the prostate has become a health concern across the world for the last two decades. In 70% of the cases, prostate cancer is a disease of men aged above 65 years. The major risk factor remains race, family history, and increasing age. The pathogenesis of prostate cancer involves a strong correlation between environmental and hereditary factors (Jain, Saxena and Kumar, 2014; Hariharan and Padmanabha, 2016).

Besides age family history of either prostate or breast cancer plays an equally contributing risk factor in developing prostate cancer. The median age for developing prostate cancer is 72 years. Besides, people with a family history of prostate cancer are 2-3 times more prone to have the same disease than people with no family history. Moreover, the risk is 10 times more in-person whose three immediate family members suffer from prostate cancer compared to people with no family history of the disease. It is believed that a high-fat diet also plays a crucial role in developing prostate cancer. Presently, prostate cancer is diagnosed based on the elevation of serum PSA (Vinjamoori *et al.*, 2012).

In addition to the history of smoking or alcohol consumption are also proved to be associated with prostate cancer. Prostate cancer is most prevalent in the African American population. However, this high prevalence could not be solely attributable to the race, and the influence of the socio-economic situation and the limited access to advanced medical technology also acts as a predisposing factor (Tao *et al.*, 2015).

Studies have identified several gene mutations that confer high risk for the disease. Moreover, nutritional factors such as lack of enough Vitamin D, obesity, and high intake of calcium have been reported as risk factors for prostate cancer (Tao *et al.*, 2015).

2.2 Prevalence and Epidemiology of Prostate Cancer

Torre et al (2015) described in their study that Oceania, followed by Northern America, Western Europe, Northern Europe, and the Caribbean have the highest incidence of prostate cancer. On the other hand, African countries have lower incidence and mortality than developed countries (Torre *et al.*, 2015).

Prostate cancer is the second most common cancer in the world and the sixth leading cause of death worldwide. The prostate cancer records estimated cases of 1.1 million worldwide in 2012. The death from the disease was 307,000 in the same year. A good percentage of men (70%) who are diagnosed with prostate cancer (total number approximately 759,000) are from developed countries. Approximately, 42% of the cases occur in men above 50 years of age. However, the majority is detected after the age of 60 years (Zhao *et al.*, 2016).

Jemal et. al. (2010) reported that African American men show one of the highest incidences of prostate cancer worldwide. They are very prone to develop prostate cancer at any age. They are prone to develop the disease earlier in life than men from any other ethnicity and race (Jemal *et al.*, 2010).

2.3. Diagnostic Measures

The main diagnostic modalities involved in the diagnosis of prostate cancer include digital rectal examination (DRE), determination of serum concentration of prostate specific antigens (PSA), and transrectal ultrasound (TRUS) - guided biopsy (Heidenreich *et al.*, 2014).

Previously, serum PSA value of more than 4 µg/L has been used as a primary screening tool for high-risk prostate cancer patients. Recently, the new World Health Organization (WHO) calibrated Access assays has set a cut off value for PSA as 3 or 3.1 µg/L compared to the traditionally calibrated assays where a cut off value of 4 µg/L or more was regarded as a positive predictor for prostate cancer (Stephan *et al.*, 2009).

Carvalho et al have shown that a digital rectal examination (DRE) in suspected men with low serum PSA (< 2 ng/mL) has a positive predictive value of 5% to 30% (CARVALHAL *et al.*, 1999).

2.4. Treatment Modalities of Prostate Cancer

2.4.1. Radical Treatment Options

Radical prostatectomy (RP), external beam radiation therapy (EBRT), and brachytherapy belong to the radical treatment options. As per American Urology Association (AUA) guidelines, every patient should be informed about the risks and benefits of the all available initial intervention for the management of clinically localized prostate cancer (Hsing, Tsao and Devesa, 2000).

Radical Prostatectomy

For intermediate to high-risk disease, surgical removal of the prostate and seminal vesicles is the mainstay of the treatment of prostate cancer. Presently, three main approaches are performed in RP, namely retropubic, laparoscopic, and robotic. However, some centers also perform perineal prostatectomy. Robotic and Laparoscopic approaches are gaining popularity owing to the advantages of reduced pain, reduced blood loss, shorter hospital stay and convalescence compared to open approach (Bill-Axelsson *et al.*, 2008; Coelho *et al.*, 2010).

The aim of the RP is the total eradication of disease while preserving the continence and potency, if possible. Urologists are presently showing a growing interest in treating high-risk disease with RP along with extended pelvic lymphadenectomy. It has two parts of advantages, one is much lower morbidity associated with minimally invasive techniques and the other is improvements in salvage radiotherapy to the prostatic bed for those in whom cure is not primarily achieved (Bianco, Scardino and Eastham, 2005).

External Beam Radiation Therapy

This technique requires treating the prostate with approximately 74Gy of radiation in divided fractions over a 6 to the 7-week course. Neoadjuvant (three months) or adjuvant (2.5 years) hormonal therapy is instilled concomitantly depending on the risk level of the disease (low, intermediate, or high risk). The treatment is given in the form of a luteinizing hormone-releasing hormone agonist or anti-androgen medication. For the proper planning of administration, radiotherapy target areas are defined by analyzing the images from CT scans and MRI scans. Modulation of radiation dose intensity can be achieved by newer technologies like intensity-modulated radiation therapy. More recent advances include the

use of radio-opaque markers to exactly define the extent or location of cancer (Abu-Ghanem *et al.*, 2012).

Brachytherapy

In this procedure, a low dose small radioactive “seeds” are placed into the prostate under anesthesia. The procedure is known as low-dose transperineal prostate brachytherapy. Generally, a urologist collaborates with the clinical oncologist to perform this procedure. Initially, the extent and position of the prostate are mapped. Thereafter, 80–100 seeds of iodine-125 or caesium-137 are placed.

It is confirmed that uniform coverage of the prostate and a margin around it is achieved. In this procedure urethral area is generally spared. Some initial adverse effects are observed as the seeds are permanently placed. The side effects are urinary retention, hematuria, and infection. Brachytherapy is associated with less morbidity than RP or EBRT. However, it poses some serious adverse effects such as faecal urgency, rectal symptoms, worsening of storage lower urinary tract symptoms, urethral stricture, sexual dysfunction, and treatment failure (Abu-Ghanem *et al.*, 2012).

Irreversible Electroporation (IRE)

A recent and non-invasive technique that uses short and strong pulsed electrical field to induce cell death but not thermally. Few studies performed recently as the new technique showed promising results to treat prostate cancer, despite that it can unselectively damage surrounding normal tissue which consider a disadvantage, the IRE still have less patient’s side effect compared to other modalities (Karagiannis *et al.*, 2019)

2.4.2. Conservative management

Radical treatment is not a beneficial option for men with low risk localized prostate cancer. Small localized tumors do not need radical treatment as they do not progress. In such cases, the radical approach would be overtreatment that leads to significant morbidity in terms of continence, sexual function, and quality of life.

2.5. Radiation Therapy for Prostate Cancer

Radiation therapy in prostate cancer has evolved significantly in the past few years. In the present condition, radiation therapy allows better coverage of the tumor volumes without harming the surrounding normal structures. Thereby decreasing the side effects related to radiation treatment. Three factors should be taken into consideration before going to radiation therapy; the concentration of serum level of prostate specific antigens, Gleason score, and T stage. Depending on all these parameters the patients were divided into low, intermediate, and high-risk groups (Budiharto, Haustermans and Kovacs, 2010).

