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Health-Related Quality-of-Life Related to Hypofractionated Prostate Cancer Radiotherapy

Somaya Eid

Health-Related Quality-of-Life Related to Hypofractionated Prostate Cancer Radiotherapy

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Somaya Eid DDS

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CERTIFICATE OF EXAMINATION

Supervisor

Dr. George Rodrigues

Supervisory Committee

Dr. Glenn Bauman

Dr. Varagur Venkatesan

Examiners

Dr. Richard Malthaner

Dr. JL Mahon

Dr. Joseph Chin

The thesis by

Somaya Eid
entitled:

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Date_____

_____
Chair of the Thesis Examination Board

Abstract

Introduction: The objectives of this study were to assess the health-related quality-of-life (HRQOL) and late toxicity effects of External Beam Radiation Therapy (EBRT) on prostate cancer (PC) patients treated with a hypofractionated course of EBRT ($\geq$73 Gy) and to further cross-validate the Prostate Cancer Radiation Toxicity (PCRT) questionnaire.

Methods: A cross sectional study was performed using the EPIC (generic prostate HRQOL instrument), PCRT (specific prostate radiotherapy instrument HRQOL/late toxicity), and an unvalidated exit global HRQOL/late toxicity questionnaire. The initial sample size was calculated to be 276. Baseline variables of interest were abstracted from the medical recoreds.

Results: Response rate was 69 % (190 participants). Mean age was 75.8 years (SD 5.5) and the mean time of questionnaire completion after radiotherapy was 852 days (SD 335 days). Mean scores for EPIC GU (85.1 SD 12.9), GI (84.1 SD 15.8), S (21.8 SD 20.7), and H (85.3 SD 13.7) as well as PCRT GU (66.1 SD 15.3), GI (83.6 SD 14.3), and S (39.4 SD 21.6) domains were calculated. We found significant associations between adverse effects on genitourinary tract and planning target volume-bladder overlap for PCRT GU domain scores. In comparison with the lower dose cohort no differences in GI/GU/S/H EPIC scores were observed.

Conclusion: Hypofractionated EBRT for PC resulted in excellent GI, and GU scores, and poor S scores. The PCRT domains continue to demonstrate construct/discriminant validity. The PCRT has the advantage of being a compact instrument providing normally distributed HRQOL GI/GU domain scores.

Key Words: Health-Related Quality of Life, Late toxicity, Questionnaire, Prostate Cancer, Radiation Therapy, Hypofractionated.

DEDICATION

Dedicated to my friends and beloved family who were always encouraging and thoughtful, especially my beloved son Mohamed and my mother while I isolated myself to my academic endeavors research and write this work.

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LIST OF ABBREVIATIONS AND UNITS

AJCC	American Committee for Cancer Staging
ANOVA	Analysis of Variance
AUA	American Urological Association
BPH	Benign Prostatic Hyperplasia
CARES	Cancer Rehabilitation Evaluation System
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
DRE	Digital Rectal Examination
DVH	Dose-Volume Histogram
EBRT	External-Beam Radiation Therapy
EPIC©	Expanded Prostate Index Composite
FACT-G	Functional Assessment of Cancer Therapy Scale-General
EORTC	European Organization for Research and Treatment of Cancer
G	Grade
GI	Gastrointestinal
GU	Genitourinary
GY	Gray
HD	High Dose Radiation
HRQOL	Health Related Quality of Life
HTN	Hypertension
ICC	Intra-Class Correlation
IEC	Inter-Class Correlation

IMRT	Intensity-Modulated Radiation Therapy
LD	Low Dose Radiation
LENT-SOMA	Late Effect Normal Tissue Task Force-Subjective, Objective, Management, and Analytic
LHRH	Luteinizing Hormone Releasing Hormone
LRCP	London Regional Cancer Program
LRP	Laparoscopic Radical Prostatectomy
M	Metastasis
MVA	Multivariable Analyses
N	Nodal disease
NCI CTC	National Cancer Institute Common Toxicity Criteria
PC	Prostate Cancer
PCRT	Prostate Cancer Radiation Toxicity
PIN	Prostatic Intraepithelial Neoplasia
PSA	Prostate Specific Antigen
QLQ-C30	Quality of Life Questionnaire
QOL	Quality Of Life
RP	Radical Prostatectomy
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SEER	Surveillance, Epidemiology and End-Results Program
SIB	Simultaneous In-field Boost
T	Tumour

TURP	Trasnurethral Resection of the Prostate
TRUS	Transrectal Ultrasonography of the Prostate
UVA	Univariate Analyses

REVIEW OF THE LITERATURE

1.0 Introduction

Canadian Cancer Society (CCS) reports reveal that, "Prostate cancer is the second leading cause of cancer-related deaths in men in North America, and the third leading overall cause of deaths related to cancer in Canada" (Canadian Cancer Society, 2008). The incidence of prostate cancer (PC) has been steadily increasing at an annual rate of 5.8% since 1985 (Grover et al., 2000). This year, approximately 24,700 patients in Canada will be diagnosed with prostate cancer and it is expected that prostate cancer rates will continue to rise, with estimates increasing each year (Canadian Cancer Statistics, 2008). According to the US National Cancer Institute (NCI), *Surveillance Epidemiology and End Results* publication, prostate cancer is the leading diagnosed cancer among men, with 186,320 new cases diagnosed in 2008 (Marrett et al., 1997; Ries et al., 2008). As a result approximately 25% of those diagnosed with prostate cancer will die from it. (National Cancer Institute, 2009).

Since some diagnosed prostate cancer grows at a relatively slow rate (American Cancer Society, 2008) and multiple treatment options with improvements in multidisciplinary care combining two or more of the established treatments (surgery, radiation therapy, hormonal therapy, and chemotherapy) are currently available, the mortality rate has remained stable (Grover et al., 2000).

Research has developed different risk stratification schemes to categorize prostate cancer patients into groups with different risk of various outcomes including biochemical

control and overall survival. An example of a commonly utilized system is the Canadian Consensus Guidelines which define PC as low-risk, intermediate-risk, and high-risk disease based on a combination of the baseline Prostate Specific-Antigen (PSA), disease stage (see table 1), and Gleason score (Lukka, 2001). Another commonly used stratification scheme is the one used by D'Amico (2003).

According to Dattoli (2009), combining radioactive seed implants (brachytherapy) with sophisticated external radiation, known as 4-Dimensional Image-Guided Intensity Modulated Radiation Therapy (4D IG-IMRT) with DART (Dynamic Adaptive Radiotherapy) on "high risk patients (those with high PSA values, high Gleason scores and locally advanced cancer) have enjoyed an 82% success rate out to 16 years, while low risk patients have a success rate greater than 90%" (Dattoli, 2009).

External beam radiation therapy is considered a standard treatment for cancer alongside other options such as radical prostatectomy and prostate brachytherapy (Pisansky, 2005). Multiple studies have assessed the role of dose-escalation in prostate cancer and there is growing consensus that higher radiation dosage (up to 78 Gy) with conventional dose per fraction (1.8-2.0 Gy/fraction) can lead to better biochemical (PSA)-free survival endpoints in patients with high and intermediate risk (Pisansky, 2005; Zeitlin et al., 1998; Zlotecki, n.d.; Pollack et al., 2000). However, it has not been determined that utilizing high dose radiation translates to an increase in overall survival.

Establishing the relationship between treatment toxicities and tumour control is the core of what is called the therapeutic ratio (Wei et al., 2002; Rodrigues et al, 2007). As previously indicated, various kinds of treatment methods are available for PC. These

can involve: external beam radiation therapy (EBRT), high-dose radiation (HD), radical prostatectomy (RP), permanent brachytherapy seed implant (LD), and hormonal manipulation. Consequently, therapeutic ratio is essential in explaining the costs and benefits involved in accepting the one or more of the above prescribed treatments for cure or control of the disease versus the toxicity or sequelae the treatment of the prostate may cause the patient.

Delivering a high dose of radiation to control cancer locally requires accurate patient positioning for EBRT through prostate imaging, for treatment planning and treatment verification. This improved level in technical sophistication is essential in optimizing the therapeutic ratio by precise treatment of the tumour while minimizing normal tissue treatment (Grigorov et al., 2003; Rodrigues et al., 2007). In 2006, the American Society of Clinical Oncology endorsed the concept that can allow technical sophistication for the exploration of alternate dose fractionation schemes. At the ASIO *Prostate Cancer Symposium*, Yassa stated: "An accelerated hypofractionated regimen can lead to a therapeutic gain while decreasing short term side effects, without necessarily compromising long term side effects or quality of life..." (Yassa et al., 2006). Currently, there are two clinical trials which are comparing hypofractionated dose escalated RT to standardized dose RT (low risk RTOG 0415, and intermediate risk Ontario Clinical Oncology Group (OLOG and PROFIT study) (Lee et al., 2007)

Methods utilizing high-dose per fraction in the control of localized and advanced prostate cancer must consider the late adverse effects of radiation. In addition, better methods have to be implemented in documenting the sexual, late rectal, and bladder

toxicity end points. In order for the therapeutic ratio to be optimized, the tumour control data needs to be complemented by these toxicity end points. For the sake of calculating the equivalent dosage in radiotherapy, a linear-quadratic model, "α/β ratio" has been implemented (Egawa, Shimura, Irie, et al., 2001). Regarding prostate cancer; this "α/β ratio" has been considered to be lower compared to other tumours ranging from 1.2 to 2.5 (Brenner & Hall, 1999; Leith, 1994; Hoskin, 2006). According to this model, the tumour becomes sensitive towards large doses of radiation therapy. A definite answer regarding whether this external beam radiation therapy is able to provide a better biochemical control, clinical control, as well as reasonable rates of late toxicity while still maintaining a good quality-of-life, has not yet been determined.

Toxicity scales have been used to grade sexual, late rectal and bladder effects. These scales include "*Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer* (EORTC), and *Late Radiation Morbidity Scoring Scheme or the Late Effects Normal Tissue Task Force – Subjective, Objective, Management, and Analytic* (LENT-SOMA) scales" (Rubin, Constine, Fajardo, Phillips, & Wasserman, 1995; Rodrigues et al., 2007). Though the aforementioned scales are not complicated to use, they are constrained in the type and intricacies of the information: these scales are not able to measure the impact on health-related quality-of-life (HRQOL) related to treatment side effects. For instance, these scales do not measure the bother domain; they only capture the symptoms. Patients could develop high grade symptoms with low impact/bother and vice versa. Many HRQOL questionnaires have been implemented to evaluate the HRQOL of a prostate cancer patient where the questionnaire can be administrated prior, during, and after some treatments. An example

of a generic instrument designed to assess prostate-specific cancer HRQOL is the *Expanded Prostate Index Composite* (EPIC). On the other hand, a simpler questionnaire, the *Prostate Cancer Radiation Toxicity* (PCRT), has been developed to assess the long-term effects of RT (Rodrigues et al., 2007).

The purpose of this study is to construct a new database assessing health-related quality-of-life and late toxicity in an audit of patients treated since 2003 (all treated at the London Regional Cancer Program, located at the London Health Science Centre, in London, Ontario, Canada), with a new hypofractionated prostate cancer radiation technique. Patients prior to 2003 were generally treated with 70 Gy in 35 fractions at 2 Gy/day. Since 2003, dose and dose-per fraction escalation has been utilized to a total dose of 73 Gy in 35 fractions.

Specifically, the primary goal was the further validation of the PCRT instrument versus the commonly used EPIC instrument. A secondary goal of the study was a preliminary assessment of a simple HRQoL Exit questionnaire (assessing global changes in HRQOL, GI, GU, and sexual late toxicity). A third goal was the investigation of predictive pretreatment factors and late toxicity as recorded by EPIC/PCRT using univariable (UVA) and multivariable (MVA) analysis. A fourth goal of the study was to compare post treatment HRQOL versus available (prior 2003) EPIC HRQOL data and to generate a hypothesis explaining any potential differences in HRQOL due to hypofractionated therapy. The results of this audit and HRQOL analyses may provide valuable feedback concerning the quality of current radiation treatments. This analysis

may also identify areas for improvement in care of patients receiving radiation treatments.

2.0 Prostate Cancer

2.1 Introduction:

The prostate, an essential part of the male reproductive system, assists in the production of seminal fluid and allows the sperm to be carried out of the body. Medical findings have suggested that a healthy prostate is approximately the size of a walnut, approximately 4 x 2 x 3 centimeters or 1.6 x 1 x 1.2 inches (American Cancer Society, 2008; U.S. National Institute of Health, 2005). Since the prostate surrounds the urethra, as a tumour begins to grow it may squeeze the urethra and affect the flow of urine from the bladder to the penis, thus potentially interfering with the voiding of urine. It may also interfere with the reproductive system and sexual function (U.S. National Institute of Health, 2005; U.M.D.N.J., 2007). In many men, however, prostate cancer is asymptomatic and is usually detected by PSA screening.

As a large and growing problem (Bowsher & Carter, 2006), prostate cancer tends to develop predominantly in older men by forming cancerous cells in the prostate tissues (U.S. National Institute of Health, 2005). Due to improvements in lifestyle, medical therapies, and disease prevention, the North American population continues to age and, by the year 2020, it is estimated that the number of people over the age of 60 will triple. So too, the number of men affected by prostate cancer should increase consequentially. To cope with that growing problem, clinicians, and researchers are continuously challenged to improve detection and treatment of the disease, as to study demographics and behavior of the populations affected.

The specific cause of prostate cancer is still not clearly known; however, many studies have revealed certain risk factors related to its development. Scientists have investigated various factors that could modify the risk of prostate cancer in some patients rather than others. Men older than age 45 are more likely to develop prostate cancer compared to those younger than 45 (National Institute of Health, 2005). According to the American Cancer Society, there is a greater risk for men to develop prostate cancer if there is a family history of the disease. African American men are at higher risk than males from other ethnic backgrounds, with a relative risk ratio around 1.5 to 2.0 in the United States.

An additional putative risk factor of premalignant changes, including the microscopic finding of abnormal prostate cells "high-grade prostatic intraepithelial neoplasia (PIN)" may suggest (although not proven yet) a higher risk for prostate cancer. Previous researchers have found that a diet rich in animal fat increases the risk for prostate cancer, whereas a diet rich in vegetables and fruits lowers that risk. Other possible modifiable risk factors may include sexual activity, smoking, obesity, and lack of exercise, although to date there is no clear evidence linking these factors with prostate cancer (American Cancer Society, 2008; U.S. National Institute of Health, 2005; U.M.D.N.J., 2007).

2.2 Prostate Cancer Diagnosis and Screening Tests

Fortunately, many tests have been designed to investigate prostate cancer. These include: laboratory-based tests (prostate specific-antigen (PSA); Gleason Grade; physical

examination (including digital rectal exams (DRE)); diagnostic imaging (Transrectal ultrasound (TRUS) with biopsy); MRI of the prostate, bone scan as well as CT scan of pelvis and abdomen can be utilized to investigate any local, regional, and metastatic spread.

Wang and co-workers in 1979 discovered the serum marker prostate specific-antigen (PSA), which in turn remarkably advanced prostate cancer detection and management.

2.2.1 Prostate-Specific Antigen (PSA)

Labrie (2004) stated that "The prostate-specific antigen (PSA) is the first FDA-approved tumour marker for early detection of prostate cancer through population screening". PSA was first identified in 1970, purified, characterized and named as PSA in 1979, and detected in serum in 1980. This protein is a serine protease produced by the prostate gland at very high concentrations. PSA is secreted into the seminal plasma in high concentrations (0.5-5g/L), where it plays a role in semen liquefaction. Labrie & Koutsilieris (2004) explain: "In young, healthy males the retrograde release of PSA into the bloodstream is a rare event occurring with a frequency of less than one PSA molecule per million secreted PSA molecules. This leads to a concentration of <4 ng/ml PSA in serum. However, this is not a generally observed phenomenon-the derived number was based on survey on conducted on a certain number of "healthy" individuals, which did not take into account age and other factors. Perturbation of the prostate gland architecture often results in excessive escape of PSA into the circulation." A significant increase of

serum PSA can be the result of prostate cancer or benign prostate disease, as well as physical trauma of the prostate. Nevertheless, an elevated serum PSA might be considered a reliable marker of prostate gland diseases, especially prostate cancer. Nevertheless, overlap exists between prostate cancer and Benign Prostate Hyperplasia (BPH) patients with PSA under 10ng/ml. Previous studies reported that two-thirds of patients subjected to biopsies based on a PSA level of 4-10 ng/ml have no histological proof of prostate cancer (Brawer, 1994). And so, this range became known as the "grey zone". Refinements in PSA such as PSA velocity, PSA density, and free to total PSA has been proposed to help determine whether or not to carry out biopsy for patients in the "grey zone" (Bowsher & Carter, 2006).

2.2.2 Transrectal Ultrasonography of the Prostate

Transrectal Ultrasonography of the Prostate (TRUS) allows the physician to examine images of the prostate as well as its surrounding tissue (Chen, 1997), thereby helping the physician to check for abnormalities in the prostate gland, such as: BPH, cancer of the prostate prostatitis, and prostatic abscess (Kazush, 2004).

An essential part of measuring the prostate gland is to assess the volume of the prostate; therefore, many formulae have been used, of which the ellipsoid formula is most popular, involving the measurement of three prostate dimensions (Liebross, 1999). Measuring the prostate gland volume helps determine treatment options. A prostate gland size less than 50 grams will make brachytherapy and perineal prostatectomy much easier to perform (Wang, 1997). Applying hormonal therapy to a

large gland will help decrease the prostate gland size, and although TRUS can be utilized to assist in deciding a treatment for the large BPH gland (Kazush, 2004); however, some physicians may not find it to be an acceptable tool.

The role of TRUS has changed with the use of the prostate specific-antigen (PSA) screening test and early diagnosis of prostate cancer (D'Amico, 1997). It is now largely used to visualize the prostate gland to assist in guiding the possible biopsy needle. TRUS might play a role in the early detection of the presence of prostate cancer. Further progress, including the use of end-firing probes, advanced the urologist's capability to fully monitor prostate biopsy procedures (Shetty, 2008).

2.2.3 Digital Rectal Examination

Digital rectal examination (DRE) refers to the physical examination of a patient's rectum by his physician to check the prostate gland, as well as investigate any problems existing in other organs, pelvis and/or the lower belly. It should be noted that Whitmore and Jewett's initial clinical staging was entirely dependent on the DRE outcomes (Jewett, 1997). According to Pittsburgh University Cancer Institute publications "A digital rectal examination allows a doctor to feel only the back wall of the prostate gland, so any abnormalities located in the middle or front part of the gland cannot be felt. For this reason, the DRE is performed in conjunction with PSA testing. Although the PSA test can detect many cancers which doctors cannot feel during a DRE, it has also been shown that DREs detect some cancers which are not associated with an elevated level of PSA in

the bloodstream" (UPMC Cancer Centers, 2009). Therefore, in the early PC stages DRE is crucial in detecting PC when it is asymptomatic.

2.2.4 Gleason Grading System

Histologic grade is the most vital information obtained by use of the needle biopsy as it is highly predictive of patient outcome. In taking tissue samples from the prostate gland, the Gleason grading system, the most commonly utilized classification scheme for the histologic grading of prostate cancer (Gleason, 1966; Gleason, 1992). The grade assigned to the tumour offers an explicit idea of potential tumour growth and spread, as well as the abnormality of the cancer cell (Greco & Zelefsky, 2000). Cell growth pattern should be taken into account when determining cancer grade. The Gleason grades range from 1 to 5, where 5 stands for the most aggressive and 1 for the least aggressive. Unlike grade 3 (which seldom has metastases), grade 4 or 5 tumours are commonly associated with metastases. The overall Gleason score is simply the combined of the two most predominant histologic patterns observed, ranging from 2 to 10 (Zagars, 1995). A Gleason score ≤ 6 usually typifies a low grade tumour growing sufficiently slow that it simply might not cause a major health hazard during patient's lifetime. Intermediate grades are considered to be 7, and scores from 8 to 10 are considered to be high grade (McNeal, 1990). One should keep in mind however, that tissue sample gained by tumour biopsy is not always completely representative. Sometimes, tumours could be missed (20-30% of samples are under graded). An additional opinion from other pathologists is highly recommended here to ensure the accuracy of the grading to be assigned to tissue samples. Interpretation of the overall Gleason score and the component

grade should be performed with great care, as the overall score may imply a totally different and significant outcome. For example, a Gleason score of (4+3=7) indicates a poorly differentiated primary element (pattern 4, highly cancerous), while a (3+4=7) implies a better differentiated primary (pattern 3, less cancerous). Although the total score is the same there is published evidence suggesting a significant difference in terms of patient outcome (McNeal, 1992; Grignon, 1994).

2.3 Prostate Cancer Staging

Cancer stage categorizes the degree or severity of the cancer, based on the primary tumour site and size, and extent, involvement of lymph nodes and the presence of metastases. Assigning an accurate stage of cancer is essential since at diagnosis the stage is the most influential predictor of survival. As well, treatments are often altered based on the cancer stage. There are different types of staging systems, but two main classification systems are used for clinical staging. The first is the Whitmore-Jewett system, subsequently modified since its first description in 1956 (Whitmore, 1956). Here, a Stage A rating indicates an undetectable tumour clinically restricted to the prostate gland, whereas Stage D indicates metastatic disease (Jewett, 1975).

The second system is the TNM (Tumour, Node, and Metastasis) staging system, adopted first in 1975 by the American Committee for Cancer Staging and End Results Reporting (AJCC). In 2002, the American Committee of Cancer revised the TNM staging system. T indicates the primary area of the tumour in the prostate. N indicates whether the cancer has spread to lymph nodes and if so to what degree. M indicates the distant

extension of the cancer to the bones or other organs. Overall stage grouping is referred to as Roman Number Staging. This staging system ranges use numerals I to IV, which the U.S. National Institute of Health (2005) uses to describe the progression of cancer as follows:

Stage I: At this stage, the cancer (located only in the prostate) cannot be detected through a digital rectal exam although it may be discovered during surgery for BPH. (T1a, N0, M0, G1(Well differentiated (low grade) (Gleason 2-4)).

Stage II: Despite the fact that the cancer is palpable by digital rectal examination, it is still localized within the prostate. (N0, M0, and any G with either T1 or T2)

Stage III: The cancer is no longer only in the prostate, but it has not reached the lymph nodes. (T3, N0, M0, any G)

Stage IV: The tumour may have spread beyond the seminal vesicles to be found in nearby organs and muscles or it may have affected the lymph nodes or other parts of the body. (T4, N0, M0, any G. Or any T, N1, M0, any G/ any T, any N, M1, any G)

Table 1: TNM Prostate Cancer Staging System;

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer Science and Business Media LLC, www.springerlink.com. (See permission Appendix 2)

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour neither palpable nor visible by imaging
T1a	Tumour incidental histological finding in ≤5% of resected tissue
T1b	Tumour incidental histological finding in >5% of resected tissue
T1c	Tumour identified by needle biopsy (e.g., because of elevated PSA)
T2	Tumour confined within prostate
T2a	Tumour involves one-half of one lobe or less
T2b	Tumour involves more than one-half of one lobe but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extended through the prostate capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall

Nodal Metastasis (N)

NX Regional lymph nodes were not assessed

N0 No regional lymph nodes metastasis

N1 Metastasis in regional lymph nodes

Distant Metastasis (M)

MX Metastasis cannot be assessed (not evaluated by any modality)

M0 No distant metastasis

M1 Distant metastasis

M1a Non-regional lymph node metastasis

M1b Bone metastasis

M1c Metastasis at other sites with or without bone disease

Histopathological grade (G)

GX Grade cannot be assessed

G1 Well differentiated (low grade) (Gleason 2-4)

G2 Moderately differentiated (moderate grade) (Gleason 5-6)

G3 Poorly differentiated or undifferentiated (marked anaplasia) (Gleason 7-10)

G4 Undifferentiated (high grade) (Gleason 7-10)

2.4 Management of Prostate Cancer

2.4.1 Risk Categories

Lukka (2001) stated that risk stratification (low, intermediate, and high) is a useful aid to precede prostate cancer management decisions. Posing a patient's condition in absolute terms of "superior case" and "inferior case" scenarios help the patients to prioritize their HRQOL concerns in relation to the risk of cancer recurrence and death; to then make the appropriate treatment decision (Klein, 2004).

A study by D'Amico (2003) stated that the prostate cancer risk strata based on Gleason score, T stage, and PSA is a valid way to predict outcome and select treatment related to the patient's particular case. Further, D'Amico in his study (2003) stratified the risk into three strata as the following:

Low risk is defined as Gleason score ≤ 6, and PSA ≤ 10, and T1 (a, b, c), T2a. It is apparent with the low risk category that long-term survival is good to excellent, with a variety of therapy modality. Consequently, the patient's awareness of each individual treatment side effect is crucial for decision making (Klein, 2004).

The intermediate risk stratum is associated with a Gleason score ≤ 7, T2b or T2c, and PSA >10, ≤ 20, but not otherwise in the low-risk strata. There is a higher risk for relapse in this category, and a good discussion of competing risk and benefits of treatment needs to occur with patients (Klein, 2004).

The high risk stratum is associated with Gleason score ≥8, PSA >20, or T3 (a, b, c) T4. Patients with high risk disease should be informed that monotherapy is likely not sufficient (Klein, 2004). Patients are generally offered hormonal therapy in addition to local prostate treatment with surgery or radiation (Rodrigues et al, 2007).

2.4.2 Treatment Options

The discovery of prostate cancer offers a difficult challenge to select the best treatment for localized prostate cancer patients. This has been difficult, given the lack of well-conducted comparative trials of available treatments. Because the physician's main aim in treatment is to "cure" prostate cancer and thus prolong life, the idea of watchful waiting seems somewhat improper or inappropriate to some. However, given the normal lifespan of the majority of prostate cancer patients and the long natural history of their cancer when compared to other types of cancer, we know this diagnosis does not always lead to metastasis or death. Consequently, many patients will choose to protect and maintain their HRQOL with surveillance only rather than focus solely on maximizing length of their survival. Patient choices depend heavily on the likelihood of good and bad outcomes related to each individual treatment option.

Watchful waiting or otherwise known as active surveillance clearly is a reasonable option for many prostate cancer patients. The determination of when the cancer becomes life-threatening is the key to decide when to intervene. Ultimately, with the physician's unbiased guidance and aid, it is clearly the patient's choice to make (Kirby, Partin, Feneley & Parsons, 2006).

There are four treatment options introduced by physicians to patients with organ-confined adenocarcinoma of the prostate. These include surgery, radiation therapy, endocrine treatment (hormonal), or an expectant treatment which in turn stands for delayed palliative therapy in formerly untreated males because there is no intention to cure. If, later on, the patient and patient's tumour features are monitored directly and treatment proposed to cure are offered to the patient, this is considered to be watchful waiting with delayed treatment (Bowsher & Carter, 2006).

2.4.3 Surgery

During the American Urology Association (AUA) meeting in 1992, Schussler et al. presented their initial attempt to perform laparoscopic radical prostatectomy (LRP). In 1997, an AUA group published their finding of nine cases (Schuessler, Schularm, Clayman, & Kavoussi, 1997). They found that the long operation times for open surgery with a range of 9.4 hours seemed to give the initial operations advantages over the open surgery. The refined and standardised LRP procedure was initiated in 1998 when Vallancien and Guillonneau (2000) used "a transperitoneal approach to the seminal vesicles, ampullae, and intra-corporeal suturing." LRP became known as a minimally invasive alternative to open surgery in 2000 (Menon, Shrivastava, & Tewari, 2005). Chin et al., 2008 revealed in his report of the Cancer Care Ontario *Surgical and Pathological Guideline* that "The main goals of radical prostatectomy (RP) are complete eradication of the cancer-containing organ with negative surgical margins, preservation of urinary function, and preservation of erectile function, where appropriate, but, in some cases, it is not possible to achieve all three. Positive surgical margins are associated with

higher rates of cancer recurrence, but techniques for the preservation of urinary and erectile function may result in positive margins" (Chin et al., 2008). Chin recommended RP to low-risk PC patients since surgery is the preferred option for those patients based on their opinion. However, the high-risk patient surgery option should be carefully considered (Chin et al., 2008).

2.4.4. Radiation Therapy (RT)

Radiotherapy (RT) is the primary fundamental non-surgical treatment in the management of cancer. During the management of a malignant disease, more than 50% of cancer patients are treated with RT (Hoskin, 2006).

RT is delivered in one of two ways, either by teletherapy or brachytherapy. Unlike brachytherapy, teletherapy is applied from a distance and is synonymous to EBRT, where brachytherapy is considered closed therapy (Vokes & Golomb, 2003). Employing the position of radioactive sources close to or within a tumour, it delivers elevated doses of radiation to a restricted volume with a fast drop in nearby tissue. Nevertheless, the best radiation modality for the treatment of prostate cancer remains a source of argument.

Furthermore, EBRT destroys cancer cells using particles or high-energy rays. Radiation is used effectively to treat prostate cancer when it is located within the prostate gland or within tissue surrounding the gland. Individuals with low and intermediate risk cancer could initially undergo RT as the treatment of choice with a cure rate equal to radical prostatectomy. It may be prescribed for those who have undergone surgery but

the cancer is still present or recurrence in the prostate gland (adjuvant therapy). In salvage cases, EBRT potentially in conjunction with hormonal manipulation can still be given for curative and a control purposes. Rectal damage may be controlled or eliminated by highly targeted RT, according to researchers in Oregon (American Cancer Society, 2007).

To date there is more information on the success of EBRT than brachytherapy in the medical literature (American Cancer Society, 2007). In advocating how to deal with a man's localized prostate cancer, whether to treat or not, one must take into consideration the pragmatic indications of the disease--as evaluated by Gleason grade, PSA level, as well as clinical stage--and the life expectancy of the patient and his choice for and between treatment choice taking into account all factors, including side-effects.

2.4.5 Hormonal Management

In 1941, Huggins and Hodges documented the palliative effect of castration and, since that time, hormone ablation has been the foundation for management of metastatic prostate cancer (Huggins, 1941; Huggins, Stevens & Hodges, 1941). Various options for androgen ablation include orchiectomy or injection of luteinizing-hormone-releasing hormone (LHRH) agonists, both resulting in responses in over 95% of hormone-native patients, bringing improved pain relief from metastatic lesions, objective tumour responses, and a fall in PSA. There are side effects, however, including fatigue, hot flashes, loss of libido, and osteoporosis. Regardless, orchiectomy remains the standard by which all other forms of hormonal therapy are measured, and it does offer

advantages—immediate hormonal control, relatively low cost, and elimination of issues of patient compliance. Nevertheless, most men choose treatment with LHRH agonists, despite their diminished convenience and significantly increased expense.

2.4.6 Watchful Waiting

The rationale of watchful waiting with delayed treatment is to avoid needless treatment with its intrinsic side effects and expense for patients with early stage prostate cancer. This is particularly applicable for those patients who are not likely to develop clinically significant cases (i.e. symptomatic metastatic disease) during their lifetime. In such cases of watchful waiting, delayed treatment can frequently offer those patients a chance at cure at a later time (Vokes & Golomb, 2003). A clinical trial conducted in 2002 showed that, the urinary obstructive symptoms, "were more prevalent among men assigned to watchful waiting versus RP" (Wei et al., 2002). Furthermore, the finding of a recent randomized control trial conducted in Scandinavia comparing RP versus watchful waiting revealed that, "the cumulative incidence of distant metastases at 12 years was 19.3% in the RP and 26% in the watchful wafting group. Furthermore, the overall mortality was 32.7% in the RP Group and 39.8% in the watchful waiting group. In conclusion, RP reduces prostate cancer mortality and risk of metastases with little or no further increase in benefit 10 or more years after surgery" (Axelsen et al., 2008).

3.0 External Beam Radiation Therapy (EBRT)

3.1 Introduction

Many recent advances in technology now exist for radiotherapy, leaving clinicians with the challenge to remain "current" in order to effectively use these new advances to optimize management of their patients' disease. Most patients taking radiotherapy need to undergo external X-ray as generated by a linear accelerator for treatment. This requires complicated and highly precise physics planning systems combined with state-of-the-art problem-solving algorithms to take precedence to protect tissue during treatment. In addition, we need to take into careful consideration inhomogeneities and beam variables, as well as the use of multileaf collimators, now widespread and highly used because of their ability to conform using intensity-modulated radiation therapy. The main treatment still include the determination of a precise patient site and a method targeting that site day after day with suitable treatment, following both precise localizing and determination of the volume, and the cooperation with medical physicists to distinguish optimal conveyance of applying available beams with proper treatment modifiers (Hoskin, 2006).

Hoskin (2006) states succinctly and well: "The process of daily implementation of the treatment plan is often neglected but of vital importance in ensuring accurate and effective radiotherapy with verification that treatment delivery is reproducing the expected beam as defined in the planning process".

