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

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Abbreviations and Acronyms

$BE_{eff} D$ 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
The $TD_{5/5}$ is the 5% probability of a complication within 5 years after treatment.

The $TD_{50/5}$ is the 50% probability of a complication within 5 years after treatment.
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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\textsubscript{eff} 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 $2.0 \times 10^{-4}$ % and $8.3 \times 10^{-5}$ % 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 $^6\text{LiF:}\text{Mg,Cu,P}$ and $^7\text{LiF:}\text{Mg,Cu,P}$ 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

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Publications in refereed journals


Papers accepted for publication


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


Conference presentations

International


3. 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. Medical Physics and Biomedical Engineering World Congress. 2009. Munich, Germany.
National


Other presentations


* Awarded First Place Medical Physics Prize Winner.