University of Alberta

Impact of conventional fractionated RT to pelvic lymph nodes and dose-escalated hypofractionated RT to prostate gland using IMRT treatment delivery in high-risk prostate cancer

by

Nadeem Pervez

A thesis submitted to the faculty of Graduate Studies and Research in partial fulfillment of requirements for the degree of

Master of Science

Oncology

Fall 2009

Edmonton, Alberta

Examining Committee

David Murray, Oncology

Robert Pearcey, Oncology

Marc Mackenzie, Oncology

Andrew Shaw, Oncology

Jackson Wu, Oncology, University of Calgary

DEDICATION:

I owe all of my achievements to my late mother, Moyeeda Khatoon. Without her love, care and support, I would not be where I am today. May Allah reserve the highest place for her in the heavens. I also appreciate the assistance of my all family members who devoted their time and energy in supporting me.

ABSTRACT

Prostate cancer is the most common cancer among Canadian men. The standard treatment in high-risk category is radical radiation, with androgen suppression treatment (AST). Significant disease progression is reported despite this approach. Radiation dose escalation has been shown to improve disease-free survival; however, it results in higher toxicities. Hypofractionated radiation schedules (larger dose each fraction in shorter overall treatment time) are expected to deliver higher biological doses. A hypofractionated scheme was used in this study to escalate radiation doses with AST. Treatment was well tolerated acutely. Early results of self-administered quality of life reported by patients shows a decrease in QOL which is comparable to other treatment schedules. Significant positional variation of the prostate was observed during treatment. Therefore, we suggest daily target verification to avoid a target miss. Initial late effects are reasonable and early treatment outcomes are promising. Longer follow-up is required for full outcomes assessments.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude and appreciation to my mentor, Dr. Robert Pearcey, my supervisor, Dr. David Murray and my supervisory committee member, Dr. Marc Mackenzie for their continuous support. Thank you Bob, Dave and Marc for your support and direction when needed and your freedom in between.

I would also like to acknowledge my patients who increased my knowledge in Oncology, and especially those who participated in this study. I would like to take this opportunity to acknowledge physicians, physicists, statistician, research nurses and data managers who assisted in the conduction of this study.

Many thanks to the Alberta Cancer Board for the Bridge and Pilot funding for this project.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACB	Alberta Cancer Board
AST	androgen suppression treatment
BCC	basal cell carcinoma
BED	biologically equivalent dose
bNED	no biochemical evidence of disease
CCI	Cross Cancer Institute
coRT	conventional radiotherapy
CRT	conformal radiotherapy
CT	computed tomography
CTCAE v3.0	common terminology criteria for adverse events version 3.0
DICOM	digital imaging and communications in medicine
DQA	delivery quality assessment
DRE	digital rectal examination
DVHs	dose volume histograms
EORTC	European organization for research and treatment of cancer

EPIC	expanded prostate cancer index composite
Fr	fraction
GEE	generalized estimating equation
GI	Gastrointestinal
Gy	Gray – radiation unit (1 Joule energy absorbed per kilogram)
GU	Genitourinary
LI	labeling index
LQ	linear-quadratic
L5	Lumber vertebra 5
LN	lymph nodes
IGAR	image guided adaptive radiotherapy
IMRT	intensity modulated radiotherapy
KVCT	kilovoltage computed tomography
MLC	multileaf collimator
mm	millimeter
MRI	magnetic resonance Imaging
MVCT	megavoltage computed tomography
NTD	nominal total dose

OARs	organs at risk
PACS	picture archiving and communications system
PCI	prostate cancer index
PDE	Phosphodiesterase
PI	principle investigator
PROFIT	prostate fractionated irradiation trial
PSA	prostate specific antigen
QA	quality assurance
QOL	quality of life
RAR	region at risk
REB	research ethic board
ROI	region of interest
RT	radiotherapy
RTOG	radiation therapy oncology group
S1	sacral vertebra 1
SAEs	serious adverse events
SAS	statistical analysis software
SCC	squamous cell carcinoma
SD	standard deviation

SPSS	Statistical Package for the Social Sciences
SV	seminal vesicle
TURP	transurethral resection of prostate
UCLA	University of California, Los Angeles
VNC	virtual network connection
3DCRT	three-dimensional conformal radiotherapy
3T	three Tesla
α	α component of cell killing
β	β component of cell killing
α/β	ratio of α and β

1. Background and introduction

1.1. Incidence:

Prostate cancer is the most common cancer among Canadian men. In 2009, it is estimated that 25,500 men will be diagnosed with prostate cancer. An estimated 4,400 men will die of the disease within the same year. One in 7.4 men will develop prostate cancer and it is predicted that one in 27 will die as a result of it (1).

1.2. Risk group (Appendix 1 & 2):

Localized prostate cancer is classified using the Canadian consensus criteria into low, intermediate, and high-risk groups (2). This classification is based on:

a) Prostate specific antigen (PSA) levels in serum detected by a blood test.

b) Clinical stage established by clinical test including digital rectal examination (DRE) and radiological examinations including computed topography (CT) or magnetic resonance imaging (MRI) scans and bone scans.

c) Pathology report from which Gleason scores (overall tumor differentiation) is derived.

Patients who have PSA >20 ng/ml, and/or clinical stage T3/T4, and/or Gleason Score 8 to 10 at presentation or diagnosis are classified as the

high-risk group (2). Whereas another group of patients who have a combination of a Gleason score of 7 and a PSA ≥15 ng/ml have approximately a 20% risk of pelvic lymph node involvement (45). These patients may benefit from radiotherapy (RT) to pelvic lymph nodes (LN).

1.3. Treatment:

The most common curative treatment option, for men with high-risk prostate cancer, is a radical course of RT, usually with androgen suppression treatment (AST). All of these patients have a more than 20% risk of subclinical metastasis to pelvic LN. Therefore, elective irradiation of pelvic LN is considered necessary in the majority of North American centres. Large multi-institutional randomized controlled trials from Europe, European organization for research and treatment of cancer (EORTC) (3) and the USA, radiation therapy oncology group (RTOG) (4, 5) have shown an improved overall and disease free survival using this approach.

1.3.1. Standard treatment:

Up until now the typical plan for RT usually consisted of two consecutive phases with a reduction in irradiated volume in the second phase. This is necessitated by the radiation tolerance limits of normal tissue "organs at risk" (OARs), namely: small bowel, rectum, bladder and femoral heads. In the first phase, the entire pelvic contents are commonly treated using the four-field box technique, targeting the prostate, seminal vesicles (SV) and pelvic LN at risk. The usual dose for this phase is 45-50 Gy in 1.8-2

Gy/fraction (Fr), five days a week. This is followed by a second phase of 20 to 27 Gy to the prostate gland and proximal SV using a conformal technique. The second phase uses the same fractionation scheme to bring the total dose to 70-75.6 Gy in 7-8 weeks. AST has been given in a neo-adjuvant, concomitant and/or adjuvant fashion when radiation treatment is used. (3, 4, 5)

1.4. Outcomes:

There are still a significant number of patients who experience disease progression despite this approach. A five-year disease free survival rate of 46.4 - 74% is reported in randomized studies in high-risk patients (3,4) Furthermore, the use of conventionally planned whole pelvic RT (four field box technique) can result in significant toxicities such as proctitis and enteritis. The recently published RTOG 94-13 study reported (Table 1) the following toxicities in patients treated with whole pelvic radiation, using the RTOG/EORTC acute and late toxicity scoring schemata. (5)

Table 1: Toxicity data from RTOG 94-13

Dose/fraction	Acute toxicities	GU[a]	GI[b]
Phase-I (Pelvis) 50.4 Gy/28Fr Phase-II (Prostate) 19.8 Gy/11Fr Total dose 70.2 Gy/39 Fr	Grade 2	31.4%	46.65%
	Grade 3	12%	2.6%
	Total ≥ Grade 2	43.4%	49.25%
	Late toxicities @ 5 years	GU	GI
	Grade 2	14.9%	15.2%
	Grade 3	3%	4.3%
	Total ≥ Grade 2	17.9%	19.5%

[a]GU = Genito-urinary and [b]GI = Gastro-intestinal.

1.5. How to improve outcome?

A higher total radiation dose using conventional fractionation (1.8-2 Gy) and higher biological dose using hypofractionation (each dose fraction of > 2Gy) is currently being tested in prospective clinical trials with the goal of improving cancer control outcomes in high-risk patients.

1.5.1. Higher total dose using conventional fractionation:

Randomized studies have consistently shown a direct dose response relationship for RT in prostate cancer. Increasing the total radiation dose to 80 Gy using conventional fractionation (1.8 -2 Gy) has been shown to improve disease-free survival in low to intermediate risk groups. However, higher doses result in higher acute and late treatment related toxicity even

when using the more precise three-dimensional conformal radiation (3D-CRT). These toxicities appear to be partially overcome by using the intensity modulated radiation treatment (IMRT) technique. (6, 7, 8, 9)

1.5.2. Higher biological doses using hypofractionation:

1.5.2.1 Radiobiology:

The so-called linear-quadratic (LQ) model of radiation cell killing has proved to be a robust theory, which can be readily applied to clinical data. The LQ cell survival equation includes the coefficients α and β (and their ratio α/β). According to the model they are mechanistically related to DNA damage. Traditionally, α/β ratio of 10 Gy is used to calculate biologically equivalent dose (BED) to compare acute toxicity and tumor response of different dose fractionation schedules. Recent literature suggests that adenocarcinoma of the prostate gland is different from most other malignancies in terms of its slow growth, low labeling index (LI), and longer potential doubling time (the estimation of time in which tumor cells double, assuming no cell loss) of weeks to months. The role of α/β to calculate equivalent biological dose is controversial (11). Clinical studies predict an average α/β ratio of 1.5 Gy (range 0.8-2.2) for prostate carcinoma, whereas and α/β ratio of 4 Gy is felt to fit more closely with rectal late radiation effects. This difference in α/β predicts for a potential therapeutic advantage for hypofractionated RT schedules compared to conventional fractionation. This means that we can expect to deliver

higher biological doses to tumors with acceptable rectal toxicity using hypofractionated RT (10). Although the total dose in the hypofractionated regimen may be lower than with conventional fractionation, each fraction size is larger, and the treatment is delivered in a shorter overall number of days, which translates to a higher biological dose. Fowler et al (11) published a comprehensive review of a proposed biologically equivalent hypofractionated treatment schedules for cancer of the prostate based on published clinical data (Tables 2 and 3).

Table 2: Future Protocols suggested by Fowler for Prostate Cancer: Iso-Effective for Late Complications at α/β ratio of 3 Gy (11).

		With NTD and bNED for	tumor α/β = 1.5 Gy		tumor α/β 1.0 Gy		tumor α/β 2.0 Gy	
No. Frs	Dose per Fr	Total dose (Gy)	NTD (Gy)	bNED (%)	NTD (Gy)	bNED (%)	NTD (Gy)	bNED (%)
33	2.00	66.00	66.0	51.6	66.0	52.8	66.0	50.9
25	2.43	60.77	68.3	58.5	69.5	62.8	68.3	58.3
20	2.83	56.60	70.2	64.4	72.3	70.0	68.4	58.4
15	3.42	51.37	72.3	69.9	75.7	77.9	69.4	62.3
10	4.44	44.37	75.3	77.1	80.4	86.0	71.4	67.4
5	6.76	33.81	79.8	85.5	87.5	94.0	74.0	74.4
36	2.00	72.00	72.0	69.2	72.0	69.4	72.0	69.1
25	2.58	64.51	75.2	77.0	77.0	80.3	73.9	73.9
20	3.00	60.00	77.1	81.0	80.0	85.4	75.0	76.7
15	3.62	54.35	79.5	85.2	83.7	90.1	76.4	79.7
10	4.69	46.85	82.8	89.6	88.8	94.3	78.3	83.4
5	7.12	35.58	87.6	94.0	96.3	97.6	81.1	87.8
39	2.00	78.00	78.0	82.6	78.0	82.5	78.0	82.2
25	2.73	68.13	82.2	88.9	84.6	90.9	80.6	86.9
20	3.16	63.28	84.3	91.2	87.8	93.6	81.7	88.6
15	3.82	57.23	86.9	93.5	91.8	95.9	83.2	90.4
10	4.92	49.23	90.3	95.7	97.2	97.8	85.2	92.4
5	7.46	37.29	95.4	97.6	105.1	99.1	88.2	94.7

Where bNED = no biochemical evidence of disease;

NTD = normalized total dose (to 2 Gy fractions)

Table 3: One of Fowler's suggestions (11):

With NTD & bNED for tumor with:			α/β ratio of 1.5 Gy		α/β ratio of 1.0 Gy		α/β ratio of 2.0 Gy	
No. of fraction	Dose each fraction	Total dose (Gy)	NTD (Gy)	bNED (%)	NTD (Gy)	bNED (%)	NTD (Gy)	bNED (%)
25	2.73	68.13	82.2	88.9	84.6	90.9	80.6	86.9

Formula used to calculate this NTD:

$$NTD = Dnew\left(1+\frac{dnew}{\alpha/\beta}\right)\Big/\left(1+\frac{2Gy}{\alpha/\beta}\right) = BED/(RE \quad for \quad 2Gy \quad fractions)$$

Where D_{new} and d_{new} are total dose and dose per fraction respectively of suggested hypofractionation regimen.