However, other than all these conditions physicians' judgments, patient preferences, and resource availability also determines the choice of the treatment in prostate cancer patients. The main radiation therapy procedure used in prostate cancer is external beam radiation therapy (EBRT). As per the National Comprehensive Cancer Network (NCCN) prostate cancer guidelines, the radiation therapy for prostate cancer patients who has a life expectancy of more than 10 years can be treated with EBRT. Intermediate risk patients might be treated with EBRT along with an androgen deprivation therapy (ADT) and high-risk patients should be treated with EBRT along with 2 -3 years of ADT ('NCCN Guidelines for Patients Prostate Cancer', 2019).

The dose used in the EBRT treatment also plays a significant role in prostate cancer patients. A radiation dose of 72Gy has shown to be effective in prostate gland patients. Kuban et al (2003) have shown that patients who had received a dose of more than 70Gy had a 61% disease-free survival rate for 5 years. In contrast, patients who received a dose of 60Gy and more had a 5-year disease-free survival rate of 59% (Kuban *et al.*, 2003).

Advancement of the radiation technology further it was possible to improve the survival outcome of the patients. Older radiation therapies were thus got replaced with 3-dimensional (3D) conformal radiation therapy (CRT). In this procedure, computer software was introduced to incorporate the volumetric data on the tumor so that specific beam angles and radiation portals can be placed. This placement was difficult in the previous version of radiotherapy procedures. Previous studies have shown that using this technology it is possible to escalate the radiation dose from 64–68 Gy to the higher doses (Pearlstein and Chen, 2013).

In a meta-analysis conducted on a randomized controlled trial by Viani et al (2009), it was reported that a higher dose of radiotherapy is more effective compared with conventional radiotherapy. However, in patients with higher dose radiotherapy had a higher chance of developing gastrointestinal toxicity compared to the patients who received the conventional dose. Further, they have also reported no significant difference between the prostate cancer mortality between two groups (Viani, Stefano and Afonso, 2009).

2.6. Risk Associated with Radiotherapy

Improved biochemical disease-free survival (BDFS) is achieved by dose escalation but the high radiation dose results in associated treatment-related morbidity. Doses greater than 70 Gy in conventional EBRT, lead to significant rectal and bladder complications. Acute gastrointestinal toxicity may develop during radiotherapy. Acute GI toxicity may be manifested as proctitis with a severity proportional to radiation dose (Fischer-Valuck, Rao and Michalski, 2018).

Moreover, with 3D-CRT, a good percentage (15% - 35%) of patients receiving > 70 Gy radiation developed moderate to severe proctitis. A study called Dutch dose-escalation trial that used 3D-CRT compared 78 Gy versus 68 Gy showed there is no significant difference in acute toxicity between two dosage groups. The study established the feasibility of applying higher radiation dose (Kapoor *et al.*, 2016).

A study that used 3D-CRT reported enhanced rectal bleeding requiring laser transfusion in patients subjected to 78 Gy compared to 68Gy. However, the difference in the incidence of overall late GI complications grade 2 was not statistically significant (Tomatis *et al.*, 2012).

There is inconsistency in reporting the dose-response relationship for acute urinary toxicity. However, few studies have reported higher acute urinary toxicity with the escalation of radiation dose (Al-Mamgani *et al.*, 2009).

2.7. Intensity-Modulated Radiotherapy (IMRT)

IMRT is an improved version of 3D-CRT that can generate a dose distribution around irregular and complex target volumes. IMRT can achieve gradual dose escalation to the prostate without irradiating the nearby normal tissue. In IMRT, the intensity of the radiation can be modulated within each treatment beam. By this modulation, a gradient of the dose is generated between PTV, rectum, and bladder. The modulation allows Planning Treatment Volume PTV to receive at least 85% to 90% dose whereas rectal and bladder doses are kept within the level of tolerance (Budiharto, Haustermans and Kovacs, 2010).

Chen et al (2007) reported that IMRT is a well-tolerated technique in patients with prostate cancer. The toxicity arising due to this procedure is also medium and at an acceptable rate. The study conducted by the authors included 125 patients, among them 58.4% presented with grade 1 or grade 2 gastrointestinal toxicity. Only in 1.6% of patients, grade 3 GI toxicity was reported. Similarly, in 77.2% of patients' grade 1 or grade 2 gastrourinary toxicity was reported, and only in 3 patients, GU toxicity of grade 3 was reported. This study also reported that strict compliance with Dose Volume Histogram DVH might prevent the late complication arising due to the radiotherapy (Chen *et al.*, 2007).

IMRT is equipped with a multi-leaf collimator with advanced inverse planning software. This enables "field in the field" techniques and beam modulation. The IMRT technique enables targeting the prescribed dose to specific structures such as the prostate and proximal seminal vesicles. On the other hand, it limits the dose of radiation to surrounding normal structures such as bladder and rectum (Fischer-Valuck, Rao and Michalski, 2018).

IMRT approach allows the delivery of varied non-uniform intensities of the radiation beam to the target volume. In contrast, 3D-CRT delivers uniform beam intensity. The collimator (which is the opening of the RT beam) is varied with a fixed gantry position to generate a non-uniform intensity of the beam. IMRT can simultaneously treat the different areas within the target with varying levels of dose by modulating the dose administered within each beam. This specific technique is known as a simultaneous integrated boost (SIB) (Fischer-Valuck, Rao and Michalski, 2018).

A combination of inverse treatment planning and computer-controlled intensity modulation work together in IMRT to deliver 3D-CRT (Cahlon, Hunt and Zelefsky, 2008).

Several techniques of IMRT have been implemented for the treatment of the prostate since its implementation. A very common technique is the application of multiple coplanar fields arranged at equal or nearly equal spacing around the patient. In this approach, 5-9 static fields are used. In general, conformality and dose homogeneity increase with the number of treatment fields used. However, the said advantage diminishes with field numbers going above 7 to 9. Volumetric-modulated arc therapy (VMAT), tomotherapy, and Noncoplanar beam arrangements have been developed and used by several centers for further up-gradation of the technique in terms of dose distribution (Cahlon, Hunt and Zelefsky, 2008).

A specialized computer programming termed as "inverse treatment planning and optimization" is used to design the treatment algorithm by IMRT. In the algorithm, objective (termed as constraints and goals) is selected by the user that delineates the required dose to each target organ to be treated. Moreover, penalties are made according to the relative importance of the objectives (Cahlon, Hunt and Zelefsky, 2008).

2.8. Intensity-Guided Radiotherapy (IGRT)

The most common phenomenon in today's highly sophisticated radiotherapy procedures is the "geographical miss". This includes an array of errors such as target delineation error, variation in the day to day target, or position variation. To overcome this imaging during radiation therapy was introduced. In addition to the position adjustment, this technique also helps in the correction of radiation delivery (Dang *et al.*, 2018).

In previous studies, the importance of using a CT scan technique while using external beam radiotherapy was studied in detail. It was shown that variations in the delivered doses to the prostate and organs associated with can be envisioned using a CT scan. Only image guidance is not sufficient to account for the variation in the actual doses administered to the rectum and the bladder. In maximum cases, the prostate dose variation is far lower than the dose variation in rectum and bladder (Kupelian *et al.*, 2006).

With the further advancement in the technology, radiotherapy machines are combined with a cone beam CT which make it possible to deliver larger doses to the prostate without harming the surrounding organs. In a clinical trial, Pollack *et al.* (2002) have described that

increase in the dose of radiotherapy from 70 Gy to 78 GY in the isocenter can be proved to be beneficial for (Pollack *et al.*, 2002).

However, this dose-escalation can affect the quality of life or late toxicity. In that case, using a CT can help in the dosimetric escalation of the dose without harming the surrounding normal tissues. It is already proved that the position and shape of the bladder and also the rectum can affect the daily dose deliver accuracy.

