

# **The Impact Of Hypofractionated Simultaneous Integrated Boost In Intensity Modulated Radiation Therapy For The Treatment Of Localized Prostate Cancer**

*Thesis*

*Submitted in partial fulfillment of the doctorate degree  
In Clinical Oncology and Radiotherapy*

By

**AHMAD SAYED KAMAL ALI**  
*Master of Clinical Oncology*

*Supervised by*

**Dr. KAMAL ALI EL-GHAMRAWY**  
*Professor of Clinical Oncology  
Faculty of medicine  
Cairo University*

**Dr. SAMEH ABDEL AZIZ HANNA**  
*Professor of Radiology  
Faculty of Medicine  
Cairo University*

**Dr. MUSTAFA SHAWKY EL-HADDAD**  
*Assistant Professor of Clinical Oncology  
Faculty of Medicine  
Cairo University*

**CAIRO UNIVERSITY**  
2014

# Acknowledgment

*First, before all, thanks be to **GOD** this work has been accomplished.*

*I wish to offer my sincere thanks to **Dr. Kamal El-Ghamrawy**, Professor of Clinical Oncology, Cairo University, for his valuable assistance and support, which have always been beyond description.*

*I could not forget the great help of **Dr. Sameh Hanna**, Professor of Radiology, Cairo University, during the accomplishment of this work.*

*I would like to express my deepest gratitude to **Dr. Mustafa El-Haddad**, Assistant Professor of Clinical Oncology, Cairo University, for his care, continuous encouragement and guidance.*

*I would also like to thank **Maha Kamal-El-Deen**, Radiation Physicist, Cairo University, whose pivotal role in accomplishing this work cannot be overemphasized*

*I would also like to thank **Dr. Rafaat Ragaie**, Lecturer of Clinical Oncology, Cairo University, for his assistance and support in accomplishing this work*

*My deepest thanks are sincerely offered to all the patients and department radiographers for their patience and cooperation.*

*Last but not least I would like to express my gratitude to my family for their love and support without which this work could not be accomplished.*

## **Abstract**

. Hypofractionated IMRT proved to be a feasible option for the treatment of localized prostate cancer since it has shown an acute toxicity profile similar to conventional fractionation, with GU toxicity  $\geq$  grade 2 at 50% and GI toxicity  $\geq$  grade 2 at 0% in the hypofractionation arm, while in the control arm GU toxicity  $\geq$  grade 2 was 40% and GI toxicity  $\geq$  grade 2 was 10%, with no statistical significance between them ( $p=0.689$ ).

## **Keyword**

**RNASEL-VMT- AMCAR- CBCT-IMRT- Hypofractionated**

# Contents

<i>Acknowledgment</i> .....	2
<i>List of figures</i> .....	6
<i>List of tables</i> .....	8
<i>List of Abbreviations</i> .....	9
<i>Introduction</i> .....	12
<b>OVERVIEW OF LOCALIZED PROSTATE CANCER</b> .....	15
Part I: BASIC SCIENCE.....	16
A. Anatomical Consideration.....	16
B. Molecular Pathogenesis Of Prostate Cancer .....	21
C. Natural History And Histopathology .....	25
D. Gleason's Score.....	28
E. Serum Prostate-Specific Antigen (PSA).....	29
Part II: Imaging Studies.....	33
1. Ultrasound .....	33
2. Computed Tomography .....	35
3. Magnetic Resonance Imaging.....	37
4. Magnetic Resonance Spectroscopy .....	41
5. ProstaScint Scanning .....	42
6. Positron Emission Tomography .....	43
7. Imaging methods during external radiotherapy .....	44
Part III: STAGING AND RISK STRATIFICATION.....	51
Staging .....	51
RISK STRATIFICATION .....	53
Part IV: TREATMENT .....	56
Guidelines.....	56
Active Surveillance.....	59
Radical Prostatectomy.....	60
Brachytherapy.....	63
External Beam Radiation .....	65
Androgen Deprivation Therapy .....	78
Rationale for Hypofractionation.....	82