A small portion of rectal wall will receive a prescribed dose to PTV 68, which is 68 Gy in 25 fractions. α/β ratio for late rectal toxicity is estimated to be 4 compared to 1.5 for prostate. This is the area which we put more emphasis on in this trial to improve therapeutic gain. Using the above NTD formula, late effects for rectal toxicity is equivalent to 76 Gy in 2 Gray per fraction for a dose of 68 Gy in 25 fractions. In this trial we decided to escalate the biological dose to high risk prostate cancer. This escalation in dose is expected to increase local control, which in turn is expected to improve disease free survival. However, dose escalation using conventional dose fractionation regimen may lead to an increase in toxicity. Differential α/β ratio of the prostate and rectum suggest that we

can escalate biological radiation doses compared to current standards without increasing rectal toxicity. The historical control used to compare this study used 78 Gy in 2 Gy per fraction. We treated the prostate gland to 68 Gy in 25 fractions which is equivalent to 82.2 Gy using 2 Gy fractions (assuming α/β ratio is 1.5). Rectal doses in this case are equivalent to 76 Gy in 2 Gy per fraction which is even lower than historical control. Therefore, our hypothesis is that we will be able to deliver a higher biological dose to the prostate gland, and keep the rectal toxicity similar to or even lower than historical control.

1.5.2.2. Clinical studies:

Several investigators have published studies that strongly support this theory. Kupelian et al reported a non-randomized comparison of 70 Gy/28 Fr (hypofractionated RT at 2.5 Gy each fraction) vs.

78 Gy/ 39 Fr (standard fractionation at 2 Gy each fraction) in a mostly intermediate-risk cohort. They reported comparable tumor control with a better rectal toxicity profile for the hypofractionated arm (12).

Pollack and colleagues recently reported preliminary acute toxicity results in intermediate to high-risk prostate cancer patients treated with the hypofractionated schedule of 70.2 Gy (mean dose delivered was 73.8 Gy) in 26 fractions with each fraction of 2.7 Gy. Many patients in these studies were in the intermediate risk group and did not receive radiation to the

whole pelvis. Results were evident that the hypofractionated radiation dose was well tolerated acutely using IMRT technique (13).

Lim et al treated 66 patients with 45 Gy in 25 fractions to the entire pelvic contents using a four field conventional technique with a simultaneous integrated IMRT boost to the prostate gland and SV of 22.5 Gy in 25 fractions. There was no concomitant androgen suppression treatment (AST) in the reported study, however all patients received AST at the end of RT. Toxicity rates were 28.4% grade 2 and 7.6% grade 3 GU toxicity and a 39% grade 2 GI toxicity (14). In contrast to Lim's report, our trial treated the pelvic LN using an IMRT technique and most patients received concomitant AST.

A phase II study from Princess Margaret Hospital showed similar results for 60 Gy/20 Fr in the intermediate risk group (15) and now a phase III study prostate fractionated irradiation trial (PROFIT) has been opened in Canadian centers to compare this schedule with conventional dose fractionation.

2. Objectives of the trial

2.1. Primary objective:

- “To estimate the rate of acute and late GI toxicity of Conventional fractionated RT to pelvic LN and dose escalated hypofractionated RT to Prostate gland in high risk prostate cancer patients.”

2.2 Secondary Objectives:

- To estimate acute and late GU toxicity.
- To estimate the biochemical control (freedom from PSA failure) rate, overall and disease free survival.
- To estimate the impact of Dynamic IMRT (TomoTherapy) on Dose volume Histograms (DVHs) of OAR in order to meet dose-constraints criteria.
- To estimate the movements of the prostate and SV and frequency of isocentre placement correction during the course of treatment using Megavoltage Computed Tomography (MVCT scan).

2.3. Patient selection criteria:

- Patient has histologically proven adenocarcinoma of prostate gland by needle core samples or transurethral resection of prostate (TURP) with assigned Gleason score. Prostate biopsy performed within 180 days of enrollment (date of consent)

- Patient has high risk prostate cancer (stage T3 or T4 and/or PSA >20 ng/ml and/or Gleason score 8 to 10 or Gleason Score 7 with PSA ≥15 ng/ml)
- No clinical or radiological evidence of nodal or distant metastasis(es).
- In the opinion of the treating oncologist, patient is fit to undergo radical RT to the prostate. Patients are accessible for treatment and follow up.
- Patient does not have history of inflammatory bowel disease, anal stenosis, colorectal surgery, or repeated endoscopic examinations / interventions related to anorectal diseases.
- No history of prostatectomy, transurethral resection of prostate on more than one occasion, or previous pelvic RT.
- No history of AST for > 6 months and willing for AST.
- No contraindication to MRI.
- No previous malignancy within last five years except basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) skin or highly curable malignancy where a prognosis for cure is > 80%.
- Signed informed consent.

3. Trial Design

A total of 60 men with a diagnosis of high-risk localized prostate cancer (cT3/4 N0 M0 and/or Gleason Score 8-10 and/or pretreatment PSA > 20 ng / ml or Gleason Score 7 with pretreatment PSA ≥ 15 ng / ml) were enrolled in this study. After diagnosis, and informed written consent, they underwent CT simulation and MRI in the treatment position. The prostate, proximal & distal SV, pelvic LN and OARs including rectum, bladder, femora and peritoneal cavity were delineated on fused images. Prostate and proximal SV (CTV 68) was grown by 10 mm radially and 5 mm posteriorly to generate PTV68 while LN and distal SV (CTV 45) was grown by 10 mm to generate PTV45. A single-phase treatment plan was generated to deliver a hypofractionated radiation dose of 68 Gy/25Fr to PTV 68 (prostate + proximal SV + margins). PTV 45 received 45 Gy / 25 Fr at the same time. Dose constraints of 55 & 60 Gy to 50% & 30% respectively of the rectal volume, 60 & 65 Gy to 50% & 30% respectively of the bladder volume, were used. Maximum dose of 54 Gy was accepted to the peritoneal cavity. Treatment was delivered on the Helical TomoTherapy unit (46), and a daily pretreatment MVCT scan was performed for optimal patient positioning. Patients received hormonal (androgen suppression) treatment for varying duration with a maximum duration of 3 years in total. They were assessed weekly during radiation; 3 and 6 months after radiation and 6 monthly thereafter to assess treatment response, and to record treatment related toxicity.

4. Therapeutic regimens (treatment details including methods and processes used)

4.1. Radiation treatment:

Non-contrast CT simulation images were obtained on a Picker PQ 5000 CT Simulator (Philips Medical Systems, Cleveland, OH). Three Tesla (3T) MRI images obtained on 3 T Intera scanner (Philips Healthcare, N.A, Bothell, WA, USA). CT and MRI images were fused to delineate OAR and target volumes. A TomoTherapy® Hi-Art® (TomoTherapy Inc., Madison, WI, USA) machine was used to plan and deliver IMRT. Daily MVCT scans were performed prior to treatment for verification.

4.1.1. Patient's preparation & positioning:

- All patients were advised not to eat solid food from midnight onward to have an empty rectum prior to simulation. Liquid was allowed after midnight.
- Patients were advised to drink approximately 8 oz of fluid 2 hours prior to have a full bladder at CT simulation.
- Patients were in supine position on a flat table couch with the arms on patient's chest during CT simulation, 3T MRI and during treatment.

- Immobilizing devices, knee and calf support were used as per Cross Cancer Institute (CCI) standard for CT simulation, 3T MRI and during treatment.
- Orthogonal laser beams were also used for positioning in CT simulation, 3T MRI and during treatment.
- MR scans were performed immediately after the CT-simulation, and a dosimetrist was present at imaging procedures.

4.1.2. Patient data acquisition:

CT Scanning: 3 mm slice thickness, 3 mm spacing, with a MR / CT fiducial marker. Scan length: top of Lumbar vertebra 5 (L5) to 2 cm below ischial tuberosity. The scan was performed on CT-simulator and transferred to the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA) for contouring.

MR scanning: 3 mm slice thickness, 3 mm spacing (no gap), with a MR / CT fiducial marker. MR scans length: top of L5 to 2 cm below ischial tuberosity. The MR lasers need to be aligned, and the MR technicians should perform daily quality assessment (QA) on the lasers. Scan performed on 3T MRI and transferred to Medical Physics picture archiving and communications system (PACS) and then transferred to Eclipse.

4.1.3. Volumes:

4.1.3.1. Definition of volumes:

CT simulation and MR images were registered (fused) on Eclipse. The CT-simulation therapist initially registered the CT and MR datasets. The Radiation Oncologist then confirmed the registration. On the registered MR and CT images, the CT therapist, dosimetrists and Radiation Oncologist manually defined the following volumes (see table 4 below) onto each CT scan slices using Eclipse planning system:

- Prostate gland: This was delineated on each slice from apex to base enclosing the whole prostate gland.
- Proximal Seminal Vesicle: A sac like structure beside prostate gland. This was drawn on initial four images proximal to prostate gland (initial 1.2 cm).
- Distal Seminal Vesicle: A sac like structure beside prostate gland. This was drawn on images distal to proximal seminal vesicle (beyond 1.2 cm).
- Pelvic LN: Internal and upper external iliac LN from above obturator foramen to L5 / S1 (sacral vertebra 1) junction were defined conformally as a continuous structure.
- Bladder: was drawn as solid lines from dome of bladder to base.

- Rectum: must be drawn as solid lines from anal canal to the recto-sigmoid flexure.
- Peritoneal cavity (including both large and small bowel): was defined from the bottom of pelvic cavity to the L5/S1 junction.
- Left femoral head/neck: was defined from femoral head to the level of the ischial tuberosity.
- Right femoral head/neck: was defined from femoral head to the level of the ischial tuberosity.
- CTV 68 was obtained by adding prostate gland and proximal seminal vesicle.
- CTV 45 was obtained by adding LN and distal seminal vesicle.
- PTV 68 was grown by 10 mm uniform margin radially and 5mm posteriorly. Anterior growth was limited to 3 mm into pubic symphysis.
- PTV 45 was grown by 10 mm uniform margin around CTV 45.

NOTE: The structures were outlined in the order that they appear in the table 4.

Table 4: Structure naming conventions - Structures as defined on Eclipse for Prostate-TomoTherapy Protocol

Ord-er	Standard Name	Description	Type	Color	Done by
1	Body	Skin surface	Body overlapping	Skin rendering	CTD Therapist
2	Bladder	From dome to base	Organ	Contour-Dark Blue	CTD Therapist
3	Rectum	From anus to recto-sigmoid flexure (as per RTOG protocols)	Organ	Contour-Brown	CTD Therapist
4	FemurL	Left femur to level of ischial tuberosity	Organ	Bone Rendering	CTD Therapist
5	FemurR	Right femur to level of ischial tuberosity	Organ	Bone Rendering	CTD Therapist
6	Prostate	Prostate	Organ	Contour Pink	Radiation Oncologist
7	SVDistal	A sac-like structure farther than 1cm from the prostate	Organ	Segment Dark Green	Radiation Oncologist
8	SVProximal	A sac-like structure within 1cm of the prostate	Organ	Segment Light Green	Radiation Oncologist
9	PenileBulb	0.9 cm in length below pelvic diaphragm	Organ	Segment Blue	Radiation Oncologist
10	CTV68	prostate & proximal 1.2cm of SV, CTV to receive 68Gy	CTV2 overlapping	Contour Magenta	Radiation Oncologist
11	CTV45	pelvic LN & distal portion of SV not included in CTV68, CTV to receive 45 Gy	CTV overlapping	Contour Red	Radiation Oncologist
12	Symphysis Pub	Cartilaginous joint uniting left and right pubic bones	None	White	Radiation Oncologist
13	PeritonCav	Contains small bowel, rectum and sigmoid colon	Avoid overlapping	Translucent-Magenta	Radiation Oncologist
14	PTV68	= CTV68 + 10mm uniform margin, except 5mm post, limit growth into Symphysis Pubis to 3mm	PTV2 overlapping	Purple	Dosimetrist
15	PTV45	= CTV45 + 10mm uniform margin	PTV overlapping	Segment-Cyan	Dosimetrist
16	Cylinder	Volume circumscribing PTV by about 2 cm	Avoid overlapping	Translucent-Green	Dosimetrist
17	Couch	box incl. CT couch over entire CT scan	None	Black	Dosimetrist

Note: when contours were drawn on every 2nd slice on Eclipse, they were interpolated before sending to Tomotherapy. Once these volumes were approved at Eclipse by the Radiation Oncologist, the CT dataset and all structures were transferred to Tomotherapy.

4.1.4. Treatment technique:

The treatment was delivered on a TomoTherapy unit using an IMRT delivery technique.

4.1.5. Dose computation:

- The PTVs were outlined in all relevant planes.
- Dose distributions were obtained in a 3-dimensional pattern with DVHs. DVHs are to be used for assessing dose to the PTVs and all normal tissues at risk.

4.1.6. Equipment and tools:

Patients were treated on TomoTherapy unit. It has following characteristics:

- Photon beam of 5.7 MV.
- High dose rate (approx. 850 cGy / min , 1.5 mm source size)
- Binary multileaf collimator (MLC) modulated fan beam
- Helical delivery since couch moves while source rotates about patient and detectors gather exit beam for MVCT

Figure 1: TomoTherapy unit

Figure 2: Schematic diagram showing helical movement of source around patient while couch is moving.