The primary aim of this technique is the accurate localization of the target organ and also monitoring the actual dose delivered. Varadhan et al(2009) in their study strongly suggested computing the actual dose delivered to the prostate, bladder, or rectum by using the CT scanning data for that particular day. The cumulative DVH thus generated from this data can be examined to identify any variation in the planned and delivered doses. In this study, the researchers have proposed a framework that can be used successfully to generate a cumulative DVH (Varadhan *et al.*, 2009).

In a study by Van Herk et al(2004), a model to calculate the effective planning target (PTV) volume was proposed. This planning target volume is the sections where the prescribed dose must be delivered to get a clinically accepted and prescribed dose. On the other hand, the clinical target volume is the prescribed dose that should be administered to the target organ. The ideal PTV margin calculation was also done by the same author and it was intended in such a way that the positional variability can be addressed (van Herk, 2004).

Previously these margins were extended in the range of 10 mm to 15mm. However, later studies showed that this extended margin can also increase the toxicity caused by the radiation. The volume of normal tissue receiving high doses results in increased toxicity. IGRT technique improved the treatment protocol while it decreased the late toxicity arising from the radiation by decreasing the PTV margin (Dang *et al.*, 2018).

2.9. Importance of Optimal Planning and Delivery in Radiotherapy

In the prostate radiotherapy, intensity modulated radiotherapy integrated the computed tomography imaging technique to aid in localizing the prostate gland more preciously. Patients undergoing radical radiotherapy procedures are mainly advised to maintain a full

bladder so that the bladder and the small bowel can be displaced from the target volume of the radiation therapy (O'Doherty *et al.*, 2006).

O'Doherty *et al.* (2006), showed in their study that in the absence of any written protocol patients were unable to maintain the bladder volume. The study advised to have proper written patient instructions that can help in the maintenance of constant bladder volume (O'Doherty *et al.*, 2006).

In another study by Mullaney *et al.* (2014), 110 patients were randomly assigned to one of two bladder filling protocols. The consistency of the bladder volume was evaluated and also the gastrointestinal and genitourinary toxicity in these patients was studied. Patients were instructed to have either 540 mL or 1080 mL of water and then the bladder volume of the patients was measured. This study results showed that larger bladder volume correlated well with the larger variations in bladder volume during the radiotherapy. The patients who had adopted the 540mL routine showed fewer variations, less toxicity, and any deterioration in the quality of life parameters (Mullaney *et al.*, 2014).

Wong *et al.* (2015) concluded that a consistent bladder volume is required to decrease the toxicity and improving the treatment outcome. This study also reported variation in the bladder volume. The reason behind this lack of consistency can be attributable to various parameters such as patient education, the time lapse between the ultrasonography and the radiation therapy, and so on (Wong *et al.*, 2015).

In another study, Heng *et al.* (2015) evaluated how the bowel and bladder preparation protocol affects the CBCT. The result of this study indicated that in the control group the dose variation was more compared to the group that received the bladder preparation protocol. In the control group, the highest bladder volume variation was 98% and rectal volume variation was +96%. In contrast, patients who received a bladder preparation protocol the maximum rectum volume variation was as low as 25% (Heng, Low and Sivamany, 2015).

In a recent study by Karin Braide *et al.* (2019) the effect of bladder filling protocol on the clinical target volume (CTV) in radiotherapy was investigated. In this study total of 29 patients were included. Two different strategies for maintenance of constant bladder filling were compared in this study. Patients were divided into two groups: group 1 drank 300 mL water 1 hour before treatment and group 2 was instructed to maintain a comfortable bladder.

A planning CT and CBCT were performed in all these patients. The variability in the bladder volume was analyzed. The result indicated no significant correlation between the bladder volume and the position or the coverage of the radiotherapy. The intra-individual variation between the bladder volumes between the two groups was almost the same. In group 1 the median bladder volume was 120 mL and in group 2 it was 123 mL (Braide *et al.*, 2019).

Hynds et al (2011) in a study evaluated the efficacy of bladder filling protocol in patients undergoing radiotherapy. The bladder filling protocol used by this study was able to reach a bladder volume of 282 mL. During the treatment time, this value got reduced and a mean bladder volume of 189 mL was achieved at the time of the radiotherapy. Thus this study was able to achieve a required bladder volume by using the bladder filling protocol they adopted (Hynds *et al.*, 2011).

Maggio et al (2017) discussed in their study that rectal and bladder preparation protocol significantly affects the biochemical disease-free survival in prostate cancer patients. In this study researchers have adopted a protocol called "empty rectum and comfortable full bladder". The study results of this group were compared with the patients no-followed no such protocol and they were grouped as control. The patients who were on the rectum and bladder protocol had a higher biochemical disease-free survival (Maggio *et al.*, 2017).

2.10. Effect of Bladder Volume on Effective Dose

Previous studies have shown that bladder volume helps to determine the dose administered to the prostate. In a study, Antolak et al have reported that for proper designing of the planning target volume it is always advisable to measure the clinical target volume. The most important consideration in planning radiotherapy is avoiding the OAR. The prostate mobility mainly depends on the rectal and the bladder volume. In most cases, the volume of rectum and bladder decreases between the pretreatment and first treatment CT scan (Antolak *et al.*, 1998).

Pinkawa et al (2006) evaluated the variability of the prostate position depending on the bladder volume in patients undergoing prostate radiotherapy. Their findings showed that there is no variation in the prostate position irrespective of the bladder volume. The treatment

plan with an empty bladder resulted in a higher dose in the bowel loops (Pinkawa *et al.*, 2006).

In prostate cancer patients it was commonly observed that the bladder filling varies in a systematic manner. This mainly affects the position of the prostate and thus the effective dose of the radiotherapy. In previous studies, an empty bladder protocol was also adapted. This protocol showed less toxicity for patients who adopted the empty bladder protocol.

In a study by Moiseenko et al (2007) the effect of bladder filling protocol on dose distribution in the rectum, and bladder was investigated. This study concluded that bladder filling does not affect the prostate Equivalent Uniform Dose EUD. Moreover, the effective dose received by either full or by empty bladder also does not affect it (Moiseenko *et al.*, 2007).

In 2006 Kupelian et al have shown that even a daily CT scan also sometimes is not useful in documenting the volume changes in bladder and rectum. This study pointed out that although the dose applied to the prostate is almost similar a large variation was observed in rectum and bladder doses which are mainly attributable to the changes in volume and also the position of these two organs (Kupelian *et al.*, 2006).

Darud et al (2009) have shown that an empty rectum does not significantly affect the overall position variability of the rectum. No statistically significant change was reported for patients who maintained the empty rectum protocol versus patients who were not on such protocol (Darud *et al.*, 2010).

Yahya et al (2013) have evaluated three different rectum strategies that can help to achieve a consistent rectal volume while undergoing radiation treatment in prostate cancer patients. They have reported in this study that the use of micro enema can be proved to be a useful strategy to gain decreased in the rectal cross-sectional area. This decreased size will eventually help in decreasing the chances of geographical miss (Yahya *et al.*, 2013).

Nakamura et al (2012) found that the mean bladder volume in the patients who received the optimal plan was 266 mL and in patients who didn't receive any optimal plan, the bladder volume was 214 mL. This study result concluded that bladder volume plays a significant role in achieving an optimal plan. Moreover, this study also reported that the bladder volume of more than 150 mL may be regarded as constraints (Nakamura *et al.*, 2012).

Chen et al (2016) in their statistical analysis showed that in every 10% increase in the bladder volume causes a mean dose reduction of 5.6%. This reduction was also found to be statistically significant. Thus this study concluded that changes in bladder volume are more significant compared to the rectum volume with respect to dosimetric changes. Only the presence of air bubbles in the rectum can cause a significant volume change. Hence, it is always recommended to check the bladder volume before the radiotherapy procedure as this is a crucial parameter for actual dose delivery (Chen *et al.*, 2016).