The EBRT works by applying radiation from an outside source far away from the

patient's body. It is similar to the procedure of taking x-ray; however, the EBRT procedure generally takes longer and at substantially higher dosages and using higher energy X-rays. Prior to determining whether this technique should be used, the physician will require a pelvic x-ray, CT scan or perhaps an MRI. This is done to determine the precise location of the patient's prostate, and an ink mark on the skin spot guides the radiation team to the exact area to which the radiation is to be applied. The painless treatment, scheduled at the outpatient center 5 days a week for 7 to 9 weeks, lasts for a few minutes a day. EBRT might be applied either alone or with a brief course of neo-adjuvant hormonal therapies for a low or intermediate-risk patient, or aggregate with adjuvant hormonal therapy for patients with aggressive localized cancers and/or high-risk patients (Hoskin, 2006).

3.2 Possible Side Effects of EBRT

Although using newer treatment methods may decrease the possibility of significant side effects (American Cancer Society, 2007), some possible effects may still occur from using the standard EBRT. These generally could include effects on the bowel, bladder, and sexual systems.

3.2.1 Bowel Problems

Post treatment side effects of EBRT may result in diarrhea, bloody stool, accidental bowel movement, flatulence, and an irritated bowel, but the majority of these problems eventually can be overcome. Historical statistics show that 10% to 20% of men

experienced bowel problems after being exposed to EBRT, whereas fewer problems may occur given the use today of newer conformal radiation techniques (American Cancer Society, 2007).

3.2.2 Bladder Problems and Urinary Incontinence

Frequent urination, blood in the urine and a burning sensation on urination is experienced by approximately one in three patients, with frequent urination being the most common side effect (American Cancer Society, 2007). Even though this side effect is less expected after surgery, the chance of incontinence increases every year (8.4%) for a couple of years after treatment before it eventually subsides (American Cancer Society, 2007; Stanford, Feng, Hamilton, Gillilan, Stephenson et al., 2000).

3.2.3 Impotence

Impotence occurs to approximately the same degree, whether treatment is surgery or radiation therapy, with impotence occurring almost immediately after surgery, whereas radiation therapy leads to its developing more gradually, usually after a year or so. Previous research has shown that 3 out of 4 men became impotent within 5 years of being exposed to EBRT. Indeed, half of the men with normal erection before treatment experienced impotence at 5 years. It is not yet known whether the newer forms of radiation will have the same effect. It is known that older men undergoing surgery are more likely to become impotent after radiotherapy (American Cancer Society, 2007).

3.2.4 Acute and Late Toxicity Adverse Effects

According to Hoskin (2006), the toxicity effect of the EBRT may be divided into two categories. The acute toxicity effect takes place immediately during and for up to 6 months after the delivery of EBRT (also called sub-acute toxicity). The late toxicity effect takes place after one year of RT and up to 6 years (Pollack et al, 2002).

3.2.4.1 Acute Toxicity Effects

Acute symptoms include radiation proctitis, tenesmus, rectal bleeding, and pelvic pain with mucous discharge. Avoiding constipation and keeping the stool soft helps in reducing the effect, and the physician may prescribe certain medication to control this toxicity. Other symptoms, such as diarrhea with flatulence, may also indicate small bowel toxicity (Hoskin, 2006). Furthermore, a combination of obstructive and irritative prostatic symptoms resulted in urinary acute toxicity symptoms, including frequency, poor stream and urgency, though seldom hematuria. Physicians generally advise their patients to maintain a well hydrated diet to reduce bladder irritation and thus prevent infections. Acute toxicity to the bowel and urinary tract usually ease within 12 to 18 weeks. While acute toxicity can lead to chronic issues, it may also be or reversible after completion of RT.

Additional acute toxicity is also expected to occur, and other commonly noticed effects during treatment include skin erythema or dry desquamation, fatigue and lethargy, as well as loss of pubic hair (Prosnitz, Schneider, Manola et al., 1999).

3.2.4.2 Late Toxicity Effects

In order to accurately determine the late toxicity effects related to radiation therapy, it is essential to rule out other baseline co-morbid conditions from being possible confounding factors (for example, late bowel toxicity occurs in approximately 30% of patients, these GI symptoms might be the result of conditions unrelated to their RT (Andreyev et al, 2005). Urinary symptoms bladder/irritative can be treated after evaluation with urodynamic studies. Urinary symptoms could improve after EBRT apparently due to prostate gland shrinkage thus decrease in obstructive symptoms (Dearnaley et al, 2005). Studies reported that almost half of the PC patients will experience erectile impotence when they receive RT with hormone therapy (Raina et al, 2003).

4.0 Health Related Quality of Life Instruments

4.1 Introduction

Over the past two decades, when mentioning outcomes in cancer treatment, it was implicit that the focus was to the endpoints of tumour response and survival. The utilization of multimodality therapies and an increased survival rate has led to both greater awareness and an increased interest in and concern for the psychosocial desires of cancer patients. The decline in health, when coupled with treatment consequences such as physical or functional impairment, disruption of social or family interactions and both physiological and psychological distress, all in turn affect a prostate cancer patient's quality of life (HRQOL). So it would seem that cancer treatment options should include both quality of life as well as the quantity of life expected during and post-treatment. And, while quality of life is not necessarily associated with an attendant survival rate, it should be an important consideration. A patient's knowledge of his disease and treatment/symptoms and thus his empowerment in understanding better both his disease and the treatment required may well be important elements, indeed as important as his therapeutic options (Vokes & Golomb, 2003).

In general, what is considered to be quality of life can vary greatly amongst individuals. In the world of science, the general consensus for HRQOL refers to how the patient perceives their ability to live life with the disease and its treatment (Vokes & Golomb, eds., 2003). There are other factors – environmental, economic, social and political variables— that play a significant role in this perception. These are excluded from this HRQOL since they do not directly affect most health care interventions.

Multidimensionality and subjectivity are considered to be two fundamental premises of health related quality of life instruments.

Multidimensionality means that HRQOL has a broad range of domains, at least three but generally four dimensions. The first is the Physical/Somatic such as pain, nausea, and fatigue. The second is the Functional, which includes energy and daily activities. The third is the Social dimension, the ability to maintain relationship with family and friends. The fourth dimension is the Psychosocial/Emotional and includes mood, anxiety, and depression. Subjectivity studies show that two people with the same disability will have different experiences and reactions. "Individual priorities, social support and ability to adapt are only some of the factors that could determine the final outcome." (Vokes & Golomb, eds, 2003). Hence, with these elements at different levels of priority for different people, any HRQOL construct must take these four elements into account (Cella, 2001; Ware, Kosinski, Bayliss et al., 1995).

Since HRQOL deals with humans, one needs to monitor and carefully examine these factors since they change over time, in the course of the disease and its treatment. Different assessment tools designed by health care providers rate function such as standard toxicity ratings or global ratings (e.g. the Karnofsky scale), both of which summarize one area only, somatic symptoms or performance (Vokes & Golomb, 2003; Lindley, Hirsch, O'Neill et al., 1992). Studies show that the side effects of disease and outcome are important to the patient and that much may be learned from that patient's experience. One may think that the control and alleviation of a symptom would improve or return the HRQOL to its former state but, given the multiplicity of side effects,

sometimes that is not the case. Studies have demonstrated that performance status is not associated with the patient's emotional or social functions. One may be progressing well in treatment, but their HRQOL may be lowered because they are for instance experiencing impotency, thus perhaps significantly interfering with their social, functional and recreational life. Assessment tools are generally not quite so accurate since they do not encompass all possible variables. For example, the standard toxicity ratings disclose nothing regarding a patient's experience of a particular side effect nor do they declare how a patient's daily life is influenced by the treatment (Vokes & Golomb, 2003).

HRQOL measurements were made to measure groups of patients and the data acquired is usually interpreted in average scores. These measurements are useful in clinical practice to screen for problems or promote patient/physician discussion, but depend heavily on the question being asked, and the population being studied. Sometimes one may need to specifically choose an instrument design so that the information being attained is relevant to the question. Sometimes more than one instrument may need to be used. Moreover, defining the population of interest (inclusion, exclusion criteria) is crucial. Based on the study question, an HRQOL assessment study must have a baseline assessment so that changes over time can be assessed. Time points chosen depend on the protocol objectives and whether it is short-term or persistent effects of treatment that are being studied. The frequency of assessments may also be dependent on how fast the disease is progressing (Vokes & Golomb, 2003).

These measurements are valuable since they provide information on functional, physical, and emotional effects of the treatment, and that information may be used to help

evaluate a new dose treatment regimen. The data can also be used for treatment modifications to minimize negative effects, to better understand where preventative interventions might be warranted, or to prepare and educate patients for possible outcomes. Since prostate cancer has shifted to become more of a chronic disease over time, rehabilitation efforts have become more important. Patients may have to cope with physical or psychosocial late effects of the disease and specific EBRT treatment. Thus, HRQOL assessment is helpful in identifying possible late effects of the EBRT and allowing one to intervene and stop the progression or perhaps make it better. As well, it can serve to alert health care providers about morbidities that may have otherwise gone unnoticed (unexpected physical or emotional difficulty). Depending on the patient's answers on a HRQOL measure, the physician may want to discuss patient's priorities and concerns (Vokes & Golomb, 2003).

4.2 General HRQOL Instruments

Since the patient is considered to be the best source of information concerning their HRQOL, self-assessment questionnaires should be used. This is a convenient method as these questionnaires can be given to large groups of patients and busy clinics, can be given directly or mailed to the patient, and may be completed in face-to-face interviews or even over the phone. The questionnaire is based on two approaches, the generic instrument and the specific instrument. The generic instrument measures a very broad spectrum of HRQOL domains, thus allowing between-group comparisons. The downside to this approach is that it does not provide enough information regarding a specific disease, condition or intervention. In the specific instrument, appropriate for use

with all cancer patients to which disease-specific or treatment-specific modules have been added, one can evaluate specific diseases, populations, functions, radiation effects, and more clearly identified problems. The results allow for comparability across types of cancer and offer sensitivity to specific concerns (Lipscomb, Golay & Snyder, 2005). There are many well-developed HRQOL instruments that can be used for cancer patients. Most provide both dimensions and are thus a valid tool for evaluation of prostate cancer. Cancer-specific HRQOL validated instruments include the following:

1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30): In 1980 the EORTC conducted a study on quality of life, using a questionnaire which included nine multi-item scales with a total of 30 items. Since then, it has been used in many studies worldwide and has been proven to be sensitive to disease status (Da Silva et al., 1993).
2. Functional Assessment of Cancer Therapy Scale (FACT-G), by Cella et al. in 1993 (Cella et al., 1993).
3. Cancer Rehabilitation Evaluation System (CARES), by Schag et al., 1994 (Schag et al., 1990, 1994).

In general, all these studies found an association between the changes in cancer-specific HRQOL and prostate cancer progression, as well as therapy (Schag, Ganz, Wing et al., 1994).

4.3 Prostate Cancer-Specific HRQOL Instruments

Fortunately the prostate cancer prognosis is favorable, especially for localized disease, and it is well known that the majority of patients will have survival measured in

years. The physician's main responsibility, aside from treating prostate cancer patients, is to deal with their concerns about treatment options and the prediction of important outcomes. Since prostate cancer can be considered a chronic disease for many patients, HRQOL becomes a major concern for prostate cancer patients and HRQOL outcomes play an important part in choosing the optimal treatment. This in turn gives both physicians and patients a means to differentiate between treatment options and to trace cancer progression (Staquet, Hays & Fayers, 1999; Schapira, Lawrence, Katz et al., 2001) (see Figure 1).

4.4 Modular Prostate Cancer HRQOL Instruments

Some generic validated instruments for use in determining the prostate cancer specific HRQOL have been developed. These include:

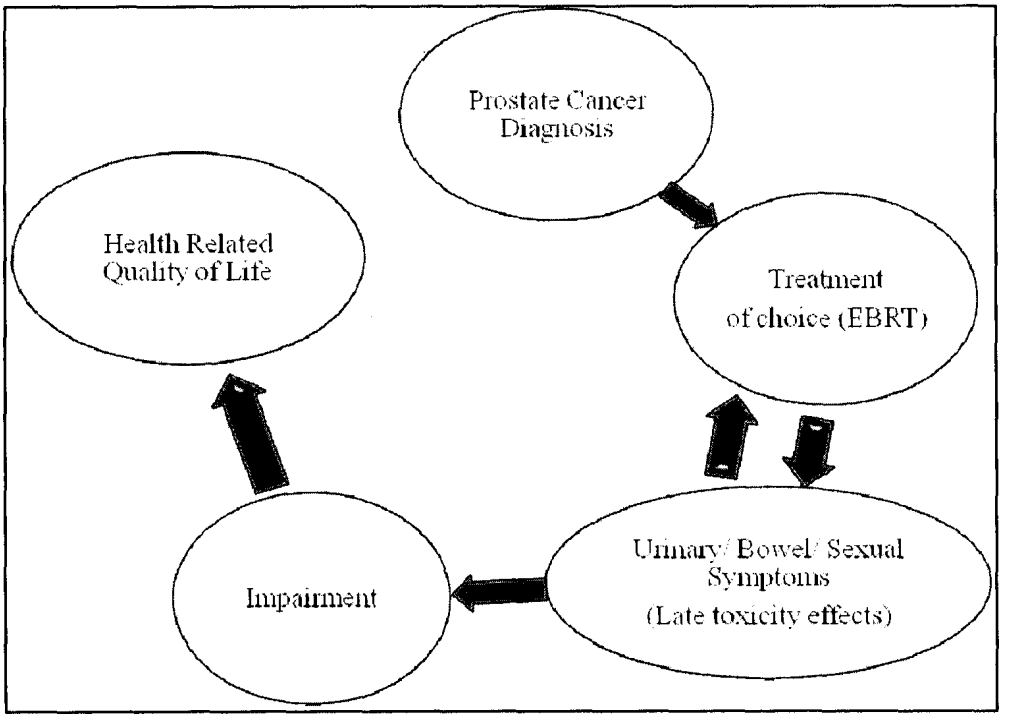
1. Prostate Cancer Index (PCI) developed by Litwin et al. in 1998 (Wei, Dunn, Litwin & Sandler, 2000). This questionnaire comprises 20 disease-specific items, and includes six scales (bowel/urinary/sexual function and bowel/urinary/sexual bother). This questionnaire proved to be reliable, with a test-retest reliability array from 0.66 to 0.93, and valid in a range of settings, with internal consistency ranging from 0.65 to 0.93. With its good reliability rating, it has been administrated widely in clinical studies.
2. Expanded Prostate Cancer Index: Composite (EPIC), by Wei et al. in 2000. This 50-item valid questionnaire was built on the framework of PCI, and developed to measure additional domains not correctly assessed on previous scales, including the irritative urinary symptoms, bowel and hormonal symptoms. The internal consistency of the

EPIC, test-retest reliability was more than 0.80. The validity of the EPIC was tested by assessing cross-correlation with both the American Urological Association symptoms index (AUA-SI), and the SF-12, FACT-P© (Wei et al., 2000).

3. Functional Assessment of Cancer Therapy Prostate Module (FACT-P) developed by Esper et al. in 1997 (Esper et al., 1997). The developed version of the FACT-P is the 2FACT-G© which is considered a modular questionnaire. It is a 33-item with functional well-being subscales, with categories including social/family, physical, emotional, and relationship with physician. Its internal consistency offers a published range from 0.65 to 0.69.
4. Prostate Cancer Outcomes Study Questionnaire (PCOS) developed by Stanford et al. in 2000 (Stanford et al., 2000).
5. Most recently, our research group (Rodrigues et al., 2007) developed a survey instrument called Prostate Cancer Radiation Toxicities (PCRT). This 29-item questionnaire has been constructed to assess late toxicities related to radiation therapy for prostate cancer patients, specifically the GU/GI/sexual late toxicities. The reliability test-retest was assessed by intraclass correlation and ranged from 0.4-0.7, as well as demonstrating fair to good internal consistency.

Most QOL instruments are in English, but the need for these tools in other languages is growing. Many groups have already begun the process of translating and validating their instruments. HRQOL data obtained can be used to describe the full range of treatment effects on patients' functioning and/or mortality, to assess rehabilitation needs and to predict future responses.

Figure 1: Conceptualization of HRQOL for Prostate Cancer Patients



4.4.1 Acute Toxicity Scales

The acute radiation toxicity scales used in clinical trials were developed by the Radiation Therapy Oncology Group (RTOG). In the case of prostate cancer, the lower gastrointestinal (GI) system and genitourinary (GU) system were considered acute toxicity scales by the RTOG. The RTOG scheme does not include sexual acute toxicity. A worldwide commonly used scale is The National Cancer Institute Common Toxicity Criteria (NCICTC) (Trotti, 2000). In this scale, 100 out of 260 individual items are potentially relevant to RT adverse effects. The RTOG and the NCICTC scales are graded on a five-point ranging from zero (absence of symptoms) to four (impairment or life threatening symptom). Grade two (moderate) and grade three (severe) commonly have a significant impact on a patient's HRQOL.

4.4.2 Late Toxicity Scales

The RTOG group and the EORTC combined their efforts to produce the first internationally approved late RT toxicity scale. This international scheme grades 17 diverse late tissue morbidities on zero to four scales in similar way to the acute toxicity scales. This scale is not exclusive to prostate cancer; it can be used widely to assess the late toxicity of all RT patients.

4.5 Reliability and Validity of HRQOL Instruments

Reliability and variability are used to ensure meaningful interpretation of findings in an HRQOL instrument (Streiner & Norman, 1995). Reliability estimates the consistency in the clinical condition. When an instrument measures the attributes it was designed for, it is considered to be valid. In the absence of an external criterion or a gold standard, validity is harder to assess than reliability. Several forms of validity exist such as face, content, convergent, criterion, concurrent, and construct, while the different forms of reliability are test-retest, internal consistency, interobserver, and intraobserver. In an ideal survey instrument, all aspects of validity and reliability are demonstrated. This is rarely achieved because it would require the instrument to be applied for many years (Streiner & Norman, 1995).

When reading many HRQOL studies, one must be aware of the potential lack of demonstrated validity and reliability being used (Yarbro & Ferrans, 1998). One must also be aware that applying a subset of items from a previously validated instrument is essentially flawed. The reason it may be flawed is because the item may not perform

reliably since it is out of context. Alternatively, there may be a rational plan to carry out the required psychometric testing of the instruments (Klein, 2004).

Our study instruments, EPIC/PCRT, demonstrated their reliability and validity through two major research studies (Wei et al., 2000; Rodrigues et al., 2005). The University of Michigan conducted a study to validate the EPIC for comprehensive assessment of HRQOL. They found in the EPIC questionnaire: "Test-retest reliability and internal consistency were high for EPIC urinary, bowel, sexual, and hormone domain summary scores (each $r \geq 0.80$ and Cronbach's alpha ≥ 0.82) and for most domain-specific subscales. Correlations between function and bother subscales within domains were high ($r > 0.60$). Correlations between different primary domains were consistently lower indicating that these domains assess distinct HRQOL components" (Wei et al., 2000). In comparison to the 12-item Short-Form Health Survey (SF-12) they conclude that the EPIC is "a robust prostate cancer HRQOL instrument that complements prior instruments by measuring a broad spectrum of urinary, bowel, sexual, and hormonal symptoms, thereby providing a unique tool for comprehensive assessment of HRQOL issues important in contemporary prostate cancer management" (Wei et al., 2000).

Rodrigues et al. developed the PCRT questionnaire. The study revealed a valid and reliable instrument. "The PCRT domains demonstrated stable and consistent mean and median scores in all domains ... with reasonable overall and individual subscale response rates. All reliability intra-class correlations were > 0.7 for all domains" (Rodrigues et al., 2007). Furthermore, they found that the PCRT questionnaire "demonstrate discriminative validity in terms of the fact that there was some low-level

correlation between all three measures ranging from 0.098 to 0.449" (Rodrigues et al., 2007). Consequently, the three subscales assess diverse but somewhat related (i.e. related to radiation toxicity) domains. Results from the PCRT questionnaire revealed progressive lower correlation among the subscales; hence demonstrating further content validity.

In conclusion, HRQOL is both multidimensional and subjective; it must be measured and assessed over time from the patient's perspective. Different instruments are to be used depending on the situation and questions being asked. Groups have been established to develop guidelines for determination of clinical or subjective relevance, reporting and interpretation of data, cross-cultural validation instruments, and comparing scores across measures, integration of measures of quality and quantity, and how to manage missing data. All the information previously listed simply add to the importance of including HRQOL data to enhance both the information gathered and to help both the patient and his physician to reach the best decision on an ideal treatment option for their particular disease (Vokes & Golomb, 2003).

MATERIALS AND METHODS

5.0 Research Study

5.1 Research Question

Does hypofractionated course of EBRT have any effect on late toxicity and respective HRQOL on PC patients?

5.1.1 Overview

The London Health Sciences Centre London Regional Cancer Program (hereafter referred to as LRCP) Genitourinary (GU) group began to use higher doses of radiation therapy as an institutional standard in conjunction with a simultaneous in-field boost (SIB) technique, in order to try to increase the tumour therapeutic gain, although this has the potential to increase late toxicity effects on HRQOL. This strategy involved the use of a higher dose per fraction with constant total number of fractions (treatments), a strategy known as hypofractionation. In 2003,a technique was introduced which involved a mild degree of hypofractionation through the introduction of the SIB technique which gave a dose per fraction of 2.3Gy during the last 10 treatments compared with the traditional 2Gy per fraction used in the past for the entire treatment.

Associated with this was a modest dose escalation in the total dose of radiation to 73Gy. The result was a modest increase in the biologically effective dose of radiation post 2003 vs. pre 2003 (124Gy vs. 117Gy). Consequently, an increased concern

regarding dose-escalation is that additional dose may lead to additional late toxicities (to the rectum as well as to the bladder and sexual function of the PC patients). This and respective HRQOL changes are part of the focus of this study.

The LRCP researchers hypothesized that, with improvements in treatment management and delivery technique (e.g. SIB delivery), any additional effect on late toxicities and HRQOL may be reduced to a minimum. To evaluate these HRQOL and late toxicities, we used the EPIC and PCRT questionnaires. Although the EPIC questionnaire is commonly used in evaluating QOL, it has limitations in detecting late toxicity effect. Therefore, we also employed the PCRT which had some advantages over the EPIC. The PCRT had been developed specifically for the purpose of detecting late toxicity effect, and the questionnaire is in fact shorter than the EPIC. Moreover, the LRCP aims to ensure these advantages of the PCRT questionnaire in fact quantifiably exist, by assessing the validity of the PCRT in detecting the RT late toxicity effect and changes in HRQOL when they exist.

In order to answer the research question, we selected the EPIC/PCRT/Exit questionnaires in order to collect information on HRQOL/ late toxicity of a study population (PC patients) who received HD EBRT. We then compared this cohort to a similar cohort treated prior to 2003 with LD EBRT.

We have chosen the abovementioned questionnaires as QOL instruments to measure HRQOL and EBRT late toxicity effects. The EPIC and PCRT questionnaires were tested for Validity and reliability and were proven to be valid and reliable. (see section 6.3)

5.2 Primary Objectives

This study had two primary objectives,

1- To assess the validity of the PCRT questionnaire versus EPIC questionnaire (gold standard) in the detection of clinical differences.

2- To assess post treatment HRQOL and late toxicity effects of EBRT on PC patients treated with a hypofractionated course of radiation therapy (equal or more than 73 Gy).

5.3 Secondary Objectives

Three secondary objectives were also identified:

1- To assess the univariable and multivariable associations between baseline variables of the study population and their HRQOL/Late toxicity scores.

2- To assess HRQOL and late toxicity of PC patients treated with a hypofractionated course of EBRT ($\geq$73Gy) in comparison to results in a pre-existing database of prostate cancer patients treated with lower dose EBRT (<73 Gy).

3- To test correlation of a simpler HRQOL scale (Exit questionnaire) with larger EPIC/PCRT scales.

6.0 Research Design and Methods

6.1. Introduction

The study design is an observational cross-sectional postal survey with retrospective baseline data collection from medical charts, and is employed to assess a change in practice within a single study population in terms of HRQOL/late toxicity related to hypofractionated EBRT. Another focus of this study is a comparison of the PCRT questionnaire with the EPIC questionnaire to ensure PCRT validity and reliability in the detection of clinical differences if they exist. The primary study population is comprised of patients treated with a higher EBRT dose (≥73 Gy) post-2003.

The foremost strength of the study design is the required relatively short time to assess frequency and characteristics of exposure and outcome without trouble of loss to follow up at the particular point in time. The rationale of using the cross-sectional design over other study designs is that it is an inexpensive and simple design, given that it is a fast way to establish a database of this hypofractionated cohort for use in future studies, while assessing the prevalence of radiation late toxicity in this population. As well, we were not interested in assessing an accurate causal temporal order; hence, our study population's exposure to EBRT preceded the HRQOL/RT-Late toxicity outcomes.
An important part of this research is to compare the study cohort patient's quality-of-life data with pre-existing database for patients treated prior to the change in EBRT (323 patients prior to 2003) in order to generate hypothesis regarding the potential increases in toxicities and HRQOL potentially related to dose per-fraction escalation. We will be able to investigate whether or not any significant changes in HRQOL or late toxicity had

occurred. In this study, we were able to gather as many as possible baseline characteristics that match our study cohort with the previous cohort (standard dose of 70Gy per 35 fractions), with comparable time lag from treatment to assessment for both groups. Thus, we were able to minimize biases due to differences in data collection time, treatment technique changes, and population changes over time. Our previous database was collected through similar methodology (employing cross-sectional study design with sample size equal to 323). This study determines the feasibility of further studies regarding the advantages of using dose escalation treatment methods versus the conventional dose.

Data collection of our study population was conducted through the survey questionnaires (EPIC/PCRT/Exit), and through abstraction of relevant demographics, and pretreatment information from study participants' charts. A letter of information describing the study was mailed out with the study questionnaires booklet to consenting study participants.

The initial sample size of 299 was determined by the number of eligible patients receiving hypofractionated radiation therapy since 2003 when this new treatment was initiated. This number was generated from the OPIS (Cancer Care Ontario) system which catalogues all radiation treatments received at the LRCP. Having identified seven deceased patients and 16 with changed addresses, we mailed out questionnaires to 276 patients, of whom 190 responded with complete questionnaires and signed consent forms to confidentially collect data.

The study investigators obtained the patient's date of birth, treatment (radiation and hormonal treatment details, side-effects) and cancer related information (cancer stage, PSA, Gleason score, PSA/clinical outcome of treatment) from each patient's chart in order to link subject's questionnaire responses to factors related to their cancer and cancer treatment.

Data analysis was performed on the database to assess study population demographics and baseline characteristics. Additional analyses assessed the correlation between the EPIC and PCRT questionnaires; we assessed the internal consistency reliability by employing Intraclass correlation analysis, construct/concurrent validity by calculating the Pearson correlation coefficient (interclass correlation) between PCRT subscales and the subscales of the EPIC and Exit questionnaires. We also assessed the convergent/discriminant validity by calculating the Pearson correlation coefficient (ICC/IEC) between all final subscales of the PCRT. Chi-square was used to compare the demographics and baseline characteristics between our study group and the previous existing data base. Furthermore, in order to correlate the base line factors of our study cohort with their respective EPIC/PCRT domain scores, we performed univariable and multivariable analyses. Additionally, in order to investigate the potential differences in HRQOL between our study cohort (post 2003) and the prior 2003 cohort, an analysis of EPIC domain scores was performed.

6.2 Summary of Methods

1. A package containing a letter of information, a booklet of three questionnaires, and stamped return envelope were mailed out to the patients. One follow-up

phone call was made by the investigator at four weeks to individuals who did not return the questionnaires, to ensure that the individual had received the package and to answer any questions about the study. This phone call was not used as a recruitment tool. The call was only to ensure that the individual received the package and was informed about the study. No other follow-up procedures were used, in order to minimize the impact on individuals who did not want to participate.

2. Data entry into a Microsoft Access database of all study participants' demographics and questionnaire information was completed by June 2008. The study investigator entered the data, ensuring its accuracy by randomly pulling and verifying the entry of 20% of the data.
3. Chart data abstraction included only patients who returned the questionnaire with signed consent form at the LRCP, beginning in October 2008 and ending by November 2008. The entry of the data was verified through randomly double-checking 20% of the data. Of the 190 charts, one was found to be missing, and thus it was excluded from the database.
4. Data entry was completed by December 2008, and identifier information on the database was removed. The Microsoft Access file was then converted using Statistical Analysis Software (SAS) for statistical analysis.

6.3 Study Questionnaires

Two validated HRQOL measurement questionnaires were used for our study. The first questionnaire was the EPIC questionnaire (generic prostate-HRQOL instrument

providing a summary of HRQOL), asked 32 questions with regard to patient's general prostate cancer health, and offered internal consistency >0.80 (Wei et al., 2000). The second validated questionnaire, the PCRT questionnaire, asked 29 questions specifically related to the late toxicity of radiation therapy in the prostate cancer setting, offering a reliability range of 0.4 to 0.7 (Rodrigues et al., 2007).

Furthermore, our Exit questionnaire asked eight questions about participants' bowel, bladder and-sexual function, and overall QOL (see section 6.3.3). Permission was obtained to use the validated EPIC questionnaire before initiating the study protocol (see Appendix 1). All multi-item scale scores for the PCRT/EPIC were transformed linearly to a 0-100 scale, with higher scores representing better HRQOL. PCRT/Late toxicity scores were recorded on the scales zero to four, zero no toxicity and four indicating life threatening toxicity.

6.3.1 The PCRT Questionnaire's Domains and Subscales

1. The GU urinary domain included five subscales defining late toxicity symptoms as follows: 1-Nocturia, 2-Frequency, 3-Dysuria, 4-Hematuria, and 5-Incontinence.
2. The GI bowel domain included four subscales defining the late toxicity as follows: 1-Diarrhea, 2-Pelvic pain, 3-Tenesmus, and 4-Bowel control.
3. The sexual function domain included three subscales, as follows: 1-Impotency, 2-Libido, and 3-Contentment.

4. RTOG GI and GU toxicity scores can be abstracted for the PCRT questionnaire by the use of additional questions imbedded into questions relating to toxicity scales (see Appendix 4).

6.3.2 The EPIC Questionnaire's Domains and Subscales

These include the following:

1. The GU/ urinary domain includes four subscales: urinary function, urinary bother, urinary irritative and urinary incontinence.
2. The GI/ bowel domain includes two subscales: bowel function and bowel bother.
3. The sexual domain includes two subscales: sexual function, and sexual bother.
4. The hormonal domain includes two subscales: hormonal function, and hormonal bother.
5. The satisfaction domain.

6.3.3 The Exit Questionnaire's Domains and Scales

These include the following domains which ranged from one to five - 1 indicated better QOL and 5 indicated poor QOL. There were eight questions in total— 2 questions per domain. The following list is the domain of interest that each question was targeting:

1. The GI QOL current/since completion RT.
2. The GU QOL current/since completion RT.
3. The sexual QOL current/since completion RT.
4. Overall QOL current/since completion RT.

6.4 Subject Recruitment and Enrollment

6.4.1 Study Population

Those patients at the LRCP diagnosed with prostate cancer, treated with EBRT for prostate cancer as per the new institutional standard of 2003 and meeting the eligible criteria were invited to participate in this study by a mailed out questionnaire booklet with a signed return envelope. Patients were asked to send back the questionnaire with the singed consent form. However, patients were asked not to send back the received package in case of refusing to participate. Inclusion and exclusion criteria were determined as follows.

6.4.2. Inclusion Criteria

- Histological diagnosis of prostate cancer.
- Radical radiation therapy hypofractionated (73 Gy in 35 fractions) as per the institutional standard set in 2003.

6.4.3. Exclusion Criteria

- Unable to complete questionnaires in English.
- Under 18 years old.

6.5 Database Creation and Management

6.5.1 Data Collection

Our data package included a letter of information and a booklet containing three different questionnaires (EPIC, PCRT, Exit questionnaire) in order to collect data (see Appendix 1). A patient chart review was then used to retrospectively collect baseline variables data (see Table 1).

6.5.2 Comprehensive Rationale for Retrospective Data Collection

The medical chart's recorded data was collected to link the questionnaire data with each patient's baseline data. Once the database was constructed, the identifiers were removed from the database. Hence, known confounder variables from previous studies, such as coexistent medical conditions; (e.g. diabetes mellitus), location of the cancer, treatment volume, adjuvant treatment (chemo/hormone therapy), age, disease stage, PSA level, surgical information, and Gleason score were collected. The directed acyclic graph (DAGs) provided us with insight into some expected confounding variables and helped eliminate the potential direct effect and controlled confounding by identifying variables, helping to ensure that adjustment of these covariates as potential confounders did not introduce bias to the effect estimate, as well as helping to prevent over control (Bauer G, 2008), (See Figure 2).

6.5.3 Data Measurements

6.5.3.1 Exposure Variable

Exposure variable is the exposure to a minimum of 73 Gy dose or higher of EBRT as an institutional standard set in 2003.

6.5.3.2 Baseline Variables

The baseline variables were identified from the study participants' hospital charts, including their imaging and laboratory results. Information of PSA was collected at three periods of time: baseline before the exposure to radiation, during the RT, and after questionnaire compilation. RTOG-baseline of GI, GU, and sexual comorbidity were collected to assess the changes of RTOG-baseline with study PCRT outcomes (See Table 2). The overlap parameter (see Figure 3) was collected since it is an important predictor factor to our study outcomes as proved by previous studies (Fang et al., 2008; Storey et al., 2000; Wachter et al., 2001).