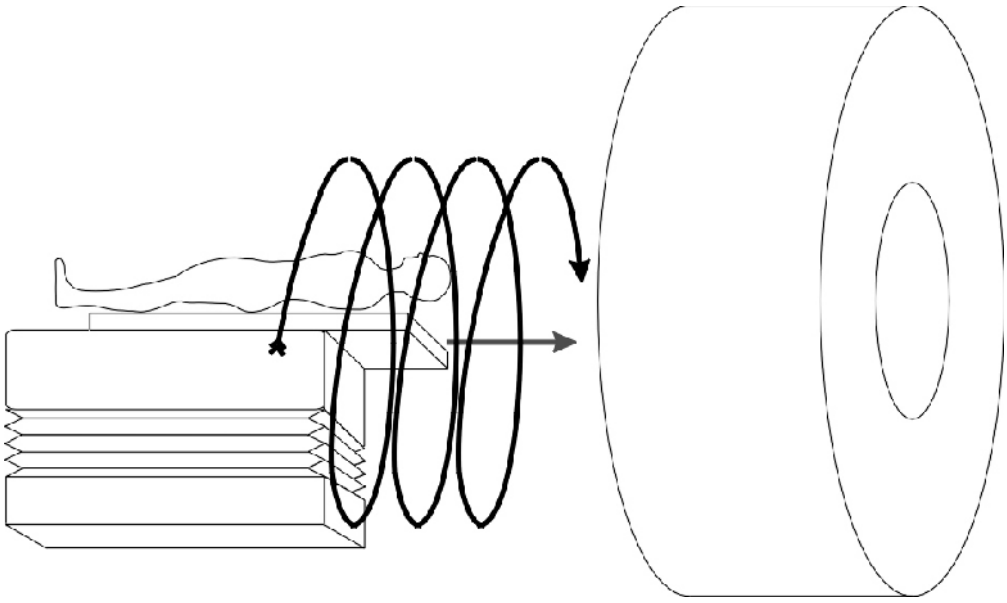
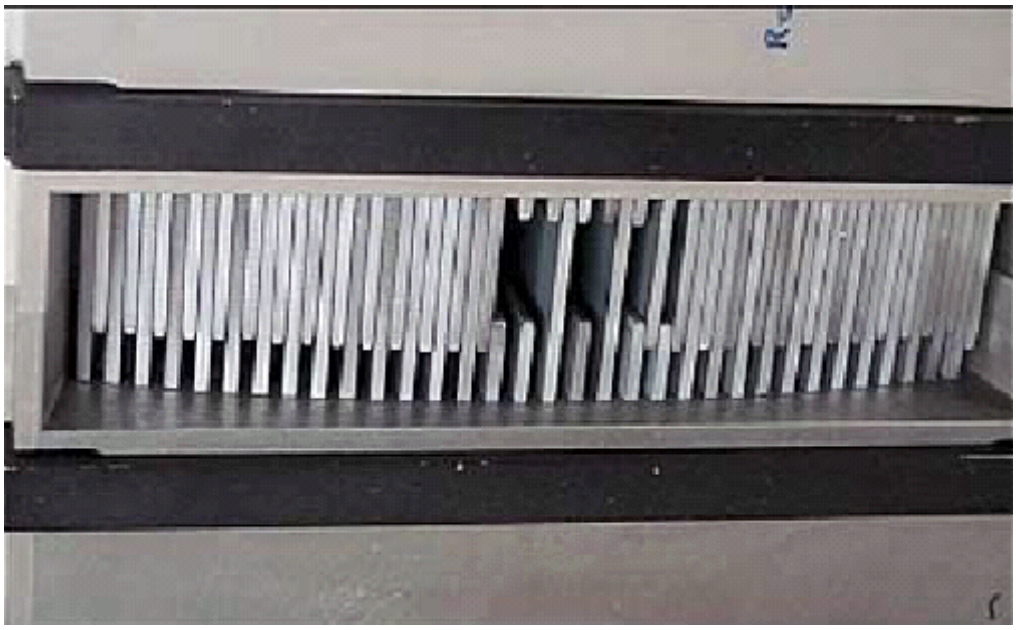


Figure 3: MLC used in TomoTherapy Unit.



4.1.7. At the Tomotherapy Planning Station:

Figure 4: TomoTherapy Operator station.

4.1.7.1. Region of interest (ROI) panel:

- Target structures, display settings, and colors were checked.
- Overlap priorities were set according to the following table 5:

Table 5: Region of Interest panel.

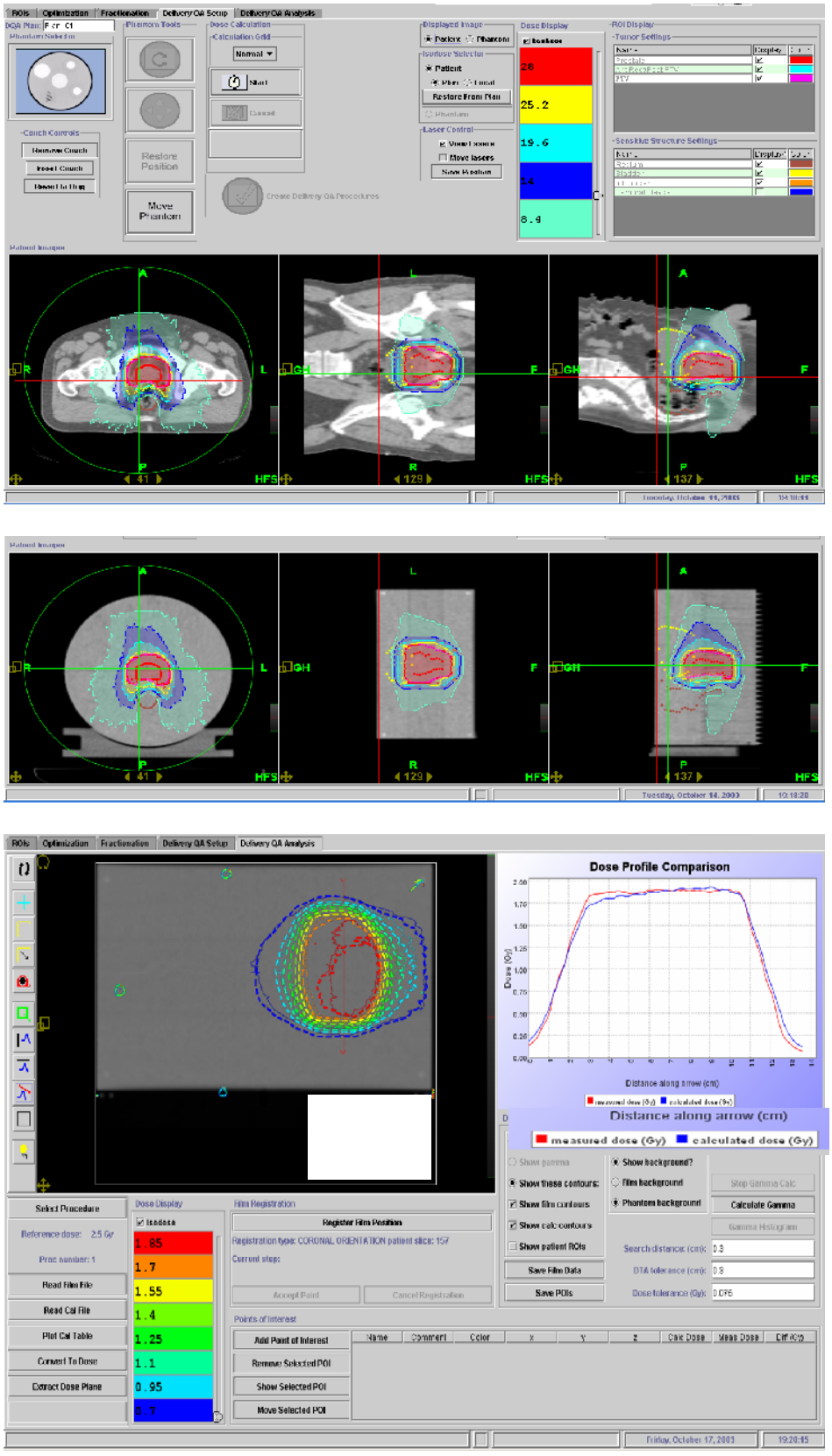
Standard Name	Type	Overlap Priority	Color	Display	Use
PTV68	Tumor	1	Purple	Y	Y
PTV 45	Tumor	2	Cyan	Y	Y
Rectum	RAR	1	Brown	Y	Y
Bladder	RAR	2	Dark Blue	Y	Y
CTV 68	Tumor	3	Magenta	Y	
PeritonCav	RAR	4	Light Purple	Y	Y
CTV 45	Tumor	5	Red		
FemurR	RAR	6	White	Y	
FemurL	RAR	7	White	Y	
SymphysisPub	RAR	8	Orange		
PenileBulb	RAR	9	Light Blue	Y	
Prostate	RAR	10	Pink	Y	
SVproximal	RAR	11	Light Green		
SVdistal	RAR	12	Dark Green		
Cylinder	RAR	13	Green		Y
Couch	RAR	14	Black		
Body	RAR	15	White	Y	

4.1.8. DQA:

After completion of planning at Tomotherapy station:

- A Medical Physicist, Associate Medical Physicist or graduate student performs the DQA under the supervision of a staff Medical Physicist. Expected agreement is 3.5% for the point dose measurement (taken in a high dose, low gradient region) and the gamma parameters were 3 mm and 5% (of nominal fraction dose).
- The person doing the DQA informed the physicist doing the 2nd check that the DQA has been completed.
- The physicist doing the 2nd check asked the responsible Radiation Oncologist to sign and approve the DQA.

Figure 5: DQA process.



4.1.9. Dose specification:

4.1.9.1. Dose prescription

Doses were prescribed to 95% of volume of PTV 68 to receive 68 Gy. The following were treatment goals to achieve:

- Bladder: Dose constraints of ≤ 60 Gy to 50% and ≤ 65 Gy to 30% of total bladder volume were used.
- Rectum: Dose constraints of ≤ 55 Gy to 50% and ≤ 60 Gy to 30% of total rectal volume were used.
- Peritoneal cavity (including both large and small Bowel): A maximum dose of ≤ 54 Gy was accepted. A minor variation was accepted on discretion of Physician where maximum dose is not falling directly on small bowel.
- Left femoral head/neck: Maximum dose was limited to 52 Gy.
- Right femoral head/neck: Maximum dose was limited to 52 Gy.
- PTV 68: 95% volume of PTV68 was prescribed to 68 Gy. Cold spot (64.6 Gy, which is 95% of prescription dose 68 Gy) was limited to ≤ 2 cm^3. Maximum dose or hot spot was limited to ≤ 72.8 Gy (107% of 68 Gy).
- PTV 45: 95% volume of PTV45 was prescribed to ≥ 45Gy. Cold spot (42.75 Gy which is 95% of prescription dose 45 Gy) was limited to ≤ 2 cm^3. Maximum dose or hot spot was limited to ≤ 68 Gy.

Table 6: Protocol dose constraints

VOI	Treatment Goal 1	Treatment Goal 2	Treatment Goal 3
PTV68	95% of PTV 68 to receive 68 Gy (by definition)	≤ 2 cm^3 to receive ≤ 64.6 Gy (95% of 68 Gy) (cold spot)	Max dose ≤ 72.8 Gy (107% of 68 Gy) (hot spot)
PTV45	95% of PTV 45 to receive ≥ 45 Gy	≤ 2 cm^3 to receive ≤ 42.75 Gy (95% of 45 Gy)	Max dose ≤ 68 Gy
Rectum	30% to receive ≤ 60 Gy	50% to receive ≤ 55 Gy	
Bladder	30% to receive ≤ 65Gy	50% to receive ≤ 60 Gy	
Small Bowel (Peritoneal Cavity)	Max dose ≤ 54 Gy		
Femurs	Max dose ≤ 52Gy		
Unspecified tissue	Max dose ≤ 68 Gy		
Penile bulb	mean dose ≤ 52.5 Gy		

4.1.9.3. Fractionation schedule:

Please refer to table 7 below.