Hypofractionated Radiotherapy Treatment in Prostate Cancer .....	84
<b>PATIENTS AND METHODS</b> .....	97
Patients .....	98
A. CTsimulation: .....	100
B. Delineation:.....	101
I. Target volumes:.....	101
II. Organs at risk: .....	106
C. Randomization .....	109
D. Prescribed dose: .....	109
E. Treatment planning.....	110
F. Plan Acceptance.....	112
G. Plan Quality Assurance.....	114
H. Treatment Verification.....	115
I. Treatment assessment.....	116
J. End points .....	118
Statistical Methods: .....	118
<b>RESULTS</b> .....	119
Clinico-pathological Data.....	120
Dosimetric Analysis.....	123
1. PTV constraints.....	123
2. Risk Structure Constraints.....	126
Toxicity.....	132
1. Urinary toxicity .....	132
2. Gastro-intestinal Toxicity .....	134
3. Sexual symptoms.....	134
Quality of life assessment .....	135
Prostaic size .....	137
Serum PSA .....	138
Isocenter Directional Shift.....	139
Treatment Interruption .....	140
Cost .....	141
<b>DISCUSSION</b> .....	142
Conclusion and Recommendations .....	154

English Summary ..... 155

References ..... 169

Mastertable ..... 155

Arabic Summary ..... 179

# List of figures

Figure 1: Lymphatic drainage of the prostate (From Green DR, Shabsign R, Scardino PT: Urological ultrasonography. In: Walsh PC, Rettic AB, Stamey CA, Vaughan ED Jr [eds]: Campbells's Textbook of Urology, 6th ed. Philadelphia, WB Saunders, 1992.) .....	17
Figure 2: Frontal section of male pelvis at right angles to perineal membrane. (From Oelrich TM. The urethral sphincter muscle in the male. Am J Anat 1980; 158: 229- 246) .....	18
Figure 3: Zones of the prostate (From Green DR, Shabsign R, Scardino PT: Urological ultrasonography. In: Walsh PC, Rettic AB, Stamey CA, Vaughan ED Jr [eds]: Campbells's Textbook of Urology, 6th ed. Philadelphia, WB Saunders, 1992.) .....	19
Figure 4: The prostate epithelium(Adapted from Nelson WG, De Marzo AM, Isaacs WB: Prostate cancer. N Engl J Med 2003; 349:366–381.) .....	21
Figure 5: Fusion of transcripts from the androgen-regulated <i>TMPRSS2</i> gene and ETS family genes <i>ETV1</i> and <i>ERG</i> in prostate cancers. (Adapted from Tomlins SA, Rhodes DR, Perner S, et al: Recurrent fusion of <i>TMPRSS2</i> and <i>ETS</i> transcription factor genes in prostate cancer. Science 2005; 310:644–648).....	23
Figure 6: Proliferative inflammatory atrophy (PIA) as a precursor to prostatic intraepithelial neoplasia (PIN) and prostate cancer. (Adapted from Nelson WG, De Marzo AM, Isaacs WB: Prostate cancer. N Engl J Med 2003; 349:366–381.).....	27
Figure 7: Gleason score for histologic grading of prostate cancer demonstrating progressive loss of glandular formation with increasing score. (Adapted from Gleason DF. Histologic grade, clinical stage, and patient age in prostate cancer. NCI Monogr 1988;7:15 .....	29
Figure 8: prostatic lesion seen by transrectal U/S .....	34
Figure 9: CT showing prostatic cancerous lesion arising from the peripheral zone.....	36
Figure 10: A: Normal T1-weighted axial magnetic resonance image. Age-related benign prostatic hyperplasia in the transition zone is evident (long arrow). The neurovascular bundles lie adjacent to the peripheral zone (short arrow). B: The T-2 weighted axial image of the same level of the gland demonstrates areas of low signal intensity adjacent to the post biopsy hemorrhage that are suspect for tumor (short arrows and arrowheads). This is an example of the hemorrhagic exclusion sign. (Courtesy of Steven Eberhardt, MD.).....	38
Figure 11 : MRS image matched to MRI indicating early stage prostate cancer .....	42
Figure 12: Choline PET-CT in localized prostate cancer.....	44
Figure 13: BAT-assisted treatment verification images. (Right) sagittal image. (Left) transverse image, with various structures contoured and ready for alignment. Bladder(orange) prostate(yellow) rectum(green) seminal vesicle(cyan) .....	47
Figure 14 : Orthogonal EPID with corresponding DRRs for a case of prostate cancer using bony landmarks with fiducial markers for patient alignment during treatment.....	49
Figure 15: Cone beam CT seen here mounted perpendicular to the treatment machine gantry .....	50
Figure 16: prostatic apex can be more accurately defined in MRI fused imaging (left) compared to CT alone (right).....	102