6.5.3.3 Outcome Variables

Although our primary objective was to assess quality-of-life overall score, we used the EPIC rectal HRQOL score as the main endpoint (for the post and prior 2003 comparison) for three reasons. First, it is clinically relevant to patients and physician. Second, the medical literature showed that the rates of the rectal toxicity have been increased with dose escalation when using non-IMRT techniques. Third and last,

sexual/GU side effects may be less responsive to changes (Fang et al., 2008; Storey et al., 2000; Wachter et al., 2001).

The secondary outcome variables consist of GU urinary and sexual domain scores. Three domains from the PCRT questionnaire (GI/GU/sexual) versus four domains from the EPIC questionnaire (urinary/bowel/sexual/hormonal) were utilized. The PCRT focuses on the symptoms relating to the late effects of EBRT after treatment for prostate cancer, whereas the EPIC questionnaire evaluates both the symptoms and bother. For the PCRT questionnaire we excluded item numbers 16-20, 22 and 23 as being non-useful through item reduction (Rodrigues et al., 2005).

Table 2: Baseline Independent Variables Collected from Participant's Medical Records

Variables	Measurements	Scales
Regional	Postal Code	Discrete
Demographic: Age	Years	Continuous
Imaging TRUS	Volume in cm^3	Continuous
Co-morbidities: Diabetes, BPH, Hypertension, Cardiovascular disease, Hypercholesterolemia.	Yes/No/Unknown Yes/No/Unknown Yes/No/Unknown	Dichotomous
Previous Pelvic cancer Site (Colon, Bladder, others) Treatment: Surgery, Hormone therapy, Chemo-therapy, RT	Yes/No/Not answered Yes/No/Not answered Yes/No/Not answered Yes/No/Not answered	Dichotomous
Laboratory: Biopsy TURP	Yes/No	Dichotomous
N Stage	(N0, NX, N1)	Dichotomous
Gleason Score Overall, Primary, Secondary	From 2-10 From 1 to 5	Categorical Ordinal
T stage	T1a/T1b/T1c/T2a/T2b/T2c/T3a /T3b/T4	Categorical
Blood thinner: Coumadin, Heparin, ASA, Others	Yes/No	Dichotomous
Pre- Treatment PSA PSA- Nadir PSA-Failure(Nadir + 2)	(01 to 10), (11 to 20) >20. ng/ml Lowest PSA after EBRT PSA Nadir +2	Continuous into Categorical
Treatment volume	1= Prostate 2= Prostate &Seminal Vesicles 3=2+Pelvic	Ordinal

Variables	Measurements	Scales
Treatment Sites	Local (yes/no/unknown) Regional (yes/no/unknown) Distant (yes/no/unknown)	Dichotomous Dichotomous Dichotomous
Metastasis: Bone Paraortic nodes	 yes/no/unknown yes/no/unknown	 Dichotomous Dichotomous
Time between questionnaire administration and end of RT	Time (In weeks, months)	Continuous
Overlap values include: (PTV, Rectal, Bladder, PTV-Rectal, PTV-Bladder)	cc	Continuous
Pre questionnaire distress scale	0 to 10	Ordinal
Pre-existing conditions (GI, GU, sexual)	RTOG-Grade from 0 to 4	Ordinal
Acute toxicity conditions (GI, GU, sexual)	RTOG-Grade from 0 to 4	Ordinal
Pre-questionnaire Edmonton Symptoms Assessment scale 11 items	0-10	Ordinal

Figure 2: Direct Acyclic Graph "DAGs" Controlling for Sufficient Confounders

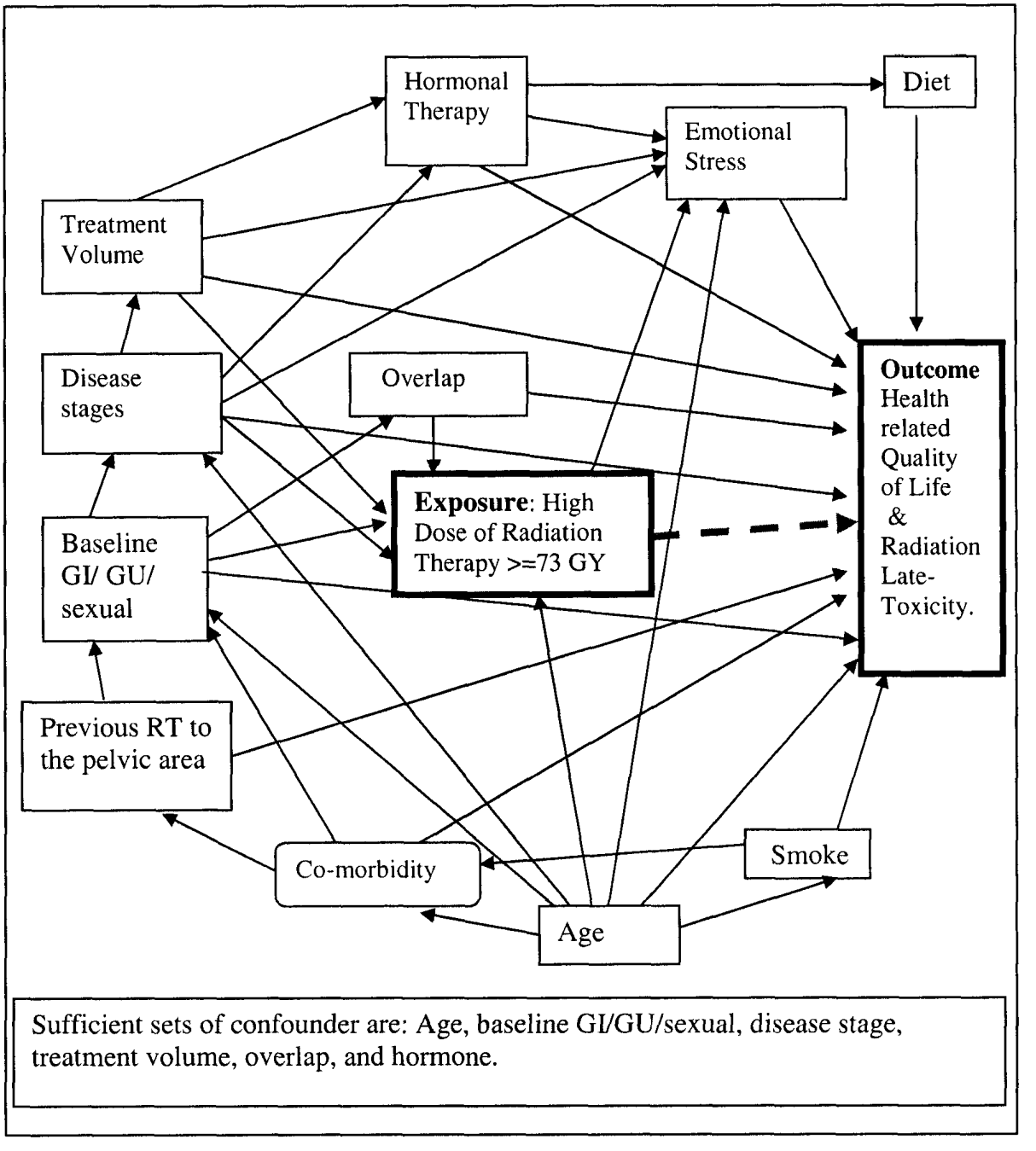
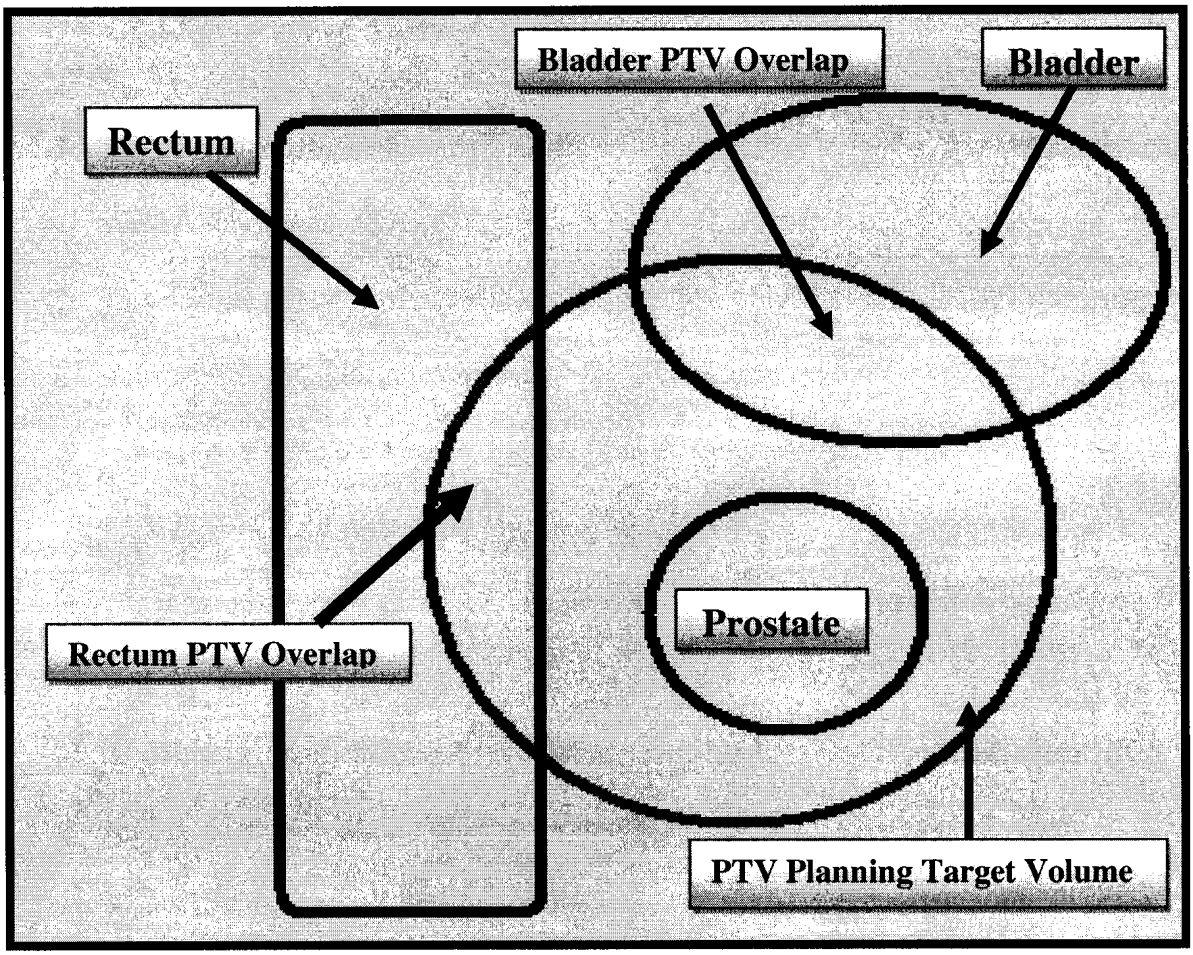


Figure 3: Conceptualization of the Overlaps with PTV Planing Target Volume (Sagittal Slice)



6.6. Treatment of the Data

6.6.1 Summary of Analyses Procedures

- Data analysis proceeded after converting the Microsoft Access file into Statistical Analysis Software (SAS).
- Descriptive analysis of demographics, baseline characteristics, PCRT domains/ subscales, EPIC domain/subscales, and Exit questionnaire for study population.
- Analysis of time between radiation completion and questionnaire completion on PCRT/EPIC/Exit responses.
- Correlation analysis of PCRT vs. EPIC vs. Exit responses to assess convergent and divergent validity.
- Univariable analysis conducted, using our study database for the EPIC and PCRT questionnaires domain. Testing for normality and outliers was performed.
- Transformation of all EPIC domains and only PCRT Sexual domain to improve normality distribution.
- To ensure that the data fitted the multiple linear regression models, diagnostic regression tests assessing confounder followed by statistical adjustment of covariates as potential confounders was performed.
- Multivariable analyses (multiple linear regressions) were used for each HRQOL domain in order to model the relationship between domains score and high radiation dose while adjusting for confounder variables.

- Combination of this study database with the previous existing database was performed to perform a statistical comparison of EPIC domains for hypofractionated versus standard dose radiotherapy.
- Destruction of all paper records at the end of the analysis started in December 2008 and finished in January 2009.

6.6.2 Statistical Analyses

6.6.2.1 Descriptive Analyses EPIC/PCRT/Exit Scores and Baseline Variables

In part, this research study tried to investigate the following questions: Are there statistically significant changes in HRQOL and late toxicity in the current hypofractionated study population compared to non dose-per-fraction escalated patients? Are there significant differences between the EPIC and PRCT questionnaires in the ability to detected differences in the GU, GI, and sexual scales scores in this study population?

To answer these questions, we carried out a descriptive, univariable, and multi-variable analyses. The descriptive analysis utilized the demographic characteristics and predictor variables of the study population. Differences in demographic variables (i.e. age, region) were assessed by computing the mean differences using t-test, and one-way ANOVA for the continuous outcome variables, whereas with categorical predictor multi-way ANOVA was used. Informative frequency tables are presented to provide an overall view of the data. The correlations between the baseline variables (disease stage T, Gleason grade, PSA, TRUS volume, N stage, treatment volume, sites), and HRQOL

outcomes (GU, GI, sexual function) were considered to assess measures of association, the nonparametric Spearman correlation coefficient tests was used for the Exit questionnaire.

We found several useful explanatory variables, and we thus investigated which of these variables would have an effect on the study outcome by fitting a multiple linear regressions model, which in turn helped in predicting the factors that might affect the outcome. The fitted multiple regression models disclosed changes in direction or strength of the estimated effect due to confounder or effect measure modification respectively.

When both the predictor variables and outcome variables were continuous, the correlation coefficient's graphical counterpart "scatter plot" was the numerical description. However, side-by-side box plots were considered as a graphical tool when the predictor variables were categorical. Another approach was to check the pairwise association. For instance, for categorical variables we looked at two-way tables taking each pair of variable in turn (Vittinghoff, 2005).

6.6.2.2 Univariable Analyses

To ensure that data fitted the proposed multiple regression model, univariate analysis took place using SAS univariate procedure. Histograms with box plots were used to report the non-normal errors of distribution. Furthermore, univariate procedure data analysis was used to test for outliers, including extreme and influential, as well as the normality distribution tests (Moments). Variables met the statistical significant

associations ($P < 0.1$) in the univariate analysis, were entered into the stepwise logistic regression analysis (see Figure 4).

6.6.2.3 Multivariable Analyses

Data transformation was used to deal with the extreme outliers or when data are highly skewed. Transformation of the dependent variable should be considered to linearize the association between the predictor variable and the outcome. However, bias in prediction was reduced by including more variables in the model, keeping in mind that inclusion of highly correlated predictors in the model severely degrades the precision of the estimated regression coefficient for some or all predictors. In order to determine if there were enough events to support the number of predictors in the model, we relied on the consistency between the Wald and likelihood ratio for the logistic model when used for the binary variables and then we explored and removed any variables responsible for multicollinearity existence.

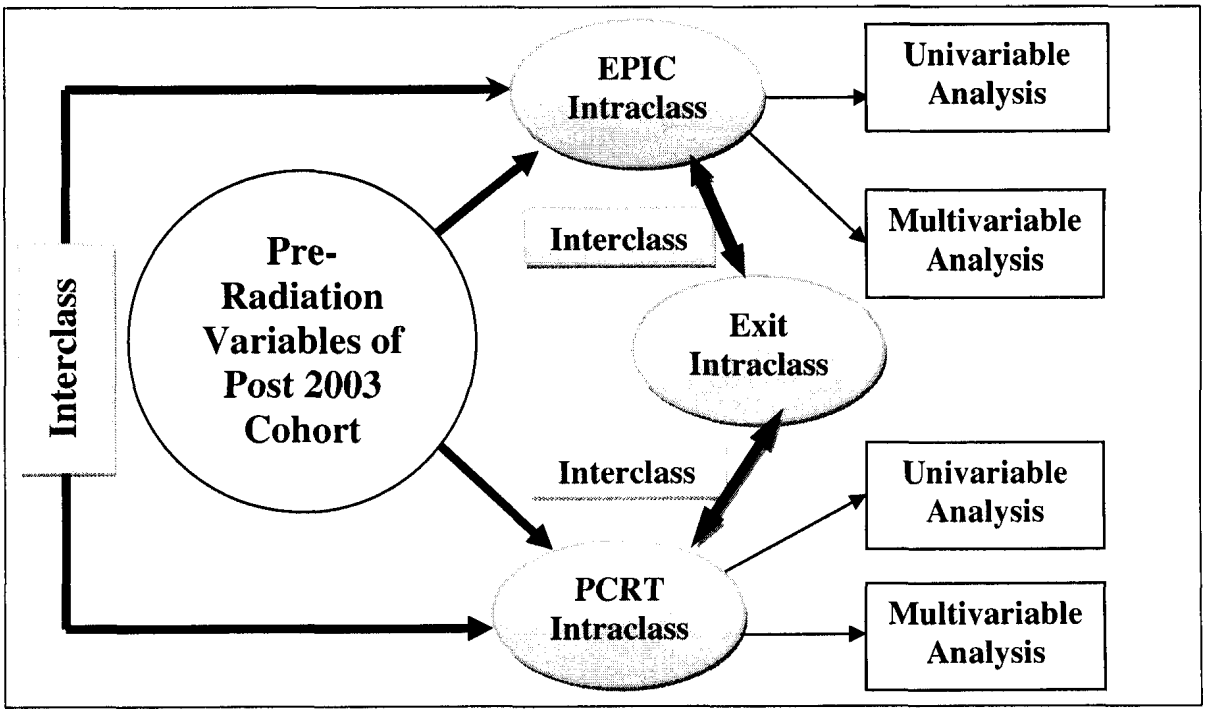
Vittinghoff and Glidden (2005) stated that backward selection has an advantage over forward and stepwise selection procedures. In the backward selection the negatively confounded sets of variables are less likely to be omitted from the model (Sun et al., 1999). Furthermore, Kennedy and Bancroft (1971) preferred backwards elimination to forward selection with regards to model building as well as recommending alpha=0.10 . Therefore, any existing differences between the study populations were explained by running a multiple regression with backward elimination at alpha value of 0.10.

The known confounders from previous studies such as age, disease stage, co-morbidities (cardiac vascular disease/ diabetic/ hypertension/ pelvic cancer/ previous pelvic radiation/ hormone therapy), treatment volume, and target volume overlap, took into account statistical adjustment of covariates as potential confounders. Once interaction was detected in the fitted model, data was stratified if it was determined to be effect measure modifiers. Consequently, determining the effect modifiers, potential covariates, and confounding factors assisted in running the regression models. Multiple linear regressions were used for continuous outcomes and logistic regression for the transformed sexual domain for both EPIC/PCRT as well as, the EPIC hormone domain (see Figure 4).

6.6.2.4 Cross- Validation Analyses

To cross-validate the PCRT we ran the inter/intra-class correlation for PCRT, EPIC, and Exit. Internal consistency was assessed by computing the intra-class correlation. The inter/intra-class correlation (product moment) was used to assess the convergent/discriminant validity and criterion validity among the PCRT scales. We considered a scale valid when scales from the same domain correlated more highly than those from different domains. We assessed the concurrent validity by subjecting each scale to a one-way analysis of covariance (ANOVA) using significant baseline variables determined previously during the study design (see Figure 4).

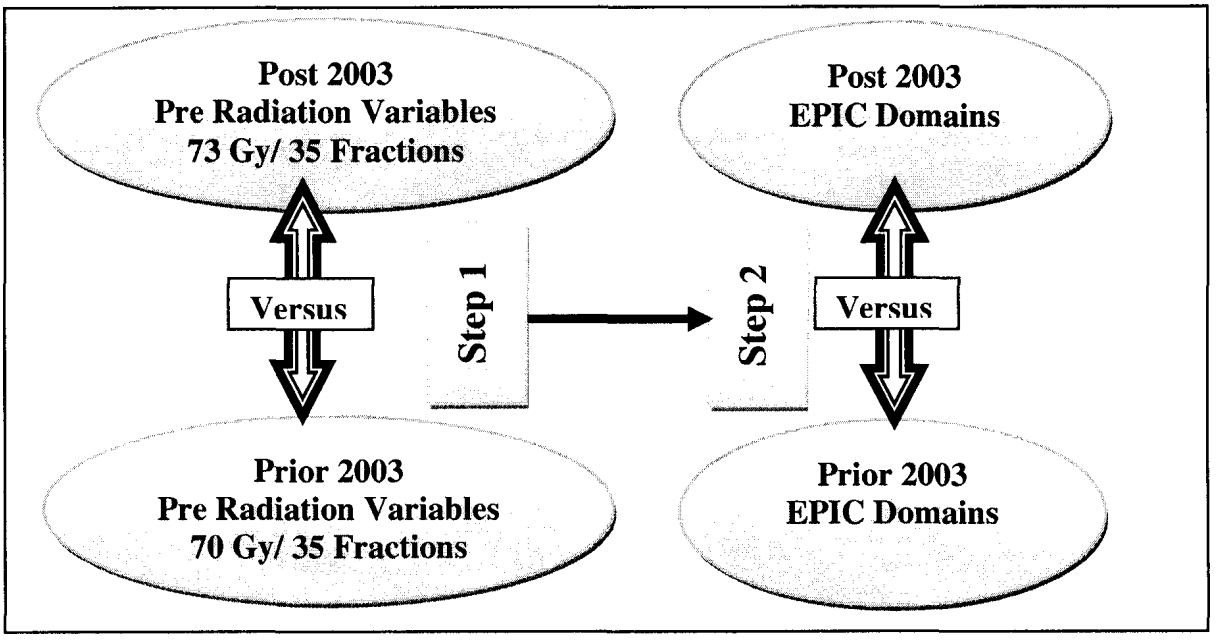
Figure 4: Conceptualization of Post 2003 (73 Gy/ 35 Fractions) Study Cohort Analyses



6.6.2.5 Comparison Analyses

We used both post and prior 2003 EPIC data to perform the comparison between the hypofractionated and the non-hypofractionated PC patients. To test the differences between the prior 2003 EPIC data and post 2003 EPIC data, we used the Chi-square and Fisher test to confirm the comparison results (see Figure 5).

Figure 5: Preliminary Assessment of HRQOL Effect and Dose-Per Fraction Escalation Procedures



6.7 Power and Sample Size Considerations

The study was cross-sectional and thus sample size will be affected by validity, whereas longitudinal studies are more affected by reliability (Hopkins, 1997). The study outcomes (domain scores) may result from the interdependency of the study variables. This in turn leads to more degraded relationships when the variable validity is lower (Hopkins, 1997). We thus needed a larger sample size to fully characterize the variable relationships. The available sample size of 299 was determined by the number of eligible patients who received hypo-fractionated radiation therapy since 2003. This number was generated from the OPIS (Cancer Care Ontario) system which catalogues all radiation treatments that have been received at the LRCP. Further calculation was done using the SISA online calculator with permission (Uitenbroek, 1997) (see Table 3), given the smallest correlation worth detection r1= 0.2 against r2= 0.00 assuming that r2 is the null

hypothesis population correlation. Results of the calculation, included in Table 3, show that, for a two-sided t-test with alpha equal to 0.05 and 80% level of power, a sample size of 194 subjects was required. Considering a potential 50% refusal to participate, the sample needed would be equal to 291 subjects (see Table 3).

Hopkins (1997) suggested the use of the following formula $N=32/ES^2$ to calculate the sample size in a cross-sectional study with valid variables. ES is the smallest clinically meaningful differences (equivalent to effect size) worth detection. Applying this formula with a 95% confidence level and alpha equaling 0.05, and for type II errors 20%, given ES=0.4 we will need ($N=32/0.4^2$) 200 subjects in both groups. Allowing a 50% loss to non-participation, we need 300 potential subjects. It is worth noting here that, for future work, we have 323 subjects from the control standard database to match the available 190 study population sample. Since the primary endpoint is the EPIC rectal HRQOL score, it is therefore worth calculating the sample size using the PCRT information, as it is has been designed to assess late toxicity of the EBRT for prostate cancer. Using the SISA sample calculation (Uitenbroek, 1997) will ensure the power of our available sample. Nevertheless, given a mean of 90, with 95% confidence level at alpha=0.05 and the power of 99%, conceding four points as clinical significant differences and a standard deviation equal to 10 with a double sided t-test, a sample size of 197, plus 50% loss to follow up, which is equal to 296 subjects, was required. We were able to invite 276 patients to participate with only 69% response, our sample size for the total analysis is 190. This sample size is more than sufficient given verification received from Dr. John T. Wei, designer of the EPIC questionnaire and based on the number of EPIC domains had been used as primary end points (see Appendix 3). Thus,

multiple approaches to estimates of sample size confirm that our study population would be sufficiently large to meet our primary objectives.

Table 3: SISA Calculation: Result for two sided t-test given 0.2 correlation

	Power	
Alpha	**80%**	**90%**
0.1	154	211
0.05	194	258
0.01	288	365
0.001	419	511

6.8. Implementation and Timeline

All data and data editing was completed within two years of this project's initiation in August 2007. With data management and analysis ongoing in December 2008 and January 2009, the intent was to attack each specific aim sequentially and devote the last six months of our project to final data quality assurance, repetition of indeterminate results, and writing final reports.

6.9. Study Strength and Limitations Summary

6.9.1. Study Strength

Every study has its own strengths which form a solid foundation for a reliable project. During the past five years, two questionnaire mailings were sent to patients to

capture the effects of using two different radiation doses. Prior to 2003 patients received 70 Gy/35 fractions (BED=117 Gy); whereas after 2003 patients were treated with 73 Gy/35 fractions (BED=129 Gy) which is an almost 6% increase in biological equivalent dose. In addition, both cohorts were treated in a standardized fashion as regards to beam arrangement and used computerized treatment planning with the exception that the post 2003 cohort received the higher dose through a simultaneous boost technique.

As far as patients with prostate cancer are concerned, important results showing the effect of higher doses upon quality of life and symptoms from late toxicity could meaningfully be used in determining in advance the best treatment modalities to ensure optimizing quality of life for the patient. An example of using a decision aid was reported in 2006, the JCO published a study of comparing two RT dose levels (70 Gy versus 74 Gy). In that study, therapeutic ratio (differences in tumour control versus toxicity) was presented to assist patients choosing an RT regimen. They found that most patients in the study chose the lower radiation dose (70 Gy) (Tol-Geerdink van et al, 2006) when all cancer control and toxicity information was provided to the patient.

Given that prostate cancer is increasing in prevalence among men, this research paper will enrich the field with valuable information as it depicts the relationship between a prostate cancer patient's quality of life and late toxicity effect of radiation. The research also provides an opportunity for further study into the field. All these results can pave the way to new discoveries that decrease the effect of late toxicity when implementing radiation therapy. Furthermore, significant available data from hospital medical charts offer the possibility of conducting information to compare prostate patients over three

years of follow-up. This study provided novel findings regarding the impact of higher radiation doses on the emergence of late toxicity and quality-of-life for men with prostate cancer. Since high dose EBRT will be more readily available over the coming years, this study helps to establish the database for further studies, both locally and internationally. It could also inspire further research highlighting what may be the beneficial effects particular to EBRT.

6.9.2. Study Limitations

Since the administrative data (chart review for baseline factors) in both studies our study and prior to 2003 were not derived specifically for the sake of this research project, this study may be subject to both random and systematic errors. To begin with, the chance of confounding is presented by observational studies that depict quality-of-life as it is not feasible to randomly choose subjects for radiation (there were no randomization for radiation or dose use). In addition, residual confounding can also be caused by not having an accurate treatment history and not being able to adjust for adherence in the final outcomes.

Furthermore, our study is subjected to biases such as selection bias because subjects were able to choose their own therapy. The selection bias is neither intrinsic nor fully correctable in cross-sectional design. However this is offset somewhat by the fact that radiation dose of treatment technique was governed by a standardized protocol (class solution) over both time periods that would have helped minimize variability in treatment.

In addition, the investigator was neither blinded nor had control over exposure or outcome assessment. The investigator could only collect data by chart abstraction of medical history recorded by other clinicians which may not be accurate nor complete (measurement bias). This limitation was minimized by confirming doctor's notes with results from lab tests, x-ray tests, and pathological tests.

Another possible limitation is that self-reporting of symptoms and treatment history in observational epidemiologic studies can be inaccurate because of a patient's limited ability to retain and recall past symptoms or experience. To minimize the recall bias, patients were asked to register their past four week's experiences from time of receipt of the questionnaire. Recall bias could still be in play in that significant toxicity more have occurred or resolved before four weeks from the survey time and would not be captured. As well, our results could be distorted by epidemiologic biases; our study is based on patients with potentially significant co-morbid illnesses. Moreover the study was subjected to reporting bias since that the respondent patients might be different from the non respondent.

In addition, the study design created an inability to provide an accurate causal temporal order. Thus, a precise evaluation cannot be accomplished in this study because of the fact that merely one factor is being examined, offering only a snapshot of the patient's health through the former year. For this reason, no one can accurately assure that the outcome was a result of being exposed to an escalated dose of radiation. The previous study (pre-2003) may prevent us from answering all pertinent questions because it was designed with another purpose in mind (i.e. to assess the HRQoL of prostate cancer

patients with the EPIC questionnaire). Thus, the results of this study as pertains to correlations between HRQOL outcomes and radiation treatment parameters should be considered exploratory and hypothesis generating.

7.0 Human Subjects Consideration

As stated earlier, subjects in our study were all patients treated at the LRCP, all diagnosed with prostate cancer, and all treated with EBRT in the Department of Radiation Oncology. All individuals were contacted prior to participating and the research study was explained in a postal information letter. All individuals were told that their participation was completely voluntary and that they could withdraw from the study at any time. A consent form clearly outlining the study, including time commitments and any risks, was reviewed by each participant. Signed informed consent was obtained from every participant, and a copy provided to each participant (See Appendix 1). A final report copy will be made available to any requesting participant.

7.1 Risks and Benefits of the Research

Risk is minimal in this study as it was in the pre-2003 study, given no medical intervention was being proposed. Questionnaires included questions regarding gastrointestinal, genitourinary, and sexual function. The study participants were informed that participation was voluntary and that they could answer all, some or none of the questions. No direct benefit to the patient was to be expected from this study. The benefit to society was to assess whether our dose escalation in prostate cancer radiation has led to extra toxicities related to that change in treatment policy. In addition, the further validation of the PCRT instrument was a main goal of this investigation.

7.2. Privacy & Confidentiality Issues

This study and the pre-2003 study included the following details:

- Full or partial name or initials.
- Full or partial date of birth or death.
- Institutional / Hospital chart or record number.
- Initial data collection, including patient name, date of birth (to calculate age), and LRCP record number ("patient's demographic information").

Any gathered information was purely for research purposes. Confidentiality was an obligatory factor in this research. All copies of questionnaires were stored in a safe place, and data saved on computer contained no personal data. Confidential passwords were provided for the study personnel to access this information. The information was depicted in a general form without mentioning any personal details.

8.0 Results

8.1 Overview

Section 8.2 provides the descriptive analysis results including the pre-treatment factors, pre-existing co-morbidities, and questionnaires HRQOL endpoints. We received 190 completed questionnaires (EPIC, PCRT, and Exit) out of 276 mailed questionnaires, thus our study response rate was 69%. The participant mean age was 76 years, ranging from 53 to 84. The mean interval time between end of RT and questionnaires completion was 852 days. According to risk distribution categories our study population were at low risk (22%). 43% of the participents received RT to prostate and seminal vesicles and 35% received whole pelvic RT.

The EPIC questionnaire endpoints GU, GI, sexual, hormonal, and satisfaction mean scores were 85, 84, 23, 85, and 82 respectively. The PCRT questionnaire endpoints GU, GI, and sexual mean scores were 66, 84, and 39 respectively. The Exit questionnaire endpoints GU, GI, and sexual were good, good, and poor respectively (see Section 8.2.3).

The cross-validation analysis results for the interclass correlation comparing EPIC/PCRT domains ranged from 0.50-0.88 (see section 8.3), while the intraclass correlation for EPIC and PCRT domains ranged from 0.16-0.43 and 0.23-0.30, respectively (see section 8.4). Section 8.5 provides the detailed results of the univariable analysis. All EPIC domains required either ASSR (GI/GU) or dichotomous (S/H)

transformations for UV/MV analyses while no such transformations were necessary for PCRT domains.

Section 8.6 provides results of the multivariable analysis; we found significant associations between pre-treatment urinary toxicity levels and planning target volume-bladder overlap for PCRT/GU domain scores. In comparison with lower dose cohort, no differences in GI/GU/S/H EPIC scores were observed (see Section 8.7).