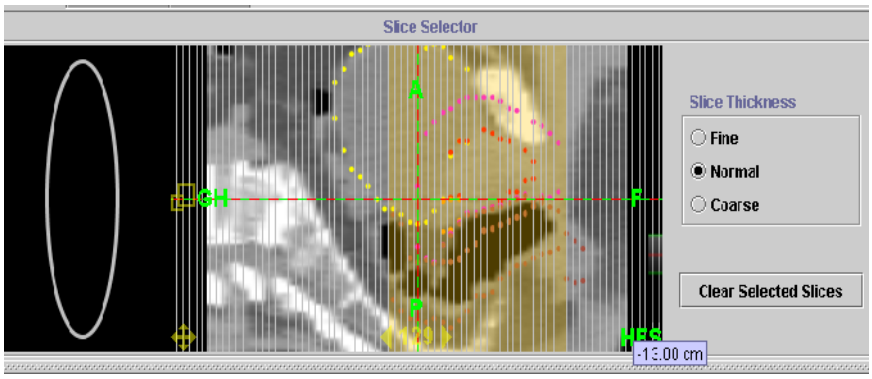
Table 7: Fractionation schedule

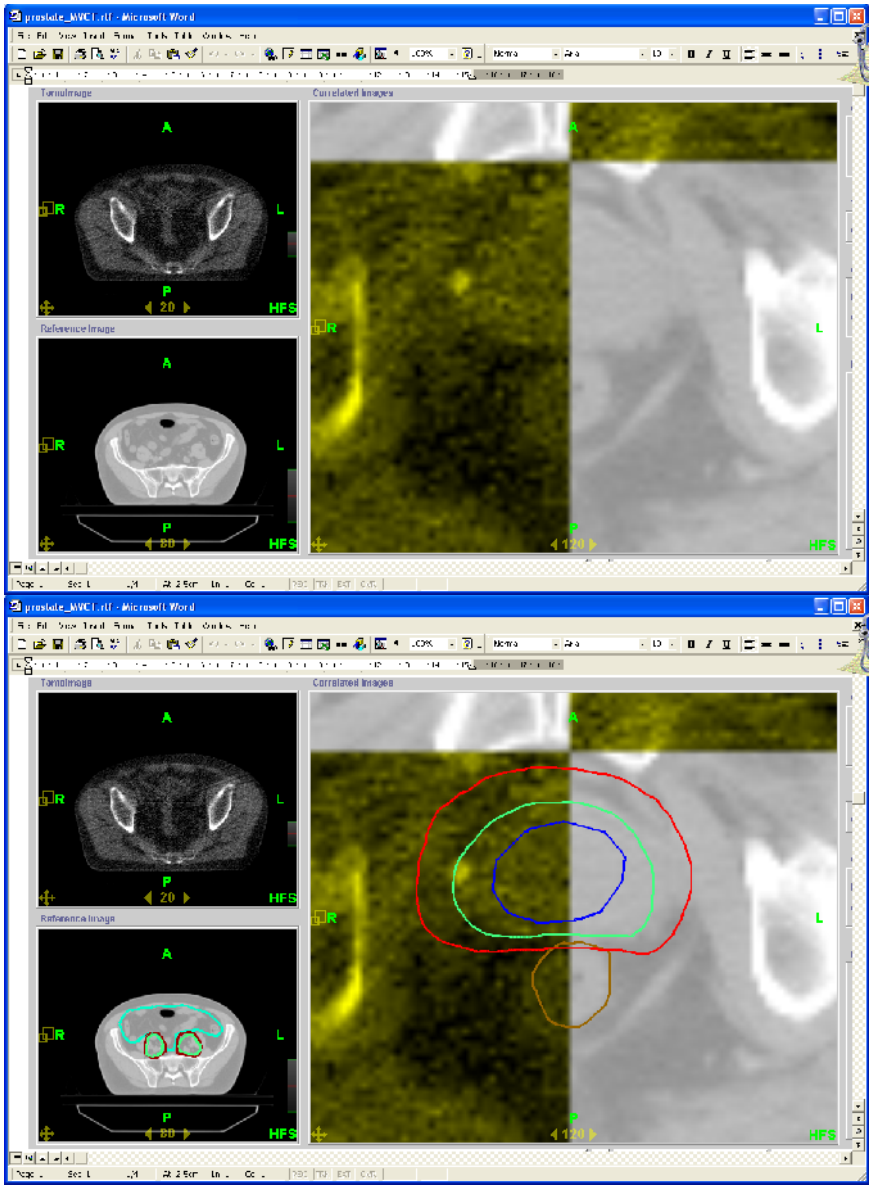
Targets	Total dose	Number of fractions	Dose per fraction	Number of fractions per day	Number of days per week
PTV 68	68 Gy	25	2.72 Gy	1	5
PTV 45	45 Gy	25	1.8 Gy	1	5

4.1.10. Treatment Verification:

MVCT images were obtained every day prior to each treatment, and were compared with the images from planning CT scan for positioning verification. Necessary table shift were applied for each treatment after manual 3D correction of the Prostate Rectal interface (figure 6). These shifts were recorded in shift form (Appendix 6)

Figure 6: Images showing daily pre-treatment verification process using MVCT images on TomoTherapy.





4.2. Androgen suppression therapy (AST):

Neoadjuvant/concurrent/adjuvant or concurrent / adjuvant or adjuvant Eligard (Lupron) injections, 22.5 mg every 3 months as a subcutaneous depot, were prescribed to patient for up to a total duration of 3 years. Duration, frequency and scheduling were left at the discretion of the treating physician. Neoadjuvant Eligard injections were not allowed for more than 6 months duration. Antiandrogen therapy scheduling, dose and duration were left at the discretion of physician. Eligard and antiandrogen therapy was allowed to be discontinued with the approval of the treating physician in cases when patients cannot tolerate hormonal treatment.

5. Clinical evaluation, laboratory tests, follow-up

5.1. Before treatment start:

A routine physical examination including DRE was performed before starting RT. All patients underwent the following investigations before starting RT:

- PSA and routine blood tests.
- Diagnostic CT or MRI scans of abdomen and pelvis
- Whole body bone scans.

These staging investigations were performed within 3 months before starting RT. Eligibility check list completed to rule out ineligibility. (See appendix 3)

All patients underwent 3T MRI before starting RT.

5.2. During treatment:

Patients were seen weekly in clinic during treatment. GI and GU toxicities were recorded using RTOG toxicity scale (Appendix 7).

5.3. After the end of treatment (Follow-up):

Routine post-treatment follow-up was arranged for 3 month after the last day of RT. Research nurses called patients at one month after treatment completion to record RTOG toxicity scores. Additional follow-up visits

during this time were at the physician's discretion. The RTOG/EORTC acute GI and GU toxicity scores were obtained within 90 days of first treatment (Appendix 8).

Subsequent follow up were arranged for every 6 months counting from the last day of RT.

For each follow up visit during the first three years, a PSA level (done 1 week prior to visit), late GI and GU toxicity scores, and findings by physical examination and DRE were obtained and recorded (Appendix 9 and 10).

University of California, Los Angeles (UCLA) Prostate Cancer Index (PCI) questionnaire to assess quality of life were given at 0, 1 month and 6 months to the patient at each follow up visit up to and including the 36-month visit (Appendix 5).

Isotope bone scan will be performed at relapse or when symptoms suggest boney metastases.

Treatment in case of progression:

In case of disease progression, the patient will be treated according to Institute treatment guidelines: http://www.cancerboard.ab.ca/Professionals/TreatmentGuidelines/Genitourinary/TreatmentGuidelines_Prostate.htm.

5.4. **Table 8:** Summary table:

Required Investigation	Pre-study	Weekly during RT	1 month	3 month	6 month	Every 6 month
Physical examination	X			X	X	X
PSA	X			X	X	X
Diagnostic CT or MRI	X					
Bone scan	X					
Toxicity form		X	X	X	X	X
Quality of Life	X		X		X	X

5.5. Criteria of evaluation:

All patients were evaluated and recorded on evaluation forms provided.

Toxicity forms: Acute and late RTOG toxicity forms were filled as per the summary table. Care was given to report the toxicity as per pretreatment symptom level. A clinical research nurse completed the toxicity form at 1 month after treatment with information gathered over the telephone.

Clinical assessment: clinical assessments were performed on each patient visit. DRE were performed to assess possible disease progression in and around the prostate gland. Any suspicious symptoms were evaluated clinically and radiologically as required.

Biochemical assessment: PSA tests were performed as per table in section 5.4. A nadir + 2 definitions are used for biochemical failure.

Patients will be restaged and further management will be at the discretion of treating Physician.

Progression free survival was recorded from date of starting RT to date of clinical and/or radiological evidence of disease progression.

Overall survival was recorded from date of starting RT until death.

Biochemical failure will be recorded as PSA rise of 2 ng/ml from lowest (nadir) PSA after treatment.

6. Registration, Statistical and Ethical Considerations

6.1. Patient registration:

All eligible patients were approached to carefully read and sign consent form by a physician or a nurse or data manager. After consent form patients were registered to IGAR Excel flow sheet for this trial at Cross Cancer Institute.

Clinical research nurse and/or Data manager collected and entered data on an Excel spread sheet for analysis.

6.2. Sample Size and Statistical Analysis of the Outcomes:

This was a single institution, single arm, non-randomized study. Primary endpoints are acute and late rectal toxicity. Secondary endpoints are acute and late bladder toxicity and biochemical control (freedom from PSA failure) rate, overall and disease free survival.

H0 (null hypothesis): There is no difference in late rectal toxicity using hypofractionated RT compared to historical control using conventional RT.

H1 (alternate hypothesis): Late rectal toxicity expected to reduce significantly using hypofractionated RT compared to historical control using conventional RT.

Numeric Results for testing H0: P = P0 versus H1: P < P0

The primary objective of the study was to test the observed acute and late rectal toxicity rate (Grade II onwards) against a recognized standard rate of 26%. A reduction in this rate to 10% was considered important and 50 patients were sufficient to perform a significance test at the 5% level with 80% power using a two-tailed single proportion t-test.

Kaplan-Meier survival estimates with 95% confidence limits and a median survival time was computed to determine the biochemical control (freedom from PSA failure) rate, overall and disease free survival.

Two sided tests were used in the statistical analysis, and were performed using the statistical analysis software (SAS) computer program, version 9.1 (SAS Institute, Cary, NC).

6.3. Accrual and Duration of Study:

The estimated accrual for this study was 2 to 3 patients a month. Thus, patient accrual was expected to be complete within 24 months. Additional time was required to allow the toxicity data to mature.

All of the patients registered in the study were accounted for. The number of patients who were not evaluable, who died or withdrew before treatment began were specified. The distribution of follow-up time was described and the numbers of patients lost to follow-up are given.

6.4. Safety Monitoring:

A research nurse and / or a radiation oncologist were responsible for regular monitoring of patients on treatment. It was the responsibility of research nurse and / or data manager to report all grade 3 or 4 toxicity and any unexpected toxicity to principal investigator (PI) no later than 24 hours. All grade 3 and 4 toxicity was marked on bigger version of stopping rule graph. If the number of events meets the stopping criteria, accrual could have been halted and PI would have immediately informed Research Ethic Board (REB). In any case, PI arranged meetings with co-investigators at first 10 patients to review trial progress.

A serious adverse events (SAEs) is any adverse event related directly to treatment or arising from treatment complication that:

- Results in death
- Is life threatening
- Requires in-patient hospitalization
- Results in persistent or significant disability/incapacity

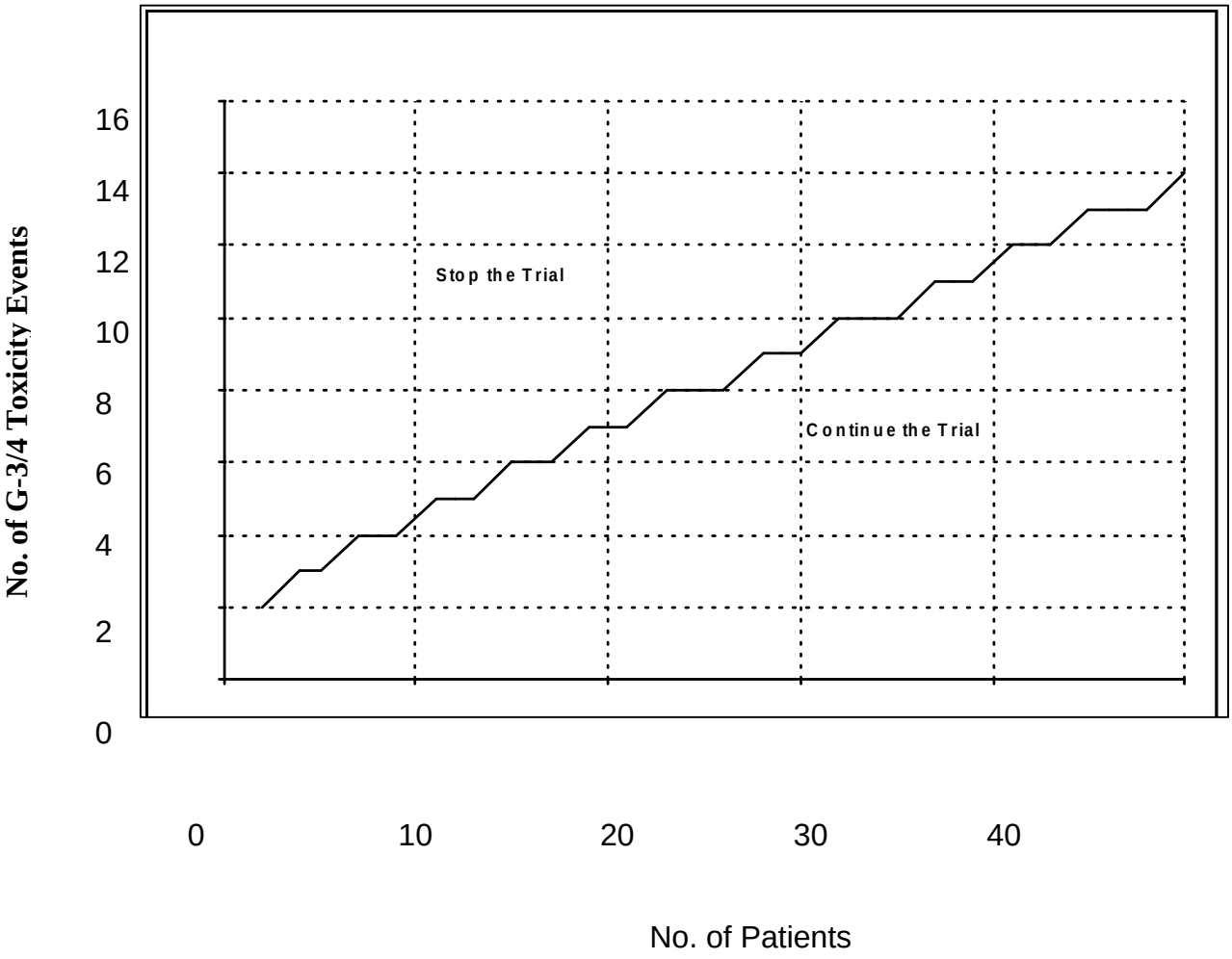
Medical and scientific judgment was exercised in deciding whether expedited reporting is appropriate. It was the investigator's (radiation oncologists) responsibility to investigate and report the date and cause of death of any patient entered on this trial (Appendix 11) to PI. It was PI's responsibility to inform REB.