Collery and Forde (2017) have shown that constructing a DVH can significantly quantify the variation in the dose administered to the rectum and bladder. This study reported a significant difference between the planned and on-treatment dose-volume histograms. However, the variation in the dose-volume constraints was not statistically significant. This study pointed out that to reduce the toxicity arising due to radiotherapy implementation of an effective rectal protocol is required (Collery and Forde, 2017).

Boladeras et al (2018) in a study evaluated the association between the DVH values with the patient's health related quality of life in patients with prostate cancer.. This study result indicated that higher DVH value is related to urinary incontinence and other obstructive symptoms. When compared with normal rectal functioning, patients with rectal incontinence showed a higher DVH dose. This study proved that DVH parameters are also closely related to the health related quality of life in patients with prostate cancer (Boladeras *et al.*, 2018).

Chapter Three:

Methodology

It was a challenge to treat the patient while they are in the same state of bladder and rectum preparations. In order to assist the effectiveness of the preparation performed at the department of radiotherapy at Assuta Medical Center, this study was undertaken. This study was designed to find the relationship between the organs volume and the doses they receive as an indicator of the effectiveness of patient preparation.

3.1. Study Center and General Protocol

The study was conducted in the Assuta Medical Center; The Prostate cancer patients undergo a Volume Modulated Arch Therapy (VMAT) to receive a total dose of 60 Gray to 73.6 Gray over 7 weeks (mild hypo-fractionation).

3.2. Patients

In this retrospective study total 15 patients with prostate cancer who visited the department from 2017 to 2019 and underwent radiotherapy at our department were included. The CBCT records of all this patients were retrospectively evaluated. All these patients were selected randomly. Among these patients 10 patients received treatment only for the prostate cancer and 5 patients received treatment for both prostate and associated lymph nodes. The only difference between the two groups is on the total dose and the number of the sessions they received.

3.3. Optimal Planning Protocol

The patients were advised before simulation and daily treatment sessions to maintain a specific bladder and rectum volume. The protocol was explained to the patients before the treatment starts and were asked to follow it strictly. The patients were asked first to evacuate the rectum and bladder. After that they were advised to drink 3 to 4 cups of water and after

waiting for 30 minutes when started to feel full they were sent for the treatment. This protocol was devised in such a way that the patients had a full bladder and empty rectum. In case the patients were not fully prepared with the planning protocol they were asked to prepare themselves again. A daily CBCT scan was conducted every day before the treatment to check the bladder and rectum situation and to correct any shifts from the isocenter point.

3.4. Irradiation Process

The first step to receiving radiotherapy after making a decision through all consultations and meetings with consultant physicians is simulation.

The simulation was done using a GE CT scanner, the patients received the preparing instructions from the radiation therapist in order to be in a full bladder empty rectum situation, patients asked to drink a water mixed with an oral Iodinated based CT contrast to delineate the Bladder. The bladder was delineated on each slide from the base of the bladder to the top of the bladder and the rectum was delineated from the anus to the sigmoid.

Three tattoos were made and cover with a small metal balls to identify the reference point. Then the images sent to the Treatment Planning System (E-clips). The radiation oncologist reviews the images and delineates the Planning Treatment Volume and all the surrounding normal tissues such as the urinary bladder, rectum and head of femur. After this protocol was done later a Medical Physicist prepares a treatment plan taking into account the PTV dose coverage (95-107 %) and doses for the normal surrounding tissue to remain within the dose constrains. The doses are represented by a Dose Volume Histogram, which is a graph that shows the relationship between the dose and the volume.

Before the plan become ready to treatment. The radiation oncologist reviews the plan and checks the dose distribution to the PTV and OAR before approving it. The plan then underwent few QA procedures to insure nothing is missing or incorrectly unplanned.

Retrospectively, each CBCT was reviewed, and the Bladder and rectum was delineated on each slide exactly as each was delineated on the original plan. Afterword, A DVH was created to each new structure as shown in the figure (3.1) and (3.2). The maximum, minimum and average dose to Urinary Bladder and Rectum were checked and compared to the DVH

at the original plan which was calculated on the CT simulation images for each patient. So we could monitor what the patient actually received and compared it to what was planned as shown in figure as shown in figure (3.3) and (3.4).

To test the association between bladder volume and the average dose (relative and absolute), and rectum volume and the average dose (relative and absolute). The linear mixed effects model were fit by maximum likelihood approach.

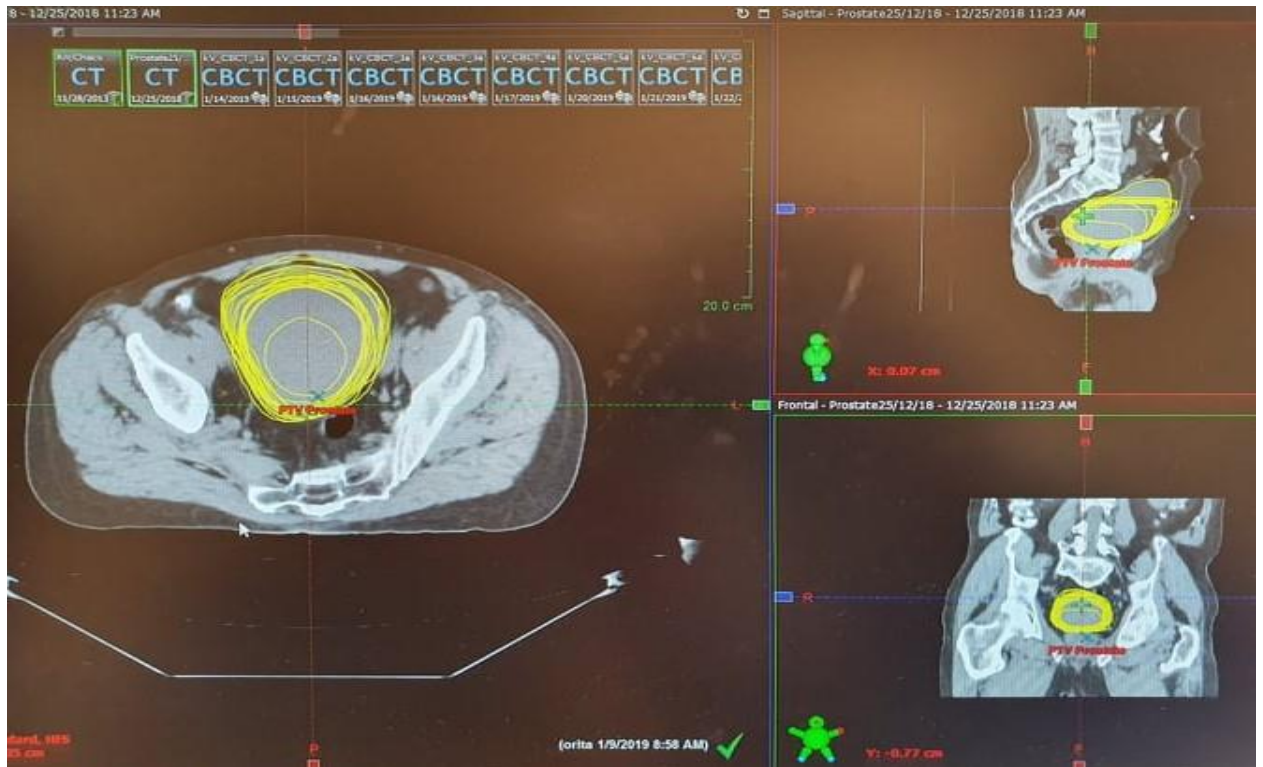


Figure 3.1: All the new bladder structure for one patient which was delineated on CBCTs shown on the original plan.



Figure 3.2: All the new rectum structure for one patient which was delineated on CBCTs shown on the original plan.