8.2 Descripitve Analyses of The Study Population

8.2.1 Pretreatment Factors

The study sample charecteristics are provided in Table 4. The mean age of the study population is 76 years, with ages ranging from 53 to 84. The TRUS volume mean was 51cc with range (18-238). Pre-treatment PSA mean was 12.5 ng/ml range (0.01-77.5). The mean interval time between end of RT and EPIC/PCRT/Exit completion was 851.6 days with range (212-1454). PTV and rectal overlap is an estimate of the percentage volume of that organ included in the high dose region of treatment and as such, it was postulated overlap volumes may correlate with subsequent toxicity and quality of life. PTV-Bladder overlaps mean was 18.27cc with range (6.96-35.8). While PTV-Rectal overlap mean was 8.6 cc with range (2.8-25). PTV volume, bladder volume, and rectall volume means were 153, 70, and 162 respectievly. The majority of our study population distribution according to T stage were T1, T2 with relative frequency of 36%, 53% respectively, and only 12 % , 1% were T3,T4 respectively (see Table 5 and Figure 3). Regarding baseline GI/GU/sexual comorbidity according to RTOG-toxicity grade, patient medical records

documented that 89%, 36%, and 74% respectively did not have pre-existing GI, GU, and sexual comorbidity. However, 48 % reported mild baseline-GU comorbidity, 16% reported mild baseline sexual morbidity, and 10% experienced mild baseline-GI morbidity. Only one patient reported having life-threatening GI comorbidity due to rectal bleeding (see Table 6).

Table 7 provides frequency and relative frequency of the study population according to treatment site, hormone therapy, Gleason grade, T/N stage. Most study patients received treatment to prostate and seminal vesicles with a prevalence of 59 %. A small portion (26%) received additional whole pelvic treatment. This segment of the study sample would have higher probability to develop GI toxicity due to the large area of treatment. The distribution of the study population according to Gleason score 2 - 6 was 36%, Gleason score 7 was 41%, and Gleason score 8-10 were 23%. Of 189 patients, 25 had received TURP (13 %). Thus the percentage of patients with low risk, intermediate risk, and high risk were 22%, 43%, and 35% respectively according to the Canadian Consensus Stratification (see Table 5). While the majority of participants (71%) had no regional lymph node metastasis (by CT, N0), 24.9% of the patients had no regional lymph node assessment (Nx). Only 4 % had metastasis in regional lymph nodes. Moreover, 47 % of participants used blood thinner (68.5% ASA, 19% Coumadin, and 8.99% Heparin). Five out of 189 patients had had a PSA failure (3%), with 1% clinical failure. Of the study population, 96 % are alive with no evidence of relapse, and 4 % had relapsed. Three percent of the patients had a contraindication to EBRT because they either had diverticular disease or were using testosterone replacement; therefore, patients were asked to stop the medications before delivering the EBRT.

Although 52.4% of participants had received hormonal therapy, 96.0% of them received neoadjuvant hormone therapy (62% for 3 months), 67.7% received adjuvant hormone therapy (37% for 24 months, 25% for 36 months), and 60.6% received concurrent hormone therapy (56.7% for two months). Furthermore, 18.0% of the study cohort received hormonal therapy at the time of the questionnaire.

8.2.2 Prevalence of Pre-existing Co-morbidity among Study Cohort

More than half of study participants had hypertension (55.0%). The cardiovascular disease prevalence was 40.7%. The hypercholesterolemia prevalence was 28.0%. Other co-morbidities revealed were diabetes, BPH, and previous pelvic cancer (15.9%, 9.0%, and 9.0% respectively). To evaluate the baseline GI comorbidity, the RTOG toxicity scale was used yielding 22 out of 184 cases had baseline GI disturbance. The baseline RTOG toxicity GU co-morbidity was significantly higher at 123 out of 189 with prevalence of 66.9%. The baseline sexual co-morbidity was 51 with prevalence of 27.7%. Patient's distress scores were collected prior to questionnaire administration at their last clinical follow-up. Results of baseline GU were consistent with expectation of symptoms of prostate enlargement (BPH) in this age demographics. Results showed that 62 % (89/143) did not suffer any emotional stress, 25 % (36/143) slightly distressed, 8 % (11/143) had moderate distress, and 5% (6/143) were highly distressed.

Table 4: Pre-Treatment Patient Demographics & Characteristics

Variables	N	Mean	Std Dev	Min	Median	Max
Age	189	75.77	5.54	53.00	77.00	84.00
TRUS Volume (cm^3)	167	51.15	31.52	18.00	42.00	238.0
PSA Pre-Treatment (ng/ml)	189	12.48	12.07	0.01	8.79	77.50
PSA Nadir (ng/ml)	188	0.70	1.18	0	0.18	11.50
PSA- at Failure (ng/ml)	5	6.59	3.19	2.030	6.50	10.90
PSA Prior to Questionnaire (ng/ml)	188	0.59	0.95	0	0.20	7.38
Most Recent PSA (ng/ml)	188	0.54	1.07	0	0.24	10.90
Biopsy Gleason Score Distribution	188		1.01	4.0	7.0	10.0
Interval Between End of RT & EPIC (Days)	189	851.6	335.0	212.0	896.00	1454
PTV Volume (cm^3)	96	153.13	44.56	57.46	146.65	312.0
Rectal Volume (cm^3)	96	69.74	47.17	27.86	61.86	482.7
Bladder Volume (cm^3)	96	161.86	82.67	45.70	144.99	467.7
PTV- Rectal Overlap Volume (cm^3)	96	8.55	3.21	2.81	7.98	25.05
PTV- Bladder Overlap Volume (cm^3)	96	18.27	7.30	6.96	17.84	35.75
N= number of observations, Min= Minimum, Max= Maximum. Std Dev= Standard deviation.						

Table 5: Risk Stratification among Study Population

Risk Categories	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Low risk	42	22.22	42	22.22
Intermediate	81	42.86	123	65.3
High risk	66	34.92	189	100

Table 6: Stratification of the Pre-existing Co-morbidity Prevalence's (GI/GU/Sexual) by RTOG Toxicity Scale

Grade	Baseline-GI Frequency (%)	Baseline-GU Frequency (%)	Baseline-Sexual Frequency (%)
(0) None	163 (88.59%)	66 (35.87%)	136 (73.91%)
(1) Mild	18 (9.78%)	88 (47.83%)	29 (15.76%)
(2) Moderate	2 (1.09%)	26 (14.13%)	18 (9.78%)
(3) Severe	-	3 (1.63%)	1 (0.54%)
(4) Life Threatening	1 (0.54%)	1 (0.54%)	-

Table 7: Study Cohort Treatment and Risk Stratification Variables n=189

Variable	N	Frequency	Percent
Treatment volume	189		
Prostate only		27	14.29
Prostate and Seminal Vesicles		112	59.26
Prostate and Seminal Vesicles and Pelvic		50	26.46
Hormonal Therapy	189		
Neo-adjuvant/adjuvant/concurrent		99	52.38
Biopsy Gleason score distribution	188		
2-6		68	36.17
7		77	40.96
8-10		43	22.87
Clinical T-stage distribution	189		
T1		64	33.86
T2		101	53.44
T3		22	11.64
TX		2	1.06
N-stage	189		
N0		135	71.43
N1		7	3.70
NX		47	24.87

8.2.3 Questionnaires HRQOL Outcomes Descriptive Analyses

Tables 8 to 10 present the descriptive statistical analyses of the EPIC, PCRT, and Exit domains scores respectively. The number of survey booklets returned was 190, giving a response rate of 69% (190/276). Out of these returned booklets, 190, 190, and 186 patients answered the EPIC, PCRT, and Exit questionnaires respectively. There was 9% missing (un-answered) questions in the EPIC questionaire portion of the survey booklet. Similarly, there was 4.3% missing (un-answered) questions in the PCRT questionaire portion of the survey booklet, and 4.0% for the Exit questionaire. For EPIC/PCRT/Exit single items response frequencies, please see Appendix 4.

EPIC-Domains and Subscales

The EPIC domains GU, GI, sexual, hormonal, and satisfaction mean, standard deviation, and 95% CI scores were 85±13 (83.27 to 87.09), 84±16 (81.77 to 86.43), 23±21(18.65 to 24.89), and 85±14 (83.29 to 87.35), respectively. (See Table 8) Higher scores indicate better QOL for a given domain. The highest urinary subscale mean and standard deviation was 92±12 for urinary function, indicating better HRQOL, and the lowest was 81±18 for urinary bother. Sexual subscales showed patient HRQOL scores with average and standard deviation of 14±19.4 and 41±38 for sexual function and sexual bother, respectively.

PCRT Domains and Subscales

The PCRT domains GU, GI, and sexual mean, standard deviation, and 95% CI

scores were 66±15 (63.92 to 68.28), 84±14 (81.5 to 85.8), and 39±22 (36.15 to 42.63), respectively (see Table 9).

Exit Scales

The average stated response for current QOL in terms of GI, GU, and sexual as poor were good, good, and poor, respectively. Overall, the QOL average was good (see Table 10). The Exit questions were able to capture a range (1-5) of answers for all eight questions.

RTOG Late Toxicity Grades

Table 11 provides an GI/GU-late toxicity grade descriptive analysis. The prevalence of PCRT/GI grade (none, mild, moderate, severe, and life threatening) are 42%, 46%, 3%, 6%, and 3% respectively. The prevalence of PCRT/GU-grade (none, mild, moderate, severe, and life threatening) are 2%, 28%, 59%, 10%, and 1% respectively. These probabilities showed that, for the GI-grade, the highest distributions were among grade none (42%) and mild (46%). Unlike the GI-grade, the GU-grade highest distribution was found in the moderate grade at 59%.

Table 12 provides the RTOG late toxicity grade and descriptive analysis from the PCRT questionnaire. The median of the GI-grade is 1; the GU-grade median is 2. Both ranged from minimum 0 to maximum 4 with 190 responses. (See Tables 11-12).

Table 8: EPIC Domain-Specific Summary and Subscale Scores (N=190)

HRQOL Domains	Scoring Min	Mean score	Std Dev	Scoring Max	Upper Qua	Lower Qua	N	Med
HRQOL Domain Summary Scores								
Urinary	41.67	85.18	12.93	100	95.83	78.99	176	87.8
Bowel	25	84	15.79	100	96.43	75.89	176	89.3
Sexual	0	21.77	20.68	86.54	31.09	5.77	171	16
Hormonal	36.36	85.32	13.69	100	97.73	77.27	175	88.6
Domain-specific HRQOL Subscales								
Urinary subscales								
Urinary Function	41.75	91.72	11.98	100	100	88.40	190	100
Urinary Bother	28.57	80.57	15.64	100	92.86	71.43	175	83.3
Urinary Irritative	35.71	84.76	11.87	100	92.86	78.57	175	87.5
Urinary Incontinence	8.25	87.71	18.05	100	100	79.25	175	100
Bowel subscales								
Bowel Function	35.71	86.26	13.69	100	96.43	78.57	186	89.3
Bowel Bother	14.29	82.08	19.65	100	96.43	71.43	175	89.3
Sexual subscales								
Sexual Function	0	13.8	19.39	80.56	22.22	0	169	5.56
Sexual Bother	0	40.47	37.80	100	75	6.25	162	25
Hormonal subscales								
Hormonal Function	20	81.64	16.52	100	100	70	175	85
Hormonal Bother	33.33	87.92	13.42	100	100	79.17	175	91.7
Satisfaction								
Satisfaction	0	81.78	23.64	100	100	75	175	75

Min=Minimum, Max=Maximum, Std Dev= Standard Deviation, Med= Median, Qua= Quartile

Table 9: PCRT Domain-Specific Summary and Subscale Scores (N=189)

HRQOL Domain Summary Scores	N	Mean Score	Std Dev	Score Min	Lower Qua	Med Score	Upper Qua	Score Max
PCRT-GI	169	83.64	14.3	33.3	77.08	85.7	95.83	100
PCRT-GU	189	66.10	15.3	6.25	56.25	68.8	75.00	100
PCRT-Sexual	171	39.39	21.6	0	25.00	40.0	55.00	100
Dysuria (S) How often pain during urination?	187	94.52	14.4	0	100.0	100	100	100
Dysuria (S) Severity of pain on urination?	37 (i)	90.54	19.0	25	100.0	100	100	100
Dysuria (B) Upset in daily activities has pain on urination caused?	52 (i)	84.14	21.0	25	75.00	100	100	100
Hematuria (S) Blood in urine?	186	98.79	5.38	75	100.0	100	100	100
Hematuria (B) Upset urine in blood cause?	187	99.33	4.80	50	100.0	100	100	100
Incontinence (S) Amount of incontinence pads used per day	182	97.53	11.2	0	100.0	100	100	100
Incontinence (B) Upset in daily activities has use of incontinence pads?	182	97.25	11.4	25	100.0	100	100	100

S= Symptoms; B= Bother. Min=Minimum, Max=Maximum, Std Dev= Standard Deviation, Med= Median. Qua=Quartile. i= patients were asked to skip these questions if they answered no to previous question

Table 10: Characteristics of Exit Domain-specific Summary and Subscale Scores

Exit-HRQOL Domains	N	Mean score	St Dev	Median score	Score Min	Score Max
(Q1): My current QOL in terms of bowel movement.	186	2.50	0.999	2.5	1	5
(Q2): Since completion of the prostate RT, my QOL in terms of bowel movement.	186	3.15	0.754	3	1	5
(Q3): My current QOL in term of urination.	186	2.68	0.808	3	1	5
(Q4): Since completion of the prostate RT, my QOL in terms of urination.	186	3.03	0.788	3	1	5
(Q5): My current QOL in term of sexual function.	174	4.31	0.929	5	1	5
(Q6): Since completion of the prostate RT, my QOL in terms of sexual function.	169	3.90	0.792	4	2	5
(Q7): My overall QOL right now.	186	2.55	0.889	3	1	5
(Q8): Since completion of the prostate RT, my overall QOL.	186	2.93	0.781	3	1	5

Table 11: Frequency and Prevalence of RTOG Late Toxicity Grades Abstracted from PCRT Questionnaire

Grade	GI-Grade		GU-Grade	
	Frequency (%)	Cumulative Frequency (%)	Frequency (%)	Cumulative Frequency (%)
(0) None	79 (41.58)	79 (41.58)	3 (1.58)	3 (1.58)
(1) Mild	88 (46.32)	167 (87.89)	54 (28.42)	57 (30)
(2) Moderate	6 (3.16)	173 (91.05)	112 (58.95)	169 (88.95)
(3) Severe	12 (6.32)	185 (97.37)	19 (10)	188 (98.95)
(4) Life Threatening	5 (2.63)	190 (100)	2 (1.05)	190 (100)

Table 12: RTOG Late Toxicity Grade "Descriptive Statistics Summary"

Variable	N	Median	Std Dev	Minimum	Maximum	Sum
GI-Grade	190	1	0.954	0	4	156
GU-Grade	190	2	0.674	0	4	343

8.3 Cross-Validation Analyses

8.3.1 Convergent/Discriminant Validity of PCRT Questionnaire

Inter-Class Correlation Coeffecients

The validity analysis conducted by calculating the interclass correlation coeffecients among the three questionnaires (EPIC-PCRT/EPIC-Exit/ PCRT-Exit) offered a Probability>[*r*] under the null hypothesis H0=0. Results are included in Tables 13 through 15 respectively, with the EPIC-grade/ PCRT-grade/ Exit-grade shown in Tables 16 through 18.

Table 13 presents the correlation between the PCRT scales and the 10 EPIC scales. Vittinghoff et al. (2005) stated that Pearson Correlation Coefficint equal to 0.7 and higher is considered to be a strong linear association. These correlation matrixes indicate significant evidence of a strong and moderate linear association between PCRT GI, GU, sexual domains and EPIC domains as follows.

The PCRT GI Domain association with EPIC/ bowel was the strongest positive linear association's *r* at alpha equal to 0.05 with *r* value of 0.9 which demonstrates an almost perfect correlation. As well, the PCRT/GI and EPIC/ bowel bother have significant strong association with almost perfect correlation of 0.9. Moreover, the association between the PCRT/GI and EPIC/ bowel function correlation of 0.7 indicates significant evidence of strong positive linear association. The PCRT GI Inter-class Correlation Coefficients linear association strength ranged from the lower value of correlation of 0.18 (EPIC-sexual) to the higher value of correlation of 0.9 (EPIC-bowel).

The above strong correlations of the GI organ system indicate that scales tend to converge between the two questionnaires. On the other hand the scales belonging to different organ systems tend to diverge or in other words to correlate less as may be expected (i.e. the correlation PCRT GI with EPIC GU, and PCRT GI with EPIC sexual ranged from 0.2-0.3 and 0.1-0.2 respectively).

The PCRT GU Domains association with both the EPIC/urinary, EPIC/urinary bother are equal to 0.7 for each association, indicating significant evidence of strong positive linear association at alpha=0.05. The moderate direct linear associations at alpha equal to 0.05 are 0.5 between the PCRT/GU and EPIC/ urinary function, 0.6 for the PCRT/GU and EPIC/urinary irritative, and 0.6 for the PCRT/GU and EPIC/urinary incontinence association. The PCRT/GU and EPIC domains Pearson Correlation Coefficients linear association strength ranged from the lower value of correlation of 0.23 with EPIC-sexual function to the higher value of correlation of 0.71 (EPIC-GU). The above moderate to strong correlations of the GU organ system indicate that scales tend to converge between the two questionnaires. But scales belonging to a different organ system tended to diverge or in other words to correlate less (i.e. the correlation of PCRT/GU with EPIC/sexual, and PCRT/GU with EPIC/hormonal ranged from 0.1-0.2 and 0.2-0.3 respectively).

The PCRT Sexual Domains provide significant evidence of a strong direct association with the EPIC-sexual domain equal to (0.7) at alpha equal to 0.05. PCRT-sexual domain and EPIC-sexual function $r = 0.5$ indicate significant evidence of moderate direct linear association, at alpha=0.05. PCRT-sexual domain and EPIC-sexual

bother correlation of 0.6 also indicate significant evidence of more than moderate direct linear association, at alpha=0.05. The Correlation Coefficients association strength of the PCRT-sexual domain with EPIC-domains ranged from the lower value of 0.18 (EPIC-bowel) to the higher value of correlation of 0.7 (EPIC-sexual). The above moderate to strong correlations of the Sexual organ system again indicate that scales tend to converge between the two questionnaires, while scales belonging to a different organ system tend to diverge or to correlate less (i.e. the correlation of PCRT-sexual and EPIC-hormonal ranged from 0.1-0.2).

8.3.2 Convergent/Discriminant Validity of Exit Questionnaire

Table 14 indicates significant evidence of strong and moderate reverse linear association between EPIC Domains and the Exit questionnaire. The correlation coefficients for the EPIC-bowel Bother, EPIC-bowel, and EPIC-bowel function with the Exit-bowel current were $r = -0.7$, $r = -0.68$, and $r = -0.57$ respectively, indicating a significant evidence of strong and moderate reverse linear association at alpha=0.05 ($P<.0001$), respectively. Since the lowest score on the Exit questionnaire is an indication of better HRQOL, this statistically significant strong reverse association shows that, with the higher scores in the EPIC-GI domain (indication of better QOL) there will be a decrease in the Exit score for patient's current QOL in terms of bowel movement.

The correlation coefficients for the EPIC-bowel bother, EPIC-bowel, and EPIC-bowel function with the Exit-bowel changes since RT were -0.57, -0.57, and -0.48 respectively. This significant evidence of strong and moderate reverse linear association

at alpha=0.05(P<.0001) respectively strengthen the potential validity of the Exit questionnaire. These statistically significant reverse associations show that, with the higher scores in the EPIC-GI domain, there will be a decrease in patient QOL in terms of bowel movement following completion of prostate RT as shown by the existing validated HRQOL questionnaires.

The correlation coefficients for the EPIC-Urinary, EPIC-urinary bother, and EPIC-urinary function, and the Exit-urinary current are r =-0.624, -0.62712, and -0.4593 respectively. These indicate significant evidence of moderate reverse linear association at alpha=0.05 (P<.0001). These statistically significant moderate reverse associations prove that, with the higher scores in the EPIC-GI domain there will be a decrease in patients QOL in terms of urination.

Table 15 shows significant evidence of moderate to strong reverse linear association between PCRT Domains and Exit questionnaire at alpha= 0.05 (P<.0001), as follows: PCRT-GI and Exit Q1 alpha=0.05 (P<.0001) r = -0.648. This offers significant evidence of a moderate to strong reverse linear association. PCRT-GI and Exit Q2 P<.0001 r = -0.565, offers significant evidence of a moderate reverse linear association. PCRT-GU and Exit Q1 P<.0001 r = -0.431, offer significant evidence of a low to moderate reverse linear association. PCRT-GU and Exit Q3 P<.0001 r = -0.540 also offer significant evidence of a moderate reverse linear association, as do PCRT-Sexual and Exit-sexual current P<.0001 r = -0.599. PCRT-Sexual and Exit Q6 P<.0001 r = -0.431, offer significant evidence of low to moderate reverse linear association. The correlation

coefficient for the EPIC-sexual and Exit sexual QOL since completion RT ranged from 0.3-0.4 with $P < .0001$.

Table 13: Interclass Correlation between EPIC-PCRT HRQOL Summary Scores. Pearson correlation coefficients Prob > [r] under H0: Rho=0. Number of observations=187

EPIC Domains			
	GI–PCRT *r.* (N/*P*)	**GU–PCRT** *r.*(N/*P*)	**Sexual– PCRT** *r.* (N/*P*)
Urinary	0.297 (155, P= 0.002)	**0.717** (176, P<.0001)	0.311 (159, P<.0001)
Urinary Function	0.178 (169, P=0.02)	**0.523** (189, P<.0001)	0.258 (171, P=0.007)
Urinary Bother	0.321 (154, P<.0001)	**0.727** (175, P<.0001)	0.291(158 P=0.0002)
Urinary Irritative	0.296 (154, P=0.0002)	**0.647** (175, P<.0001)	0.238 (158, P=0.003)
Urinary Incontinence	0.184 (154, P=0.0221)	**0.593** (175, P<.0001)	0.260 (158, P=0.001)
Bowel	**0.877** (155, P<.0001)	0.401 (175, P<.0001)	0.242 (158, P=0.002)
Bowel Function	**0.742** (165, P<.0001)	0.353 (185, P<.0001)	0.179 (167, P=0.021)
Bowel Bother	**0.882** (154, P<.0001)	0.373 (174, P<.0001)	0.250 (157, P=0.002)
Sexual	0.179 (153, P=0.02)	0.266 (170, P=0.0004)	**0.667** (159, P<.0001)
Sexual Function	0.135 (150, P=0.099)	0.231 (169, P=0.0025)	**0.497** (160, P<.0001)
Sexual Bother	0.164 (146, P=0.048)	0.216 (161, P=0.006)	**0.623** (151, P<.0001)
Hormonal	0.289 (154, P=0.0003)	0.353 (174, P<.0001)	0.228 (158, P=0.004)
Hormonal Function	0.211 (164, P=0.007)	0.335 (184, P<.0001)	0.185 (168, P=0.016)
Hormonal Bother	0.313 (156, P<.0001)	0.325 (176, P<.0001)	0.269 (159, P=0.001)
Satisfaction	0.259 (167, P=0.0007)	0.173 (187, P=0.018)	0.120 (169, P=0.119)

Table 14: Interclass Correlation between EPIC-Exit HRQOL Summary Scores
Pearson correlation coefficients. Prob > [r] under H0: Rho=0. Number of observations

EPIC Domains								
Exit	Urinary	Urinary Function	Urinary Bother	Urinary Irritative	Urinary Incontinence	Bowel	Bowel Function	Bowel Bother
Q1	-0.429 P<.0001 N=172	-0.306 P<.0001 N=186	-0.434 P<.0001 N=171	-0.359 P<.0001 N=171	-0.354 P<.0001 N=171	**-0.683** P<.0001 N=172	**-0.565** P<.0001 N=182	**-0.700** P<.0001 N=171
Q2	-0.275 P= 0.002 N=173	-0.178 P=0.015 N=186	-0.291 P=0.000 N=172	-0.211 P=0.0054 N=172	-0.229 P=0.0025 N=172	**-0.566** P<.0001 N=173	**-0.480** P<.0001 N=182	**-0.569** P<.0001 N=171
Q3	**-0.624** P<.0001 N=173	**-0.459** P<.0001 N=186	**-0.627** P<.0001 N=172	**-0.568** P<.0001 N=172	**-0.475** P<.0001 N=172	-0.339 P<.0001 172	-0.294 P<.0001 N=182	-0.330 P<.0001 N=171
Q4	**-0.418** P<.0001 N=186	-0.280 P=0.000 N=186	**-0.427** P<.0001 N=172	**-0.3817** P<.0001 N=172	-0.275 P=0.000 N=172	-0.156 P=0.042 N=172	-0.152 P=0.041 N=182	-0.152 P=0.047 N=171
Q5	-0.251 P=0.001 N=162	-0.217 P=0.004 N=174	-0.2365 P=0.003 N=161	-0.177 P=0.0249 N=161	-0.239 P=0.0022 N=161	.-0.251 P=0.001 N=160	-0.238 P=0.002 N=170	-0.224 P=0.005 N=159
Q6	-0.175 P=0.028 N=158	-0.148 P=0.056 N=169	-0.3804 P<.0001 N=172	-0.115 P=0.1511 N=157	-0.161 P=0.0445 N=156	-0.156 P=0.051 N=157	-0.185 P=0.018 N=165	-0.142 P=0.077 N=156
Q7	-0.420 P<.0001 N=173	-0.354 P<.0001 N=186	-0.3804 P<.0001 N=172	-0.327 P<.0001 N=172	-0.389 P<.0001 N=171	-0.382 P<.0001 N=173	-0.298 P<.0001 N=182	-0.391 P<.0001 N=172
Q8	**-0.390** P<.0001 N=173	-0.3182 P<.0001 N=186	**-0.3682** p<.0001 N=172	-0.331 P<.0001 N=172	-0.276 P=0.000 N=171	**-0.322** P<.0001 N=173	-0.246 P=0.000 N=182	**-0.347** P<.0001 N=172

EPIC Domains							
Exit	Sexual	Sexual Function	Sexual Bother	Hormonal	Hormonal Function	Hormonal Bother	Satisfaction
Q1	-0.214 P=0.005 N=169	-0.144 P=0.064 N=166	-0.218 P=0.006 N=160	-0.402 P<.0001 N=172	0.298 P<.0001 N=181	-0.436 P<.0001 N=174	-0.239 P=0.0010 N=185
Q2	-0.126 P=0.103 N=169	-0.137 P=0.078 N=167	-0.083 P=0.297 N=160	-0.256 P=0.0007 N=171	-0.248 P=0.0008 N=181	-0.245 P=0.0011 N=174	-0.298 P<.0001 N=184
Q3	-0.144 P=0.062 N=169	-0.079 P=0.309 N=167	-0.153 P=0.053 N=160	-0.339 <.0001 171	-0.301 P<.0001 N=181	-0.337 P<.0001 N=173	-0.158 P=0.0319 N=184
Q4	-0.105 P=0.174 N=169	-0.125 P=0.108 N=167	-0.063 P=0.431 N=160	-0.216 P=0.005 N=171	-0.233 P=0.002 N=181	-0.199 P=0.009 N=173	-0.167 P=0.024 N=184

Q5	**-0.683** P<.0001 N=163	**-0.624** P<.0001 N=161	**-0.526** P<.0001 N=153	-0.259 P=0.0009 N=161	-0.218 0.0044 N=170	-0.269 P=0.0005 N=162	-0.113 P=0.1396 N=172
Q6	-0.359 <.0001 N=159	-0.290 P=0.000 N=157	-0.315 P<.0001 N=151	-0.206 P=0.0099 N=155	-0.163 P=0.0361 N=165	-0218 P=0.0062 N=157	-0.047 P=0.5445 N=167
Q7	-0.278 0.0002 N=170	-0.179 P=0.021 N=167	-0.308 P<.0001 N=161	-0.427 P<.0001 N=171	-0.381 P<.0001 N=181	-0.431 P<.0001 N=173	-0.267 P=0.0003 N=184
Q8	-0.144 P=0.060 N=170	-0.112 P=0.152 N=167	-0.128 P=0.105 N=161	-0.256 P=0.000 N=171	-0.218 P=0.003 N=181	-0.24479 P=0.0012 N==173	-0.206 P=0.0051 N=184

Q1: My current QOL in terms of bowel movement is. Q2: since completion of the prostate RT, my QOL in terms of bowel movement is. Q3: My current QOL in terms of urination is. Q4: Since completion of the prostate RT, my QOL in terms of urination is. Q5: My current QOL in terms of sexual function is. Q6: since completion of the prostate RT, my QOL in terms of sexual function is. Q7: My overall QOL right now is. Q8: Since completion of the prostate RT, my overall QOL is.

Table 15: Interclass Correlation between PCRT-Exit HRQOL Summary Scores
Pearson Correlation Coefficients Prob > [r] under H0: Rho=0. N observations=186

Exit	PCRT-GI			PCRT-GU			PCRT-Sexual Domains		
	r	*P* value	N	*r*	*P* value	N	*R*	*P* value	N
Q1	**-0.646**	<.0001	166	**-0.431**	<.0001	167	-0.323	0.0007	183
Q2	**-0.565**	<.0001	166	-0.267	0.0002	185	-0.165	0.0322	168
Q3	-0.278	0.0003	166	**-0.540**	<.0001	186	-0.247	0.0013	168
Q4	-0.118	0.1293	166	**-0.377**	<.0001	186	-0.131	0.0903	163
Q5	-0.249	0.0016	157	-0.233	0.0020	174	**-0.599**	<.0001	164
Q6	-0.088	0.2805	153	-0.126	0.1019	169	**-0.432**	<.0001	159
Q7	-0.304	<.0001	166	**-0.378**	<.0001	185	-0.353	<.0001	167
Q8	-0.281	0.0002	185	-0.301	<.0001	185	-0.287	0.0002	167

Q1: My current QOL in terms of bowel movement is. Q2: since completion of the prostate RT, my QOL in terms of bowel movement is. Q3: My current QOL in terms of urination is. Q4: Since completion of the prostate RT, my QOL in terms of urination is. Q5: My current QOL in terms of sexual function is. Q6: since completion of the prostate RT, my QOL in terms of sexual function is. Q7: My overall QOL right now is. Q8: Since completion of the prostate RT, my overall QOL is
r =Correlation Coefficients N= number of observations

8.3.3 Concurent Validity of PCRT

The bolded correlations in Table 17 demonstrate a negative strong correlation between the PCRT domains and the RTOG-toxicity grades (GI/GU). Patients experiencing better HRQOL in GI and GU organs had lower toxicity grades, as might be expected. The correlation between GU-toxicity grade and GU domain was -0.7, and for the GI-toxicity grade and GI domain was -0.6. These reverse correlations between the PCRT GI/GU domains and the GI/GU toxicity grades assure the concurrent validity of the PCRT with the results of PCRT-Intraclass correlation. Moreover, Table 16 results provide concurrent validity of the PCRT, with the bolded numbers indicating patients reporting better quality of life through EPIC-GI/GU domains and subscales of these domains offering a moderate to strong reverse association with the PCRT-Late toxicity grades. We also found that the Exit questionnaire indicated a moderate positive correlation between GI-toxicity grade and Q1, and Q2 with the equal values of 0.4 (P<.0001/observation=189) for both questionnaires, where the GU-toxicity grade had a positive small association with Q3, and Q4 of 0.2 (P=0.002/observation=186), and 0.3(P<.0001/observation=186) respectively.

Correlations are not as strong as the comparision between HRQOL scales EPIC versus PCRT. This indicates that objective toxicity does not always translate into QOL effects in toxicity scales and QOL scales, but also captures related but not exactly same information.