In addition to the above SAEs, any grade 3 or 4 late toxicity events (e.g. rectal necrosis requiring hyperbaric oxygen therapy, bleeding requiring blood transfusion) were discussed between the PI and the co-investigators. During the accrual phase of the study, if and when 5 patients are observed to have grade 3 or 4 late toxicity, the PI and co-investigators were supposed to review all relevant dosimetric parameters and determine whether accrual should be held.

6.5. Stopping Rule:

Although late toxicity is the endpoint of interest, acute toxicity was used as a proxy due to the length of the time needed to determine late toxicities. Acute GI and GU toxicity are reported to be significant predictors of late toxicity by several investigators [16-18]. The majority of acute toxicities should occur within 2 months of treatment initiation. We implemented early stopping rules for unacceptable acute toxicity following the method of Thall, Simon & Estey (JCO 1996) [19]. For a maximum of 50 patients with mean Toxicity Rate = 0.15 and π_*= 0.95 the resulting stopping boundaries are:

Figure 7: Toxicity Stopping Rule



6.6. Ethical considerations

6.6.1. Patient protection:

The responsible investigator was ensuring that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) or the laws and regulations of the country; whichever provides the greatest protection of the patient.

The protocol has been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (ref: http://www.ifpma.org/pdfifpma/e6.pdf).

The protocol was approved by the Alberta Cancer Board (ACB) Ethics Committees (see appendix 12 for modified consent form).

6.6.2. Subject identification:

Patient information was allowed to use by the researchers who are carrying out this study, and may be disclosed to others as described below. ACB Research Ethics Board must approve any research proposal to use information that identifies a patient for a purpose other then this study in advance. Direct access to patient identifiable health information collected for this study was restricted to the researchers who are directly involved in this study except in the following circumstances.

Patient identifiable health information may need to be inspected or copied from time to time for quality assurance (to make sure the information being used in the study is accurate) and for data analysis (to do statistical analysis that will not identify patient). The following organizations were allowed for this inspection:

- ACB Research Ethics Board, the institutional review board at this centre
- Health Canada
- Office of the Information and Privacy Commissioner

Any disclosure of patient identifiable health information was in accordance with the Alberta Health Information Act. As well, any person from the organizations looking at records on-site at the Cross Cancer Institute follows the relevant ACB policies and procedures that control these actions. Any disclosure of patient identifiable health information to another individual or organization not listed needed the approval of the ACB Research Ethics Board.

The researchers who are directly involved in the study may share information about patient with other researchers, but not identified in that shared information except by a number. The key that indicates what number each patient has been assigned was kept secure by the researchers directly involved with study and will not be released.

Although absolute confidentiality can never be guaranteed, the ACB made every effort to keep patient identifiable health information confidential, and to follow the ethical and legal rules about collecting, using and disclosing this information in accordance with the Health Information Act and other regulatory requirements.

7.0. Acute toxicity results, statistics, discussions and conclusions

Toxicity data was gathered prospectively on all patients using the RTOG toxicity criteria (20). Toxicity occurring within 90 days of the end of RT was classified as acute toxicity. The patients were reviewed weekly during RT and again at 3 months post RT by the treating physician.

7.1. Statistical Analysis:

The GI and GU toxicity scores were ordinal, hence the correlation of the toxicity scores with other parameters were tested using ordinal by ordinal Kendal Tau-b test of correlation. A univariate test of toxicity score and other parameters were conducted, hence a p-value < 0.10 was considered for statistical significance. All statistical tests were conducted using Statistical Package for the Social Sciences (SPSS) version 15.

7.2. Results:

Patient characteristics are outlined in Table 9, and Table 10 outlines the breakdown of PSA, Gleason score and T-stage.

Table 9: Patient characteristics

Characteristic	Value
Mean age (Range)	68.2 (55-88) years.
Mean Gleason Score (Range)	7.6 (6-10)
Mean initial PSA (Range)	21.61 (4.3-80.0) ng/ml
Stage	No. of patients
T1	12
T2	30
T3	17 (including 7 T3b)
T4	1

Note: see appendix 1 for T stages.

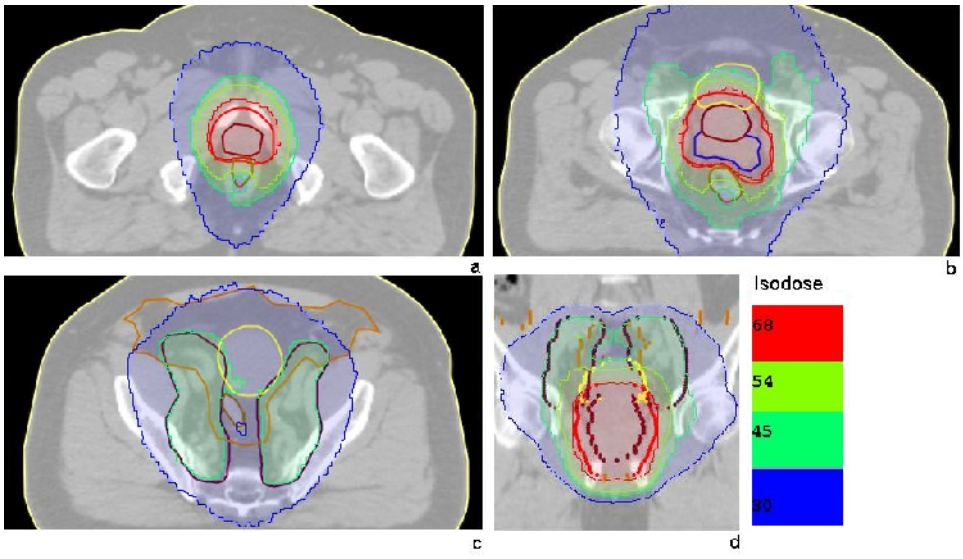
Table 10: Patient breakdown

		Clinical Stage				
Gleason Score	PSA	T1	T2	T3	T4	Total
6	0 - ≤10	-	-	-	-	-
	>10 to ≤ 20	-	-	1	-	1
	>20 to ≤ 40	1	4	-	-	5
	>40	-	-	-	-	-
7	0 - ≤10	-	-	3	-	3
	>10 to ≤ 20	3	1	2	-	6
	>20 to ≤ 40	3	7	2	-	12
	>40	1	2	1	-	4
8	0 - ≤10	1	4	1	1	7
	>10 to ≤ 20	1	4	3	-	8
	>20 to ≤ 40	-	1	-	-	1
	>40	-	-	1	-	1
9	0 - ≤10	-	3	2	-	5
	>10 to ≤ 20	-	2	-	-	2
	>20 to ≤ 40	1	-	1	-	2
	>40	-	1	-	-	1
10	0 - ≤10	1	-	-	-	1
	>10 to ≤ 20	-	1	-	-	1
	>20 to ≤ 40	-	-	-	-	-
	>40	-	-	-	-	
Total		12	30	17	1	60

All treatment objectives for PTV 45 and OARs were satisfied according to the dosimetric parameters outlined above in Table 6. The PTV68 parameters were met in all but 2 patients who had a minor deviation in their coverage due to error in overlap priorities (see figure 8 for dose distributions). The prostate gland did receive the prescribed dose in these 2 patients. Fifty-two patients commenced AST prior to starting RT (neo-

adjuvant), 3 patients started AST concomitantly, 3 patients started adjuvantly and 2 patients declined AST. Neo-adjuvant AST was commenced on average at 66 days prior to RT (range 13-189 days).

Figure 8: Axial and Coronal images showing PTV, OAR and isodoses. Axial CT image of pelvis at level of (a) prostate gland (b) prostate and proximal seminal vesicles and (c) pelvic LN and (d) coronal CT image showing prostate and pelvic LN. Contours: Red is PTV68; Maroon is prostate; Blue is proximal seminal vesicle; Dark Brown is PTV 45; Yellow is bladder; Brown is rectum; Light brown is peritoneal cavity. Isodose are shown as colour map.



Acute toxicity was analysed prospectively using the RTOG toxicity criteria, the maximum acute toxicities are outlined in Table 11. There were 31

(51.7%) grade 1 GI toxicities, 21 (35%) grade 2 GI toxicities and no grade 3 or higher GI toxicities. Twenty-eight (46.67%) patients developed grade 1 GU toxicity, 20 (33.33%) patients had grade 2 GU toxicity and 4 (6.67%) patients developed grade 3 GU toxicity; there were no grade 4 toxicities.

Table 11: Maximum acute toxicities during treatment using RTOG and common terminology criteria for adverse events version 3.0 (CTCAE v3.0) grading criteria

Acute Toxicities- Number (%)					
Grade	GI		GU		Max Toxicity (RTOG)
	RTOG	CTCAE-v3.0	RTOG	CTCAE-v3.0	
0	8(13.33%)	8(13.33%)	8(13.33%)	8(13.33%)	2(3.33%)
1	31(51.67%)	31(51.67%)	28(46.67%)	28(46.67%)	24(40%)
2	21(35%)	21(35%)	20(33.33%)	22(36.67%)	30(50%)
3	0(0%)	0(0%)	4(6.67%)	2(3.33%)	4(6.67%)

Acute toxicity settled quickly after finishing RT, and at 3 months of follow-up there where no grade 3 or higher GU toxicities and only 5 (8.62%) grade 2 and 11 (18.97%) grade 1 toxicities. There was no grade 2 or higher GI toxicities with only 8 (13.6%) grade 1 toxicities (Table 12).

Table 12: Maximum acute toxicities at 3 months using RTOG and CTCAE v3.0 grading criteria

	Number (%)*	
Grade	GI	GU
0	51(86.4%)	43 (70.69)
1	8(13.6%)	11 (18.97)
2	0	5 (8.62)
3	0	0

*1 patient was un-contactable for his 3 month follow-up

The mean bladder volume was 338.45 ± 33.76 cm^3, the mean D30% (dose to 30% of the volume) was 56.6 Gy (range 44.94 Gy – 65 Gy), and the mean D50% (i.e. median dose) was 48.2 Gy (range 39.95 Gy – 55.92 Gy). The mean rectal volume was 86.27 ± 3.96 cc, the mean D30% was 53.53 Gy (range 40.24 Gy – 59.49 Gy) and the mean D50% was 45.56 Gy (range 36.39 Gy – 52.13 Gy) (Table 13).

Table 13: Dosimetric parameters for PTV68, bladder and rectum

Parameter	Mean	SEM
Prostate Volume	52.45cc	±4.17
Bladder Volume	338.45cc	±33.76
Rectal Volume	86.27cc	±3.96
PTV68 min (D99%)	66.03 Gy	±0.39
PTV68 max (D1%)	70.46 Gy	±0.17
Rectal D30%	53.53 Gy	±0.52
Rectal D50%	45.56 Gy	±0.43
Rectal V60Gy	18.35%	±0.63
Bladder D30%	56.6 Gy	±0.71
Bladder D50%	48.2 Gy	±0.46
Bladder V65Gy	18.44%	±0.98
All Constraints Met	58 (96.67%)	
Unable to meet PTV68 constraints	2 (3.33%)	

An analysis was performed to identify any correlation between dose received by the bladder, rectum and PTV68 and toxicity. The analysis included volume, mean and median doses, dose to 30% of the volume, and 10 separate dose points between V6.8 Gy to V68 Gy. There was no statistically significant correlation seen between dose to the PTV68 and bladder and toxicity. There was a correlation shown between the rectal V60 and GI toxicity (using Kendall's Tau-b with a $p=0.085$, $p<0.1$ is significant).

7.3. Discussion:

We have compared our toxicity data with previous trials looking at pelvic LN RT or dose escalation with or without AST (summarised in Table 14). Dose escalation in prostate cancer has been assessed by a number of recent prospective randomised trials. In 2002 Pollack et al (6) randomly assigned 301 patients to either 70 Gy or 78 Gy (2 Gy per fraction), with an update by Kuban et al (21) in 2006. With a median follow-up of 8.7 years the bNED was 73% in the 78 Gy arm as compared to 50% in the 70 Gy arm ($p=0.004$); there was no difference in overall survival. This means that patients in higher dose arm have better PSA control but no significant overall survival benefit.