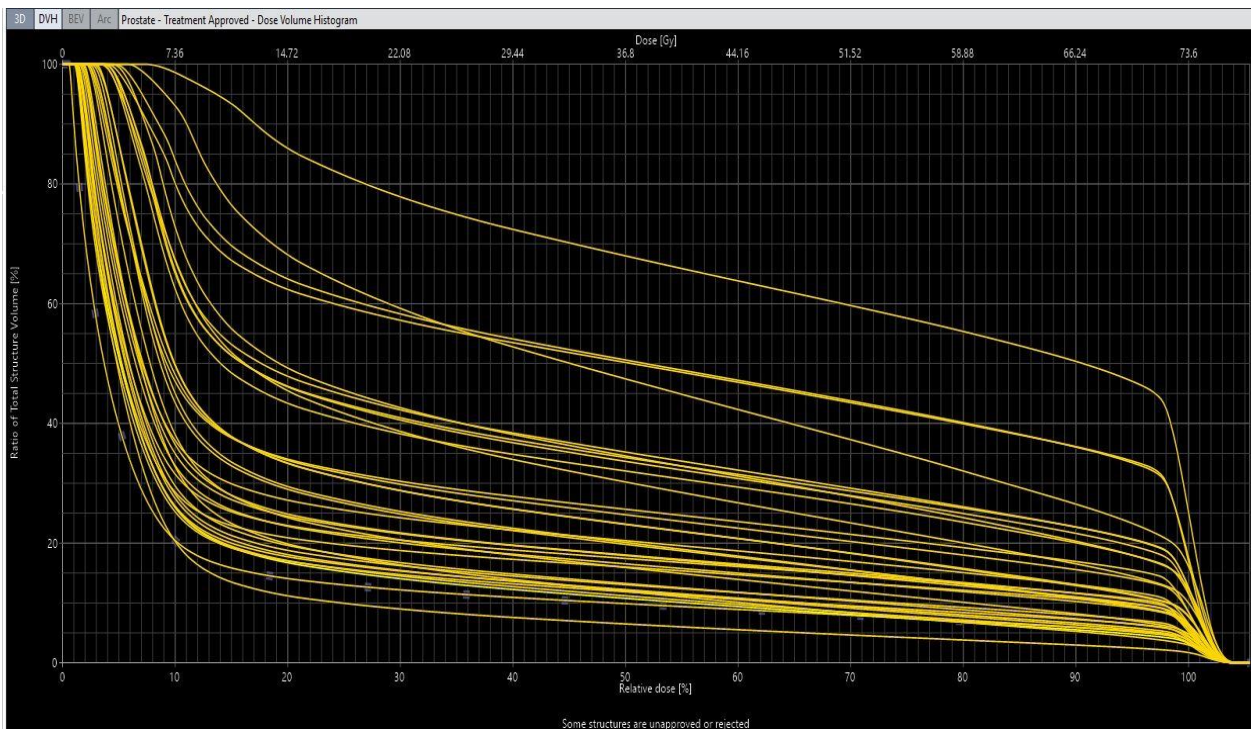


Figure 3.3: All the new bladder structure DVH for one patient demonstrate the day to day variations.

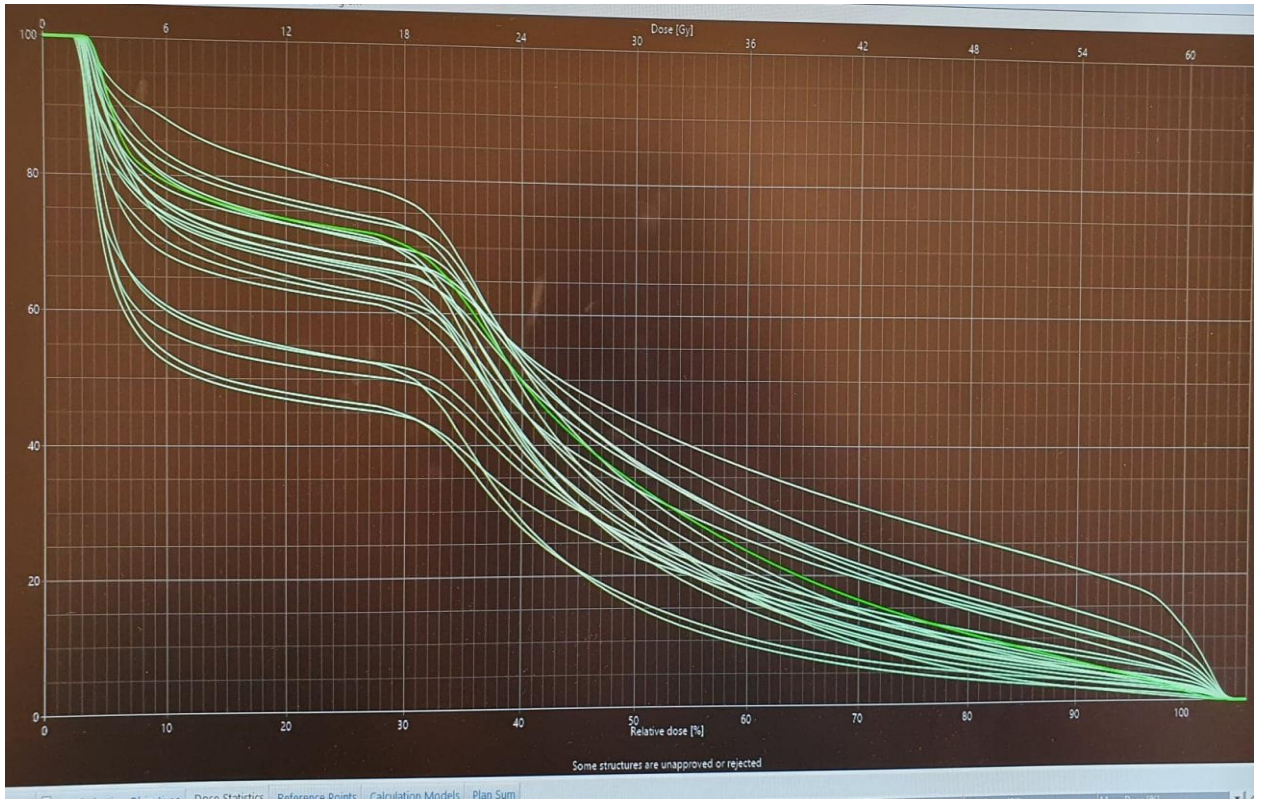


Figure 3.4: All the new rectum structure DVH for one patient demonstrate the day to day variations.

Chapter Four:

Results and Discussion:

4.1. Statistical analysis

Data were analyzed using descriptive statistics and Linear mixed models to assess all study relations and hypotheses. Statistical significance was set at a P value < 0.05 . Analyses were performed using R software and IBM SPSS version 23 for Windows.

4.2. Volume Evaluation

For each patient, descriptive statistics for bladder and rectum volumes were calculated on CBCT, results are presented in Table (4.1). Among all patients, variances of volumes for the bladder are larger than those of the rectum. The whisker-and-box-plots in Figures (4.1) and (4.2) also show the medians and variations among the bladder and the rectum volumes for all the patients.

Table 4.1: Descriptive Statistics of Bladder and Rectum Volumes.