Table 16: Validity Analysis- EPIC-RTOG Toxicity Grade Analysis. Pearson Correlation Coefficient Prob > [r] under H0: Rho=0. Number of observations=19

EPIC	GI-Grade (RTOG-Toxicity Scale)			GU-Grade (RTOG-Toxicity Scale)		
Variable	**Correlation Coefficients**	***P* value**	**N**	**Correlation Coefficients**	***P* value**	**N**
Urinary	-0.2522	0.0007	176	**-0.4240**	<.0001	176
Urinary Function	-0.1489	0.0404	190	**-0.2518**	0.0005	190
Urinary Bother	-0.2777	0.0002	175	**-0.4633**	<.0001	175
Urinary Irritative	-0.2618	0.0005	175	**-0.4438**	<.0001	175
Urinary Incontinence	-0.1584	0.0363	175	**-0.2608**	0.0005	175
Bowel	**-0.6707**	<.0001	176	-0.1441	0.0565	176
Bowel Function	**-0.6253**	<.0001	186	-0.1601	0.0291	186
Bowel Bother	**-0.6356**	<.0001	175	-0.1229	0.1052	175
Sexual	-0.0995	0.1954	171	-0.1643	0.0318	171
Sexual Function	-0.0814	0.2926	169	-0.1211	0.1169	169
Sexual Bother	-0.0904	0.2528	162	-0.112	0.1548	162
Hormonal	-0.2294	0.0023	175	-0.1897	0.0119	175
Hormonal Function	-0.2285	0.0018	185	-0.2589	0.0004	185
Hormonal Bother	-0.2099	0.005	177	-0.1302	0.0841	177
Satisfaction	-0.1944	0.0075	188	-0.1166	0.1109	188

Table 17: Validity Analysis- PCRT- RTOG Toxicity Grade Analysis Pearson Correlation Coefficients. Prob > [r] under H0: Rho=0. Number of observations=189

PCRT	GI-Grade (RTOG-Toxicity Scale)			GU-Grade (RTOG-Toxicity Scale)		
Variable	**Correlation Coefficients**	***P* value**	**N**	**Correlation Coefficients**	***P* value**	**N**
PCRT-GI	**-0.64023**	<.0001	169	-0.10346	0.1807	169
PCRT-GU	**-0.30834**	<.0001	189	**-0.71198**	<.0001	189
PCRT-sexual	-0.11469	0.1353	171	-0.12464	0.1043	171
PCRT-pain during urination	-0.17699	0.0154	187	-0.17944	0.0140	187
PCRT-dysuria symptoms	**-0.32081**	0.0529	37	-0.17394	0.3032	37
PCRT-urinary bother	-0.22147	0.1146	52	**-0.31628**	0.0224	52
PCRT-hematuria symptoms	-0.09450	0.1995	186	-0.10425	0.1567	186
PCRT-hematuria bother	**-0.5423**	0.4610	187	**-0.4127**	0.5749	187
PCRT-incontinence symptoms	-0.10523	0.1574	182	-0.24793	0.0007	182
PCRT-incontinence bother	-0.11705	0.1156	182	-0.20893	0.0046	182

Table 18: Validity Analysis- Exit-RTOG Toxicity Grade Analysis Pearson Correlation Coefficients. Prob > [r] under H0: Rho=0. Number of observations=186

EXIT	GI-Grade (RTOG-Toxicity Scale)			GU-Grade (RTOG-Toxicity Scale)		
Variable	**Correlation Coefficients**	***P* value**	**N**	**Correlation Coefficients**	***P* value**	**N**
Q1	**0.4358**	<.0001	186	0.2278	0.0018	186
Q2	**0.3702**	<.0001	186	0.0701	0.3418	186
Q3	0.1956	0.0075	186	**0.3321**	<.0001	186
Q4	0.0990	0.1786	186	**0.1971**	0.0070	186
Q5	0.1219	0.1092	174	0.1424	0.0608	174
Q6	0.0365	0.6605	169	-0.0340	0.6605	169
Q7	0.1746	0.0171	186	0.2198	0.0026	186
Q8	**0.1718**	0.0191	186	**0.1565**	0.0329	186

8.4 Intra-class Correlation Coefficient Inferences

8.4.1 Internal Consistency of PCRT Questionnaire

Correlations between PCRT-GU, and PCRT-sexual subscales diverged with correlation values of 0.3 (P<.0001/observation=168), and 0.2 (P=0.003/observation=154) respectively. Correlation between the PCRT-GI and PCRT-sexual diverged with correlation values of 0.3 (P<.0001/observation=168), and 0.3(P<.0001/observation=171), respectively. (See Table 19.) The PCRT principal domains demonstrate internal consistency. The results in internal consistency ICC=0.30 between GU domain and the GI domain indicates significant evidence of a direct satisfactory association. The strength of the association is similar to the correlation between GU domain and Sexual domain with the value of 0.29 (P<.0001). The correlation between the Sexual domain and the GI domain is the weakest at value 0.24 (P=0.003). Thus, we conclude that the PCRT offers fair reliability. A limiting factor in this study is that another wave of the PCRT questionnaire was not administered to the study cohort to investigate test-retest reliability. However, this was previously performed in the validation of the PCRT questionnaire (Rodrigues et al, 2007)

Table 19: Internal Consistency Analysis Intraclass Correlation Coefficient of PCRT Questionnaire

PCRT Domains	PCRT-GI	PCRT-GU	PCRT-Sexual
PCRT-GI Correlation P value N	1	0.30349 <0.0001 168	0.23795 0.003 154
PCRT-GU Correlation P value N	0.30349 <0.0001 168	1	0.29527 <0.0001 171
PCRT-Sexual Correlation P value N	0.23795 0.003 154	0.29527 <0.0001 171	1

8.4.2 Internal Consistency of Exit Questionnaire

Table 20 presents the ICC which quantifies the nature and strength of the linear association between variables. The value of 0.0919 which is close to zero denotes the absence of association between q4 (quality of life in terms of urination since completion of RT) and q5 (current QOL in terms of sexual function), with no statistically significant evidence of this poor association at p with a value of 0.227.

In this table, none of the ICC values are equal or above 0.7. The many values close to 0.7, however, indicate some degree of association among the variables with significant evidence of these association at alpha=0.05 with two sided t-test. The ICC values represent a moderate direct relationship between the variables as listed below: the strongest asociation is between q1 and q7 0.57469 ($P<.001$), providing evidence of significant moderate linear association between patients' current overall QOL and their current QOL in terms of bowel movement at alpha=0.05.

With q1 and q2 at 0.5094 ($P<.0001$); however, there is evidence of a significant moderate linear association between patient's current QOL in terms of bowel movement and their QOL since prostate EBRT completion in terms of bowel movement at alpha=0.05.

Likewise, q2 with q8 at 0.500 ($P<.001$) offers evidence of a significant linear association between patient's QOL in terms of bowel movement and their overall QOL since completion of their prostate RT at alpha=0.05. Again, q3 with q4 at 0.51489 ($P<0.001$) offers further evidence of a significant linear association between patient's

QOL in terms of urination and patient's QOL in terms of urination since completion of their prostate RTat alpha=0.05 (q3 with q7).Likewise, 0.5232 ($P<.001$) r value indicates evidence of a significant linear association between patient's QOL in terms of urination and overall QOL now, at alpha=0.05. Q4 with q8, 0.6058 ($P<.001$), the $r=0.6058$ indicates a somewhat stronger association between patient's QOL since completion of prostate RT in terms of urination and their overall QOL since completion of prostate RT. The significant association between q1 and all other variables ranged from 0.21 to 0.571, and the significant association between q2 and the other variables ranged from 0.30 to 0.50.

The significant associations between q3, and the other variables ranged from 0.26 to 0.51. The signifficant associations between q4 and the other variables ranged from 0.26 to 0.60 . The significant associations between q5 and the other variables ranged from 0.16 to 0.39. The significant associations between q6 and the other variables ranged from 0.26 to 0.39. The significant associations between q7 and the other variables ranged from 0.31 to 0.57. The signifficant associations between q8 and the other variables ranged from 0.34 to 0.60. The significant associations occurred in the q1-q2 (bowel), q3-q4 (rectal), q5-q6 (sexual) doublets and same q7-q8 pairs as all. The fact that, not all GI/GU/sexual groups were highly unrelated shows the validity of the Exit questionnaire in measuring different aspects of HRQOL. Comparison of intra-class correlation coefficients could also be correlated between the general Exit QOL questions (q7, q8) and the subscales Exit questions bowel (q1, q2), bladder (q3, q3), and sexual (q5, q6).

Table 20: Internal Consistency AnalysisIntraclass Correlation of Exit Questionnaire -Pearson Correlation Coefficients Discrimination

CI Exit Q	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Q1 *r* *P* N	-	**0.509** <.0001 185	**0.493** <0.0001 185	0.214 0.0034 185	0.294 <0.0001 173	0.189 0.0147 167	**0.575** <0.0001 184	0.345 <0.0001 184
Q2 *r* *P* N	-	-	0.3047 <0.0001 185	**0.362** <.0001 185	0.168 <.0001 185	0.180 0.0270 173	0.3423 0.0198 184	**0.500** <.0001 184
Q3 *r* *P* N	-	-	-	**0.515** <.0001 186	0.157 0.0388 174	0.265 0.0005 168	**0.523** <.0001 184	**0.446** <.0001 184
Q4 *r* *P* N	-	-	-	-	0.092 0.2274 174	0.269 0.0004 168	0.324 <.0001 184	**0.606** <.0001 184
Q5 *r* *P* N	-	-	-	-	-	**0.394** <.0001 166	0.311 <.0001 172	0.183 0.0165 172
Q6 *r* *P* N	-	-	-	-	-	-	0.197 0.0104 169	0.246 0.0013 169
Q7 *r* *P* N	-	-	-	-	-	-	-	**0.457** <.0001 186
Q8 *r* *P* N	-	-	-	-	-	-	-	-

r = correlation coefficient, *P* = *P* value, N= number of observations

Exit Non-parametric Testing.(Spearman Correlation Coefficients Inferences)

Some of the study ordinal variables with few response options do not follow normal distribution. Therefore, these variables were candidates for Spearman Correlation Coefficient analysis. D'Agostion (2006) stated: "Extreme values can have a substantial impact on the value of the sample correlation coefficient. When data subjected to extremes, an alternative measure of correlation between variables is based on ranks called Spearman correlation."

In this section, we interpret the Spearman correlation r_s outcomes. The result of the Spearman correlation test proved the moderate linear association between q1 with q7 and between q2 with q8 (bowel vs general QOL), as well as q3 with q7, and q4 with q8 (urinary vs. general QOL). However, it shows a slight reduced in the strength of association between q1 with q2 and between q3 with q4, which indicate the existence of extreme value.

In addition, the Spearman correlation coefficients $r_s = 0.074$ showed no association between q3 and q5 where the Pearson correlation coefficient $r = 0.15684$ reflects a very slight linear association between these two variables (see Table 16).

Table 21: Spearman Correlation for the Exit Questionnaire

Exit	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Q1 *r* *P* N	-	**0.485** <0.0001 185	0.488 <0.0001 185	0.193 0.0087 185	0.233 0.0021 173	0.184 0.0176 167	**0.597** <0.000 184	0.268 0.0002 184
Q2 *r* *P* N	-	-	0.262 0.0003 185	0.332 <.0001 185	0.253 0.0008 173	0.164 0.0340 167	0.376 <.0001 184	**0.525** <.0001 184
Q3 *r* *P* N	-	-	-	**0.490** <.0001 186	0.074 0.3294 174	0.257 0.0008 168	**0.534** <.0001 184	0.406 <.0001 184
Q4 *r* *P* N	-	-	-	-	0.112 0.1412 174	0.259 0.0007 168	0.323 <.0001 184	**0.613** <.0001 184
Q5 *r* *P* N	-	-	-	-	-	0.357 <.0001 166	0.236 0.0018 172	0.153 0.0453 172
Q6 *r* *P* N	-	-	-	-	-	-	0.212 0.0058 169	0.239 0.0018 169
Q7 *r* *P* N	-	-	-	-	-	-	-	0.434 <.0001 186
Q8 *r* *P* N	-	-	-	-	-	-	-	

r = correlation coefficient, *P* = *P* value, N= number of observations

8.4.3 Internal Consistency of EPIC Questionnaire

In the validation analysis, the EPIC questionnaire showed satisfactory survey characteristics. Internal consistency for the urinary, bowel, sexual and hormonal domain scores compared to those reported by Wei et al. in their 2000 study, as well as showing test-retest reliability. These principal domains (Urinary/Bowel/Sexual/Hormone) demonstrate internal consistency (Cronbach's alpha<.0001) (See Table 22). Our data analysis confirms the previously known validity of the EPIC questionnaire.

Table 22: Intraclass Correlation Coefficient of EPIC Questionnaire

EPIC Domains	EPIC-Urinary	EPIC-Bowel	EPIC-Sexual	EPIC-Hormonal
EPIC – Urinary ICC P value Number of observation	1	**0.43315** <.0001 170	**0.2591** 0.001 159	**0.42599** <.0001 167
EPIC-Bowel ICC P value Number of observation	**0.43315** <0.0001 170	1	0.16761 0.0341 160	**0.32172** <0.0001 166
EPIC-Sexual ICC P value Number of observation	**0.2591** 0.001 159	0.16761 0.0341 160	1	**0.31149** <.0001 160
EPIC-Hormonal ICC P value Number of observation	**0.42599** <0.0001 167	**0.32172** <0.0001 166	**0.31149** <0.0001 160	1

8.5 Univariable Analyses (UVA)

Univariable analyses were used to identify the predicted variables that meet the 0.1 significant levels, to be fitted into the multivariable analyses models. The following section will present the outcomes of these analyses for each study individual questionnaire and domains, and includes information regarding data transformation model if employed.

8.5.1 Univariable Analysis of EPIC-Questionnaire Domains

8.5.1.1 EPIC Bowel

Tables 23a and 23b provide UVA analyses of the EPIC-bowel domain after, and before transformation, respectively. The sample size is 175 with the mean EPIC bowel score=85.27. The value of the Skewness indicated the degree of asymmetry in the sample distribution. The Skewness value=-1.2195 is far from 0 and thus it is not indicative of symmetry, The Kurtosis value=1.24738442, far from 0, indicated thickness in the tails of the distribution (the degree of clustering observation at the tails of the distribution). The range is 100-79.2. The interquartile range (the difference between the first and third quartile) is 16.6666 (95.8333-79.1667). To investigate the significant variable to predict the EPIC-GI, the SAS Univariate procedure was used to test the following hypothesis: H0= No relationship between baseline variables and outcome variables, Ha= There is relationship between baseline variables and outcome variables.

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The SAS output for the Wilcoxon Signed-Rank test showed a Signed Rank=7700 with a two sided p value= "Pr>=[S] <.0001. Based on the observed p value, $P<.0001<0.05$, we reject the H0: The median are equal in favor of the alternative, H1. The median EPIC-GI is lower post-treatment as compared to baseline for the significant variables.

Testing the null hypothesis H0; Differences follow a normal distribution, and the Shapiro-Wilk test, with test statistics W=0.86 and *P* value<.0001. We reject H0 based on the observed *P* value; therefore we have significant evidence to show that the data do not follow a normal distribution.

8.5.1.2 EPIC Sexual

Tables 23a and 23b provide a descriptive analysis of the EPIC-sexual domain after, and before transformation, respectively. The sample size is 171 with the mean=21.77. The value of the Skewness indicated the degree of asymmetry in the sample distribution. The Skewness value=-1.14 is far from 0; therefore, it is not indicative of symmetry, The Kurtosis value=0.82, close to zero, do not indicate thickness in the tails of the distribution. The range is 86.54. The interquartile range is 25.32. To study the differences between the EPIC-sexual we ran the SAS univariate procedure.

The SAS output for the Wilcoxon Signed-Rank test showed a "Signed Rank=5076.5 with a two sided p value= "Pr>=[S] <.0001. Based on the observed p value, $P<.0001<0.05$, we reject the H0: The median are equal in favor of the alternative, H1: The median EPIC-sexual is lower post-treatment as compared to baseline. A test was

done for normality output. The null hypothesis is H0: Differences follow a normal distribution. The Shapiro-Wilk test, with test statistics W=0.88 and *P* value<.0001. We reject H0 based on the observed P value; therefore we have significant evidence to show that the data do not follow a normal distribution.

8.5.1.3 EPIC Urinary

Table 23a and 23b provide a descriptive analysis of the EPIC-urinary domain after, and before transformation, respectively. The sample size is 175 with the mean=85.26. The value of the Skewness indicated the degree of asymmetry in the sample distribution. The Skewness value=-1.22 is far from zero therefore, it is not indicative of symmetry, The Kurtosis value=1.25, far from zero, indicated thickness in the tails of the distribution. The range is 58.3. The interquartile range is 16.77. To study the differences between the EPIC-urinary we run the SAS Univariate procedure. The SAS output for the Wilcoxon Signed-Rank test showed a "Signed Rank=7700 with a two sided p value= "Pr>=[S] <.0001. Based on the observed *P* value, *P*<.0001<0.05, we reject the H0: The median are equal in favor of the alternative, H1: The median EPIC-Urinary is lower post-treatment as compared to baseline.

Testing the null hypothesis H0; Differences follow a normal distribution. The Shapiro-Wilk test, with test statistics W=0.89 and *P* value<.0001. We reject H0 based on the observed *P* value; therefore we have significant evidence to show that the data do not follow a normal distribution.

8.5.1.4 EPIC Hormonal

Table 23a provides a descriptive analysis of the EPIC-hormone domain after transformation, and table 23b provides information of the non transformed hormone domain. The sample size is 175 with the mean=85.32. The value of the Skewness indicated the degree of asymmetry in the sample distribution. The Skewness value=--0.98 is close to zero therefore, it is indicative of symmetry, The Kurtosis value= 0.74, close to zero, does not indicate thickness in the tails of the distribution. The range is 63.64. The interquartile range is 20.55.

The SAS output for the Wilcoxon Signed-Rank test showed a "Signed Rank=7700 with a two sided p value= "Pr>=[S] <.0001. Based on the observed p value, $P<.0001<0.05$, we reject the H0: The median are equal in favor of the alternative, H1: The median epic-hormone is lower post-treatment as compared to baseline.

Testing the null hypothesis, H0: Differences follow a normal distribution. The Shapiro-Wilk test, with test statistics W=0.98 and *P* value<.0001. We reject H0 based on the observed *P* value; therefore we have significant evidence to show that the data do not follow a normal distribution.

8.5.1.5. EPIC-Domains Transformation

All EPIC domains demonstrated non-normal distribution; therefore, we had to transfer these domains to improve normality of the distribution and run adjusted UVA analysis to determine the significant variables that have *P* value equal to or less than 0.1

to be fitted in the multivariable analysis (see Table 25-29). Arcsin-square root transformation helps with normality for the urinary and bowel domains.

For the urinary domain, only blood thinner, baseline-GI co-morbidity, baseline-GU co-morbidity and acute toxicity variables were significant at the 0.1 levels. These variables were fitted in the multivariable analyses of the EPIC-Urinary model (see Table 26).

For the bowel domain, the variables that meet the 0.1 significant levels are the baseline-GU, hypercholesterolemia, hormone during radiation, acute toxicity, and bladder value l (see Table 27). Moreover, for the hormone domain outcomes there were quite a few with the value of 100. As a result, any transformation will not yield a normal distributed endpoint. We ran the analysis on the untransformed values. The significant variables at .10 levels were: overall Gleason score, baseline GI co-morbidity, hypercholesteremia, BPH, diabetes, treatment volume, hormone (neo-adjuvant, adjuvant, and hormone therapy at EPIC), PTV value, and PTV bladder.

For the sexual domain, a group of zero values caused problems with normality. We therefore dichotomized the domain to <=15 and >15, and the same for hormone domain (>90/<=90); then we ran logistic regression procedures (see Table 23b). Results of estimated odds ratio for overall Gleason, hormone during radiation and duration of hormone therapy, the results of which are fitted in the multivariable analyses (see Tables 28, 29).

Table 23a: The Univariate Analysis EPIC (No adjustment) Linear Regression of Transformed EPIC-domains (Scores) as a Function of the Independent Variable.

Model Without Adjustment	Transformed EPIC Intercept variables							
	EPIC- Sexual		EPIC- Urinary		EPIC-Bowel		EPIC-Hormonal	
Independent Variables	Regression Coefficient	Pr > [t]	Regression Coefficient	Pr > [t]	Regression Coefficient	Pr > [t]	Regression Coefficient	Pr > [t]
TRUS Volume	1.007	1.018	-0.001	0.267	-0.000	0.659	0.0050	0.719
TURP	-0.1668	0.240	-0.016	0.170	-0.017	0.218	-0.1230	0.330
T2	0.4703	0.056	-0.013	0.687	-0.019	0.611	**0.0653**	**0.018**
T3	0.2005	0.378	0.058	0.246	-0.062	0.317	**0.5803**	**0.029**
Overall Gleason	**-0.3703**	**0.03**	-0.014	0.365	-0.015	0.448	**-0.5164**	**0.003**
Blood thinner	0.00375	0.954	-0.011	0.077	**-0.015**	**0.04**	-0.0210	0.739
Baseline- GI	-0.5232	0.267	**-0.122**	**0.009**	-0.072	0.196	-0.9297	0.068
Baseline-GU	-0.1912	0.567	**-0.10**	**0.001**	**-0.093**	**0.01**	-0.0383	0.906
Baseline-sexual	-0.2384	0.487	-0.059	0.131	-0.065	0.153	0.0151	0.965
Hypertension	0.1839	0.229	-0.008	0.512	-0.011	0.444	-0.1349	0.335
Hypercholesterolemia	0.034	0.812	-0.008	0.545	-0.038	0.058	-0.0840	0.517
BPH	0.1722	0.186	0.004	0.704	-0.001	0.909	-0.2208	0.127
Cardiovascular	0.0969	0.355	0.006	0.558	-0.005	0.650	-0.0361	0.697
Diabetes	0.2040	0.454	-0.017	0.426	-0.034	0.178	-0.3509	0.294
Prostate/seminal	-0.0023	0.994	-0.027	0.547	-0.005	0.923	**-0.9992**	**0.000**
Whole pelvic	-0.0023	0.994	-0.077	0.177	-0.067	0.359	0.4335	0.153
Hormone during RT	**-0.763**	**0.02**	-0.016	0.591	**-0.067**	**0.05**	**-1.4968**	**<.0001**
Time of Hormone therapy	**-0.0287**	0.036	0.000	0.956	-0.000	0.706	**-0.0793**	**<.0001**
Hormone therapy at questionnaire	-0.503	0.392	0.007	0.900	-0.046	0.565	**-2.8922**	**0.006**
Acute toxicity during radiation	0.1645	0.784	**-0.166**	**0.002**	**-0.213**	**0.002**	-0.1355	0.821
PTV Volume	0.00164	0.728	0.000	0.14	0.000	0.301	**0.0112**	**0.031**
Rectal Volume	-0.00486	0.425	-0.000	0.862	-0.000	0.365	-0.00616	0.389
PTV Rectal	-0.0314	0.646	0.008	0.255	0.009	0.205	0.1073	0.159
Bladder value	-0.00297	0.276	0.000	0.462	0.001	0.059	0.00258	0.338
PTV Bladder	-0.0048	0.869	0.003	0.225	0.002	0.576	**0.0814**	**0.011**
Interval of RT to EPIC	-0.00049	0.286	0.000	0.771	-0.000	0.333	2.047	0.996

Table 23 b: The Univariate Analysis EPIC (No adjustment) Linear Regression of Non-Transformed EPIC-Sexual domain (Scores).

Model Without Adjustment	EPIC Non-Transformed Intercept variables			
	EPIC- Sexual		EPIC-Hormone	
Independent Variables	Regression Coefficient	Pr > [t]	Regression Coefficient	Pr > [t]
TRUS Volume	0.032	0.562	-0.002	0.95
TURP	-1.177	0.359	-0.510	0.51
T2	-0.644	0.852	-1.033	0.66
T3	**-10.798**	**0.040**	**-6.902**	**0.05**
Overall Gleason	**-3.888**	**0.020**	**-4.893**	**<.0001**
Blood thinner	0.425	0.532	-0.379	0.48
Baseline- GI	**-9.551**	**0.049**	**-7.741**	**0.02**
Baseline-GU	-2.226	0.522	-1.976	0.38
Baseline-sexual	-4.146	0.246	-0.512	0.83
Hypertension	-0.186	0.886	-0.641	0.45
Hypercholesterolemia	-0.504	0.725	**-1.751**	**0.04**
BPH	-0.430	0.688	-1.234	0.08
Cardiovascular	0.244	0.809	-0.581	0.35
Diabetes	-0.935	0.682	**-3.311**	**0.03**
Treatment volume seminal	5.588	0.212	4.904	0.10
Treatment volume seminal+ Pelvic	-2.283	0.647	**-6.24**	**0.052**
Hormone during RT	**-8.518**	**0.007**	**-9.630**	**<.0001**
Time of Hormone therapy	**-0.402**	**0.002**	**-0.408**	**<.0001**
Hormone therapy at questionnaire	-10.004	0.092	**-13.310**	**<.0001**
Acute toxicity during radiation	-7.857	0.206	-3.359	0.41
PTV Value	0.022	0.675	0.0553	0.06
Rectal value	-0.052	0.293	-0.019	0.50
PTV Rectal	-0.014	0.985	0.499	0.25
Bladder value	-0.049	0.099	0.012	0.47
PTV Bladder	0.229	0.484	**0.488**	0.007
Interval of RT to EPIC	-0.003	0.500	-0.001	0.645

8.5.2 Univariable Analysis of PCRT Questionnaire Domains

8.5.2.1 PCRT-Urinary and Bowel Domains

We looked at possible transformation to improve normality of the PCRT scores. The GI/GU domains transformation did not make any difference regarding normality distribution. Regressions were based on the untransformed data for these two domains. The predicted variables that were significant at .10 levels for the PCRT-Bowel are TURP, diabetes, treatment volume, acute toxicity, baseline-GU co-morbidity, bladder volume, PTV-bladder, and interval between radiation and questionnaire administration. For the Urinary domain the predicted variables that were significant at .10 levels were acute toxicity, baseline-GU co-morbidity, bladder volume, PTV-bladder, and interval between radiation and questionnaire administration (see Table 24).

8.5.2.2 PCRT-Sexual Domains

For the sexual data, the appropriate transformation is the arcsin-square root transformation. The regressions for the sexual domain are based on this transformation (see Table 24). None of the independent variables meet the <.10 significance.

Table 24: The Univariate Analysis PCRT (No Adjustment) Linear Regression of PCRT-domains (Scores) as a Function of the Independent Variables.

Individual Model Without Adjustment	PCRT Intercept variables					
	PCRT- Sexual Transformed		PCRT- GI Un-transformed		PCRT-GU Un-transformed	
Independent Variables	Regression Coefficient	Pr > [t]	Regression Coefficient	Pr > [t]	Regression Coefficient	Pr > [t]
TRUS volume	0.0003	0.652	-0.025	0.478	-0.063	0.128
TURP	-0.003	0.857	**-2.035**	**0.011**	-0.623	0.468
T2	0.022	0.632	-0.434	0.858	0.193	0.712
T3	-0.080	0.251	-3.314	0.366	-1..107	0.791
Overall Gleason score	0.009	0.686	-0.779	0.521	-0.920	0.446
Blood thinner was used	-0.002	0.804	-0.387	0.371	-0.148	0.742
Baseline-GI	-0.107	0.118	-3.509	0.341	-6.184	0.086
Baseline-GU	-0.035	0.433	-1.550	0.519	**-9.162**	**<.0001**
Baseline-sexual	-0.030	0.518			-1.66	0.508
Hypertension	-0.008	0.659	-1.303	0.195	-1.048	0.271
hypercholesterolemia	-0.011	0.466	-0.612	0.536	-0.160	0.881
BPH	-0.004	0.814	-0.141	0.862	-0.45	0.55
Cardiovascular	-0.000	0.982	0.086	0.896	-0.068	0.923
Diabetes	-0.005	0.825	-1.064	0.377	0.407	0.75
Prostate/seminal	0		0		0	-
Whole pelvic	-0.016	0.804	-5.237	0.166	-2.912	0.426
Hormone during RT	0.012	0.779	-2.729	0.217	-2.196	0.328
Time of hormone therapy	-0.000	0.854	0.062	0.436	-0.075	0.432
Hormone therapy during questionnaire	0.020	0.796	1.976	0.606	-3.01	0.497
Acute toxicity during RT	-0.032	0.705	**-10.118**	**0.039**	**-16.022**	**0.0001**
PTV value	0.001	0.289	0.010	0.762	0.053	0.104
Rectal value	-0.001	0.320	-0.032	0.251	-0.048	0.13
PTV rectal	0.004	0.716	0.238	0.603	0.121	0.798
Bladder value	-0.000	0.720	0.020	0.234	0.031	0.084
PTV bladder	0.001	0.784	0.115	0.566	**0.478**	**0.020**
Interval between end of RT & EPIC	**-0.000**	**0.022**	-0.003	0.417	-0.007	0.274

8.6 Multivariable Analyses (MVA)

8.6.1 EPIC- Bowel MVA

Model 1: Out of a possible 189 observations, 86 observations were used while the remaining 103 observations were missing values and could not be used or analyzed. The dependent variable is the EPIC-Bowel domain score. Expected variables from UVA introduced into the model included (EPIC-Bowel toxicity given blood thinner, baseline-GU co-morbidity, Hypercholesterolemia, Hormone, Acute Toxicity during radiation, Bladder value) is

$= \beta 0 + \beta$ blood thinner$+ \beta$ baseline-GU$+ \beta$ Hypercholesterolemia, β Hormone, β Acute Toxicity, β Bladder value.

Results: ANOVA Analysis of Variance

Source	DF	Sum of squares (SS)	Mean Square (MS)	F MS_M/MS_E	Sig (Pr>F)
Model(Regression)	6	0.88654	0.14776	3.24	0.0067
Error(Residual)	79	3.60184	0.04559		
Corrected total	85	4.48838			

Model refers to the variation in the dependent variable (outcome) accounted for by the regression equation, and Error refers to the variation in the outcome variable not accounted for by the regression. The F-test= 3.24>2.22 (p=0.0067) suggested that the regression value of the EPIC-Bowel score differed among each of the predicted variable in the fitted model (see Tables 25, 27); which leads to rejecting the null (H_0 all the estimated parameter of the independent variables are equal).

From the parameter estimating the slope of blood thinner with p value of 0.28 indicated that there is no statistically significant association between the change of 1-unit in the EPIC-Bowel and using blood thinner. It was the same as the association with the hypercholesterolemia, hormone, acute toxicity, and bladder value since *P* values are 0.41, 0.08, 0.15, and 0.16 respectively. The only significant association found is the baseline-GU co-morbidity. Therefore the change in EPIC-Bowel score associated with a 1-unit change in baseline-GU grade P=0.008.

Stepwise selection step 1 baseline –GU entered. Since that the regression of baseline-GU is significant we quantified how much variation in the dependent variable (EPIC-bowel) is explained by the independent variable (baseline-GU). In the coefficient of determination the R^2 is equal to 0.097 thus 9.7% of the variation in the EPIC-Bowel toxicity is explained by the baseline-GU. The estimate of the regression parameter associated with baseline-GU is -0.14704. On average, existing GU co-morbidity have the EPIC-Bowel domain 0.14 units lower than for patients who do not have baseline- GU co-morbidity holding the other variable constant. To verify the indication of the baseline-GU, we ran the backward removal stepwise selection o-5, and excluding each of the independent variable from the model we found no other variable other than the baseline-GU met the 0.050 significance level of entry into the model (see Table 25, 27).

8.6.2 EPIC Sexual MVA

Model 2: Number of observations used was 66 out of 189 number of observation with missing values was 123. The dependent variable is the EPIC-Sexual, and the

expected variables from UVA introduced into the model included EPIC-sexual toxicity given T1, T2, Overall Gleason grade, baseline-GI, Treatment volume-seminal, Treatment volume-pelvic, Hormone during radiation therapy, hormone, hormone therapy at the time of feeling questionnaire, Bladder value).

Results: ANOVA Analysis of Variance

Source	DF	Sum of squares (SS)	Mean Square (MS)	F MS_M/MS_E	Sig (Pr>F)
Model(Regression)	10	4038.56354	403.85635	0.85	0.5857
Error(Residual)	55	26198	476.32831		
Corrected total	65	30237			

Running the model using SAS REG procedure indicated that all variables in the model are significant at .10 levels. F=0.85<2.03 $F_{10, 55}$ P= 0.58>0.05; therefore, we do not reject the null hypothesis (H_0 all the estimated parameter of the independent variables are equal). The independent variable divided into six in group one included T1, T2. Group two included the Gleason overall grade; group three included the baseline-GI; group four included treatment volume; group five included hormone therapy; and group six included the bladder value.

Stepwise selection, step 1 was performed by entering group six into the model. The outcomes showed that all groups of variables left in the model are significant at the 0.005 level. However, no other group of variables met the 0.005 significance level for entry into the model. The estimate regression =-0.479 F=6.63>3.93, P=0.012<0.05; therefore, we reject the null hypothesis. The coefficient of determination the R^2 is equal to 0.094, thus 9.4%, (Mallow's C (P) =-4.4789) of the variation in the EPIC-Sexual

toxicity is explained by the hormone therapy. The estimate of the regression parameter associated with hormone therapy is -0.047902. On average, hormone therapy offers the EPIC-Sexual domain' score 0.05 units lower than patients who do not have hormone therapy, holding the other variable constant. Step 2, entering group 7 into the model resulted in a non-significant variable in the model, with all *P* values more than 0.1. Therefore, we started the backward removal to check for variables that meets 0.05 significant. None of the independent variables meet the 0.05 significance (see Table 25, 28).

8.6.3 EPIC Urinary MVA

Model 3: Number of observation used was 170 out of 189; number of observation with missing values was 19. The dependent variable is the EPIC-urinary. Expected variables from UVA introduced into the model included EPIC-urinary toxicity given blood thinner, baseline-GU Co-morbidity, baseline- GI Co-morbidity, and acute toxicity during radiation.

Results: ANOVA Analysis of Variance

Source	DF	Sum of squares (SS)	Mean Square (MS)	F MS_M/MS_E	Sig (Pr>F)
Model(Regression)	4	0.82650	0.20662	6.34	<.0001
Error(Residual)	165	5.37989	0.03261		
Corrected total	169	6.20639			

Running the model using SAS REG procedure indicated that all variables in the model are significant at .05 levels. However, F=6.34<2.42 $F_{4, 165}$ *P*= .0001<0.05;

therefore, we reject the null hypothesis (H_0: all the estimated parameter of variables is equal).

The independent variables are Blood thinner, baseline-GU co-morbidity, baseline-GI co-morbidity, acute toxicity during radiation. All the variables in the model are significant at the 0.05 level (see Table 25 and Table 26).

