Evaluation of Normal Tissue Complication Probability and Risk of Second Primary Cancer in Prostate Radiotherapy

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Abbreviations and Acronyms

$BE_{ff}D$	Biologically Effective Dose
D_{eq}	Equivalent Dose
3D-CRT	Three-Dimensional Conformal Radiotherapy
3D-CRT/70 Gy	4-field Three-Dimensional Radiotherapy to total dose of 70 Gy
3D-CRT/74 Gy	4-field Three-Dimensional Radiotherapy to total dose of 74 Gy
A-bRFS	ASTRO-biochemical Relapse-Free Survival
BCF	Batch Correction Factor
BEIR	Biological Effects of Ionizing Radiations
bNED	Biochemical No-Evidence-of-Disease
CT	Computed Tomography
CTV	Clinical Target Volume
DVH	Dose-Volume Histogram
EBRT	External Beam Radiotherapy
FFPF	Freedom From PSA Failure
FS	Field-Size
FSU	Functional Subunit
GI	Gastrointestinal
GTV	Gross Tumour Volume
GU	Genitourinary
HDR-BT	High-Dose-Rate Brachytherapy
ICRP	The International Committee on Radiation Protection
IMRT	Intensity-Modulated Radiotherapy
LDR-BT	Low-Dose-Rate Brachytherapy
Linac	Linear Accelerator
LQ	Linear-Quadratic
MOSFET	Metal Oxide Semiconductor Field Effect Transistor
MU	Monitor Unit
N-bRFS	Houston nadir+2 biochemical Relapse-Free Survival

NCRP	National Council of Radiation Protection and Measurements
NTCP	Normal Tissue Complication Probability
OARs	Organs-At-Risk
OED	Organ Equivalent Dose
PPFS	PSA Progression-Free Survival
PSA	Prostate Specific Antigen
PSA-DFS	Prostate Specific Antigen-Disease-Free Survival
PTV	Planning Target Volume
RBE	Relative Biological Effectiveness
RE	Relative Effectiveness
RR	Relative Risk
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
S.D	Standard Deviation
SSD	Source-to-Skin Distance
SCF	Sensitivity Correction Factor
SEER	Surveillance, Epidemiology, and End Results Programs
SIR	Standardized Incidence Ratio
SPC(s)	Second Primary Cancer(s)
TCP	Tumour Control Probability
$TD_{5/5}$	The 5% probability of a complication within 5 years after treatment.
$TD_{50/5}$	The 50% probability of a complication within 5 years after treatment
TLDs	Thermoluminescence Dosimeters
UNSCEAR	The United Nations Scientific Committee on Effects of Atomic Radiation

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Abstract

The probabilities of developing radiation-induced normal tissue complications and second primary cancers were evaluated using dose-volume histograms as well as dose measurements covering a range of radiotherapy techniques including External Beam Radiotherapy (EBRT) and Brachytherapy (BT) for prostate cancer.

There are two major parts in this thesis. In the first part, the Dose-Volume Histograms (DVHs) of the Organs-At-Risk (OARs) such as rectum, bladder, urethra, and femoral heads were retrieved from the radiation treatment plans of 4-field standard fractionated (2 Gy/fraction) Three-Dimensional Conformal Radiotherapy (3D-CRT) to total dose of 64 Gy, 4-field hypofractionated (2.75 Gy/fraction) 3D-CRT to total dose of 55 Gy, 5-field 3D-CRT to total dose of 70 Gy, 4-field 3D-CRT to total dose of 70 and 74 Gy, Low-Dose-Rate Brachytherapy (LDR-BT) with I-125, High-Dose-Rate Brachytherapy (HDR-BT) with Ir-192, and combined-modality treatment (3D-CRT & HDR-BT) techniques. The DVHs of these normal organs/tissues were converted to Biologically Effective Dose based DVHs ($BE_{ff}DVHs$) and Equivalent Dose based DVHs ($D_{eq}VHs$) respectively in order to account for differences in radiation treatment modality and fractionation schedule. For assessment of the Normal Tissue Complication Probability (NTCP), the Lyman and Relative Seriality NTCP models were applied to the differential $D_{eq}VHs$ of the OARs. For the assessment of risk of radiation-induced Second Primary Cancer (SPC), the Competitive Risk model was used. In total, 223 DVHs from 101 patients were analysed in this thesis.

In the second part, a radiation dosimetry technique was developed and used in measuring the doses delivered to distant organs/tissues (e.g. lungs and thyroid) as a result of prostate irradiation. In this case, simulation of prostate cancer radiotherapy was performed with the anthropomorphic Rando phantom using 4-field 3D-CRT technique to the total dose of 80 Gy with the 18 MV X-ray beam from Varian iX linear accelerator (linac). Radiation doses at different locations in the Rando phantom resulting from scattered and leakage photon and neutron radiations were measured using enriched ^{6}Li and ^{7}Li LiF:Mg,Cu,P glass-rod thermoluminescence dosimeters (TLDs).

Results indicated that with hypofractionated 3D-CRT (20 fractions of 2.75-Gy fraction and 5 times/week to total dose of 55 Gy) NTCP of rectum, bladder and urethra were less than those for standard fractionated 3D-CRT using 4-field technique (32 fractions of 2-Gy fraction and 5 times/week to total dose of 64 Gy) and dose-escalated 3D-CRT. Rectal and bladder NTCPs (5.2% and 6.6% respectively) following the dose-escalated 4-field 3D-CRT (2 Gy per fraction to total dose of 74 Gy) were the highest amongst the analysed treatment techniques. The average NTCP for rectum and urethra were 0.6% and 24.7% for LDR-BT and 0.5% and 11.2% for HDR-BT. Although brachytherapy techniques resulted in delivering larger equivalent doses to normal tissues, the corresponding NTCPs were lower than those of external beam techniques except in the case of urethra due to much smaller volumes irradiated to higher doses. Amongst normal tissues analysed, femoral heads were found to have the lowest probability of complications as most of their volume was irradiated to lower equivalent doses compared to other tissues.