Patient No.	No. of Measurements	Bladder Volume (mL)			Rectum Volume (mL)		
		Mean	Std. Deviation	Std. Error	Mean	Std. Deviation	Std. Error
1	20	199.8150	96.78522	21.64183	42.1900	8.81213	1.97045
2	20	129.2550	46.12279	10.31337	60.7800	7.13225	1.59482
3	20	200.4950	101.85328	22.77509	47.9300	6.07654	1.35876
4	20	167.6350	61.43613	13.73754	49.6750	9.01051	2.01481
5	20	194.3100	66.11807	14.78445	30.4900	3.60991	0.80720
6	20	463.1100	112.54335	25.16546	48.3400	8.67825	1.94052
7	32	238.4344	110.61591	19.55432	46.9344	13.17734	2.32945
8	32	236.1000	78.21318	13.82627	46.9875	6.97793	1.23353
9	32	171.0375	125.65737	22.21329	44.3719	9.20705	1.62759
10	20	117.5600	48.48197	10.84090	48.8850	8.32114	1.86066
11	32	146.4313	68.72996	12.14986	45.0406	6.43302	1.13721
12	32	263.6344	58.99127	10.42828	44.6531	15.07427	2.66478
13	32	274.5687	97.87695	17.30236	60.4750	14.55167	2.57240
14	32	143.7781	64.29293	11.36549	64.5438	12.12943	2.14420
15	32	167.6875	94.15262	16.64399	67.8687	6.35891	1.12411

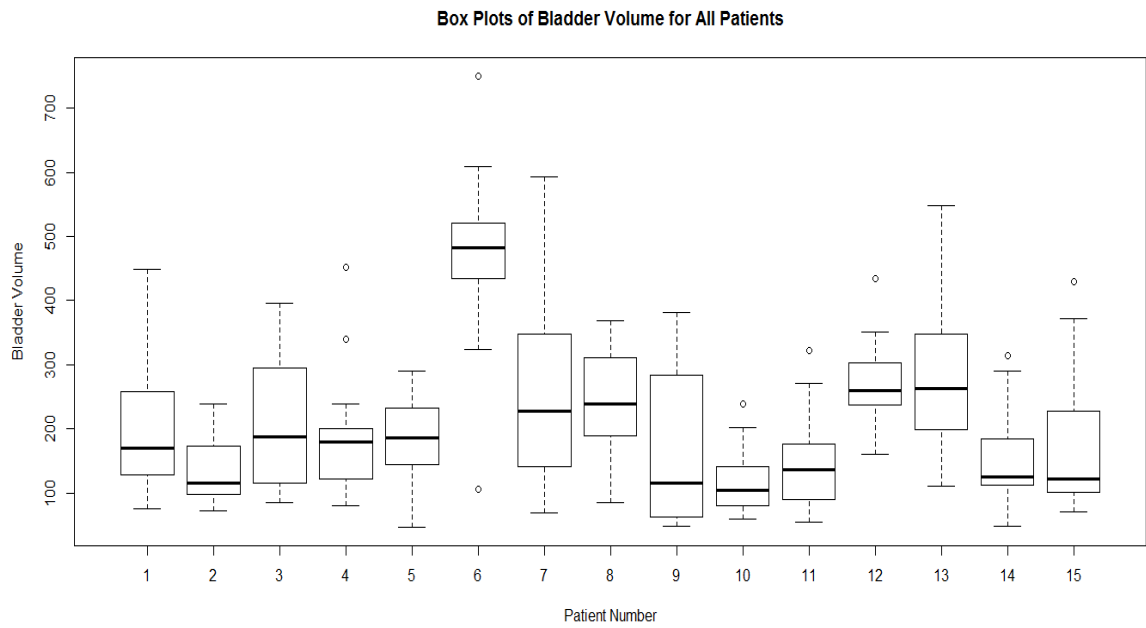


Figure 4.1: The variation of the volumes for the bladder.

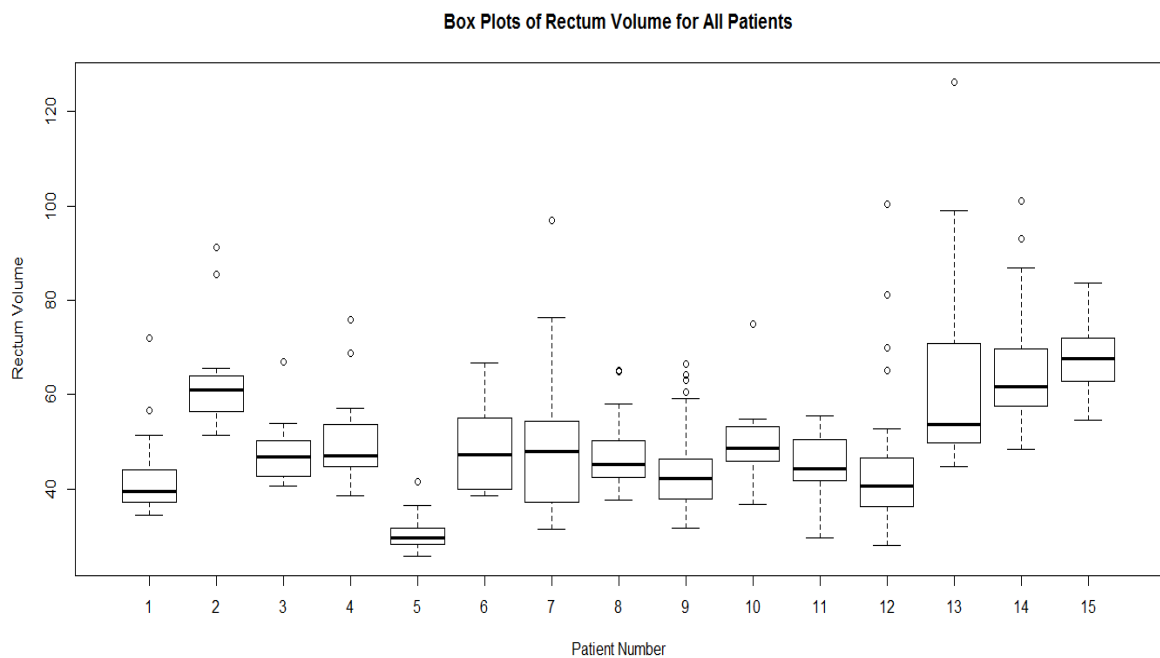


Figure 4.2: The variation of the volumes for the rectum.

Descriptive statistics for the Dose (Relative and Absolute) average related to bladder and rectum volume for each patient was calculated. It was noticed that the variations were increased with the increase of the volume for the bladder and rectum as shown in table (4.2) and (4.3).

Table 4.2: Descriptive Statistics of Dose Relative and Absolute Average related to Bladder Volumes.

Patient No.	No. of Measurements	Dose Relative Average (%)			Dose Absolute Average (Gy)		
		Mean	Std. Deviation	Std. Error	Mean	Std. Deviation	Std. Error
1	20	36.4050	12.01799	2.68730	21.8500	7.21267	1.61280
2	20	44.0100	4.23891	.94785	26.4150	2.54667	0.56945
3	20	22.5900	8.49253	1.89899	13.5555	5.10742	1.14205
4	20	18.4550	6.14093	1.37315	11.0800	3.67031	0.82071
5	20	14.5250	5.67384	1.26871	8.7100	3.40787	0.76202
6	20	10.8050	5.15491	1.15267	6.4800	3.08419	0.68965
7	32	29.2562	13.89418	2.45617	21.5219	10.21589	1.80593
8	32	24.4813	8.64424	1.52810	18.4344	6.26380	1.10729
9	32	20.8469	9.28422	1.64123	15.3344	6.82810	1.20705
10	20	41.0250	11.80209	2.63903	24.6100	7.08341	1.58390
11	32	63.0844	5.71840	1.01088	46.4250	4.22092	0.74616
12	32	59.7563	3.26684	0.57750	43.9781	2.41497	0.42691
13	32	49.9250	3.48906	0.61678	36.6687	2.60996	0.46138
14	32	45.1625	3.80091	0.67191	33.2375	2.78831	0.49291
15	32	58.7313	2.86080	0.50572	43.2250	2.09454	0.37027

Our results showed that there were 18.9% variations of bladder volume between the planning phase and the treatment phase, the mean bladder volume at the planning phase was 318.21 mL compared with 207.59 mL at the treatment phase. Same variations also found regarding the rectum with 14.8% variation in volume between the planning phase and the treatment phase as shown in table (4.4) and (4.6).