Stepwise selection: Step 1 was performed by entering baseline-GU variable into the model. The outcomes showed that all groups of variables left in the model are significant at the 0.005 level. The estimate regression = -0.099 F=10.93>3.93, P=0.0012<0.05, and we therefore reject the null hypothesis. The coefficient of determination the R^2 is equal to 0.0611 thus 6.11%, (Mallow's C (P) =12.7256) of the variation in the EPIC-Urinary toxicity is explained by the baseline –GU. The estimate of the regression parameter associated with baseline-GU is -0.0988. On average, baseline-GU have the EPIC-Urinary domain score 0.11 units lower than patients who do not have baseline-GU, holding the other variable constant. Step 2, entering baseline-GI into the model resulted in a significant variable in the model, all p value are less than 0.05. Step 3, acute toxicity entered into the model resulted in significant variables at 0.05 levels.

Table 25: Multivariable Analyses Un-Transformed EPIC-Domains *β*

Individual model with adjustment	EPIC dependent variables							
	EPIC-Sexual intercept: 20.359/Pr= 0.446		EPIC-Urinary intercept: 1.391/ Pr <.0001		EPIC-Bowel intercept: 1.435/Pr <.0001		EPIC-Hormone intercept: 79.35/Pr <.0001	
Independent variables	***β***	**Pr > [t]**	***β***	**Pr > [t]**	***β***	**Pr > [t]**	***β***	**Pr > [t]**
T2	-2.377	0.725	-	-	-	-	-	-
T3	1.509	0.914	-	-	-	-	-	-
Overall Gleason score	1.159	0.767	-	-	-	-	1.0469	0.58
Blood thinner was used			-0.011	0.06	-0.0104	0.29	-	-
Baseline-GI	-5.492	0.531	**-0.098**	0.03	-	-	-7.5002	0.06
Baseline-GU	-	-	**-0.08**	0.01	**-0.138**	0.01	-1.0195	0.44
Hypercholesterolemia	-	-	-	-	0.042	0.42	-	-
BPH	-	-	-	-	-	-	0.0934	0.94
Diabetes	-	-	-	-	-	-	0.630	0.85
Prostate, seminal vesicle	-	-	-	-	-	-	3.61305	0.37
Whole pelvic	-	-	-	-	-	-	5.4112	0.31
Hormone Rx	-7.131	0.388	-	-	-0.082	0.08	-5.234	0.20
Hormone therapy	-0.399	0.353	-	-	-	-	**-0.325**	**0.03**
Hormone therapy during questionnaire	3.106	0.827	-	-	-	-	4.3133	0.48
Acute toxicity during radiation	-	-	**-0.110**	**0.04**	-0.147	0.15	-	-
Bladder value	-0.025	0.462	-	-	0.0004	0.16		
PTV volume							0.0110	0.81
PTV-Bladder							0.0719	0.75

***β* =Regression coefficient.**

Table 26: Multivariable Analyses EPIC Transformed Urinary Domain

Individual model with adjustment	**Dependent variable (Transformed EPIC-Urinary)**		
Independent variable	**Parameter estimate**	**Pr>[t]**	**95% confidence limits**
Intercept	1.468	<.0001	1.334, 1.60
Blood thinner used	**-0.017**	0.018	-0.032, -0.003
Baseline-GU	**-0.08**	0.034	-0.153, -0.006
Hypercholesterolemia	-0.026	0.086	-0.056, 0.004
Hormone during RT	-0.036	0.298	-0.103, 0.03
Acute toxicity during radiation	**-0.161**	0.024	-0.2, 0.3
Bladder value	0.0004	0.161	-0.0001, 0.001

Table 27: Multivariable Analyses EPIC Transformed Bowel Domain

Individual model with adjustment	**Dependent variable (Transformed EPIC-Bowel)**		
Independent variable	**Parameter estimate**	**Pr>[t]**	**95% confidence limits**
Intercept	1.435	<.0001	1.20 , 1.67
Blood thinner used	-0.010	0.285	-0.03, -0.009
Baseline-GU	**-0.138**	0.008	-0.24, -0.34
Hypercholesterolemia	-0.042	0.417	-0.06, 0.14
Hormone during RT	-0.082	0.084	-0.18, 0.01
Acute toxicity during radiation	-0.147	0.153	-0.35, 0.06
Bladder value	0.0004	0.161	-0.0001, 0.001

Table 28: Multivariable Analyses EPIC Transformed Sexual Domain

Logistic procedure EPIC-Sexual ≤15 EPIC-Sexual >15	Parameter estimate	Pr >Chi-Square	Odds ratio estimate	95% Wald confidence limits
Intercept	0.892	0.598	-	-
Overall Gleason	-0.054	0.836	0.948	0.57, 1.57
Hormone during RT	-0.221	0.678	0.801	0.28, 2.23
Time of hormone	-0.02	0.361	0.980	0.94, 1.02
Number of observations was128/189. Number of EPIC-Sexual ≤15 was 55. Number of EPIC-Sexual >15 was 73.				

Table 29: Multivariable Analyses EPIC Transformed Hormone Domain

Logistic procedure EPIC-Hormone ≤90 EPIC-Hormone >90	Parameter estimate	Pr > Chi-Square	Odds ratio estimate	95% Wald confidence limits
Intercept	-15.1944	0.9457	-	-
T3	12.1179	0.9567	>999.99	<0.001, >999.99
Overall Gleason	0.6238	0.2840	1.87	0.596, 5.842
Baseline GI	**-2.2888**	**0.0341**	0.10	0.012, 0.842
Whole pelvic	-0.8672	0.4837	0.42	0.037, 4.757
Treatment prostate	1.4858	0.1982	4.419	0.460, 42.49
Hormone during RT	-1.9577	0.0708	0.141	0.017, 1.181
Time of hormone	-0.0354	0.5778	0.97	0.852, 1.093
Hormone at EPIC	-11.3310	0.9711	<0.001	<0.001, >999.99
PTV volume	0.00140	0.9098	1.111	0.978, 1.026
PTV bladder overlap	0.0244	0.6757	1.03	0.914, 1.149

Number of observations was 69/189.
Number of EPIC-Hormone ≤90 was 35.
Number of EPIC-Hormone >90 was 34.

8.6.4 PCRT GI-Domain MVA

Model 1: Number of observation used were 168 out of 189, number of observation with missing values is 21. The dependent variable is the PCRT-GI. Expected variables from UVA introduced into the model included (PCRT-GI given TURP, diabetes, treatment volume seminal, treatment volume whole pelvis, Acute Toxicity during radiation) is = β0+ β TURP + β treatment volume seminal + β treatment volume whole pelvis + β Acute Toxicity during radiation.

Results: ANOVA Analysis of Variance

Source	DF	Sum of squares (SS)	Mean Square (MS)	F MS_M/MS_E	Sig (Pr>F)
Model(Regression)	5	3374.93	674.99	3.55	0.0045
Error(Residual)	162	30768	189.93		
Corrected total	167	34143			

The F-test= 3.55 suggested that the regression value of the PCRT-GI score differed among each of the predicted variables in the fitted model (see Table 30), which leads us to reject the null (H_0: all the estimated parameters of the independent variables are equal).

From the parameter estimating the slope of TURP *P* value = 0.01 indicated a statistically significant association between the change of 1-unit in the PCRT-GI and TURP. The association between the PCRT-GI and the other independent variables in the models were not statistically significant.

Stepwise selection Step 1 TURP entered. Since the regression of TURP is significant we quantified how much variation in the dependent variable (PCRT-GI) is

explained by the independent variable (TURP). The coefficient of determination the R^2 is equal to 0.039, thus 3.9 % of the variation in the PCRT-GI toxicity is explained by the TURP. The estimate of the regression parameter associated with TURP is -2.035. On average, TURP has the PCRT GI domain score 2 units lower than patients who do not have TURP holding the other variable constant (see Table 30).

8.6.5 PCRT GU-Domain MVA

Model 1: Number of observation used was 94 out of 189; number of observations with missing values was 95. The dependent variable is the PCRT-GI. Expected variables from UVA introduced into the model included (PCRT-GU given baseline-GU, Acute Toxicity, bladder volume, PTV bladder, radiation to questionnaire administration) is = $\beta 0 + \beta$ baseline-GU + β bladder volume + β PTV bladder + β Acute Toxicity + β radiation to questionnaire administration.

Results: ANOVA Analysis of Variance

Source	DF	Sum of squares (SS)	Mean Square (MS)	F MS_M/MS_E	Sig (Pr>F)
Model(Regression)	5	4404.75	880.95	4.86	0.0006
Error(Residual)	88	15966	181.43		
Corrected total	93	20370			

The F-test= 4.86 suggested that the regression value of the PCRT-GU score differed among each of the predicted variables in the fitted model (see Table 30), which led us to reject the null (H_0: all the estimated parameters of the independent variables are equal).

From the parameter estimate the slope of baseline-GU p value = 0.003 indicated statistically significant association between the change of 1-unit in the PCRT-GU when baseline-GU changed. The association between the PCRT-GU and PTV bladder was statistically significant, with *P* value of 0.013. The other independent variables in the models were not statistically significant.

Stepwise selection (forward and backward) showed only baseline-GU and PTV bladder were statistically significant. The estimate of the regression parameter associated with PTV bladder is 0.50007. On average, PTV bladder increased the PCRT domain score by 0.5 units holding the other variable constant (see Table 30). And on average baseline-GU decreased the PCRT-GU score 10 units lower than patients who do not have baseline-GU holding the other variable constant (see Table 30).

Table 30: Multivariable Analyses of PCRT Urinary and Bowel Domains

Individual model with adjustment	PCRT dependent variable			
	PCRT-Bowel intercept: 93.23/Pr <.0001		PCRT- Urinary intercept: 73.12/ Pr <.0001	
	Regression Coefficient	Pr > [t]	Regression Coefficient	Pr > [t]
TURP	**-2.04**	**0.0095**	-	-
Diabetes	-2.565	0.095	-	-
Treatment volume-seminal	1.072	0.730	-	-
Treatment volume-pelvic	-3.24	0.359	-	-
Acute toxicity	-8.572	0.076	**-6.559**	**0.264**
Baseline-GU	-	-	**-10.162**	**0.0025**
Bladder-value	-	-	0.004	0.835
PTV-Bladder	-	-	**0.5001**	**0.0125**
RT to EPIC	-	-	-0.003	0.5111

8.7 Primary Comparisons Analysis

Analyses comparing our study cohort (hypofractionated EBRT prostate cancer patients' post 2003) outcome to the previous existing EPIC database (conventional dose of EBRT prior 2003) had been carried out in order to generate hypothesis regarding the potential increases in toxicities and HRQOL potentially related to dose per-fraction escalation. We carried out these analyses after we gathered as much as possible similar baseline factors that match our study cohort with the previous cohort, with comparable time lag from treatment to assessment for both groups. Thus, we were able to minimize biases due to differences in data collection time, treatment technique changes, and population changes over time.

8.7.1 Baseline Variables

The primary results of the combined data are all provided in Tables 31 through 36. Based on the assumption of equal variance we ran the t-test and Fisher test to test the Null: all baseline variables means are equal. We found that we had statistical significant evidence to reject the null for the following variables: age at diagnosis, PSA at questionnaire administration, and RT to EPIC completion with *P* value equal to <.0001, 0.05, and <.0001. We obtained the same results by employing the non-paramedic test Wilcoxon Scores on these variables. We failed to reject the null for the PSA pre RT, age at EPIC administration, TRUS volume (see Table 31). The Chi-square test was carried out to test the following hypothesis concerning the risk in the two populations.

8.7.2 Pretreatment Factor Analysis

Null hypothesis H0: The two populations are homogeneous with respect to risk. We found that for Gleason 2-6 the mean and standard deviation were 86±13, 85±14, for LD pre-2003, HD post-2003 respectively. Gleason 7 averages were 85.5±15, 84±18 for LD, HD respectively. And for Gleason 8-10 averages were 84±17, 83±16 for LD, HD respectively (see Table 32). Given x^2 =3.695 <5.99 with two degrees of freedom we do not find statistical significant evidence at alpha 0.05 to reject the null. Therefore, the two populations are homogeneous with respect to risk based on Gleason score.

In the pre-2003 cohort, 46% (250/547) of the patients had received hormone therapy versus 18% (99/547) of our study cohort Pr<.0001. The x^2=16.312>3.84 with one degree of freedom we have significant evidence to reject the null at alpha 0.05. Therefore, we conclude there is a difference in risk among hormone therapy groups (see Table 33).

The frequency of RT treatment site "whole pelvic" was so close with 12% (66/544) and 9% (50/544) for LD, HD respectively. Given x^2=4.456>3.84 with one degree of freedom, we have significant evidence to reject the null at alpha 0.05. Therefore there is a difference in risk among whole pelvic treatments group (see Table 34).

Patients with diabetes had 11% (55/512), and 6% (30/512) for LD and HD respectively Pr=0.77 (see Table 36). Testing the independent variable diabetes x^2=0.089<3.84 with one degree of freedom, we found no significant evidence to reject

the null at alpha 0.05. Therefore, we conclude there is no difference in risk among diabetes groups.

8.7.3 Analyses of EPIC-HRQOL Scores Differences among the Two Cohorts

Null hypothesis: No differences in the mean EPIC-HRQOL scores in the post-2003 cohort (HD) versus pre-2003 cohort (LD). We assumed the equality of the variances between the two groups' EPIC scores and then ran a t-test. We found that, no matter if we assume equal or unequal variance, the test results keep giving us the same result: none of the EPIC scales were significant, and therefore we fail to reject the null. Then we ran the equality of variance test; the only variable providing significant evidence to reject the null was the satisfaction domain with alpha value of $0.04<0.05$. Thus, we did not assume the equality of variance for this particular domain (see Table 36).

The result obtained from running the Wilcoxon Rank Sums test supported our conclusion that we did not reject the null hypothesis. Therefore, there are no apparent differences in the HRQOL between the HD post 2003 PC patients and LD prior 2003 PC patients based on this analysis of the two databases.

Table 31: Summary Statistics of Baseline Characteristics

Variables	Study cohort (73> Gy/35)	Control cohort (70< Gy/35)
	N, {Minimum, Maximum} Mean, ±Std, 95% Confidence limit	N, {Minimum, Maximum} Mean, ±Std 95% Confidence limit
Age EPIC Pr> [t] 0.230 / Pr>F 0.67 Pr>Chi-Square 0.0716	(189), {53-84} 75.76 ±5.54 (74.96 to 76.55)	(313), {66-88} 75.15 ± 5.39 (74.55 to 75.75)
PSA pre treatment Pr> [t] 0.303/ Pr>F 0.042 Pr>Chi-Square 0.106	(189), {0.01 - 77.5} 12.5 ± 12.15 (10.75 to 14.21)	(358), {0.6-115} 13.7± 13.77 (12.27 to 15.14)
PSA at questionnaire Pr> [t] 0.09/ Pr>F <.0001 Pr>Chi-Square <.0001	(188), {0-7.4} 0.59 ± 0.95 (0.45 to 0.73)	(334), {0.01-49.1) 0.998± 3.16 (0.61to1.38)
RT to EPIC Pr>[t] <.0001/ Pr>F <.0001 Pr> Chi-Square <.0001	(189), {212.0-1454.0} 851.5±335 (803.4 to899.52)	(340), {132.0-2778.0} 1508.67±636.1 (1440.8 to 1576.5)
TRUS volume Pr>[t] 0.96/ Pr>F 0.46 Pr> Chi-Square 0.774	(167), {18-238} 51.15±31.52 (46.3 to 55.96)	(98), {6.50-200} 51.33±29.42 (45.4 to 57.23)

Table 32: Summary Statistics of Groups Comparing Gleason Score Distributions.

Analysis variable: EPIC-Bowel domain (Pre-2003)						
Biopsy - Gleason score	**N**	**Mean**	**Std Dev**	**Minimum**	**Median**	**Max**
Low Risk (2-6)	147	86.107	13.228	48.2143	89.286	100.000
Intermediate Risk (7)	116	85.479	14.666	32.143	89.286	100.000
High Risk (8-10)	59	84.026	16.798	21.429	91.071	100.000

Analysis variable: EPIC-Bowel domain (Post-2003)						
Biopsy - Gleason score	**N**	**Mean**	**Std Dev**	**Minimum**	**Median**	**Max**
Low Risk (2-6)	64	84.857	13.8529	39.2857	89.2857	100.00
Intermediate Risk (7)	73	84.026	17.6812	25.0000	91.0714	100.00
High Risk (8-10)	37	82.834	15.5958	44.6429	87.5000	100.00

Table 33: The Frequency of Subjects between Groups by Hormone Usage

Hormone	Groups		Total
Frequency percent	Pre-2003	Post-2003	
No	108 19.74 %	90 16.45 %	198 36.20 %
Yes	250 45.70 %	198 36.20 %	349 63.80 %
Total	358 65.45 %	349 63.80 %	547 100.00
Frequency missing = 2. (Chi-Square=16.3 Pr<.0001)			

Table 34: The Frequency of Subjects between Groups by Treatment Volume

Primary radiation therapy treatment volume	Groups		Total
Frequency percent	Pre-2003	Post-2003	
Not whole pelvic	289 53.13%	139 25.55	428 78.68
Whole pelvic	66 12.13%	50 9.19	116 21.32
Total	355 65.26	189 34.74	544 100
Frequency missing = 5. (Chi-Square=4.55 Pr=0.03)			

Table 35: The Frequency of Subjects between Groups by Diabetes

Diabetes	Groups		Total
Frequency percent	Pre-2003	Post-2003	
No	269 52.54 %	158 30.86 %	427 83.40 %
Yes	55 10.74 %	30 5.86 %	85 16.60 %
Total	324 63.28	188 36.72	512 100
Frequency missing = 37 (Chi-Square=0.089 Pr=0.77)			

Table 36: HROL-EPIC Domains Statistics comparing Prior-2003 Cohort to Post-2003 Cohort

EPIC domains variable	Post-2003		Pre-2003	
	N	Mean ± Std 95% CL	N	Mean ± Std 95% CL
Urinary	175	85.26±12.92 83.27 to 87.09	317	84.23±14.19 82.7 to 85.8
Urinary function	189	91.79±11.97 90.1 to 93.51	336	90.73±13.47 89.28 to 92.17
Urinary bother	174	80.67±15.64 78.33 to 83.01	318	79.73±16.77 77.88 to 81.58
Urinary irritation	174	84.81±11.88 83.03 to 86.59	317	83.53±13.3 82.05 to 85
Urinary incontinence	174	87.83±18.04 85.13 to 90.53	318	87.38±18.93 85.3 to 89.47
Bowel	175	84.14±15.82 81.78 to 86.43	324	85.4±14.55 83.77 to 86.94
Bowel function	185	86.28±13.72 84.29 to 88.28	336	87.05±12.48 85.73 to 88.39
Bowel bother	174	82.14±19.69 79.2 to 85.09	322	83.62±18.16 81.63 to 85.61
Hormonal	175	85.32±13.69 83.29 to 87.35	330	84.75±13.63 83.27 to 86.22
Hormonal function	184	81.64±16.56 79.24 to 84.05	338	81.68±15.51 80.02 to 83.34
Hormonal bother	177	87.91±13.41 85.93 to 89.91	329	87.43 ±13.34 85.98 to 88.88
Sexual	171	21.77±20.68 18.65 to 24.89	320	21.30± 18.9 19.22 to 23.36
Sexual function	168	13.88±19.41 10.92 to 16.84	307	13.8± 18.75 11.69 to 15.9
Sexual bother	162	40.47±37.80 34.61 to 46.34	309	38.25±34.55 34.38 to 42.12
Satisfaction	187	81.68±23.66 78.27 to 85.1	338	79.29±27.17 76.38 to 82.2

9.0 DISCUSSION

9.1 Late Toxicity Effect

Minimizing the dose to normal prostate gland tissue while utilizing radiation dose escalation has rapidly become the leading trend in radiation therapy treatment in the past decade. The promise shown by 3D conformed Intensity modulated RT in improving disease survival while decreasing the associated late toxicity effect on the GI, GU, and sexual function have been reported in several studies (Deborah, 2004). More recently a strategy of increasing dose per fraction (hypofractionated RT) has been an area of active research. Consequently, an assessment of hypofractionated RT late toxicity has become a priority in cancer research.

The main focus of the study was on the late toxicities of EBRT for PC patients. The study investigated the associated adverse effects on the surrounding related organ systems, the rectum-sigmoid-bowel (GI), the bladder (GU), and the sexual organ system (bilateral neurovascular bundles and penile bulb). Based on literature review and urologists' expert opinion, these adverse effects have included the following symptoms: GI included diarrhea, pelvic pain, rectal bleeding, tenesmus, and bowel control; GU included nocturia, frequency, hematuria, dysuria, and incontinence; and sexual included libido impairment, level of sexual interest, and impotency.

9.1.1 GI-Toxicity

The presence of RTOG late toxicity grade 2 and more in the gastrointestinal organ system has a significant impact on a patient's HRQOL. Our findings of EBRT-HD suggested that EBRT had only a small impact on toxicity. Only 3.16% (6/190) reported grade 2 (moderate problem patients requiring outpatient conservative medication) compared to 1% (2/189) baseline grade 2, 6.32% (12/190) reported grade 3 (severe problem patients requiring blood transfusion / minor surgical intervention), and one case reported grade 4 (life threatening; patient hospitalized and major surgical intervention required). This one life-threatening case was reported to have baseline severe rectal bleeding prior to exposure to RT. Furthermore, the primary aim of dose escalation in increasing survival without an increase in toxicity grade ($\geq$ grade 3) sequelae was supported by our findings. All 189 study participants survived, with 92% (174/189) alive with no evidence of disease recurrence, 4% (8/189) alive without clear evidence of relapse, and 4% (7/189) alive with disease still present.

We explored the association of some predicted variables to the PCRT-Late toxicity outcome by employing the MVA Cox regression model including TURP, diabetes, treatment volume (seminal vesicle site or whole pelvic), and acute toxicity. The only predictor baseline factor with significant impact on the GI-grade toxicity end point was prior TURP with P=0.0095 (see Table 30), while the rest of the fitted exploratory variables in the model were not significant at alpha=0.05. The observed relationship between TURP and GI toxicity has not been previously reported and will need future confirmation.

9.1.2 GU-Toxicity

Our findings suggested a trend in the GU endpoint late toxicity from baseline co-morbidity, with 59% (112/190) reporting grade 2 toxicity compared to 14% (26/189) with baseline urinary co-morbidity. Only 10% (19/190) reported grade 3 GU toxicity compared to 2 % (3/189) with baseline urinary grade 3, indicating that radiation had some impact on the urinary system of our study participants, though the patient mean age of 76 years undoubtedly accounts for some of these symptoms, as suggested in the literature (Sanda, 2008). We explored the association of some predicted variables to the GU-outcome (variables meeting the <.01 levels of significance in the UVA models and put into MVA Cox regression model), including: baseline GU co-morbidity, bladder-volume, acute toxicity, PTV-bladder, and time interval between radiation completion and questionnaire administration. The only predictors that had a significant impact on the GU-grade toxicity end point were pretreatment RTOG toxicity levels and planning target volume-bladder overlap (PTV-bladder) with P=0.0025, and P= 0.013 respectively for non-transformed PCRT GU domain scores. The rest of the fitted exploratory variables in the model were not significant at alpha=0.05(see Table 30).

9.2. Health Related Quality of Life Assessment

9.2.1 Assessment of Study Cohort HRQOL

The assessment of HRQOL changes related to EBRT late toxicity effect is mandatory in determining the expected QOL changes associated with the EBRT. Consequently, physicians and patients alike would have better understanding of the

tradeoff concerning the new treatment approaches and their adverse effects prior to implementation.

The assessment of these changes in HRQOL/Late toxicity required a valid and reliable instrument to provide us with accurate data. This ideal valid instrument should be specific, simple and quick to be administered in different clinical and research settings. Therefore, our objectives were to assess HRQOL by patient reports and to cross-validate the PCRT questionnaire. To minimize reporting and recall biases, patients were asked to report their symptoms and corresponding bother over the last four weeks of questionnaire reception. The study finding from the EPIC/ PCRT/ Exit questionnaire descriptive analysis proved that hypofractionated EBRT is a satisfactory treatment for this study cohort in terms of their rectal/bowel, urinary, and hormonal endpoints, while there was a big impact on the sexual endpoint results, as presented in Tables 8, 9, and 10.

The outcome results of the Exit questionnaire (see Section 8.2.2) was supported by the correlation with both EPIC and PCRT. Patients rated their overall quality of life since EBRT completion, regarding bowel movement with average score of 3 indicating good QOL (3.15± 0.75), urinary with average score of 3 indicating good QOL (3.03±0.78), and sexual with average score of 4 indicating poor QOL (4±0.79). However, patients rated their overall quality of life as good, with the average 3 (3±0.78). MVA analysis on the EPIC-GU domain revealed that 11% of these domains variation (decreased scores) is explained by the existing of baseline-GU. Five percent of the variation in the sexual domain scores (decreased scores) is explained by the hormone therapy factor. In regards the PCRT-GI domain only 3.9% of the variation is explained by

TURP; and 50% of the PCRT-GU domain variation is explained by PTV bladder overlap factor. Thus, only a small percentage of QOL is explained by known variables and some variables postulated to be influential (i.e. organ domain values and overlap were not). Thus, there is a considerable room for further research into other variables that would predict for post-treatment HRQOL.

9.2.2 Comparison QOL Assessment between Groups

The EPIC-HRQOL scores results of our study cohort (HD post 2003) were similar to those reported by the previous conducted study to (LD pre 2003), implying that HD is favorable over the LD in that it provides potentially better curative rates without an increase in the late toxicity effects and respective worse HRQOL for PC patients (see Table 36).

9.3 PCRT Cross Validation

Based on our primary end point GI domain, our study results showed no difference between EPIC-GI mean (84±16) versus PCRT GI mean (84±14) in detecting HRQOL changes among study population (see Table 9 and Figure 7). Results of the correlation matrixes between the PCRT domains and EPIC domains indicate significant evidence of a strong and moderate linear association between PCRT GI, GU, sexual domains and EPIC domains. Given PCRT is shorter, may be preferable for use. Also facilitates comparisons between HRQOL studies that use PCRT scale vs. EPIC scale.

Also GI/GU domains did not need transformation prior to UVA and multivariable analysis.

9.3.1Convergent/Divergent Validity of PCRT

The PCRT-EPIC interclass correlation results reflect a strong to almost perfect correlation to the GI organ system (function / bother) between the two questionnaires, indicating that scales tend to converge between the two questionnaires. Conversely, the scales belonging to a different organ system tend to diverge or in other words to correlate less (i.e.. the correlation of PCRT GI with EPIC GU, and PCRT GI with EPIC sexual ranged from 0.2-0.3 and 0.1-0.2 respectively). Similarly, Inter-class correlation results ranging from moderate to strong correlations of the GU organ system indicate that GU-scales tend to converge between the two questionnaires. However, scales belonging to different organ systems tended to diverge or correlate less (i.e. the correlation of PCRT GU with EPIC sexual, and PCRT GU with EPIC hormonal ranged from 0.1-0.2, and 0.2-0.3 respectively). Furthermore, for the sexual organ system, results of IEC ranged from moderate to strong correlations, indicating that scales tend to converge between the two questionnaires. Scales belonging to different organ systems tend to diverge or to correlate less (i.e. the correlation of PCRT sexual and EPIC hormonal ranged from 0.1-0.2). Divergence between different organ systems is expected.

9.3.2 Concurent Validity of PCRT

As reported previously in the results section (8.2.3) those patients who

experienced better HRQOL in GI, and GU organs had a lower toxicity grade, with the lowest grade indicating no toxicity. These reverse correlations between the PCRT GI/GU domains and the GI/GU toxicity grades ensure the concurrent validity of the PCRT with the results of PCRT-Intraclass correlation. Furthermore, patients who reported better quality of life through EPIC-GI/GU domains and subscales of these domains indicate a moderate to strong reverse association with the PCRT-Late toxicity grades.

9.4 Convergent/Discriminant Validity of Exit Questionnaire

It was not our aim to fully validate the Exit questionnaire, although our complete analysis performed an initial assessment of the Exit questionnaire. A potential very short questionnaire that could be employed in the clinical setting presented in Section 8.2.2 ,we found a significant evidence of strong and moderate reverse linear association ranging from -0.5 to -0.6 with $P<.0001$ between the Exit versus the EPIC, which demonstrates score validity to the Exit questionnaire. These statistically significant reverse associations prove that, with higher scores in the EPIC-GI domain, there will be a decrease in patient QOL score in terms of bowel movement following completion of prostate RT. Similarly to GI domain, the results of the EPIC-GU and Exit urinary QOL score following RT completion showed statistically significant moderate reverse associations, which indicated that with higher scores in the EPIC-GU domain there will be a decrease in the patients QOL score in terms of urination. The correlation coefficient for the EPIC-sexual and Exit-sexual QOL following completion of RT ranged from 0.3-0.4 with $P<.0001$, which is consistent with the EPIC sexual scores, indicating poor QOL in term of sexual

function. Our findings suggest the Exit questionnaire might be a valid alternative to the longer HRQOL questionnaires that could be explored by further follow up studies.

9.5 Conclusion

We found that a high dose of EBRT for prostate cancer resulted in excellent bowel/rectal, hormonal, and urinary scores (based on patient reports), and overall survival with minimal severe, acute, or late complications. These findings thus demonstrate and support the feasibility of high-dose EBRT in a large number of PC patients. Late rectal toxicities seem to be significantly minimal compared to baseline rectal toxicity. The changes in HRQOL related to the bowel/rectal, urinary, hormonal, sexual domains significantly influenced patient satisfaction with treatment outcomes, with 40% satisfied and 48% extremely satisfied. These results concur with the results of Sanda (2008). Based on this positive hazard/benefit ratio, EBRT appears safe as our standard treatment delivery for localized PC patients, though a history of TURP may be remains a significant concern when considering a patient for EBRT.

The PCRT domains continue to demonstrate constructive/discriminant validity. The PCRT has the advantage of being a compact instrument that provides normally distributed HRQOL domain scores that can be utilized for MVA modeling without transformation or dichotomization. Comparing the HD post 2003 treatment to LD prior 2003 we found that, EBRT was associated with a similar model of change in HRQOL domains related to bowel/rectal, urinary, hormonal, and sexual function.

Our findings will empower the patient by making him a closer part of the early treatment decision-making process because he is better informed, and understands that his clinical team is making fully informed treatment decisions which match his lifestyle and his expectations. This alone in turn optimizes the clinician's ability to choose the optimal treatment modality because of enhanced awareness of the patient's expectations. The realistic outcome produced is earlier comfort levels for the patient as part of his treatment team, better ability to optimize treatment modalities on the part of the clinician. Along the way, we discover that we are not simply treating the disease called prostate cancer. We are treating a human being in the hopes of returning him to full and optimal health. Potentially, our studies translate across a number of disease boundaries. That avenue remains to be explored, but it is exciting in the anticipation. And all this is possible because we have designed an exquisite, short, comprehensive, easy-to-use tool to assist both the patient and his clinical treatment team.

9.6 Future Work and Recommendation

The comparison analysis between our study cohort versus the two pre-existing databases should be further studied. Therefore, to overcome the limitations of our study and to generalize the findings of the EBRT benefit, randomized multicenter prospective studies should compare hypofractionated HD EBRT versus LD EBRT with standardization of RT delivery technique, nurses' training, and EBRT dose/fraction; and with prostate cancer conformal and HRQOL endpoints to be registered. Further work could include examining the reliability of the PCRT questionnaire. It could be administered to the patients in four waves. First wave administered prior to treatment to

establish baseline information. Second administration should take place at 6 months after EBRT completion to detect the acute toxicity. The third wave should be administrated at two years after completion of EBRT, in order to detect late toxicity effects. A fourth wave could be administered at 3-5 years post EBRT completion. This longitudinal assessment of QOL may provide valuable data on the time course and natural history of acute and late toxicities. Our findings suggest the Exit questionnaire might be a valid alternative to longer HRQOL questionnaires and should explore in further studies. Our current standard of mildly hypofractionated EBRT appears to be as safe as normally fractionated standardized dose radiotherapy.

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APPENDIX 1

LETTER OF INFORMATION

AND QUESTIONNAIRES BOOKLET

Health-Related Quality-of-Life and Late Toxicity Related to Hypofractionated Prostate Cancer Radiation Therapy.

Study Investigators:

Dr. Somaya Eid DDS
Departments of Radiation Oncology and Epidemiology/Biostatistics
London Regional Cancer Program
London Health Sciences Centre
790 Commissioners Road East. London, Ontario

Dr. George Rodrigues, MD, FRCPC. MSc
Departments of Radiation Oncology and Epidemiology/Biostatistics
London Regional Cancer Program
London Health Sciences Centre
790 Commissioners Road E London, ON

Introduction and Purpose of Study:

You are being invited to participate in our research study looking at health related quality-of-life and late toxicity subsequent to your previous prostate radiation therapy. The purpose of this letter is to provide information with regards to this study. It is important for you to understand why this study is being conducted and what it will involve. Please take the time to read this carefully and feel free to ask questions to the study investigators if anything is unclear. This letter of information should be read by the patient who had previously received radiation therapy at the London Regional Cancer Program.