Table 14: Acute GI / GU toxicity comparison of recent studies

	Current study	Pollack[$]	Lim†	Kupelian&	RTOG 9413 [*]	RTOG 9406[#]	Beckendorf [^]
Dose/Fr	68/25	70.2/26	67.5/25	70/28	70.2/39	79.2/44	80/40
EQD2 Gy!	82	84.2	81	80	66.2	74.7	80
No patients	60	50	66	166	309	67	153
Concurrent AST	83.3%	44%	0%	60%	100%	69%	None
GI Acute Toxicities- Percent							
Grade 0	13.3%	42%	5%	30%	-	49.3%	32.7%
Grade 1	51.7%	40%	56%	55%	-	29.6%	37.3%
Grade 2	35%	18%	39%	15%	44%	20.9%	28.1%
Grade 3	0%	0%	0%	0%	2.6%**	0%	1.97%
GU Acute Toxicities- Percent							
Grade 0	13.37%	8%	5%	15%	-	31.82 %	20.26%
Grade 1	46.67%	44%	59%	62%	-	42.42 %	42.48%
Grade 2	33.33%	40%	28.4%	22%	27.5%	25.76 %	30.07%
Grade 3	6.67%	8%	7.6%	1%	3.9%**	0%	7.19%

Legend: $34% had pelvic irradiation to 50-52 Gy; †No AST during RT; &Prostate +/- SV only; *Whole pelvis receiving neoadjuvant and concurrent AST; #Prostate and SV only; ^Prostate and SV only; !With alpha/beta of 1.5; ** Grade 3 or higher

Zietman et al (22,23) randomly treated 393 low to intermediate risk (T1b – T2b, PSA <15 ng/ml) prostate cancer patients to dose equivalent to 70.2 Gy or 79.2 Gy. Patients were treated with a proton beam in phase I to a dose equivalent to 19.8 Gy (conventional arm) or 28.8 Gy (high dose arm) in 11 and 16 fractions respectively. Both arms received 50.4 Gy 3D-CRT in phase II using photon beams. The 5-year bNED was 78.8% in the conventional dose arm versus 91.3% in the high dose arm ($p<0.001$); there was no difference in overall survival. Peeters et al (24) reported the results of a phase III multi-centre Dutch trial comparing 78 Gy vs. 68 Gy in 664 patients. The bNED was 64% in the high dose arm and 54% in the conventional arm ($p=0.02$); the bNED was 74% vs. 64% in the high dose arm and conventional arm respectively; however, the p value was not given.

One study by Hong (25) which looked at pelvic LN RT (56 Gy in 23 fractions) with hypofractionation and dose escalation using IMRT to the prostate (70 Gy in 28 fractions at 2.5 Gy per fraction) only included 8 patients in a Phase I trial. Pollack (13) had previously reported a clinical trial of hypofractionated radiotherapy (70.2 Gy in 26 fractions at 2.7 Gy per fraction) using IMRT; the hypofractionation arm in this trial had a similar GU toxicity profile as ours, with a decreased GI toxicity (18% grade 2 GI toxicity vs. 35% grade 2 GI toxicity in our study). The reduced GI toxicity observed in the Pollack trial may be due to the fact that only the high-risk

patients (34%) received pelvic irradiation (to 50-52 Gy) as opposed to all patients in our trial.

Lim et al (14) treated 66 patients with 45 Gy in 25 fractions to the whole pelvis using a four field conventional technique with a simultaneous integrated IMRT boost to the prostate gland and SV of 22.5 Gy in 25 fractions. This differed from our trial were we treated the pelvic LN using an IMRT technique. There was no concomitant AST; however, all patients received AST at the end of RT. Toxicity rates were similar to the present trial with a 28.4% grade 2 and 7.6% grade 3 GU toxicity and a 39% grade 2 GI toxicity.

Kupelian (12) used a hypofractionated RT schedule of 70 Gy in 28 fractions at 2.5 Gy per fraction to the prostate +/- SV using IMRT and reported a GI toxicity rate of 15% grade 2 and 0% grade 3. The GU toxicity was grade 2 22% and grade 3 1%. These toxicities are less than in the present trial, however none of patients in Kupelian study received pelvic LN RT and only 60% had AST.

The RTOG 9413 (5) trial is a four arm study of pelvic LN RT vs. prostate only RT in combination with either neo-adjuvant or concurrent or adjuvant hormonal AST. The fraction schedule used was 70.2 Gy in 39 fractions (at 1.8 Gy per fraction). There were 309 patients in the pelvic LN RT with Neoadjuvant and concurrent AST arm, and analysis of GU toxicity showed a similar profile to our trial (grade 2 27.5% vs. 33.3% and grade 3 3.9% vs. 6.7% respectively). Similarly there was little difference in the GI toxicity,

44% grade 2 and 2.6% grade 3 in the RTOG 9413 vs. 35% grade 2 and 0% grade 3 in this trial.

The RTOG 9406 (26) trial treated 169 patients to the level III dose of 79.2 Gy in 44 fractions (1.8 Gy per fraction) to the prostate only (101 patients) or prostate plus SV to 55.8 Gy with a volume decrease to prostate only to 79.2 Gy (68 patients) using a 3D-CRT. The grade 2 GI acute toxicity rate was 20.9%; there were no grade 3 or higher GI toxicities. There was a 25.76% grade 2 GU toxicity rate and again there were no grade 3 or higher toxicities. The improved toxicity profile observed in this trial may be due to the fact that no patient had pelvic LN RT and only 45% of patients received neo-adjuvant AST.

Michalski et al (27) reported the RTOG 9406 dose level V where 78 Gy was delivered using a minimum dose per fraction of 2 Gy. They analysed 219 patients of which 119 patients (group 1) received 78 Gy to the prostate only and 100 patients (group 2) received to 54 Gy to prostate plus SV with a cone down to prostate only to 78 Gy using a 3D-CRT. The grade 2 acute toxicity rates were 36-45%, grade 3 acute GI toxicity rates were 2-4% and there were no grade 4 or higher GI toxicities.

Beckendorf (28) compared 80 Gy in 40 fractions vs. 70 Gy in 35 fractions (2 Gy per fraction) to the prostate and SV only using a 3D-CRT with no AST. Grade 2 GU toxicity was 30% and grade 3 was 7.19%, similar to our own study. GI toxicity was 28.1% grade 2 and 1.97% grade 3, lower grade 2 but higher grade 3 toxicities compared to our study.

Cahlon et al (29) analyzed data from 478 patients treated with IMRT to a dose of 86.4 Gy in 48 fractions. There was no pelvic LN RT and 66% of patients received ADT. Acute toxicity was scored using the CTCAE v3.0. There was a 59% grade 1 and 22% grade 2 acute GU toxicity. There was a 34% grade 1 and 8% grade 2 GI toxicity. These results do appear better than in this current trial despite using a higher dose; however it must be recognized that 2 different grading systems were used and they cannot be directly compared.

All of the discussed studies used RTOG or modified RTOG scores to report toxicity expect Cahlon et al (29) who used CTCAE v3.0 scores. This enables us to make some general comparisons of toxicity between the trials using RTOG criteria (Table 14).

Acute GU and GI toxicity results of our study are comparable to the above discussed studies which used either hypofractionated or dose escalated schedules. The use of concomitant hormonal treatment and pelvic LN RT was variable throughout the studies, whereas all patients received pelvic LN RT and most received AST (83.3%) in our study.

7.4. Conclusion:

This study demonstrates that it is possible to deliver hypofractionated and dose escalated radiation therapy to the prostate while treating the pelvic LN with a standard dose in the setting of AST with an acceptable acute toxicity rate. The acute toxicity rates were comparable to dose escalation trials using standard and hypofractionated schedules and in trials in which patients received pelvic RT. The acute toxicity recorded was transient with only 5 patients having persistent grade 2 or higher toxicity by 3 months of follow-up. Long-term toxicity results will be reported in due course.

Note: A version of this chapter has been accepted for publication in International Journal of Radiation Oncology Biology and Physics. PMID: 19395192, 2009 April 21 [Epub ahead of print].

8. Early results of Quality of Life

8.1. Study design:

Patients completed Quality of Life (QOL) questionnaires before commencing RT (baseline), at 1 month and at 6 months after completion of RT. These questionnaires were self-administered by the patients themselves at their own time with no assistance from clinical staff.

8.2. QOL assessment:

QOL assessments were obtained based on the University of California, Los Angeles (UCLA) Prostate Cancer Index (PCI) questionnaire (30). The questionnaire consists of 18 items subdivided into 3 sections: urinary function (5 items), bowel function (5 items) and sexual function (8 items). Patient completions of QOL forms were optional (Appendix 6).

8.3 Statistical Analysis:

Each of the items in the QOL questionnaire was assigned a nominal score of one to six, depending on the number of possible responses available for each item. These nominal scores were converted to continuous scores to obtain a composite of all the scores. A poor nominal score was assigned a low continuous score and vice versa. The higher the continuous score the better the QOL or vice versa. Table 15 explains the assignment of continuous scores to corresponding nominal scores of the PCI (smaller

numbers represent a poor QOL and higher numbers represent a better QOL).

Table 15: Continuous scores assigned to the corresponding nominal scores (1 to 6) of the Prostrate Cancer Index depending on the number of available responses per question (smallest numbers represent a poor QOL and higher numbers represent better QOL).

Nominal variables	1	2	3	4	5	6
3 categories	33	66	100	-	-	-
4 Categories	25	50	75	100	-	-
5 Categories	20	40	60	80	100	-
6 Categories	17	34	51	68	83	100

Means and standard errors were calculated for all 18 items of the PCI questionnaires for baseline. The one and 6 month follow-up was based on the scoring system described above (table 15). The QOL scores for each of the 18 items for 1 and 6-month follow-up were compared to the baseline using the generalized estimating equation (GEE) approach (31). The GEE approach accounts for the within-subject correlation arising due to repeated measurements on the same individual. This approach provides robust parameter estimates and their standard errors were then obtained; this is a statistical analysis for repeated measurements. All statistical analyses were conducted using SAS version 9.1.3. A p-value of <0.05 was considered to be the level of statistical significance.

8.4. Results:

The mean age at enrollment was 68 years (range 55-88), and all 60 patients completed the 6-month follow-up period. Fifty-eight patients received AST (Leuprolide 22.5 mg subcutaneously every 3 months), prescribed for a total duration of 2 to 3 years. Of the sixty patients, 3 patients were excluded from analyses because they were not approached to complete QOL questionnaire at baseline due to administrative reasons. Fifty patients completed the baseline QOL questionnaire after starting AST (median time 48 days) while 7 patients completed before starting AST. Nine patients declined to complete the sexual function portion of the questionnaire. There were some unanswered questions, mainly in the sexual function section due to unknown personal reasons. These absent responses were excluded from statistical analysis for that time point.

The mean score and standard errors of each item in the questionnaire at baseline, 1 and 6 months are shown in Table 16. The QOL scores for 1 month and 6 months were compared to the baseline scores, the results are summarized in Table 17. Significant differences between these comparisons are marked with an asterisk. The difference between time points was deemed statistically significant if the p value was <0.05.

Table 16: Mean scores and standard deviations for each item in the Prostate Cancer Index QOL questionnaire at baseline, 1 month and 6 months.

QOL item	Baseline		1 month		6 months	
	mean score	se	mean score	se	mean score	se
Urine leakage	87	34	86	35	98	23
Urinary control	91	23	90	19	94	16
# of pads or adult diapers	99	06	97	16	100	00
Dripping urine or wetting pants	93	25	92	22	96	13
Urine leakage interfering with sexual activity	98	17	94	29	100	00
Urinary function as a problem overall	39	32	42	29	32	27
Rectal urgency	95	22	73	40	82	42
Stools loose or liquid	82	23	73	26	77	28
Distress secondary to bowel movements	93	17	79	28	83	32
Crampy pain	93	21	85	31	90	31
Bowel function as a problem overall	88	25	77	31	82	34
Sexual desire	34	30	27	23	27	23
Ability to have an erection	35	27	24	26	24	15
Ability to reach orgasm	35	29	28	28	25	17
Quality of erections	52	45	40	37	39	38
Frequency of erections	38	33	28	25	26	24
Morning erections	33	24	27	20	25	17
Sexual intercourse unassisted by medical interv	43	32	38	24	37	20
Sexual intercourse assisted by medcal interver	98	12	98	11	98	11
Ability to function sexually	31	25	25	18	24	16
Sexual function as a problem overall	57	48	58	51	52	51

Table 17: Parameter estimates and their standard errors obtained from the QOL scores using the Generalized Estimating Equation (GEE) approach (statistical analysis for repeated measurements). Negative beta value indicates worsening quality of life.

	baseline vs. 1 month		baseline vs. 6 months	
	beta	**p-value**	**beta**	**p-value**
Urine leakage	-1.3	0.74	4.8	0.2031
Urinary control	-1.2	0.5967	2.3	0.3326
# of pads or adult diapers	-2.6	0.0893	0.4	0.3896
Dripping urine or wetting pants	-0.5	0.8672	2.7	0.2035
Urine leakage interfering with sexual activity	-3.4	0.3092	2.5	0.1485
Urinary function as a problem overall	4.6	0.1758	-6.7	0.0266*
Rectal urgency	-21.6	<0.0001*	-12.8	0.0024*
Stools loose or liquid	-9.9	0.0002*	-5.9	0.0153*
Distress secondary to bowel movements	-14.1	<0.0001*	-10.0	0.0011*
Crampy pain	-7.6	0.0066*	-4.4	0.1546
Bowel function as a problem overall	-11.6	0.0001*	-6.7	0.0671
Sexual desire	-7.2	0.0074*	-7.1	0.0201*
Ability ot have an erection	-6.2	0.0487*	-10.6	<0.0001*
Abiliy to reach orgasm	-7.8	0.0115*	-11.0	<0.0001*
Quality of erections	-10.9	0.0028*	-14.8	0.0016*
Frequency or erections	-10.2	0.0023*	-12.4	0.0002*
Morning erections	-6.3	0.0046*	-8.9	0.0002*
Sexual intercourse unassisted by medical interv	-4.6	0.0676	-5.9	0.1122
Sexual intercourse assisted by medical interven	0.7	0.6039	0.3	0.8598
Ability to function sexually	-6.5	0.003*	-7.1	0.003*
Sexual function as a problem overall	1.5	0.7333	-3.2	0.5091

Statistically significant trends towards decreased QOL were observed for bowel and sexual function as shown in Figures 10 and 11. Urinary function remained largely unaffected except “urinary function as a problem overall” as shown in Figure 9. The percentage of patients choosing each available response in the QOL questionnaire (dealing with urinary function, bowel function and sexual function) at each time point surveyed is shown in Figure 12.

