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

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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 ≥ grade 2 at 50% and GI toxicity ≥ grade 2 at 0% in the hypofractionation arm, while in the control arm GU toxicity ≥ grade 2 was 40% and GI toxicity ≥ grade 2 was 10%, with no statistical significance between them *(p=0.689)*.

Keyword

RNASEL-VMT- AMCAR- CBCT-IMRT- Hypofractionated

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

Abbreviation	Definition
SWOG	South Western Oncology Group
TE	Echo Time
TPS	Treatment Planning System
TR	Repetition Time
TRUS	Trans-Rectal Ultrasound
U/S	Ultrasound
UCSF	University Of California, San Francisco
WPI	Whole Pelvic Irradiation
VMAT	Volumetric Modulated Arc Therapy
2D	Two Dimensional
3D-CRT	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 **(Zelefsky, 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 iscalled the simultaneous integrated boost (SIB) technique**(MohanandWu, 2005).**

The dose distributions of IMRT treatment planscan be expected to be significantly superior in terms of higherconformity if designed to deliver different dose levels todifferent tissues simultaneouslyin a single treatment session. This permits delivery of gradeddose levels to tumor-bearing tissues and tissues at riskof subclinical tumor spread, and spares normaltissues to the greatest extent possible. The SIB-IMRT strategy not only producessuperior dose distributions but also is an easier, more efficient,and perhaps less error-prone way of planning anddelivering IMRT because it involves the use of the same planfor the entire course of treatment**(MohanandWu, 2005).**

Regarding the specificoption of external beamradiotherapy, the current widelyaccepted standard regimen for organ-confined prostate cancerinvolves approximately eight weeks of fractionatedtreatments with a daily dose of 1.8–2.0Gy to a totaldose in the range of 70–80Gy**(Mohler, et al., 2013).**For patients with an intermediate or high risk of recurrence and spread, dose escalation has been demonstrated to improve biochemical controlwith 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 faction **(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 andquality of life and its overall cost benefit.