Background Study Information:

At this point we would like to summarize the research and the purpose of this study for your understanding. At the London Regional Cancer Program, radiation treatment for prostate cancer have changed over time to reflect as new information suggesting higher Radiation doses delivered with shaped (conformal) radiation field has emerged. Based on information, we changed our radiation technique in 2003 and we are interested in determining whether this change had any effect on the quality of life or side effect of patients treated after 2003 compared to before 2003

Research Question:

The research would compare your quality-of-life data to patients treated prior to this change in order to see whether or not any significant changes in health related quality-of-life or late toxicity has occurred. The number of participants that will participate is 299 and all study patients will have been treated at the London Regional Cancer Program.

Study Population:

The patients who were treated with external radiation therapy for prostate cancer as per the new institutional standard are invited to participate in this study. Patient should also have been diagnosed with prostate cancer. Patients who are ineligible for this study include patients who are not able to fill out the questionnaires due to a language barrier.

Study Procedures:

If you take part of this study you will have the following questionnaires to fill out. The first questionnaire is called the EPIC Questionnaire which will ask you 32 questions in regards to your general prostate cancer health. The second questionnaire is the PCRT questionnaire which will ask 29 questions that specifically are related to the late toxicity of radiation therapy in the prostate cancer setting. In addition there will be an Exit questionnaire of 8 questions that will ask you general questions with regards to your bowel, bladder and-sexual function, and overall quality-of-life. The study investigators will obtain patient (date of birth), treatment (radiation and hormonal treatment details, side-effects) and cancer related information (cancer stage, PSA, Gleason score, PSA/clinical outcome of treatment) from your chart in order to link your questionnaire responses to factors related to your cancer and cancer treatment. By consenting to this study you agree to allow us to confidentially collect this data. If you do not consent to this data collection, then you cannot participate in this study. There will be no other further questionnaires.

Research Methods, Benefits and Risks:

In terms of specific research technique involved in this study all patients will receive all three questionnaires. You will be asked to complete all 3 questionnaires at home. The first 2 questionnaires approximately take 10 minutes each, the final Exit questionnaire takes approximately 5 minutes therefore a total of 25 minutes will be required for you to fill out these questionnaires. Once these questionnaires have been completed we would ask you to mail them in the provided stamped envelope at your earliest convenience in order for us to enter the data for analysis. We also ask you to send us a copy of a signed letter of information with the questionnaire. No known risk or harms would be related to this study. There are no known benefits to you associated with your participation in this research.

Voluntary Participation, Privacy and Confidentiality:

Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions, or withdraw from this study at any time with no effect on your future medical care. If you are participating in another study at this time; that is acceptable as we are only collecting health related quality-of-life data. All data that will be collected from these questionnaires will be considered confidential. We will maintain your confidentiality by using a unique identifier number on all documents instead of your name. A separate secure document will contain the linkage between your name and identifier number in order to minimize the possibility of a breach of you privacy. Your research records will be stored in a locked cabinet at the clinical trials unit. Once the data has been put into the research database, any identifying information will be removed from the database in order to protect your confidentially. If the results of the study are published, your name will not be used and no information that discloses your identity will be released or published without your explicit consent. By sending in the questionnaires; you hereby consent to participation in this study.

Patient Rights:

If you have any questions about your rights as a research participant or the conduct of the study you may contact VP Research, c/o Lawson Health Research Institute, 519-667-6649.

Compensation and Costs:

There is no compensation to you in relation to this research study. You do not waive any legal rights by completing this study. A copy of this letter is for you to keep. By sending in the completed questionnaires you are therefore consenting in the participation of this research study. Dr. Eid will be calling in 4 weeks to ensure that you received this package and to answer any questions regarding this study. If you do not wish to receive a phone call you may return the questionnaire uncompleted as a method of letting us know that you do not wish to participate.

Consent Statement:

I have read the Letter of Information, have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction.

Participant (Print name) Participant Signature

Person Conducting Informed Consent Discussion (Print)

Person Conducting Informed Consent Discussion (Sign)

Western

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London Health Sciences Centre | London Health Sciences Foundation

Questionnaire Booklet

Subject ID #

EPIC

The Expanded Prostate Cancer Index Composite

This questionnaire is designed to measure Quality of Life issues in patients with Prostate cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

Remember, as with all medical records, information contained within this survey will remain strictly confidential.

URINARY FUNCTION

This section is about your urinary habits. Please consider **ONLY THE LAST 4 WEEKS**.

1. Over the **past 4 weeks**, how often have you leaked urine?

More than once a day.....	1	
About once a day.....	2	
More than once a week.....	3	(Circle one number)
About once a week.....	4	
Rarely or never.....	5	

2. Over the **past 4 weeks**, how often have you urinated blood?

More than once a day.....	1	
About once a day.....	2	
More than once a week.....	3	(Circle one number)
About once a week.....	4	
Rarely or never.....	5	

3. Over the **past 4 weeks**, how often have you had pain or burning with urination?

More than once a day.....	1	
About once a day.....	2	
More than once a week.....	3	(Circle one number)
About once a week.....	4	
Rarely or never.....	5	

4. Which of the following best describes your urinary control **during the last 4 weeks**?

No urinary control whatsoever.	1	
Frequent dribbling.....	2	
Occasional dribbling.....	3	(Circle one number)
Total control.....	4	

5. How many pads or adult diapers <u>per day</u> did you usually use to control leakage **during the last 4 weeks**?

None.....	0	
1 pad per day.....	1	
2 pads per day.....	2	(Circle one number)
3 or more pads per day.....	3	

6. How big a problem, if any, has each of the following been for you during the last 4 weeks? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Dripping or leaking urine.....	0	1	2	3	4
b. Pain or burning on urination.....	0	1	2	3	4
c. Bleeding with urination.....	0	1	2	3	4
d. Weak urine stream or incomplete emptying.....	0	1	2	3	4
e. Waking up to urinate.....	0	1	2	3	4
f. Need to urinate frequently during the day.....	0	1	2	3	4

7. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

No problem.....	1	
Very small problem.....	2	
Small problem.....	3	(Circle one number)
Moderate problem.....	4	
Big problem.....	5	

BOWEL HABITS

The next section is about your bowel habits and abdominal pain. Please consider **ONLY THE LAST 4 WEEKS.**

8. How often have you had rectal urgency (felt like I had to pass stool, but did not) **during the last 4 weeks**?

More than once a day.....	1	
About once a day.....	2	
More than once a week.....	3	(Circle one number)
About once a week.....	4	
Rarely or never.....	5	

9. How often have you had uncontrolled leakage of stool or feces?

More than once a day.....	1	
About once a day.....	2	
More than once a week.....	3	(Circle one number)
About once a week.....	4	
Rarely or never.....	5	

10. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) **during the last 4 weeks**?

Never.....	1	
Rarely.....	2	
About half the time.....	3	(Circle one number)
Usually.....	4	
Always.....	5	

11. How often have you had bloody stools **during the last 4 weeks**?

Never.....	1	
Rarely.....	2	
About half the time.....	3	(Circle one number)
Usually.....	4	
Always.....	5	

12. How often have your bowel movements been painful **during the last 4 weeks**?

Never.....	1	
Rarely.....	2	
About half the time.....	3	(Circle one number)
Usually.....	4	
Always.....	5	

13. How many bowel movements have you had on a typical day **during the last 4 weeks**?

Two or less.....	1	
Three to four.....	2	(Circle one number)
Five or more.....	3	

14. How often have you had crampy pain in your abdomen, pelvis or rectum **during the last 4 weeks**?

More than once a day.....	1	
About once a day.....	2	
More than once a week.....	3	(Circle one number)
About once a week.....	4	
Rarely or never.....	5	

15. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

		No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a.	Urgency to have a bowel movement.....	0	1	2	3	4
b.	Increased frequency of bowel movements.....	0	1	2	3	4
c.	Watery bowel movements.....	0	1	2	3	4
d.	Losing control of your stools.....	0	1	2	3	4
e.	Bloody stools.....	0	1	2	3	4
f.	Abdominal/pelvic/rectal pain.....	0	1	2	3	4

16. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem.....	1	
Very small problem.....	2	
Small problem.....	3	(Circle one number)
Moderate problem.....	4	
Big problem.....	5	

SEXUAL FUNCTION

The next section is about your current sexual function and sexual satisfaction. Many of the questions are very personal, but they will help us understand the important issues that you face every day. Remember, THIS SURVEY INFORMATION IS COMPLETELY **CONFIDENTIAL**.
Please answer honestly about **THE LAST 4 WEEKS ONLY**.

17. How would you rate each of the following **during the last 4 weeks**? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good
a. Your level of sexual desire?	1	2	3	4	5
b. Your ability to have an erection?	1	2	3	4	5
c. Your ability to reach orgasm (climax)?	1	2	3	4	5

18. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?

None at all	1	
Not firm enough for any sexual activity	2	
Firm enough for masturbation and foreplay only	3	(Circle one number)
Firm enough for intercourse	4	

19. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?

I NEVER had an erection when I wanted one	1	
I had an erection LESS THAN HALF the time I wanted one	2	
I had an erection ABOUT HALF the time I wanted one	3	(Circle one number)
I had an erection MORE THAN HALF the time I wanted one.	4	
I had an erection WHENEVER I wanted one	5	

20. How often have you awakened in the morning or night with an erection **during the last 4 weeks**?

Never	1	
Less than once a week	2	
About once a week	3	(Circle one number)
Several times a week	4	
Daily	5	

21. **During the last 4 weeks**, how often did you have any sexual activity?

Not at all	1	
Less than once a week	2	
About once a week	3	(Circle one number)
Several times a week	4	
Daily	5	

22. **During the last 4 weeks**, how often did you have any sexual intercourse?

Not at all	1	
Less than once a week	2	
About once a week	3	(Circle one number)
Several times a week	4	
Daily	5	

23. Overall, how would you rate your ability to function sexually **during the last 4 weeks**

Very poor	1	
Poor	2	
Fair	3	(Circle one number)
Good	4	
Very good	5	

24. How big a problem **during the last 4 weeks,** if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Your level of sexual desire?	0	1	2	3	4
b. Your ability to have an erection?	0	1	2	3	4
c. Your ability to reach orgasm?	0	1	2	3	4

25. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?

No problem	1	
Very small problem	2	
Small problem	3	(Circle one number)
Moderate problem	4	
Big problem	5	

HORMONAL FUNCTION

The next section is about your hormonal function. Please consider ONLY THE LAST 4 WEEKS.

26. **Over the last 4 weeks,** how often have you experienced hot flashes?

More than once a day	1	
About once a day	2	
More than once a week	3	(Circle one number)
About once a week	4	
Rarely or never	5	

27. How often have you had breast tenderness **during the last 4 weeks**?

More than once a day	1	
About once a day	2	
More than once a week	3	(Circle one number)
About once a week	4	
Rarely or never	5	

28. **During the last 4 weeks,** how often have you felt depressed?

More than once a day	1	
About once a day	2	
More than once a week	3	(Circle one number)
About once a week	4	
Rarely or never	5	

29. **During the last 4 weeks,** how often have you felt a lack of energy?

More than once a day	1	
About once a day	2	
More than once a week	3	(Circle one number)
About once a week	4	
Rarely or never	5	

30. How much change in your weight have you experienced **during the last 4 weeks,** if any?

Gained 10 pounds or more	1	
Gained less than 10 pounds	2	
No change in weight	3	(Circle one number)
Lost less than 10 pounds	4	
Lost 10 pounds or more	5	

31. How big a problem **during the last 4 weeks,** if any, has each of the following been for you? (Circle one number on each line)

		No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a.	Hot flashes.....	0	1	2	3	4
b.	Breast tenderness/enlargement.	0	1	2	3	4
c.	Loss of body hair.....	0	1	2	3	4
d.	Feeling depressed.....	0	1	2	3	4
e.	Lack of energy.....	0	1	2	3	4
f.	Change in body weight.....	0	1	2	3	4

Overall Satisfaction

32. Overall, how satisfied are you with the treatment you received for your prostate cancer?

Extremely dissatisfied.....	1	
Dissatisfied.....	2	
Uncertain.....	3	(Circle one number)
Satisfied.....	4	
Extremely satisfied.....	5	

THANK YOU VERY MUCH!!

Prostate Cancer Radiation Toxicity Questionnaire (PCRT)

The following self-reporting questionnaire looks at the long-term side effects you may have experienced from your prostate cancer radiation therapy. The questions ask about your bowel and urinary habits, and your sexual functioning. While these questions are very personal in nature, answering them as honestly as possible is important to us in choosing the best possible follow-up care for you.

Please check your answer.

The following questions deal with your daily bowel habits. Some questions are very personal in nature and you may leave them blank if they make you uncomfortable. Your responses will be kept confidential.

Please check the answer that best describes your situation.

1. In the past 4 weeks, how often have you had blood in your bowel movements?

☐ Never

☐ Sometimes

☐ Frequently

☐ Most of the time (i.e. at least once a week)

☐ All or almost all of the time (i.e. daily)

IF NEVER, SKIP TO QUESTION 4

2. On average, over the past 4 weeks, how much blood have you had in your bowel movements?

☐ None

☐ Slight tinge

☐ Light bleeding

☐ Medium bleeding

☐ Heavy bleeding

3. On average, over the past 4 weeks, how much upset or disruption in your daily activities has the blood in your bowel movements caused you?

☐ No upset or disruption
☐ Very little upset or disruption
☐ Small upset or disruption
☐ Moderate upset or disruption
☐Severe upset or disruption

3a. Have you required any interventions for the bleeding (circle any that apply)
Tests to investigate the bleeding (endoscopy/scope or xray test/barium enema)?
Prescription medications (other than Metamucil or hemorrhoidal suppositories)?
Transfusions because of heavy bleeding?
Laser treatments or chemical (formalin) treatments to the rectum for the bleeding?
Rectal surgery because of bleeding?

4. On average, over the past 4 weeks, how many loose or liquid bowel movements per day did you have?

☐ None (or constipated)
☐ Less than one loose or liquid bowel movement per day
☐ One loose or liquid bowel movement per day
☐ Between two and four loose or liquid bowel movements per day
☐ Five or more loose or liquid bowel movements per day

IF NONE, SKIP TO QUESTION 6

4a. How frequently did you move your bowels BEFORE starting radiotherapy
☐ Once a day
☐ Twice a day
☐ Three times a day
☐ Four or more times a day

4b. Did you have problems with loose or liquid stools BEFORE starting radiotherapy

☐ Yes ☐ No

5. On average, over the past 4 weeks, how much upset or disruption in your daily activities have the loose or liquid bowel movements caused you?

☐ No upset or disruption
☐ Very little upset or disruption
☐ Small upset or disruption
☐ Moderate upset or disruption
☐ Severe upset or disruption

5a. Do you take anti-diarrhea pills such as Lomotil or Imodium?

☐ Never
☐ Occasionally
☐ Every week
☐ Daily

5b. Are there some foods that you avoid because they will cause diarrhea?

☐ Yes ☐ No

6. Over the past 4 weeks, how often have you experienced pelvic pain or cramping?

☐ Never
☐ Sometimes
☐ Frequently
☐ Most of the time
☐ Always or almost always

IF NEVER, SKIP TO QUESTION 9

7. On average, over the past 4 weeks, how severe has the pelvic pain or cramping been?

☐ Not uncomfortable

☐ Mildly uncomfortable

☐ Somewhat uncomfortable

☐ Moderately uncomfortable

☐ Very uncomfortable

8. On average, over the past 4 weeks, how much upset or disruption in your daily activities has your pelvic pain or cramping caused you?

☐ No upset or disruption

☐ Very little upset or disruption

☐ Small upset or disruption

☐ Moderate upset or disruption

☐ Severe upset or disruption

9. On average, over the past 4 weeks, how often have you felt the urge to have a bowel movement and not had one?

☐ Never

☐ Rarely

☐ Frequently

☐ Most of the time

☐ All or almost all of the time

IF NEVER, SKIP TO QUESTION 11

10. On average, over the past 4 weeks, how much upset or disruption in your daily activities has having the urge to have a bowel movement caused you?

☐ No upset or disruption

☐ Very little upset or disruption

☐ Small upset or disruption

☐ Moderate upset or disruption

☐ Severe upset or disruption

11. On average, over the past 4 weeks, how much control have you had over your bowels?

☐ Total control

☐ Control most of the time

☐ Some control

☐ Very little control

☐ No control

IF YOU HAVE HAD TOTAL CONTROL, SKIP TO QUESTION 13

12. On average, over the past 4 weeks, how much upset or disruption in your daily activities has your degree of bowel control caused you?

☐ No upset or disruption

☐ Very little upset or disruption

☐ Small upset or disruption

☐ Moderate upset or disruption

☐ Severe upset or disruption

Urinary and Bladder Habits

The following questions deal with your daily urinary and bladder habits. Some questions are very personal in nature and you may leave them blank if they make you uncomfortable. Your responses will be kept confidential.

Please check the answer that best describes your situation.

13. On average, over the past 4 weeks, how often did you urinate during the course of your day?

☐ Two or fewer times

☐ Between three and five times

☐ Between six and eight times

☐ Between nine and twelve times

☐ Thirteen times or more

13a. Since your radiotherapy, do you feel that your urinary stream is:

☐ Slower than before

☐ The same

☐ Improved

14. On average over the past 4 weeks, how often did you have to get up in the night to go to the bathroom to urinate?

☐ Never

☐ Occasionally getting up once in the night

☐ Getting up once in the night

☐ Getting up between two and four times in the night

☐ Getting up five or more times in the night

15. On average, over the past 4 weeks, how much upset or disruption in your daily activities has the frequency with which you urinate both during the day and the evening caused you?

☐ No upset or disruption

☐ Very little upset or disruption

☐ Small upset or disruption

☐ Moderate upset or disruption

☐ Severe upset or disruption

16. On average, over the past 4 weeks, how often have you experienced pain or discomfort upon or during urination?

☐ Never

☐ Sometimes

☐ Frequently

☐ Most of the time

☐ All or almost all of the time

IF NEVER, SKIP TO QUESTION 19

17. On average, over the past 4 weeks, how severe has your pain or discomfort upon or during urination been?

☐ Very mild pain or discomfort

☐ Mild pain or discomfort

☐ Somewhat uncomfortable pain or discomfort

☐ Moderately uncomfortable pain or discomfort

☐ Severe pain or discomfort

18. On average, over the past 4 weeks, how much upset or disruption in your daily activities has your pain upon or during urination caused you?

☐ No upset or disruption

☐ Very little upset or disruption

☐ Small upset or disruption

☐ Moderate upset or disruption

☐ Severe upset or disruption

18a. If you have pain on urination, have you needed to take painkillers?

☐ Never

☐ Occasionally

☐ Daily

19. On average, over the past 4 weeks, how often have you had blood in your urine?

☐ Never

☐ Rarely

☐ Frequently

☐ Most of the time

☐ All or almost all of the time

IF NEVER, SKIP TO QUESTION 21

20. On average, over the last 4 weeks, how much upset or disruption in your daily activities has the blood in your urine caused you?

☐ No upset or disruption

☐ Very little upset or disruption

☐ Small upset or disruption

☐ Moderate upset or disruption

☐ Severe upset or disruption

21. On average, over the past 4 weeks, how often did you leak urine?

☐ Never

☐ Once a day

☐ Twice a day

☐ Three to five times a day

☐ Constantly leak urine

IF NEVER, SKIP TO QUESTION 24

22. On average over the past 4 weeks, how many incontinence pads or diapers would you use throughout the course of the day?

☐ None

☐ One

☐ Two

☐ Three to five

☐ Six or more

IF NONE, SKIP TO QUESTION 24

23. On average, over the past 4 weeks, how much upset or disruption in your daily activities has the use of incontinence pads or diapers caused you?

☐ No upset or disruption

☐ Very little upset or disruption

☐ Small upset or disruption

☐ Moderate upset or disruption

☐ Severe upset or disruption

Sexual Functioning

The following questions deal with your sexual functioning. Some questions are very personal in nature and you may leave them blank if they make you uncomfortable. Your responses will be kept confidential.

Please check the answer that best describes your situation.

24. On average, over the past 4 weeks, what has been your ability to obtain and maintain an erection?

☐ Very good ability to obtain and maintain an erection

☐ Good ability to obtain and maintain an erection

☐ Moderate ability to obtain and maintain an erection

☐ Poor ability to obtain and maintain an erection

☐ No ability or very poor ability to obtain and maintain an erection

25. On average, during the past 4 weeks, how much upset or disruption in your sexual functioning has your ability to achieve and maintain erections caused you?

☐ No upset or disruption

☐ Very little upset or disruption

☐ Small upset or disruption

☐ Moderate upset or disruption

☐ Severe upset or disruption

26. On average, during the past 4 weeks, how would you rate your level of sexual interest?

☐ Very high level of interest
☐ High level of interest
☐ Moderate level of interest
☐ Low level of interest
☐ No interest

27. On average, during the past 4 weeks, how much has your level of sexual interest caused upset or disruption to your sexual activities?

☐ No upset or disruption
☐ Very small upset or disruption
☐ Small upset or disruption
☐ Moderate upset or disruption
☐ Severe upset or disruption

28. On average, over the past 4 weeks, how happy and contented were you with your sex life?

☐ Extremely happy or satisfied
☐ Somewhat happy or satisfied
☐ Neither happy or unhappy
☐ Somewhat unhappy or dissatisfied
☐ Not happy or satisfied at all

29. Since your radiotherapy, have you tried treatments of any kind to help your sexual function?

☐ Yes ☐ No

29a. If yes, have these been effective?

☐ Never ☐ Some of the time
☐ Most of the time ☐ Always

29b. Over the past 4 weeks, which of the following statements best describes your level of sexual intercourse?

☐ Not having sexual intercourse by choice

☐ Not having sexual intercourse due to lack of interest

☐ Not having sexual intercourse due to lack of opportunity

☐ Not having sexual intercourse due to inability to obtain and maintain an erection

☐ Having sexually intercourse to some degree

Exit Questionnaire

Please check only the most applied answer to your condition in the following:

1. My current quality-of-life in terms of bowel movements is:

   - ☐ Excellent
   - ☐ Very good
   - ☐ Good
   - ☐ Poor
   - ☐ Extremely poor

2. Since completion of the prostate radiation treatment, my quality-of-life in terms of bowel movements is:

   - ☐ Much better
   - ☐ Better
   - ☐ About the same
   - ☐ Worse
   - ☐ Much worse

3. My current quality-of-life in terms of urination is:

   - ☐ Excellent
   - ☐ Very good
   - ☐ Good
   - ☐ Poor
   - ☐ Extremely poor

4. Since completion of the prostate radiation treatment, my quality-of-life in terms of urination is:

   - ☐ Much better
   - ☐ Better
   - ☐ About the same
   - ☐ Worse
   - ☐ Much worse

5. My current quality-of-life in terms of sexual function is:

   - ☐ Excellent
   - ☐ Very good
   - ☐ Good
   - ☐ Poor
   - ☐ Extremely poor

6. Since completion of the prostate radiation treatment, my quality-of-life in terms of sexual function is:

- ☐ Much better
- ☐ Better
- ☐ About the same
- ☐ Worse
- ☐ Much worse

7. My overall quality-of-life right now is:

- ☐ Excellent
- ☐ Very good
- ☐ Good
- ☐ Poor
- ☐ Extremely poor

8. Since completion of the prostate radiation treatment, my overall quality-of-life is:

- ☐ Much better
- ☐ Better
- ☐ About the same
- ☐ Worse
- ☐ Much worse

Checklist for Returning Documents to the London Regional Cancer Program

- ☐ Please sign and date Letter of Information
- ☐ Retain Second Copy of Letter of Information for your records
- ☐ Please complete Questionnaire Booklet
- ☐ Place Signed Copy of Letter of Information and Questionnaire Booklet in Stamped Return Envelope and Mail at your convenience

APPENDIX 2

LETTERS OF PERMISSION

AND ETHICS APPROVAL

Springer
the language of science

Date: 05 February 2009

Dear Dr. Eid,

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Print run: 30

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Permission is contingent upon compliance with the aforementioned terms.

Sincerely,

Special Licensing Department
PS. Please be certain to include our reference in all correspondence.

From: "John Wei" Monday - February 2, 2009 2:17 PM

To: "Somaya Eid"
Subject: Re: Permission

You have our permission to use EPIC. Please refer to our website for supporting materials:
http://www.med.umich.edu/urology/research/EPIC.html
Please reference our developmental manuscript when you need a reference.
thanks and good luck on your work,
J

John T. Wei, M.D., M.S.
Associate Professor of Urology
Associate Chair for Research
University of Michigan Department of Urology
2301 Commonwealth Blvd - Rm 1021
Ann Arbor, MI 48105-2967

"It is not from the benevolence of the butcher, the brewer, or the baker, that we expect our dinner, but from their regard to their own interest." – Adam Smith, Wealth of Nations

>>> "Somaya Eid" 2/2/09 11:55 AM >>>
Dear John T Wei,

I am a student in the Epidemiology MSc program at the University of Western Ontario. I'm writing up a Clinical thesis on the; Health Related Quality of Life and Late Toxicity Related to hypofractionated Prostate Cancer Radiation Therapy", at the London Research Cancer Program. I am looking forward to obtain your permission to use the EPIC questionnaire as an appendix into my thesis to back up my thesis. Please feel free to email me with any questions. A simple email permission would be adequate. Thanks

From: "Will Hopkins" Wednesday - February 4, 2009 2:43 AM

To: "'Somaya Eid'"
Subject: RE: Permission

No problem Somaya. If you want a recent peer-reviewed paper (in Med Sci Sports Exerc, the journal of the American College of Sports Medicine) in which the thresholds are mentioned, you can download it and a summary slideshow from http://sportsci.org/2009/ProgressiveStats.zip. To reduce the risk of a copyright battle, which I would inevitably lose, I have not shown this link at the Sportscience site. The file is zipped to keep it hidden from search robots, for the same reason.

Will
Will G Hopkins, PhD FACSM
Institute of Sport and Recreation Research
AUT University, Akoranga Drive
Private Bag 92006
Auckland 0627, New Zealand

Skype WillTheKiwi
will@clear.net.nz, will.hopkins@aut.ac.nz
Sportscience http://sportsci.org
Statistics http://newstats.org
Be creative: break rules.

-----Original Message-----
From: Somaya Eid [mailto:Somaya.Eid@schulich.uwo.ca]
Sent: Wednesday, 4 February 2009 4:47 p.m.
To: will@clear.net.nz
Cc: George Rodrigues
Subject: Re: Permission

Dear Will G Hopkins,

I am a student in the Epidemiology MSc program at the University of Western Ontario. Im writing up a Clinical thesis on the; Health Related Quality of Life and Late Toxicity Related to hypofractionated Prostate Cancer Radiation Therapy, at the London Research Cancer Program. I am looking forward to obtain your permission to use your tables of the correlation corresponding to an effect size into my thesis to back up my thesis analysis part. Please feel free to email me with any questions.
A simple email permission would be adequate. Thanks.

From: office Monday - February 2, 2009 12:54 PM

Subject: permission granted

Attachments: Mime.822 (3238 bytes) [View] [Save As]

Dear Somaya,

Please use the SISA calculator and reproduce the web page in your thesis as you wish. We are
honored.

Success with your research!

Yours sincerely,

Daan Uitenbroek PhD
Quantitativeskills.com

Somaya Eid
> Dear SISA members,
>
> I am a student in the Epidemiology MSc program at the University of
> Western Ontario. I'm writing up a Clinical thesis on the; Health Related
> Quality of Life and Late Toxicity Related to hypofractionated Prostate
> Cancer Radiation Therapy", at the London Research Cancer Program. I am
> looking forward to obtain your permission to use your power calculator
> in order to calculate the sample size I would like to reproduce the
> webpage results into my thesis to back up my thesis rational for the
> sample size. Please feel free to email me with any questions. A simple
> email permission would be adequate. Thanks
> Best regards
> Dr. Somaya Eid
> London Regional Cancer Center
> University of Western Ontario, Department of Epidemiology and
> Biostatistics
> London, ON

Office of Research Ethics

The University of Western Ontario
Room 00045 Dental Sciences Building, London, ON, Canada N6A 5C1
Telephone: (519) 661-3036 Fax: (519) 850-2466 Email: ethics@uwo.ca
Website: www.uwo.ca/research/ethics

Western

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. G.B. Rodrigues
Review Number: 13465E **Review Level:** Expedited
Review Date: July 25, 2007
Protocol Title: Health-Related Quality of Life and Late Toxicity Related to Hypofractionated Prostate Cancer Radiation Therapy
Department and Institution: Oncology, London Health Sciences Centre
Sponsor:
Ethics Approval Date: August 07, 2007 **Expiry Date:** August 31, 2010
Documents Reviewed and Approved: UWO Protocol, Letter of Information and Consent
Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. John W. McDonald
Deputy Chair: Susan Hoddinott

Ethics Officer to Contact for Further Information

Jennifer McEwen ([illegible]@uwo.ca) Denise Grafton ([illegible]@uwo.ca) Ethics Officer (ethics@uwo.ca)

APPENDIX 3

SAMPLE SIZE CALCULATION BASED ON EPIC DOMAINS ENDPOINTS

Sample Size Table & Suggested Endpoint based on EPIC domains
Adapted from http://www.med.umich.edu/urology/research/EPIC.html

Number of EPIC domains as primary endpoints	Domain-specific significance level (for overall significance of 5%)	Potential Endpoints	Required Sample Size Per Treatment Group (Based on Effect Size of 0.5)	
			80% Power	90% Power
1	0.05	Any 1 of the summary scores - Urinary, Bowel, Sexual, Hormonal	64	86
4	0.0125	Urinary, Bowel, Sexual, and Hormonal Summary Scores	91	116
5	0.01	Urinary Irritative, Urinary Incontinence, Bowel, Sexual, and Hormonal Summary Scores	96	121
6	0.0083	Urinary Irritative, Urinary Incontinence, Bowel, Sexual, and Hormonal Summary Scores and SF-12 PCS	99	125
10	0.005	Urinary Irritative, Urinary Incontinence, and Function and Bother subscales for Urinary, Bowel, Sexual, and Hormonal Domains	109	136
12	0.0042	Urinary Irritative, Urinary Incontinence, Function and Bother subscales for Urinary, Bowel, Sexual, and Hormonal Domains, and SF-12 PCS and MCS Scores	112	140

If less than 100% response rate is anticipated, then sample sizes will need to be adjusted. For example, an expected 75% response rate at 2 years for a study with a single endpoint and 80% power would require 86 subjects (64/0.75 = 85.33). Last Retrieved April 2009

APPENDIX 4

EPIC/PCRT/EXIT SINGLE ITEMS RESPONSE FREQUENCY

SIMPLE STATISTICS OF QUESTIONNAIRE

EPIC GI Domain Simple Statistics Item Responses

EPIC questionnaire: How often had rectal urgency? Missing= 4				
Q8	Frequency	Percent	Cumulative frequency	Cumulative percent
More than once a day	5	2.69	5	2.69
About once a day	19	10.22	24	12.90
More than once a week	15	8.06	39	20.97
About once a week	22	11.83	61	32.80
Rarely or never	125	67.20	186	100

EPIC questionnaire: How often had uncontrolled leakage of stool. Missing=5				
Q9	Frequency	Percent	Cumulative frequency	Cumulative percent
More than once a day	5	2.70	5	2.70
About once a day	7	3.78	12	6.49
More than once a week	10	5.41	22	11.89
About once a week	20	10.81	42	22.70
Rarely or never	143	77.30	185	100

EPIC questionnaire: How often had loose stools? Missing=3				
Q10	Frequency	Percent	Cumulative frequency	Cumulative percent
Never	66	35.29	66	35.99
Rarely	85	45.45	151	80.75
About half the time	25	13.37	176	94.12
Usually	8	4.28	184	98.40
Always	3	1.60	187	100

EPIC questionnaire: How often had bloody stools? Missing=3				
Q11	Frequency	Percent	Cumulative frequency	Cumulative percent
Never	125	66.84	125	66.84
Rarely	39	20.86	164	87.70
About half the time	10	5.35	174	93.05
Usually	9	4.81	183	97.86
Always	4	2.14	187	100

EPIC questionnaire: How often had painful bowel movement? Missing=3				
Q12	Frequency	Percent	Cumulative frequency	Cumulative percent
Never	135	72.19	135	72.19
Rarely	46	24.60	181	96.79
About half the time	2	1.07	183	97.86
Usually	3	1.06	186	99.47
Always	1	0.53	187	100

EPIC questionnaire: How many bowel movement/day? Missing=3				
Q13	Frequency	Percent	Cumulative frequency	Cumulative percent
Two or less	140	74.87	140	74.87
Three to four	44	23.53	184	98.40
Five or more	3	1.60	187	100

EPIC questionnaire: How often had crimpy pain? Missing=5				
Q14	Frequency	Percent	Cumulative frequency	Cumulative percent
More than once a day	3	1.62	3	1.62
About once a day	7	3.78	8	4.32
More than once a week	10	5.41	17	9.19
About once a week	20	10.81	40	21.62
Rarely or never	143	77.30	185	100