Figure 17: CT causes overestimation of the postero-lateral aspect of the prostate (right) compared to MRI (left)	102
Figure 18: The external & internal iliac nodes are delineated from the bifurcation of the common iliac nodes on the axial plane(left) which is usually at the level of L5/S1 space as seen in the sagittal plane (middle right)	103
Figure 19: The presacral LN are delineated anterior to the sacral bone from the level of S1 to S3 together with the iliac nodes.....	104
Figure 20:The presacral LN end at S2/S3 as seen on the sagittal plane (middle right) with the appearance of the pyriformis muscle and disappearance of the sacral neural foramina in the axila plane (left) .....	104
Figure 21: The iliac nodes end at the top of the femoral head. Volume continues caudally as the obturator nodes.....	105
Figure 22: Obturator nodes end at the level of symphysis pubis fusion.....	105
Figure 23: MRI image(left) helps better identification of the prostate-rectum interface compared to CT (right)	106
Figure 24: MRI image(left) helps better identification of the penile bulb, which appears hyperintense, compared to CT (right).....	107
Figure 25: femoral head delineation should include the space between the ball of the femur and acetabulum	108
Figure 26: the optimization process using an eclipse TPS version 8.6 with dose volume constraints and priorities input (left) and iterations results (right).....	112
Figure 27: Accepted dose distribution demonstrated by isodose colorwash in axial (top), coronal (middle) and sagittal (bottom) view.....	113
Figure 28: Cumulative DVH for an accepted treatment plan.....	114
Figure 29: IMRT plan QA using portal dosimetry showing the portal intensity map (left) and gamma evaluation (right).....	115
Figure 30: Treatment verification by orthogonal anterior (above) and lateral (below) EPID using bony landmarks .....	117
Figure 31: Performance Status distribution in the 2 study groups.....	121
Figure 32: Gleason Score distribution in the 2 study groups .....	122
Figure 33: T-Stage distribution in the 2 study groups .....	122
Figure 34: Risk Group distribution in the 2 study groups.....	122
Figure 35: Mean value for PTV-T Dose Coverage for the 2 study groups .....	124
Figure 36: Mean value for PTV-T Dose Coverage for the 2 study groups .....	125
Figure 37: Mean value for Rectal Wall sparing for the 2 study groups .....	127
Figure 38: Mean value for Bladder sparing for the 2 study groups.....	128
Figure 39: Mean value for Bowel Bag sparing for the 2 study groups .....	129
Figure 40: Mean value for Penile Bulb sparing for the 2 study groups .....	130
Figure 41: Mean value for Femoral Heads sparing for the 2 study groups.....	131
Figure 42: GUT toxicity incidence up to 6 months of treatment (above) and GUT toxicity grade occurrence during treatment (below).....	134



Figure 43: Mean Quality of life score for the 2 study groups .....	136
Figure 44: Mean prostatic volume in cubic centimeters for the 2 study groups.....	137
Figure 45: Mean PSA for the 2 study groups.....	138
Figure 46: Mean Value for Isocenter shift for the 2 study groups.....	140
Figure 47: Comparison between Mean Total Monitor Unit Usage in the 2 study arms .....	141