The average estimated radiation-induced SPC risk was no greater than 0.6% for all treatment plans corresponding to various treatment techniques but was lower for either LDR or HDR brachytherapy alone compared with any EBRT technique. For LDR and HDR brachytherapy alone, the risk of SPC for rectum was approximately 2.0×10^{-4} % and 8.3×10^{-5} % respectively compared with 0.2% for EBRT using 5-field 3D-CRT to total dose 74 Gy. Treatment plans which deliver equivalent doses of around 3 – 5 Gy to normal tissues were associated with higher risks of development of cancers.

Results from TLDs measurements in the Rando phantom indicated that photon doses were highest close to the irradiation volume and the photon dose equivalent ratio (dose equivalent per unit of target dose) decreases proportionally with the distance from the isocentre (e.g. 6.5 mSv/Gy for small intestine to 0.2 mSv/Gy for thyroid). In contrast, the dose equivalent ratio of neutrons in the Rando phantom was observed to be constant at approximately 5.7 mSv/Gy for up to 50 centimeters from the edge of the treatment field (from pancreas to oesophagus).

The total dose equivalent (photon and neutron) for each organ/tissue approximated for the 4-field standard fractionated 3D-CRT technique to total dose of 80 Gy using 18 MV X-ray beam from Varian iX linac ranged between 323.0 mSv (for thyroid) and 1203.7 mSv (for colon). Based on the competitive risk model and on the assumptions that the dose equivalents were uniformly distributed in the volumes of these organs/tissues, the estimated risks of SPC range from 1.5% (in thyroid) up to 4.5% (in colon).

Different radiation treatment techniques for prostate cancer are associated with different probabilities of developing radiation-induced normal tissue complications and second primary cancers. In the case of brachytherapy for prostate cancer, due to its specific dose-volume characteristics in addition to not having the leakage or neutron radiation associated with external beam radiotherapy, this treatment modality is associated with a reduced risk of NTCP and SPC compared with EBRT techniques for both organs situated close to and organs situated at a distance from the treatment field.

In this current work, the radiation dosimetry technique based on the ^{6}LiF:Mg,Cu,P and ^{7}LiF:Mg,Cu,P glass-rod TLDs was developed to determine the radiation doses received by organs/tissues positioned away from the irradiation field due to scattered and leakage photons and neutrons. This radiation measurement technique enables the evaluation of the prostate radiation treatment plan to include the assessment of organs/tissues of interest in both high and low dose regions.

It was demonstrated in this thesis that the relative seriality (NTCP) and the competitive risk (SPC) are useful models which can be used for the purpose of relative comparison and evaluation of prostate radiation treatment plans even though they may need to be further verified and fine tuned against clinical data.

Declaration

NAME: Rungdham Takam PROGRAM: Doctor of Philosophy (Medical Physics)

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Publications in refereed journals

1. Takam R, Bezak E, Yeoh EE, Marcu L. Assessment of normal tissue complications and second cancer risks following prostate cancer irradiation - a review. *Austral – Asian Journal of Cancer* 2008; **7**: 171 – 184.
2. Takam R, Bezak E, Yeoh EE. Risk of second primary cancers following prostate cancer radiotherapy. *Physics in Medicine and Biology* 2008; **54**: 611 – 625.

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1. Takam R, Bezak E, Yeoh EE, Marcu L, "Assessment of normal tissue complications following prostate cancer irradiation: comparison of radiation treatment modalities using NTCP models" accepted for publication in Australian Physics and Engineering Sciences in Medicine.
2. Takam R, Bezak E, Yeoh EE, Liu G, "In-phantom peripheral organ doses from prostate irradiation using 18 MV external beam radiotherapy measured with ^{6}LiF:Mg,Cu,P & ^{7}LiF:Mg,Cu,P glass-rod TLDs" full paper accepted for publication in Proceeding of Medical Physics and Biomedical Engineering World Congress 2009.

Papers submitted in refereed journals

1. Takam R, Bezak E, Yeoh EE, Liu G, "Enriched ^{6}Li and ^{7}Li LiF:Mg,Cu,P glass-rod thermoluminescent dosimeters for out-of-field radiation dose measurements" submitted to Physics in Medicine and Biology.
2. Takam R, Bezak E, Yeoh EE, Liu G, "Risk of second cancer in prostate radiotherapy due to peripheral photon and neutron doses" to be submitted to Physics in Medicine and Biology. (in preparation)

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1. Takam R, Bezak E, Yeoh EE. Rectal normal tissue complication probability after prostate radiotherapy. *12th International Conference on Optimal Use of Advanced Radiotherapy in Multimodality Oncology*. 2007. Rome, Italy.
2. Takam R, Bezak E, Liu G, Yeoh EE. Risk of second primary cancer following prostate radiotherapy. *10th Biennial ESTRO Meeting on Physics and Radiation Technology for Clinical Radiotherapy*. 2007. Barcelona, Spain.
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1. Takam R, Bezak E, Yeoh EE. Risk of second primary cancer following prostate radiotherapy”. *Postgraduate Student Papers Night*. Adelaide, Australia. 2007. Sponsored by ACPSEM, SMBE and IEAUST (SA Branch).

2. Takam R, Bezak E, Yeoh EE, Liu G. Out-of-field photon and neutron radiations and peripheral lung’s dose in prostate cancer radiotherapy with high-energy medical linac”. *Postgraduate Student Papers Night*. Adelaide, Australia. 2008. Sponsored by ACPSEM, SMBE and IEAUST (SA Branch).*

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