Table 4.3: Descriptive Statistics of Dose Relative and Absolute Average related to Rectum Volumes.

Patient No.	No. of Measurements	Dose Relative Average (%)			Dose Absolute Average (Gy)		
		Mean	Std. Deviation	Std. Error	Mean	Std. Deviation	Std. Error
1	20	23.4950	4.69933	1.05080	14.1000	2.82619	0.63196
2	20	45.1900	4.31252	0.96431	27.1000	2.59656	0.58061
3	20	22.6950	3.68089	0.82307	13.6350	2.21485	0.49526
4	20	20.6950	3.85220	0.86138	12.3950	2.31095	0.51674
5	20	34.5550	5.70747	1.27623	20.7200	3.42754	0.76642
6	20	37.9200	6.14188	1.37337	22.7450	3.67301	0.82131
7	32	40.9844	7.01874	1.24075	30.1656	5.16187	0.91250
8	32	44.9844	5.45593	0.96448	33.1063	4.02388	0.71133
9	32	32.4187	4.33243	0.76587	23.8750	3.18980	0.56388
10	20	40.7850	8.43809	1.88681	24.4700	5.06984	1.13365
11	32	65.1813	5.73430	1.01369	47.9781	4.22242	0.74643
12	32	51.5375	5.06071	0.89462	37.0000	6.12415	1.08261
13	32	54.4688	4.73930	0.83780	40.0844	3.49812	0.61839
14	32	42.0375	6.01931	1.06407	30.9344	4.43560	0.78411
15	32	56.6781	3.88078	0.68603	41.7188	2.86373	0.50624

There was a statistically significant differences in Bladder volume in planning phase and the treatment phase. These differences are in both real values and proportions to planned values with respectively P values of 0.009 and 0.043. Moreover, the planned volume was greater in mean than the volume at the treatment phase by 110.623 and also greater in percentage by about 19% or the volume at the treatment phase represents about 81.1% of the volume at the planning phase as shown in table (4.4).

Whereas, the results showed that there are no statistically significant differences in Bladder dose in planning phase (relative and absolute) and treatment phase (relative and absolute) with respectively P values of 0.151, 0.077, 0.145, and 0.076. Even the differences in proportions were large but these differences are not statistically significant as shown in table (4.5).

Table 4.4: Bladder Samples Statistics.

Variable	Mean	Relative Proportion / Planned	Std. Deviation	Std. Error Mean
Planned Volume (mL)	318.21	100%	201.41	52.00
Average Volume (mL)	207.59	81.1%	85.17	21.99
Planned Relative Dose (%)	33.05	100%	18.81	4.87
Average Relative Dose (%)	35.94	119.9%	17.27	4.46
Planned Absolute Dose (Gy)	22.82	100%	14.06	3.63
Average Absolute Dose (Gy)	24.77	120%	13.22	3.41

Table 4.5: Paired Samples t Test for Bladder Differences.

Paired	Test	Paired Differences					t	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% confidence Interval of the Difference			
					Lower	Upper		
Planned V. – Average T.V.	Values	110.623	140.771	36.347	32.667	188.58	3.044	0.009
	Percentage	18.9%	0.347	0.080	-0.002	0.381	2.367	0.043
Planned R. – Average R.D.	Values	-2.884	7.362	1.901	-6.961	1.193	-1.517	0.151
	Percentage	-20.0%	0.405	0.105	-0.424	0.025	-1.910	0.077
Planned A. – Average A.D.	Values	-1.948	4.887	1.262	-4.655	0.758	-1.544	0.145
	Percentage	-20.2%	0.407	0.105	-0.427	0.024	-1.919	0.076

Regarding the rectum, the result showed that there was a statistically significant differences in Rectum volume in planning phase and the average volume at the treatment phase, these differences are in both real values and proportions to planned values with respectively P values of 0.024 and 0.007. Moreover, the planning volume was greater in mean than the average volume at the treatment phase by 12.076 and also greater in percentage by about 14.8% or the average volume at the treatment phase represents about 85.2% of planned volume as shown in table (4.6).

Table 4.6: Rectum Samples Statistics.

Variable	Mean	Relative Proportion / Planned	Std. Deviation	Std. Error Mean
Planned Volume (mL)	62.020	100%	5.842	22.627
Average Volume (mL)	49.944	85.2%	2.498	9.673
Planned Relative Dose (%)	37.747	100%	3.626	14.045
Average Relative Dose (%)	40.908	111.4%	3.335	12.917
Planned Absolute Dose (Gy)	25.960	100%	2.914	11.287
Average Absolute Dose (Gy)	28.002	111.1%	2.767	10.716

Also results report that there were statistically significant differences in Rectum dose in planning phase (relative and absolute) and rectum doses at the treatment phase (relative and absolute). These differences are in both real values and proportions to planned values with respectively P values of 0.032 and 0.018. Moreover, the planned dose smaller in mean than the average dose at the treatment phase by 3.162 and also lower in percentage by about 11.4% or the average dose at the treatment phase represents about 111.4% of planned dose as shown in table (4.7).

Table 4.7: Paired Samples t Test for Rectum Differences.

Paired	Test	Paired Differences					t	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% confidence Interval of the Difference			
					Lower	Upper		
Planned V. – Average T.V.	Values	12.076	18.433	4.759	1.868	22.284	2.537	0.024
	Percentage	14.8%	0.183	0.047	0.047	0.249	3.139	0.007
Planned R. – Average R.D.	Values	-3.162	5.133	1.325	-6.004	-0.319	-2.386	0.032
	Percentage	-11.4%	0.166	0.043	-0.206	-0.022	-2.667	0.018
Planned A. – Average A.D.	Values	-2.042	3.497	0.903	-3.979	-0.105	-2.261	0.040
	Percentage	-11.1%	0.167	0.043	-0.204	-0.019	-2.588	0.021

4.3 Discussion

The present study evaluated the day to day variation in the bladder as well as rectum volume and its effect on the dose distribution. Moreover, this study also computed a dose-volume histogram that can help in understanding the exact doses received by these organs. In previous studies, it was mentioned that a bladder and rectum protocol can help in patients undergoing radiotherapy. Moreover, it was also reported that a written instruction to maintain the bladder volume can significantly affect the consistency of bladder volume. Studies have also advised having proper written patient instruction that can help in the maintenance of constant bladder volume (O'Doherty *et al.*, 2006).

In another study, Heng et al (2015) evaluated how the bowel and bladder preparation protocol affects the dose volume histograms DVH prepared from the CBCT based on intensity modulated radiotherapy treatment regimen. The result of this study indicated that in the control group, that didn't receive the preparation protocol, the dose variation was more compared to the group that received the bladder preparation protocol. In the control group, the highest bladder volume variation was 98% and rectal volume variation was +96%. In contrast, patients who received a bladder preparation protocol the maximum rectum volume variation was as low as 25% (Heng, Low and Sivamany, 2015).

In our study, the patients were instructed to follow a planning protocol for both bladder and rectum volume. A total of 15 patients was included in this study. For all the 15 patients total of 396 scanning data was recorded. The result in this study indicates that there are statistically significant differences in Bladder volume is planned volume and average volume these differences are in both real values and proportions to planned values as shown in table (4.5) with respectively P values of 0.009 and 0.043. Moreover, the planned volume greater in mean than the average volume by 110.623 and also greater in percentage by about 19%, or the average volume represents about 81.1% of planned volume table (4.4).