Figure 9: Scores obtained in the urinary function portion of the QOL questionnaire at baseline (0 months), 1 month and 6 months after treatment completion.

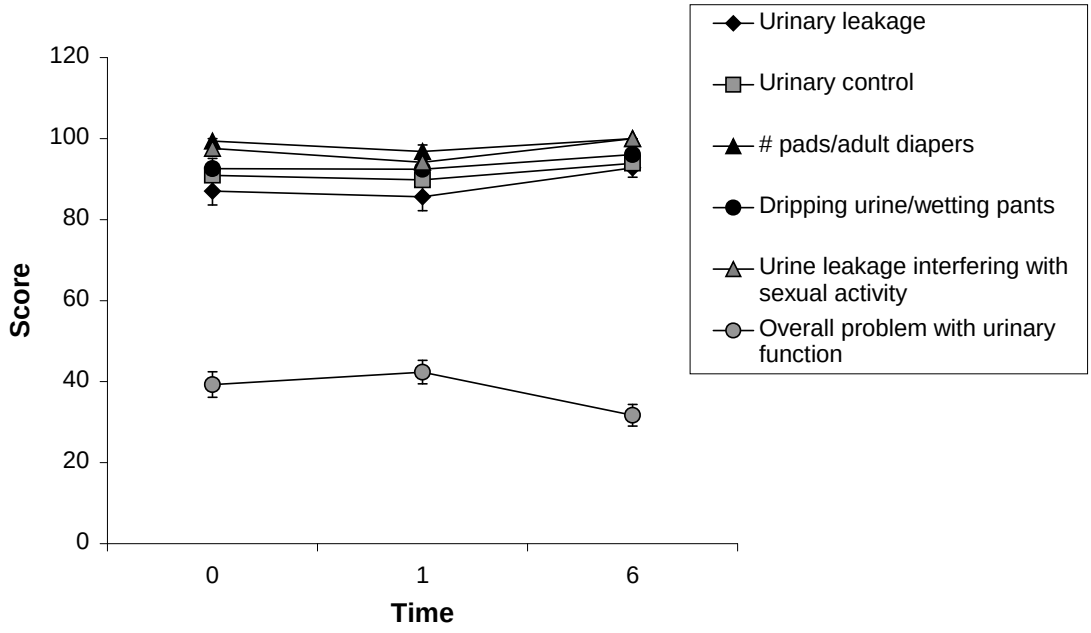


Figure 10: Statistically significant scores obtained in the gastrointestinal function portion of the QOL questionnaire (Rectal urgency, Loose or liquid stools, a distress due to bowel movements) at baseline (0 months), 1 month and 6 months after radiation treatment completion.

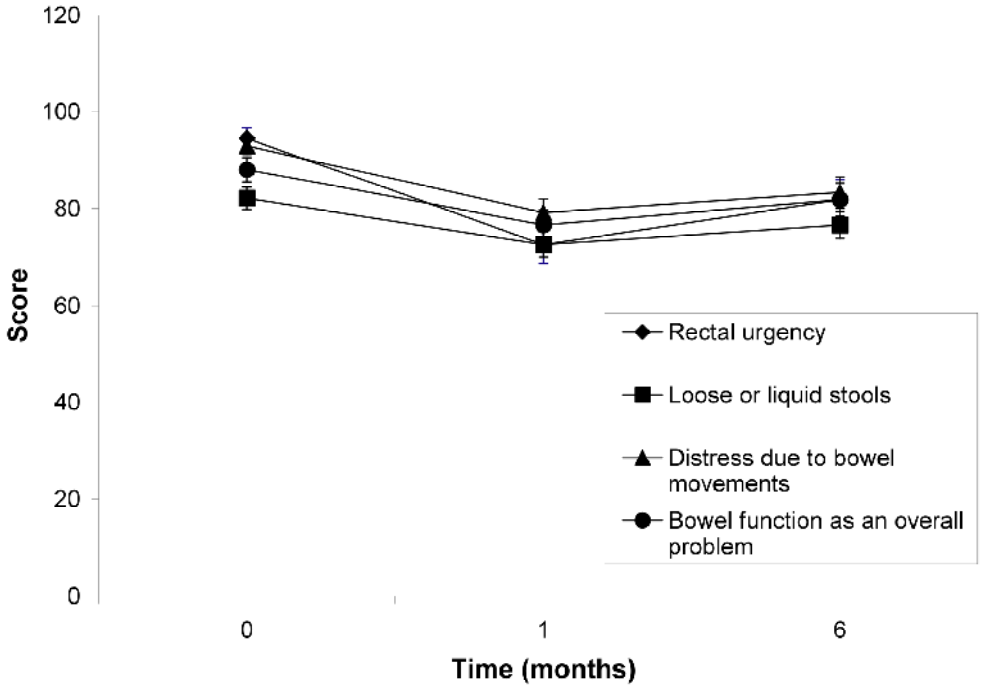


Figure 11: Statistically significant scores obtained in the sexual function portion of the QOL questionnaire (quality of erections, frequency of erections, morning erections, overall ability to function sexually) at baseline (0 months), 1 month and 6 months after radiation treatment completion.

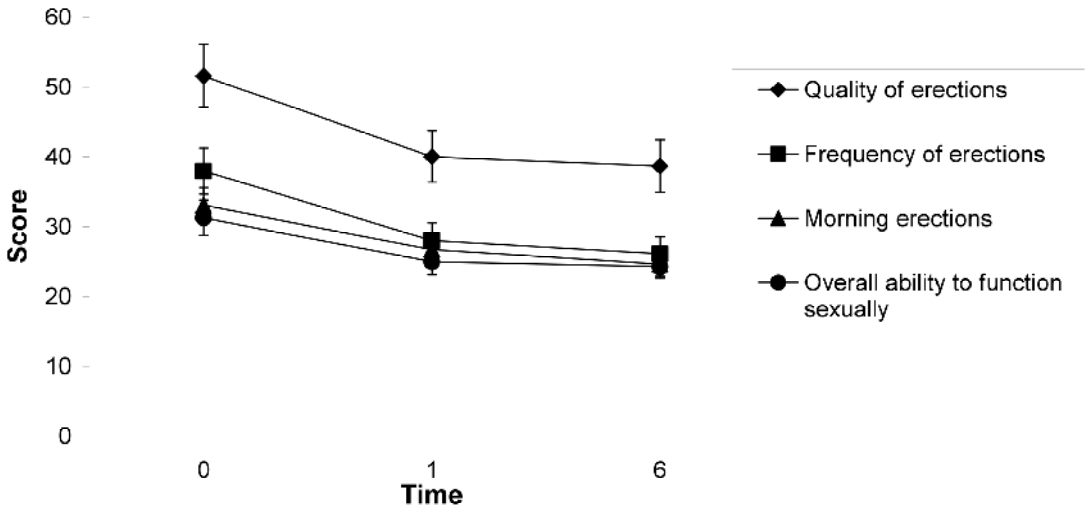
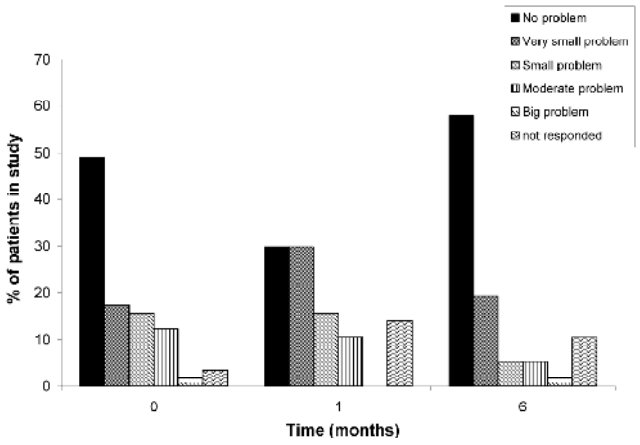
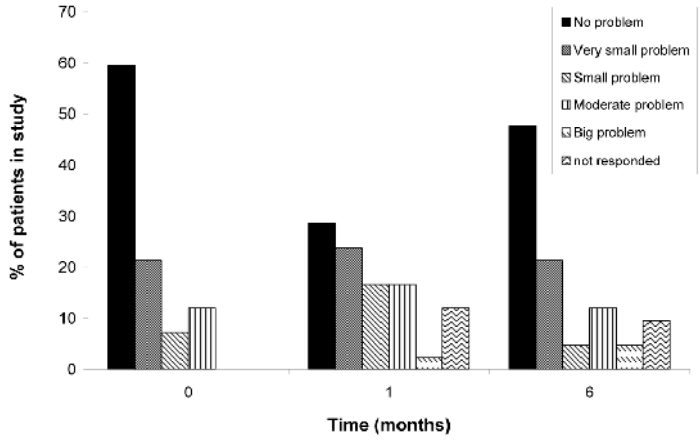


Figure 12: The percentage of patients corresponding to each questionnaire response for overall urinary function (A), overall bowel function (B), overall sexual function (C) at each time point surveyed: 0 months (before radiation treatment), 1 month and 6 months after radiation treatment completion.

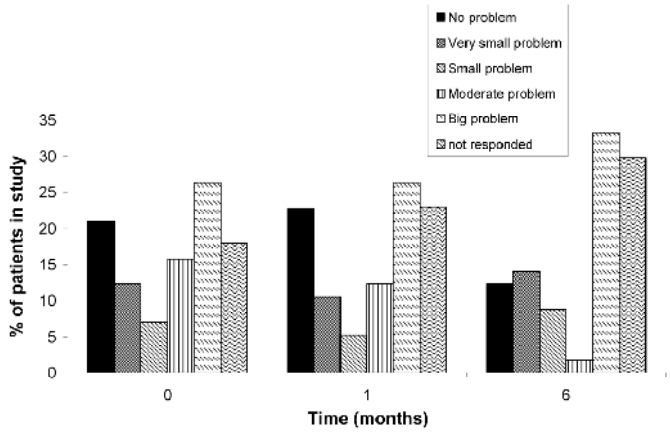
A.



B.



C.



Statistically significant differences in the scores were observed at both 1 and 6 months for items concerning rectal urgency, loose bowel movements and distress caused by bowel movements. Bowel function as a problem overall was adversely affected at one month but not at six months. In terms of sexual function, significant differences were observed for most items as well as the overall ability to function sexually, but not in the perception of sexual function as a problem overall.

8.5. Discussion:

To our knowledge there are no other published reports of QOL in high-risk prostate cancer patients where all patients received pelvic LN treatment using IMRT treatment delivery with a hypofractionated schedule and AST (hormonal treatment). In our study the use of a hypofractionated schedule resulted in a significant decrease in early post-treatment QOL largely in terms of bowel and sexual function. Urinary function was largely unaffected other than a decrease in QOL in terms of urinary function as a problem overall at 6 months. The general trend for most QOL items (Figures 10 and 11) showed a decreased score at 1 month, with a return to baseline thereafter. No significant difference is observed in terms of urine leakage, urinary control, or the number of pads or adult diapers used. The calculated scores reveal that dripping urine, wetting pants, or urine leakage interfering with sexual activity did not affect the QOL (Figure 9). Overall statistical comparison of baseline with 1 month and baseline with 6 months shows that more patients had decreased urinary function

overall at 6 months (Table 16). Usual adverse effects of RT (increased frequency, nocturia, burning sensation, urgency and slow urinary streams) are not separately listed in the questionnaire, which may be the cause for worsening urinary function overall without affecting individual functions. These questions were later included in a modified and newly validated expanded prostate cancer index composite (EPIC) questionnaire. The percentage of people who maintained that they had no difficulties with urinary function at baseline (49%), decreased to 30% at one month, with patients distributing more into the “small problem” category. Still only less than 2% reported a “big problem” with urinary function at 6 months (Figure 12A). Therefore, our data shows that there is some urinary function impairment, but is not necessarily affecting the patient’s QOL.