EPIC questionnaire: How big a problem was urgency to have bowel movement? Missing=11				
Q15a	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	64	35.75	64	35.75
Very small problem	55	30.73	119	66.48
Small problem	26	14.53	145	81.01
Moderate problem	26	14.53	171	95.53
Big problem	8	4.47	179	100

EPIC questionnaire: How big a problem was increased frequency of bowel movement.				
Q15b Missing=15	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	96	54.86	96	54.86
Very small problem	35	20.00	131	74.86
Small problem	28	16.00	159	90.86
Moderate problem	11	6.29	170	97.14
Big problem	5	2.86	175	100

EPIC questionnaire: How big a problem was watery bowel movement Missing=13				
Q15c	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	123	69.49	123	69.49
Very small problem	25	14.12	148	83.62
Small problem	18	10.17	166	93.79
Moderate problem	7	3.95	173	97.74
Big problem	4	2.26	177	100

EPIC questionnaire: How big a problem was losing control for your stool Missing= 14				
Q15d	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	119	67.51	119	67.61
Very small problem	32	18.18	151	85.80
Small problem	13	7.39	164	93.18
Moderate problem	7	3.98	171	97.16
Big problem	5	2.84	176	100.00

EPIC questionnaire: How big a problem was bloody stools Missing=14				
Q15e	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	121	68.75	121	68.75
Very small problem	24	13.64	145	82.39
Small problem	14	7.95	159	90.34
Moderate problem	10	5.68	169	96.02
Big problem	7	3.98	176	100.00

EPIC questionnaire: How big a problem was Abdominal/pelvic rectal pain?				
Q15 Missing=14	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	135	76.70	135	76.70
Very small problem	31	17.61	166	94.32
Small problem	7	3.98	173	98.30
Moderate problem	3	1.70	176	100.00

EPIC questionnaire: Overall, How big a problem have your bowel habits been				
Q16 Missing=2	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	84	44.68	84	44.68
Very small problem	59	31.38	143	76.06
Small problem	19	10.11	162	86.17
Moderate problem	16	8.51	178	94.68
Big problem	10	5.32	188	100.00

EPIC GU Domain Simple Statistics Item Responses

EPIC questionnaire: How often leaked urine. Missing=1				
q1	Frequency	Percent	Cumulative frequency	Cumulative percent
More than once a day	11	5.82	11	5.82
About once a day	20	10.58	31	16.4
More than once a week	7	3.7	38	20.11
About once a week	17	8.99	55	29.1
Rarely or never	134	70.9	189	100

EPIC questionnaire: How often urinated blood				
q2	Frequency	Percent	Cumulative frequency	Cumulative percent
More than once a day	1	0.53	1	0.53
About once a week	2	1.05	3	1.58
Rarely or never	187	98.42	190	100

EPIC questionnaire: Pain with Urination?.				
q3	Frequency	Percent	Cumulative frequency	Cumulative percent
More than once a day	4	2.11	4	2.11
About once a day	3	1.58	7	3.68
More than once a week	2	1.05	9	4.74
About once a week	7	3.68	16	8.42
Rarely or never	174	91.58	190	100

EPIC questionnaire: Urinary control				
Q4	Frequency	Percent	Cumulative frequency	Cumulative percent
Frequent dribbling	9	4.74	9	4.74
Occasional dribbling	69	36.32	78	41.05
Total control	112	58.95	190	100

EPIC questionnaire: How many pad per day. Missing=1				
Q5	Frequency	Percent	Cumulative frequency	Cumulative percent
None	178	94.18	178	94.18
1 pad per day	9	4.76	187	98.94
3 or more pads per day	2	1.06	189	100

EPIC questionnaire: Dripping or leaking urine. Missing=14				
Q6a	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	110	62.5	110	62.5
Very small problem	49	27.84	159	90.34
Small problem	9	5.11	168	95.45
Moderate problem	6	3.41	174	98.86
Big problem	2	1.14	176	100

EPIC questionnaire: Pain or burning on urination. Missing=16				
q6b	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	152	87.36	152	87.36
Very small problem	15	8.62	167	95.98
Small problem	6	3.45	173	99.43
Moderate problem	1	0.57	174	100

EPIC questionnaire: Bleed with urination. Missing=12				
Q6c	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	171	96.07	171	96.07
Very small problem	2	1.12	173	97.19
Small problem	3	1.69	176	98.88
Moderate problem	2	1.12	178	100

EPIC questionnaire: Weak urine stream. Missing=17				
Q6d	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	84	48.55	84	48.55
Very small problem	50	28.9	134	77.46
Small problem	21	12.14	155	89.6
Moderate problem	15	8.67	170	98.27
Big problem	3	1.73	173	100

EPIC questionnaire: Waking to urinate. Missing=11				
Q6e	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	20	11.17	20	11.17
Very small problem	63	35.2	83	46.37
Small problem	50	27.93	133	74.3
Moderate problem	37	20.67	170	94.97
Big problem	9	5.03	179	100

EPIC questionnaire: Need to urinate frequently. Missing=12				
Q6f	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	57	32.02	57	32.02
Very small problem	54	30.34	111	62.36
Small problem	27	15.17	138	77.53
Moderate problem	37	20.79	175	98.31
Big problem	3	1.69	178	100

EPIC questionnaire: Overall, How big a problem has your urinary function been				
q7	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	85	44.97	85	44.97
Very small problem	66	34.92	151	79.89
Small problem	19	10.05	170	89.95
Moderate problem	17	8.99	187	98.94
Big problem	2	1.06	189	100

EPIC Sexual Domain Simple Statistics Item Responses

EPIC questionnaire: Level of **sexual** desire. Missing=9				
Q17a	Frequency	Percent	Cumulative frequency	Cumulative percent
Very poor to none	96	53.04	96	53.04
Poor	35	19.34	131	72.38
Fair	25	13.81	156	86.19
Good	17	9.39	173	95.58
Very good	8	4.42	181	100.00

EPIC questionnaire: Ability to have an erection. Missing=17				
Q17b	Frequency	Percent	Cumulative frequency	Cumulative percent
Very poor to none	119	68.79	119	68.79
Poor	30	17.34	149	86.13
Fair	12	6.94	161	93.06
Good	9	5.20	170	98.27
Very good	3	1.73	173	100.00

EPIC questionnaire: Ability to reach orgasm. Missing=21				
Q17c	Frequency	Percent	Cumulative frequency	Cumulative percent
Very poor to none	119	70.41	119	70.41
Poor	23	13.61	142	84.02
Fair	11	6.51	153	90.53
Good	12	7.10	165	97.63
Very good	4	2.37	169	100.00

EPIC questionnaire: Describe quality of your erections. Missing=8				
Q 18	Frequency	Percent	Cumulative frequency	Cumulative percent
None at all	105	57.69	105	57.69
Not firm enough for any sexual activity	39	21.43	144	79.12
Firm enough for masturbation and foreplay only	20	10.99	164	90.11
Firm enough for intercourse	18	9.89	182	100.00

EPIC questionnaire: Frequency of erections. Missing=14				
Q 19	Frequency	Percent	Cum FR	Cum%
I NEVER had an erection when I wanted one	137	77.84	137	77.84
I had an erection LESS THAN HALF the time I wanted one	11	6.25	148	84.09
I had an erection ABOUT HALF the time I wanted one	10	5.68	158	89.77
I had an erection MORE THAN HALF the time I wanted one	7	3.98	165	93.75
I had an erection WHENEVER I want one	11	6.25	176	100.00

EPIC questionnaire: Hoe often any sexual activity. Missing=7				
Q20	Frequency	Percent	Cumulative frequency	Cumulative percent
Never	140	76.50	140	76.50
Less than once a week	26	14.21	166	90.71
About once a weak	12	6.56	178	97.27
Several times a week	4	2.19	182	99.45
Daily	1	0.55	183	100

EPIC questionnaire: Awake with erections? Missing=7				
Q 21	Frequency	Percent	Cumulative frequency	Cumulative percent
Not at all	143	78.14	143	78.14
Less than once a week	25	13.66	168	91.80
About once a week	12	6.56	180	98.36
Several times a week	2	1.09	182	99.45
Daily	1	0.55	183	100.00

EPIC questionnaire: How often – sexual intercourse? Missing= 7				
Q 22	Frequency	Percent	Cumulative frequency	Cumulative percent
Not at all	157	85.79	155	85.79
Less than once a week	17	9.29	174	95.08
About once a weak	8	4.37	182	99.45
Several times a week	1	0.55	183	100.00

EPIC questionnaire: Rate ability to function sexually? Missing= 7				
Q 23	Frequency	Percent	Cumulative frequency	Cumulative percent
Very poor	141	77.05	141	77.05
Poor	22	12.02	163	89.07
Fair	10	5.46	173	94.54
Good	8	4.37	181	98.91
Very Good	2	1.09	183	100.00

EPIC questionnaire: How big a problem was your level of sexual desire? Missing= 17				
Q 24a	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	54	31.21	54	31.21
Very small problem	22	12.72	76	43.93
Small problem	18	10.40	94	54.34
Moderate Problem	21	12.14	115	66.47
Big Problem	58	33.53	173	100.00

EPIC questionnaire: How big a problem was ability to have erection? Missing=24				
Q 24b	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	36	21.69	36	21.69
Very small problem	11	6.63	47	28.31
Small problem	13	7.83	60	36.14
Moderate Problem	15	9.04	75	45.18
Big Problem	91	54.82	166	100.00

EPIC questionnaire: How big a problem was ability to reach an orgasm? Missing= 24				
Q 24c	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	37	22.29	37	22.29
Very small problem	16	9.64	53	31.93
Small problem	13	7.83	66	39.76
Moderate Problem	13	7.83	79	47.59
Big Problem	87	52.41	166	100.00

EPIC questionnaire: Overall, how big a problem has your sexual function been? Missing=9				
Q 25	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	54	29.83	54	29.83
Very small problem	17	9.39	71	39.23
Small problem	15	8.29	86	47.51
Moderate Problem	22	12.15	108	59.67
Big Problem	73	40.33	181	100.00

EPIC Hormonal Domain Simple Statistics Item Responses

EPIC questionnaire: How often – Hot Flashes? Missing= 4				
Q 26	Frequency	Percent	Cumulative frequency	Cumulative percent
More than once a day	30	16.13	30	16.13
About once a day	11	5.91	41	22.04
More than once a week	6	3.23	47	25.27
About once a week	5	2.69	52	27.96
Rarely or never	143	72.04	186	100

EPIC questionnaire: How often – breast tenderness? Missing=12				
Q 27	Frequency	Percent	Cumulative frequency	Cumulative percent
More than once a day	4	2.25	4	2.25
About once a day	1	0.56	5	2.81
More than once a week	3	1.69	8	4.49
About once a week	1	0.56	9	5.06
Rarely or never	169	94.94	178	100.00

EPIC questionnaire: How often - felt depressed? Missing=4				
Q 28	Frequency	Percent	Cumulative frequency	Cumulative percent
More than once a day	6	3.23	6	3.23
About once a day	5	2.69	11	5.91
More than once a week	10	5.38	21	11.29
About once a week	27	14.52	48	25.81
Rarely or never	138	74.19	186	100.00

EPIC questionnaire: How often – lack of energy? Missing=2				
Q 29	Frequency	Percent	Cumulative frequency	Cumulative percent
More than once a day	29	15.43	29	15.43
About once a day	30	15.96	59	31.38
More than once a week	20	10.64	79	42.02
About once a week	36	19.15	115	61.17
Rarely or never	73	38.83	188	100.00

EPIC questionnaire: How much change in your weight? Missing= 0				
Q 30	Frequency	Percent	Cumulative frequency	Cumulative percent
Gained 10 pounds or more	5	2.63	5	2.63
Gained less than 10 pounds	26	13.68	31	16.32
No change in weight	140	73.68	171	90
Lost less than 10 pounds	15	7.89	186	97.89
Lost 10 pounds or more	4	2.11	190	100.00

EPIC questionnaire: How big a problem – Hot Flashes? Missing=10				
Q 31a	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	130	72.22	130	72.22
Very small problem	21	11.67	151	83.89
Small problem	9	5.00	160	88.89
Moderate problem	17	9.44	177	98.33
Big problem	3	1.67	180	100.00

EPIC questionnaire: How big a problem – breast tenderness? Missing=13				
Q 31b	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	164	92.66	164	92.66
Very small problem	8	4.52	172	97.18
Small problem	4	2.26	176	99.44
Moderate problem	1	0.56	177	100.00

EPIC questionnaire: How big a problem – Loss of body hair? Missing=13				
Q 31c	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	161	90.96	161	90.96
Very small problem	11	6.21	172	97.18
Small problem	1	0.56	173	97.74
Moderate problem	3	1.69	176	99.44
Big problem	1	0.56	177	100.00

EPIC questionnaire: How big a problem – feeling depressed? Missing=12				
Q 31d	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	126	70.79	126	70.79
Very small problem	26	14.61	152	85.39
Small problem	15	8.43	167	93.82
Moderate problem	7	3.93	174	97.75
Big problem	4	2.25	178	100.00

EPIC questionnaire: How big a problem – Lack of energy? Missing=8				
Q 31e	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	75	41.21	75	41.21
Very small problem	40	21.98	115	63.19
Small problem	30	16.48	145	79.67
Moderate problem	24	13.19	169	92.86
Big problem	13	7.14	182	100.00

EPIC questionnaire: How big a problem – change in body weight? Missing=11				
Q 31f	Frequency	Percent	Cumulative frequency	Cumulative percent
No problem	144	80.45	144	80.45
Very small problem	21	11.73	165	92.18
Small problem	6	3.35	171	95.53
Moderate problem	4	2.23	175	97.77
Big problem	4	2.23	179	100.00

Q 31 Percent	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
Hot Flashes	72.22	11.67	5	9.44	1.67
Brest Tenderness	92.66	4.52	2.26	0.56	
Loss of Body Hair	90.96	6.21	0.56	1.69	0.56
Feeling Depressed	70.79	14.61	8.43	3.93	2.25
Lack of Energy	41.21	21.98	16.48	13.19	7.14
Change in Body Weight	80.45	11.73	3.35	2.23	2.23

Q 31 Frequency	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
Hot Flashes	130	21	9	17	3
Brest Tenderness	164	8	4	1	
Loss of Body Hair	161	11	1	3	1
Feeling Depressed	126	26	15	7	4
Lack of Energy	75	40	30	24	13
Change in Body Weight	144	21	6	4	4

EPIC Satisfaction Simple Statistics Item Responses

EPIC questionnaire: Overall, How satisfied are you with the treatment you received for your prostate cancer? Missing=2				
Q 32	Frequency	Percent	Cumulative frequency	Cumulative percent
Extremely dissatisfied	8	4.26	8	4.26
Dissatisfied	1	0.53	9	4.79
Uncertain	14	7.45	23	12.23
Satisfied	74	39.36	97	51.60
Extremely satisfied	91	48.40	188	100.00

PCRT Simple Statistics Item Responses

PCRT questionnaire: How often had you had blood in your bowel movement? Missing= 6				
RT1 (Hematochezia)	Frequency	Percent	Cumulative frequency	Cumulative percent
Never	127	69.02	127	69.02
sometimes	39	21.20	166	90.22
Frequently	5	2.72	171	92.93
Most of the time	2	1.09	173	94.02
All or almost all of the time	11	5.98	184	100

PCRT questionnaire: How much blood have you had in your bowel movements? Missing=92				
RT2 (Hematochezia)	Frequency	Percent	Cumulative frequency	Cumulative percent
None	43	43.88	43	43.88
Slight tinge	24	24.49	67	68.37
Light bleeding	18	18.37	85	86.73
Medium bleeding	11	11.22	96	97.96
Heavy bleeding	2	2.04	98	100

PCRT questionnaire: How much upset in your daily activities has the blood caused you? Missing=100				
RT3 (Hematochezia)	Frequency	Percent	Cumulative frequency	Cumulative percent
No upset or disruption	56	62.22	56	62.22
Very little upset or disruption	21	23.33	77	85.56
Small upset or disruption	3	3.33	80	88.89
Moderate little upset or disruption	7	7.78	87	96.67
Sever upset or disruption	3	3.33	90	100

PCRT questionnaire: Required any tests to investigate the bleeding?				
Tests	Frequency	Percent	Cumulative frequency	Cumulative percent
No	3	1.58	3	1.58
Yes	36	18.95	39	20.53
Not answered	151	79.47	190	100

PCRT questionnaire: Transfusion because of heavy bleeding?				
transfuse	Frequency	Percent	Cumulative frequency	Cumulative percent
No	5	2.63	5	2.63
Yes	4	2.11	9	4.74
Not answered	181	95.26	190	100

PCRT questionnaire: Prescription medications for the bleeding? Missing=2				
med	Frequency	Percent	Cumulative frequency	Cumulative percent
No	4	2.13	4	2.13
Yes	9	4.79	13	6.91
Not answered	175	93.09	188	100

PCRT questionnaire: Laser or chemical treatments to rectum for bleeding?				
laser	Frequency	Percent	Cumulative frequency	Cumulative percent
No	5	2.63	5	2.63
Yes	12	6.32	17	8.95
Not answered	173	91.05	190	100

PCRT questionnaire: Rectal surgery because of bleeding?				
Rectalsurg	Frequency	Percent	Cumulative frequency	Cumulative percent
No	7	3.68	7	3.68
Yes	5	2.63	12	6.32
Not answered	178	93.68	190	100

PCRT questionnaire: How much loose or liquid bowel movements/day? Missing=11				
RT4 (Diarrhea)	Frequency	Percent	Cumulative frequency	Cumulative percent
None	102	56.98	102	56.98
< 1 loose or liquid bowel movement per day	46	25.70	148	82.68
1 loose or liquid bowel movement per day	17	9.50	165	92.18
Between 2 and 4 loose or liquid bowel movement per day	13	7.26	178	99.44
5 or > loose or liquid bowel movement per day	1	0.56	179	100

PCRT questionnaire: How frequently did you move your bowel Before starting radiotherapy?				
RT4a (Diarrhea)	Frequency	Percent	Cumulative frequency	Cumulative percent
Once a day	75	39.47	75	39.47
Twice a day	32	16.84	107	56.32
Three times a day	6	3.16	113	59.47
Four or more times a day	1	0.53	114	60
Not answered	76	40	190	100

PCRT questionnaire: Did you have problems with loose or liquid stools Before starting radiotherapy?				
RT4b (Diarrhea)	Frequency	Percent	Cumulative frequency	Cumulative percent
No	107	56.32	107	56.32
Yes	11	5.79	118	62.11
Not answered	72	37.89	190	100

PCRT questionnaire: How upset is your daily activities by loose bowel movement? Missing=65				
RT5	Frequency	Percent	Cumulative frequency	Cumulative percent
No upset or disruption	63	50.40	63	50.40
Very little upset or disruption	31	24.80	94	75.20
Small upset or disruption	16	12.80	110	88
Moderate little upset or disruption	12	9.60	122	97.60
Sever upset or disruption	3	2.40	125	100

PCRT questionnaire: Do you take anti-diarrhea pills such as Lomotil or Imodium?				
RT5a (Diarrhea)	Frequency	Percent	Cumulative frequency	Cumulative percent
Never	104	54.74	104	54.74
Occasionally	21	11.05	125	65.79
Every week	1	0.53	126	66.32
Daily	3	1.58	129	67.89
Not answered	61	32.11	190	100

PCRT questionnaire: Are there some foods that you avoid because they will cause diarrhea				
RT5b (Diarrhea)	Frequency	Percent	Cumulative frequency	Cumulative percent
No	104	54.74	104	54.74
Yes	27	14.21	131	68.95
Not answered	59	31.05	190	100

PCRT questionnaire: How often have you experienced pelvic pain or cramping?				
RT6 (Pelvic pain)	Frequency	Percent	Cumulative frequency	Cumulative percent
Never	135	72.58	135	72.58
Some times	47	25.27	182	97.85
Frequently	4	2.15	186	100.00

PCRT questionnaire: How sever has the pelvic pain ? Missing=102				
RT7 (Pelvic pain)	Frequency	Percent	Cumulative frequency	Cumulative percent
Not uncomfortable	45	51.14	45	51.14
Mildly uncomfortable	31	35.23	76	86.36
Somewhat uncomfortable	8	9.09	84	95.45
Moderately uncomfortable	3	3.41	87	98.86
Very uncomfortable	1	1.14	88	100.00

PCRT questionnaire: How much upset in your daily activities has pelvic pain caused?				
RT8 (Pelvic pain) Missing=104	Frequency	Percent	Cumulative frequency	Cumulative percent
No upset or disruption	60	69.77	60	69.77
Very little upset or disruption	17	19.77	77	89.53
Small upset or disruption	3	3.49	80	93.02
Moderate little upset or disruption	4	4.65	84	97.67
Sever upset or disruption	2	2.33	86	100.00

PCRT questionnaire: How often have you felt the urge to have a bowel movement and not had one? Missing= 2				
RT9 (Bowel tenesmus/control)	Frequency	Percent	Cumulative frequency	Cumulative percent
Never	89	47.34	89	47.34
Rarely	78	41.49	167	88.83
Frequently	18	9.57	185	98.40
Most of the time	1	0.53	186	98.94
All or almost all of the time	2	1.06	188	100.00

PCRT questionnaire: How much upset in your daily activities has having urge to have a b.m? Missing=67				
RT10 RT9 (Bowel tenesmus/control)	Frequency	Percent	Cumulative frequency	Cumulative percent
No upset or disruption	55	44.72	55	44.72
Very little upset or disruption	44	35.77	99	80.49
Small upset or disruption	8	6.50	107	86.99
Moderate little upset or disruption	16	13.01	123	100

PCRT questionnaire: How much control have you had over your bowel? Missing=6				
RT11 RT9 (Bowel tenesmus/control)	Frequency	Percent	Cumulative frequency	Cumulative percent
Total control	104	56.52	104	56.52
Control most of the time	66	35.87	170	92.39
Some control	8	4.35	178	96.74
Very little control	5	2.72	183	99.46
No control	1	0.54	184	100

PCRT questionnaire: How much upset in your daily activities has your degree of bowel control? Missing=94				
RT12	Frequency	Percent	Cumulative frequency	Cumulative percent
No upset or disruption	32	33.33	32	33.33
Very little upset or disruption	36	37.50	68	70.83
Small upset or disruption	15	15.63	83	86.46
Moderate little upset or disruption	12	12.50	95	98.96
Sever upset or disruption	1	1.04	96	100

PCRT questionnaire: How often did you urinate during the course of your day? Missing=6				
RT13 (frequency/nocturia)	Frequency	Percent	Cumulative frequency	Cumulative percent
Two or fewer times	8	4.35	8	4.35
Between three and five times	95	51.63	103	55.98
Between six and eight times	63	34.24	166	90.22
Between nine and twelve times	15	8.15	181	98.37
Thirteen times or more	3	1.63	184	100

PCRT questionnaire: Since your radiotherapy, do you feel that your urinary stream is?				
RT13a(frequency/nocturia)	Frequency	Percent	Cumulative frequency	Cumulative percent
Slower than before	69	36.32	69	36.32
The same	88	46.32	157	82.63
Improved	31	16.32	188	98.95
Not answered	2	1.05	190	100

PCRT questionnaire: How often did you get up during the night to urinate?				
RT14(frequency/nocturia)	Frequency	Percent	Cumulative frequency	Cumulative percent
Never	6	3.17	8	3.17
Occasionally getting up once in the night	28	14.81	34	17.99
Getting up once in the night	50	26.46	84	44.44
Getting up between two and four times in the night	100	52.91	184	97.35
Getting up 5 or more times in the night	5	2.65	189	100

PCRT questionnaire: How much upset in your daily activities has frequency caused? Missing=3				
RT15(frequency/nocturia)	Frequency	Percent	Cumulative frequency	Cumulative percent
No upset or disruption	66	35.29	66	35.29
Very little upset or disruption	74	39.57	140	74.87
Small upset or disruption	24	12.83	164	87.70
Moderate little upset or disruption	22	11.76	186	99.47
Sever upset or disruption	1	0.53	187	100

PCRT questionnaire: How often pain during urination? Missing=3				
RT16	Frequency	Percent	Cumulative frequency	Cumulative percent
Never	156	83.42	156	83.42
sometimes	25	13.37	181	96.79
Frequently	3	1.60	184	98.40
Most of the time	2	1.07	186	99.47
All or almost all of the time	1	0.53	187	100

PCRT questionnaire: How severe pain or urination? Missing=153				
RT17	Frequency	Percent	Cumulative frequency	Cumulative percent
Very mild pain or discomfort	28	75.68	28	75.68
Mild pain or discomfort	5	13.51	33	89.19
Somewhat uncomfortable pain or discomfort	3	8.11	36	97.30
Moderately uncomfortable pain or discomfort	1	2.70	37	100

PCRT questionnaire: How much upset in your daily activities has your urination caused? Missing=138				
RT18	Frequency	Percent	Cumulative frequency	Cumulative percent
No upset or disruption	28	53.85	28	53.85
Very little upset or disruption	18	34.62	46	88.46
Small upset or disruption	3	5.77	49	94.23
Moderate little upset or disruption	3	5.77	52	100

PCRT questionnaire: If you have pain on urination, Have you needed to take painkillers?				
RT18a	Frequency	Percent	Cumulative frequency	Cumulative percent
Never	53	27.89	53	27.89
Occasionally	1	0.53	54	27.42
Daily	1	0.53	55	28.95
Not answered	135	71.05	190	100

PCRT questionnaire: How often blood in urine? Missing=20				
RT19	Frequency	Percent	Cumulative frequency	Cumulative percent
Never	177	95.16	177	95.16
Rarely	9	4.84	186	100

PCRT questionnaire: How much upset has blood in urine caused? Missing=3				
RT20	Frequency	Percent	Cumulative frequency	Cumulative percent
No upset or disruption	183	97.86	183	97.86
Very little upset or disruption	3	1.60	186	99.47
Small upset or disruption	1	0.53	187	100

PCRT questionnaire: How often did you leak urine? Missing=8				
RT21	Frequency	Percent	Cumulative frequency	Cumulative percent
Never	120	65.93	120	65.93
Once a day	44	24.18	164	90.11
Twice a day	10	5.49	174	95.60
Three or five times a day	6	3.30	180	98.90
Constantly leak urine	2	1.10	182	100

PCRT questionnaire: How many incontinence pads used per day? Missing=8				
RT22 Incontinence	Frequency	Percent	Cumulative frequency	Cumulative percent
None	170	93.41	170	93.41
One	9	4.95	179	98.35
Two	1	0.55	180	98.90
Three to five	1	0.55	181	99.45
Six or more	1	0.55	182	100

PCRT questionnaire: How much upset in your daily activities has your urination caused? Missing=8				
RT23 Incontinence	Frequency	Percent	Cumulative frequency	Cumulative percent
No upset or disruption	170	93.41	170	93.41
Very little upset or disruption	6	3.30	176	96.70
Small upset or disruption	4	2.20	180	98.90
Moderate little upset or disruption	2	1.10	182	100

PCRT questionnaire: Ability to obtain and maintain an erection? Missing=20				
RT24 sexual impairment	Frequency	Percent	Cumulative frequency	Cumulative percent
Very good ability	1	0.59	1	0.59
Good ability	8	4.71	9	5.29
Moderate ability	13	7.65	22	12.94
Poor ability	24	14.12	46	27.06
No ability or very poor ability	124	72.94	170	100

PCRT questionnaire: How much upset in your sexual functioning has your ability to obtain and maintain an erection ? Missing=23				
RT25 sexual bother	Frequency	Percent	Cumulative frequency	Cumulative percent
No upset or disruption	57	34.13	57	34.13
Very little upset or disruption	33	19.76	90	53.89
Small upset or disruption	13	7.78	103	61.68
Moderate little upset or disruption	36	21.56	139	83.23
Sever upset or disruption	59	16.77	167	100

PCRT questionnaire: On average, during the past 4 weeks, how would you rate your level of sexual interest? Missing=14				
RT26 sexual impairment	Frequency	Percent	Cumulative frequency	Cumulative percent
Very high level of interest	2	1.14	2	1.14
High level of interest	17	9.66	19	10.80
Moderate level of interest	47	26.70	66	37.50
Low level of interest	51	28.98	117	66.48
No interest	59	33.52	176	100

PCRT questionnaire: How much has your level of sexual interest caused upset of sexual activities? Missing=26				
RT27 sexual bother	Frequency	Percent	Cumulative frequency	Cumulative percent
No upset or disruption	75	45.73	75	45.73
Very little upset or disruption	22	13.41	97	59.15
Small upset or disruption	14	8.54	111	67.68
Moderate little upset or disruption	30	18.29	141	85.98
Sever upset or disruption	23	14.02	164	100

PCRT questionnaire: How happy and contented were you with your sex life? Missing=23				
RT28 sexual impairment	Frequency	Percent	Cumulative frequency	Cumulative percent
Extremely happy or satisfied	12	7.19	12	7.19
Somewhat happy or satisfied	18	10.78	30	17.96
Neither happy or unhappy	47	28.14	77	46.11
Somewhat unhappy or dissatisfied	31	18.56	108	64.67
Not happy or satisfied at all	59	35.33	167	100

PCRT questionnaire: Since your radiotherapy, have you tried any RX to help your sexual function?				
RT29	Frequency	Percent	Cumulative frequency	Cumulative percent
No	168	88.42	168	88.42
Yes	12	6.32	180	94.74
Not answer	10	5.26	190	100

PCRT questionnaire: If you had Rx to aid sexual function: Have these been effective				
RT29a	Frequency	Percent	Cumulative frequency	Cumulative percent
Never	9	4.74	9	4.74
Some of the time	4	2.11	13	6.84
Always	2	1.05	15	7.89
Not answered	175	92.11	190	100

PCRT questionnaire: Over past 4weeks, which statement best describes your sexual Intercourse?				
RT29b	Frequency	Percent	Cumulative frequency	Cumulative percent
Not having sexual intercourse by choice	21	11.05	21	11.05
Not having sexual intercourse due to lack of interest	37	19.47	58	30.53
Not having sexual intercourse due to lack of opportunity	14	7.37	72	37.89
Not having sexual intercourse due to inability to obtain and maintain an erection	86	45.26	158	83.16
Not having sexual intercourse	17	8.95	175	92.11
Not answered	15	7.89	190	100

PCRT questionnaire: RTOG Late toxicity grades				
GI-Grade	Frequency	Percent	Cumulative frequency	Cumulative percent
0	79	41.58	79	41.58
1	88	46.32	167	87.89
2	6	3.16	173	91.05
3	12	6.32	185	97.37
4	5	2.63	190	100

PCRT questionnaire: RTOG Late toxicity grades				
GU-Grade	Frequency	Percent	Cumulative frequency	Cumulative percent
0	3	1.58	3	1.58
1	54	28.42	57	30
2	112	58.95	169	88.95
3	19	10	188	98.95
4	2	1.05	190	100

Exit Questionnaire Simple statistics Item responses

Q1: My current QOL in terms of bowel movement is:				
Bowel movement	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Excellent	33/186	17.74	33	17.74
Very good	60/186	32.26	93	50
Good	65/186	34.95	158	84.95
Poor	24/186	12.9	182	97.85
Extremely poor	4/186	2.15	186	100

Q2: Since completion of the prostate RT, my QOL in terms of bowel movement is:				
Bowel movement	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Much better	7/186	3.76	7	3.76
Better	11/186	5.91	18	9.68
About the same	125/186	67.2	143	76.88
Worse	34/186	18.28	177	95.16
Much worth	9/186	4.84	186	100

Q3: My current QOL in terms of urination is:				
Urination	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Excellent	14/186	7.53	14	7.53
Very good	57/186	30.65	71	38.17
Good	91/186	48.92	162	87.1
Poor	23/186	12.37	185	99.46
Extremely poor	1/186	0.54	186	100

Q4: Since completion of the prostate RT, my QOL in terms of urination is:				
Urination	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Much better	8/186	4.30	8	4.30
Better	26/186	13.98	34	18.28
About the same	110/186	59.14	144	77.42
Worse	37/186	19.89	181	97.31
Much worse	5/186	2.69	186	100

Q5: My current QOL in terms of sexual function is:				
Sexual	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Excellent	3/174	1.72	3	1.72
Very good	8/174	4.6	11	6.32

Good	14/174	8.05	25	14.37
Poor	56/174	32.18	81	46.55
Extremely poor	93/174	53.45	174	100

Q6: Since completion of the prostate RT, my QOL in terms of sexual function is:				
Sexual Function	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Better	1/169	0.59	1	0.59
About the same	59/169	34.91	60	35.50
Worse	65/169	38.46	125	73.96
Much worse	44/169	26.04	169	100

Q 7: My overall QOL right now is:				
Over all QOL	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Excellent	22	11.83	22	11.83
Very good	66	35.48	88	47.31
Good	74	39.78	162	87.1
Poor	22	11.83	184	98.92
Extremely poor	2	1.08	186	100

Q 8: Since completion of the prostate RT, my overall QOL is:				
Over all QOL	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Much better	8	4.3	8	4.3
Better	33	17.74	41	22.04
About the same	117	62.9	158	84.95
Worse	21	11.29	179	96.24
Much worth	7	3.76	186	100