## *List of tables*

Table 1: Age-Specific Reference Ranges for Serum PSA and PSA Density Data(Adapted from Oesterling J, Jacobsen S, Klee G, et al: Free, complexed, and total serum prostate specific antigen: the establishment of appropriate reference ranges for their concentrations and ratios using newly developed immunofluorometric assays (IFMA). J Urol 1995; 154:1090.).....	31
Table 2: Probability of Cancer Based on Total PSA and Percent of free PSA Results. (Adapted from Catalona WJ, Partin AW, Slawin KM, et al: Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA 1998;279:1542.) .....	32
Table 3: American Joint Committee TNM Staging System for Prostate Cancer (2003) .....	52
Table 4: Risk Group Definitions (D'Amico, et al., 2004) .....	54
Table 5: University of California San Francisco recommendations for ADT.....	80
Table 6: Hypofractionation Trials: Schedules and Equivalent Doses in 2-Gy Fractions .....	95
Table 7: Ultrahypofractionation Trials: Schedules and Equivalent Total Doses in 2-Gy Fractions.....	96
Table 8: D'Amico Risk Classification.....	99
Table 9: Organs at risk dose –volume constraints (Marks, et al., 2010) .....	111
Table 10: Clinicopathological Data of the study groups.....	120
Table 11: PTV-T constraints comparison by volume percent coverage in the 2 study groups.....	124
Table 12: PTV-LN constraints comparison by volume percent coverage in the 2 study groups .....	125
Table 13: Rectal constraints comparison by volume percent coverage in the 2 study groups.....	127
Table 14: Bladder constraints comparison by volume percent coverage in the 2 study groups .....	128
Table 15: Bowel Bag constraints comparison by volume percent coverage in the 2 study groups.....	129
Table 16: Penile Bulb constraints comparison by volume percent coverage in the 2 study groups.....	130
Table 17: Femoral Heads constraints comparison by volume percent coverage in the 2 study groups .....	131
Table 18: Genito-urinary toxicity profile for the 2 study groups.....	133
Table 19: Quality of life score comparison between the 2 study groups.....	136
Table 20: Prostatic size comparison between the 2 study groups .....	137
Table 21: PSA in ng/dL comparison between the 2 study groups .....	138
Table 22: Isocenter shift in millimeters comparison between the 2 study groups .....	139
Table 23: Radiation treatment interruption in days comparison between the 2 study groups.....	140
Table 24: Total Monitor Units expenditure in the 2 study groups .....	141
Table 25: Acute toxicity rates for various hypofractionation trials .....	151

# List of Abbreviations

Abbreviation	Definition
AMCAR	A-MethylacylCoARacemase
ADT	Androgen Deprivation Therapy
ASCO	American Society Of Clinical Oncology
AUA	American Urological Association
BAT	B-Mode Acquisition And Targeting
BED	Biological Effective Dose
b-DFS	Biochemical Disease Free Survival
BPH	Benign Prostatic Hyperplasia
BT	Brachytherapy
CBCT	Cone Beam CT
CT	Computer Tomography
CTCAE	Common Terminology Criteria For Adverse Events
CTV-LN	Lymph Node Clinical Target Volume
CTV-T	Tumor Clinical Target Volume
DRE	Digital Rectal Examination
DRR	Digitally Reconstructed Radiograph
DWI	Diffusion-Weighted Imaging
EBRT	External Beam Radiotherapy
EORTC	European Organization For Research And Treatment Of Cancer
EPIC	Expanded Prostate Cancer Index Composite
EPID	Electronic Portal Image Device
ETS	Erythroblast Transformation Specific
FDG	Fluorodeoxyglucose
GI	Gastro-Intestinal
GU	Genito-Urinary
HDR	High Dose Rate
IGRT	Image-Guided Radiotherapy
IMRT	Intensity Modulated Radiotherapy
kV	Kilovolt
LE	Egyptian Pound
LENT-SOMA	Late Effect In Normal Tissue Subjective, Objective Management And Analytic Scale
LDR	Low Dose Rate
MLC	Multi-Leaf Collimator
MRI	Magnetic Resonance Imaging