Whereas, the results in table (4.5) show that there were no statistically significant differences in Bladder dose is planning phase (relative and absolute) and average dose at the treatment phase (relative and absolute) with respectively P values of 0.151, 0.077, 0.145, and 0.076. Even the differences in proportions are large but these differences are not statistically significant. Although there was no statistically significant in the mean dose received, we

recommend measuring it on different dose constraints like v30, we believe there would be a statistically significant since the variation in the proportions is high.

Although our protocol wasn't considered a specific bladder volume during the planning phase, our results showed agreement with previous results. In a study by Nakamura et al (2012), it was reported that bladder volume plays a significant role in achieving an optimal plan. Also, this study reported that the bladder volume exceeding 150 mL during the planning phase might not meet the optimal planning and affect meeting the dose constraints during treatment (Nakamura *et al.*, 2012).

In prostate cancer patients it was commonly observed that the bladder filling varies systematically. This mainly affects the position of the prostate and thus the effective dose of the radiotherapy.

Our present study, results showed that there are statistically significant differences between the bladder and rectum volumes between the planning and the daily treatment sessions, although, among the 15 patients that we have studied, there weren't any statistically significant differences regarding the bladder dose between planning and daily treatment sessions, there was an opposite relationship between the bladder volume and the dose, the increase in the bladder volume will decrease the dose. This is because the bigger volume we have the less volume to be irradiated, the less mean dose to the bladder.

Similarly, Hatton et al (2011) have reported a dose variation in rectal DVH depending on the variation in volume (Hatton *et al.*, 2011). In another study by Pawlowski also the same type of finding was reported. Pawlowski et al (2010) proposed that variation in the bladder and also in the rectal volume gets reflected in the dosimetric variations (Pawlowski *et al.*, 2010).

Chen et al has also pointed out that change in bladder volume is associated with the dose variation in prostate cancer patients undergoing radiotherapy. The statistical analysis showed that in every 10% increase in the bladder volume causes a mean dose reduction of 5.6%. This reduction was also found to be statistically significant. Thus this study concluded that changes in bladder volume are more significant compared to the rectum volume with respect to dosimetric changes (Chen *et al.*, 2016).

In previous studies, many strategies have been described that were successfully used to decrease the rectum volume. Yahya et al (2013) have discussed how using micro enema can be proved to be a useful strategy to gain a decrease in rectal cross-sectional area (Yahya *et al.*, 2013).

As it was clear from our results, the decrease in the volume during treatment sessions compared to the original volume during the CT simulation will cause an increased dose to the bladder and rectum. Although it wasn't statistically significant over all the patients, it was clear that the dose limit in some patients was exceeded the allowed doses. It was also noticed that during the late sessions patients couldn't reach a full bladder situation which might be mainly because of the side effects of radiation.

Collery and Forde (2017), reported that constructing a DVH can significantly quantify the variation in the dose administered to the rectum and bladder. Similar to our study results this study reported a significant difference between the planned and on-treatment dose-volume histograms. However, the variation in the dose-volume constraints was not statistically significant (Collery and Forde, 2017).

It was also noticed that the bigger the bladder volume reached at the planning phase, the bigger differences in volume and doses as well we have at the daily treatment sessions. Because patients after a few sessions wouldn't be able to maintain a full bladder as before, this is considered to be one of the side effects of radiation therapy.

4.4 Conclusion

Image-guided radiation therapy or IGRT can evaluate the dose of radiation therapy to the target and OARs effectively. The dose-volume histograms thus obtained can help in assessing the effective dose of radiation given to the prostate, rectum, and bladder.

It was previously elucidated that variation in bladder volume can affect the planned dose distribution while changes in rectal volume have a significant effect on the after radiation effects. Hence, it was recommended to keep the bladder and rectum dose constant by maintaining a consistent planning protocol. The present study has thus used an optimal planning procedure to successfully evaluate the dose received by rectum and bladder and also the association of bladder and rectum volume with the administered dose.

The present study reported that rectum and bladder volume has a significant effect on the dosimetric parameters. The main contributing factor that can help in achieving the optimal plan is the bladder volume. Bigger bladder volume in the planning phase results in higher differences in volume and doses in the time of the treatment. The variation in bladder volume was more prominent in the latter part of the treatment procedure. This variation in the bladder volume in this phase can be due to the side effect of radiation therapy.

Chapter Five:

5.1 Limitations of the Study and Future Work

Despite the various positive findings the study dose have few limitations as well. The following section will discuss all the study limitations in details

1. The primary limitation is the lack of clinical correlation of the study results with the clinically proven output.
2. The future disease-free survival and biochemical marker for disease free conditions were not addressed in this study. A long term follow-up is necessary to understand the effect of optimal planning on doing.
3. This study has only addressed the change in bladder and rectum volume with the dosing and thinks that this is the first stepping stone for optimal planning. However, this might affect the survival rate and also may lower local control. Because of the time constraints we were not able to address this issue.
4. All the finding reported in this study requires large cohort research to further justify the findings.

5.2 Future Work

Based on the results of the current study, the following recommendations can be made.

- To stay within the acceptable radiation levels while keeping the dose to the target as it supposed to be, a new treatment protocol should be adopted at the department relating on our results. In this protocol, it should be kept in mind that the volume of the bladder should be maintained between 150 mL to 250 mL. This volume is easier for the patient to achieve during treatment sessions.
- Educate the radiation therapist about the risks of treating patients with lower bladder volume what was planned.

- It should also be noted that the optimal planning will vary from institution to institution and therefore, every institute should decide an optimal bladder volume before they progress with the radiotherapy for prostate cancer patients.

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الملخص

لقد اصبح العلاج بالاشعاع هو الخيار الأمثل في حالات سرطان البروستات متوسطة وقليل الخطورة. ومع التطور الكبير في مجال العلاج بالاشعاع، اصبح من الممكن علاج الخلايا السرطانية بدقة عن طريق تحديد مكان الورم وبعد ذلك تحديد كمية الاشعاع الدقيقة والمناسبة بدون احداث اضرار للانسجة والاعضاء السليمة المجاورة.

العلاج الاشعاعي الموجه بالتصوير (IGRT) يمكنه الان تقييم كمية الاشعاع الواصلة للهدف المراد علاجه والاعضاء المجاورة له والمعرضة للخطر. من خلال الرسم البياني لتوزيع الاشعاع (DVH) يمكن حساب وتقييم كمية الجرعة الاشعاعية الواصلة لكل من البروستات، المثانة والقولون.

توجهنا بهذه الدراسة بهدف بحث فاعلية تحضير المثانة والقولون من قبل المرضى قبل علاج سرطان البروستات عن طريق الاشعاع. عملت هذه الدراسة على 15 مريض حيث تم دراسة 396 صورة تطبيقية (CBCT) بأثر رجعي بهدف فحص وتقييم حجم كل من المثانة والقولون قبل كل جلسة علاج يومية حصل عليها المرضى، ومقارنة النتائج مع الصور التطبيقية التي اجريت عليها الخطة العلاجية، وتقييم اثر تغيير الحجم على الجرعة الاشعاعية الواصلة لكل من المثانة والقولون.

النتائج اظهرت أن هناك أختلاف بين متوسط حجم المثانة في مرحلة التخطيط للعلاج حيث كان المتوسط 314 مل في حين أن المتوسط ما قبل العلاج كان 207 مل. وقد أدى هذا الاختلاف لوجود اخنلاف في كمية الجرعة الاشعاعية الواصلة. وبالتالي فإن النتائج لهذه الدراسة اظهرت توافق مع العديد من الدراسات السابقة والتي ربطت زيادة حجم المثانة بتقليل الجرعة الاشعاعية الواصلة اليها.