Abbreviation	Definition
<b>MRS</b>	Magnetic Resonance Spectroscopy
<b>MSR-1</b>	Macrophage Class-A Scavenger Receptor
<b>MU</b>	Monitor Unit
<b>MV</b>	Megavolt
<b>NCCN</b>	National Comprehensive Network For Cancer
<b>NEMROCK</b>	Clinical Oncology Department, Cairo University
<b>NSAID</b>	Non-steroidal anti-inflammatory drugs
<b>OS</b>	Overall Survival
<b>PACS</b>	Picture Archiving And Communication System
<b>PAP</b>	Prostatic Acid Phosphatase
<b>PCa</b>	Prostate Cancer
<b>PET</b>	Positron Emission Tomography
<b>PIA</b>	Prostatic Inflammatory Atrophy
<b>PIN</b>	Prostatic Inflammatory Neoplasia
<b>PLND</b>	Pelvic Lymph Node Dissection
<b>PSA</b>	Prostatic Specific Antigen
<b>PSAV</b>	Prostatic Specific Antigen Velocity
<b>PSA-DT</b>	Prostatic Specific Antigen Doubling Time
<b>PSMA</b>	Prostatic Smooth Muscle Actin
<b>PPC</b>	PercentOf Positive Core
<b>PTV-LN</b>	Lymph Node Planning Target Volume
<b>PTV-T</b>	Tumor Planning Target Volume
<b>QA</b>	Quality Assurance
<b>QLQ</b>	Quality Of Life Questionnaire
<b>QOL</b>	Quality Of Life
<b>QUANTEC</b>	Quantitative Analyses Of Normal Tissue Effects In The Clinic
<b>RF</b>	Radiofrequency
<b>RNASEL</b>	Ribonuclease-L
<b>RP</b>	Radical Prostatectomy
<b>RT</b>	Radiotherapy
<b>RTOG</b>	Radiation Oncology Group
<b>SBRT</b>	Stereotactic Body Radiotherapy
<b>SD</b>	Standard Deviation

Abbreviation	Definition
<b>SWOG</b>	South Western Oncology Group
<b>TE</b>	Echo Time
<b>TPS</b>	Treatment Planning System
<b>TR</b>	Repetition Time
<b>TRUS</b>	Trans-Rectal Ultrasound
<b>U/S</b>	Ultrasound
<b>UCSF</b>	University Of California, San Francisco
<b>WPI</b>	Whole Pelvic Irradiation
<b>VMAT</b>	Volumetric Modulated Arc Therapy
<b>2D</b>	Two Dimensional
<b>3D-CRT</b>	Three Dimensional Conformal Radiotherapy

# Introduction

Prostate cancer is the most commonly diagnosed visceral cancer in men, 29%, and the second leading cause of cancer death, 11%, with a lifetime risk of 20%, in the USA according to the 2013 estimates **(Siegel, et al., 2013)**. It also has a similar ranking in Europe, being the most commonly diagnosed cancer with an incidence of 65 per 100000, and the third most common cancer death according to the 2012 estimates **(Schroder, et al., 2012)**. In Egypt the incidence rate is 8.3 per 100000 **(Curado, et al., 2007)**.

There has been a dramatic increase in the annual age-adjusted incidence rate in the last two decades owing to the use of digital rectal examination, serum PSA, transrectal U/S and biopsy as screening tools. On the other hand the introduction of such methods has allowed the treatment of patients at earlier stages, where low risk patients have become 45% of localized cases, resulting in a decrease in the age-adjusted death rate, 4% **(Parken, 2005)**.

Historically, radical prostatectomy used to be the standard treatment for localized prostate cancer, with radiation limited to locally advanced disease and the elderly, however, the expanding evidence of the competitive results for radiotherapy versus surgery reported in literature, has encouraged the use of radical radiotherapy treatment **(Peshel and Colberg, et al., 2003)**.

Megavoltage external beam radiotherapy was introduced in the late 1960s for the treatment of prostate cancer. With the development and integration of modern imaging modalities, treatment planning systems and modern treatment techniques, more accurate target definition was achieved, allowing for more normal tissue sparing and dose escalation, ultimately improving outcome **(Zelevsky, et al., 2002)**.

Compared with the conventional three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT) offers many potential benefits. IMRT can improve dose conformity around the target volume, thereby increasing the therapeutic ratio

which can permit tumor dose escalation, resulting in improved local control and reduced risk of treatment related complications **(Ezzell, et al., 2003)**.

Another advantage of IMRT is its ability to generate dose distributions of specific levels of non-uniformity in target volumes. This is due to the nature of inverse planning, in which the prescription dose is specified as an objective to be achieved by the planning process.

Accordingly, different dose levels can be prescribed to different targets or different regions of the target. An immediate application of this characteristic of IMRT is to plan and treat the boost dose together with the large field prescription dose. Simultaneous treatment of multiple targets with different prescribed doses is called the simultaneous integrated boost (SIB) technique **(Mohan and Wu, 2005)**.

The dose distributions of IMRT treatment plans can be expected to be significantly superior in terms of higher conformity if designed to deliver different dose levels to different tissues simultaneously in a single treatment session. This permits delivery of graded dose levels to tumor-bearing tissues and tissues at risk of subclinical tumor spread, and spares normal tissues to the greatest extent possible. The SIB-IMRT strategy not only produces superior dose distributions but also is an easier, more efficient, and perhaps less error-prone way of planning and delivering IMRT because it involves the use of the same plan for the entire course of treatment **(Mohan and Wu, 2005)**.

Regarding the specific option of external beam radiotherapy, the current widely accepted standard regimen for organ-confined prostate cancer involves approximately eight weeks of fractionated treatments with a daily dose of 1.8–2.0 Gy to a total dose in the range of 70–80 Gy **(Mohler, et al., 2013)**. For patients with an intermediate or high risk of recurrence and spread, dose escalation has been demonstrated to improve biochemical control with acceptable toxicity using contemporary radiotherapy techniques **(Pollack, et al., 2004) (Kupelian, et al., 2005)**. Unfortunately, dose escalation using a conventionally fractionated treatment schedule requires a lengthened treatment course that is less convenient for patients and more costly for the government and treating institutions. Emerging evidence accumulating from multiple recent

studies indicates that more convenient and efficient shortened courses of radiotherapy for prostate cancer yield outcomes that are equivalent and possibly superior to the lengthier standard regimens **(Faria, et al., 2011) (Pollack, et al., 2013)**. The scientific rationale for such “hypofractionated” treatment lies in the unique radiobiologic properties of prostate cancer.

Hypofractionation is not a new concept in the radiotherapy of prostate cancer. Several phase I and II trials have addressed this issue. They have used fractionation regimens ranging from 2.5Gy per fraction **(McCammon, et al., 2008)** to 7Gy per fraction **(Madsen, et al., 2012)** producing acceptable acute and chronic toxicities **(Mazio, et al., 2009)** and biochemical control comparable to conventional fractionation schemes **(Faria, et al., 2011)**. Encouraged by these results several large phase III trials have been set underway to assess the benefit of hypofractionation in prostate cancer **(Kupelian, et al., 2007)(Yeoh, et al., 2010)(Dearnaley, et al., 2012) (Pollack, et al., 2013)**.

## *Aim of work*

The aim of the current study is to assess the feasibility of applying hypofractionated simultaneous integrated boost in intensity modulated radiation therapy for the treatment of localized prostate cancer and comparing it to conventionally fractionated sequential IMRT, with regards to its effect on treatment toxicity, as well as impact on treatment delivery, patient convenience and quality of life and its overall cost benefit.