A significant decrease in QOL was observed in terms of bowel function as it relates to rectal urgency, loose bowel movements, distress with bowel movements, and bowel function as an overall problem. Worsening in terms of QOL scores was observed both at 1 and 6 months as compared to baseline (Table 16). The decrease in QOL is less at 6 months than at 1 month. These bowel function QOL items are still potentially below baseline at 6 months (see Figure 10). Crampy pain showed a decreased score (worse QOL) at 1 month with some improvement at 6 months (see Figure 10). At six months, however, the results were not statistically significant (see Table 4).

Hanlon et al. (32) have compared QOL of patients treated with pelvic LN vs. the prostate only. Their results show decrease in QOL related to bowel function in patients who received pelvic LN treatment. Our results are similar to their findings as patients in our study also received pelvic LN treatments. In our study we delivered hypofractionated schedules using IMRT technique while they used conventional schedule using 3DCRT technique. Significantly decreased QOL scores were observed for QOL items dealing with ability, quality, frequency, occurrence of morning erections, and the ability to function sexually. This is not surprising in a cohort of patients receiving continuous AST. Fifty patients already received AST for a median duration of 48 days before completing baseline QOL questionnaire, which may reflect low scores at baseline. Of the fifty-seven patients who were included in the study, 49 completed all items of the sexual function section of the questionnaire. The issue of obtaining a response to sexual function questions is reflected in a number of studies (33, 34) that analyzed sexual function. This problem is compounded by the fact that the QOL questionnaire was optional. Overall sexual function decreased at 1 month and remained at the same level at 6 months. As a problem overall, sexual function was not significantly affected at either time point. However the ability to function sexually was significantly decreased at 1 month and remained so at 6 months (Table 17) with no improvement towards baseline (Figure 11). There was no significant difference in the patient's perception of this being a problem. This is

reflected in the fact that while at baseline 73% of patients rate their ability to function sexually as very poor or poor, only 26% perceive this to be a big problem (Figure 12C). Six months after treatment the statistics remain about the same. This trend is reflected in the data from Namiki et al (35) and Junius et al. (34). Thus a large number of our patients do not perceive sexual function to be a problem despite significant impairment as discussed by Katz et al. (36). The sexual function results may reflect the mean age of the patients included in the study (68 years). This age group is both less likely to feel comfortable answering the questions, and also more likely to experience sexual dysfunction secondary to age and co-morbid medical conditions. According to Smith et al. (37) and Lindau et al. (38), only 37- 41 % of males around the age of 70 are sexually active. Patients in our study may have felt confused at having to answer sexual function questions and may have perceived answering these questions as irrelevant to them. Most patients (79%) were not using any assistance (injection, vacuum pump or Phosphodiesterase 5 inhibitors) to facilitate intercourse at baseline; this did not change over the course of the treatment. Fifty-eight of 60 patients on our study were receiving AST, compared to a number of studies where only some of the patients received it (33, 34, 35). As previously documented, AST represents an independent risk factor for erectile dysfunction (39, 40). In view of the use of AST and the hypofractionated schedule used, the rates of erectile dysfunction over time will be interesting to observe and compare to

existing studies (41, 42). Other studies have looked at comparing IMRT with either conformal or conventional RT (33, 43, and 35) (see Table 18). While the doses to the prostate, patient characteristics and use of concurrent AST vary, overall they show an equally decreased QOL after both types of treatment, with improvement in some QOL areas if the patient underwent IMRT. Lips et al. (33) show better QOL in a few domains (urinary symptoms and pain). Kupelian et al. (43) showed no difference in QOL between IMRT (78 Gy) and conventional RT (69.6 Gy). Namiki et al. (35) showed no difference in urinary function, but worse bowel and sexual function with conventional RT. Junius et al. (34) did not compare the two methods, but using IMRT (66 Gy to prostate) showed increased urinary symptoms at 1 month with subsequent resolution at 6 months. Although our questionnaire does not include the psychosocial categories present in other questionnaires, the patient responses largely reflect the same trends as other published data on the subject (33, 34, 43, 35). One limitation of this study is the questionnaire that was chosen at a time before recently validated questionnaires such as EPIC were available. Therefore it does not cover some of the psychosocial domains and irritable urinary symptoms included in other studies. Nevertheless our concern with increasingly long comprehensive questionnaires is that they may be less likely to be filled out by patients, unless made mandatory. Another limitation is that many patients started AST before baseline QOL that may reflect low sexual function at baseline.

Table 18: QOL literature comparing IMRT and conformal / conventional radiation therapy.

Author	Technique	Dose/ fraction (Gy)	Total prostate dose (Gy)	QOL questionnaire used	Results	Total patients	Patients received AST
Lips (33)	IMRT	2.17	76	EORTC-C30 PR 25 RAND 36	better QOL for urinary symptoms and pain, bowel function and sexual function no difference between groups	92	24
	CRT	2	70			78	9
Junius (34)	IMRT	2.64	66	EORTC-C30 PR 25	increased urinary symptoms @ 1 month, better at 6 months, no worsening bowel function, worsening sexual function at 1-6 months, better at 2-3 years	38	31
Kupelian (43)	IMRT	2.5	70	EPIC	no difference in QOL , no discussion of QOL in follow-up paper in 2007	51*	not reported
	CRT	2.0	78			46	
Namiki (35)	IMRT	not reported	78	UCLA PCI SF 36	no difference in urinary function, XRT worse bowel function at 3 and 6 months (than IMRT), sexual functions decreased after XRT, not after IMRT	30	4
	CRT		69.6			76	65
	coRT		69.6			34	
Pervez	IMRT	2.72	68	UCLA PCI	Overall urinary function affected at 6 months, bowel function affected at 1 month, improving towards 6 months, sexual function decreased at baseline, remained decreased	57	55

CRT = conformal RT; coRT = conventional RT

* only 24 completed EPIC questionaire

8.6. Summary:

In our study population where hypofractionated radiation doses were delivered using dynamic IMRT (helical TomoTherapy) with inclusion of pelvic LN, and 2 to 3 years of AST prescription, QOL was significantly affected in terms of bowel and sexual functions. Individual urinary functions were unaffected except urinary function as a problem overall. These results are comparable to published studies using hypofractionated schedules treating the prostate only (no pelvic RT) and to conventional schedules delivering both pelvic LN and prostate treatment. We are collecting long-term QOL data at regular intervals that will be updated at a later stage. Further studies looking at the long-term treatment effects on QOL with hypofractionated schedules are needed and are in progress.

Note: A version of this chapter has been submitted for review on October 19, 2008 in Radiotherapy and Oncology journal (Ms. Ref. No.: RO-D-08-00588).

9. Other results and future plans

9.1. Prostate movements and treatment verifications using daily pre-treatment MVCT:

9.1.1. Purpose and method:

In order for RT to be effective, the radiation needs to interact with the intended target. The prostate is a dynamic gland located in the pelvis adjacent to important structures such as the bladder and rectum (44). Differential filling of these structures may alter prostate gland position within the pelvis. This may lead to the under dosing of target volumes, compounded by the overdosing of normal tissues. This is of great importance when delivering higher radiation doses in fewer fractions (hypofractionation). Review and adjustments of the patient's position is necessary daily in order to deliver RT accurately to the targets. This can be achieved by treatment verification using three dimensional imaging such as MVCT. In this study, we investigated the day-to-day (interfractional) movements of the prostate gland and SV using MVCT as a verification tool to accurately correct daily setup variations and organ motion in a three-dimensional manner. Patients underwent Kilo-voltage CT (KVCT) simulation followed by daily MVCT imaging on a helical tomotherapy unit prior to each treatment fraction. KVCT and daily MVCT images were fused to manually generate corrective shifts (when necessary) in patient positions before each dose was delivered (see figure

13 and 14). Measuring the required corrective shifts in patient position after fusion of KVCT and daily MVCT images assessed daily variation in prostate and SV positions.

Figure 13: Transverse view of kilovoltage (KV) CT image used for planning of radiation treatment (left panel), and megavoltage CT image taken daily before each fraction (middle panel); fusion of the two images are used to manually analyze if corrective adjustment in the patient's position is necessary prior to delivering radiation (right panel).

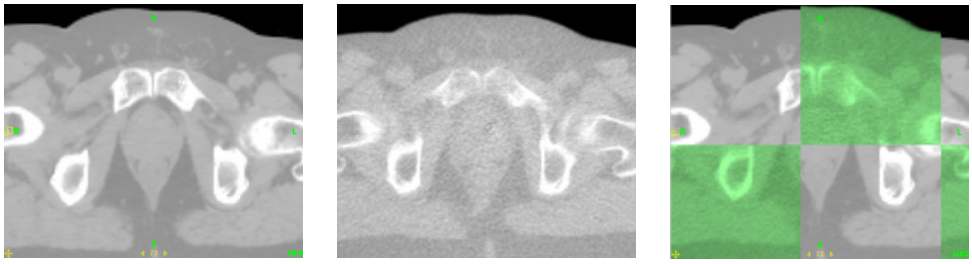
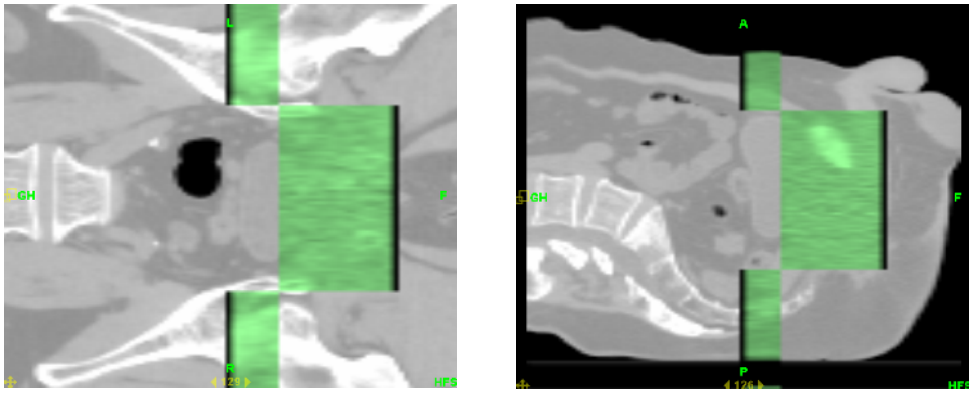


Figure 14: Fusion of kilovoltage planning images with daily megavoltage CT images for the coronal (left panel) and sagittal (middle panel) orientations are also used to assess if corrective shifts of the patient's position is warranted.



9.1.2. Results:

The applied daily corrective positional shifts for each of the 25 fractions were analyzed for the 57 patients (see figure 15 and 16). The applied shifts' means, standard deviations (SD) and ranges in millimeter (mm) were as follows:

- Anterior-posterior: mean 1.91 (2.35 SD) and range -10.6 to 21.9
- Left-right lateral: mean 2.54(2.58 SD) and range -21.0 to 16.0
- Superior-inferior: mean 2.42 (2.20 SD) and range -11.8 to 12

Of the 1,425 fractions delivered, treatments that would have exceeded the target margin resulting in a lower radiation dose to the target and higher dose to the normal tissue if adjustments were not made:

- Anterior-posterior: 48 fractions (3.4%)
- Left-right lateral: 21 (1.5%)
- Superior-inferior: 10 (0.7%)

Of the 57 patients receiving RT, 28 patients (49%) required at least one adjustment that would have exceeded treatment target and margins.

Figure 15: The range for patient positional adjustments was greatest in the right-left lateral plane.

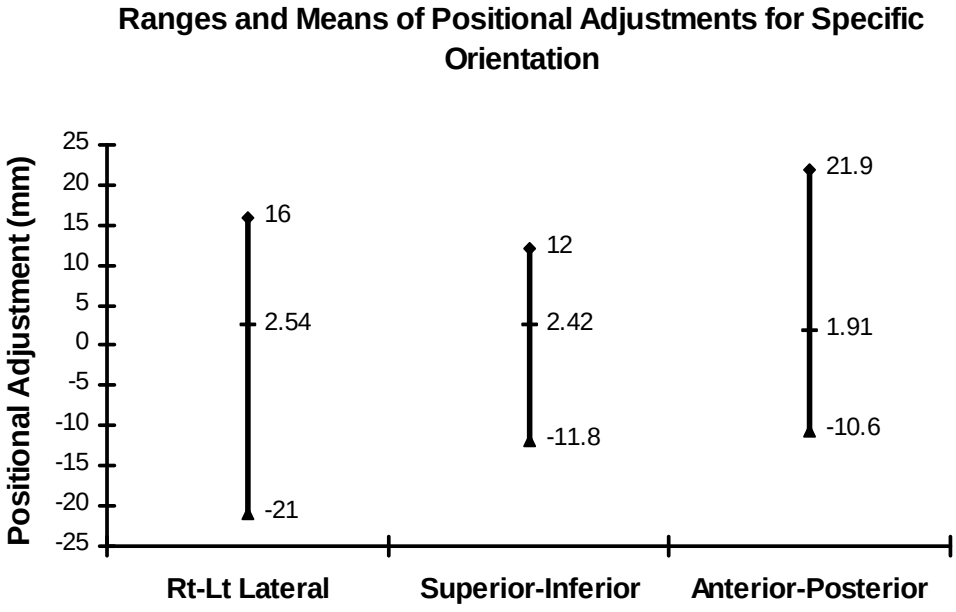
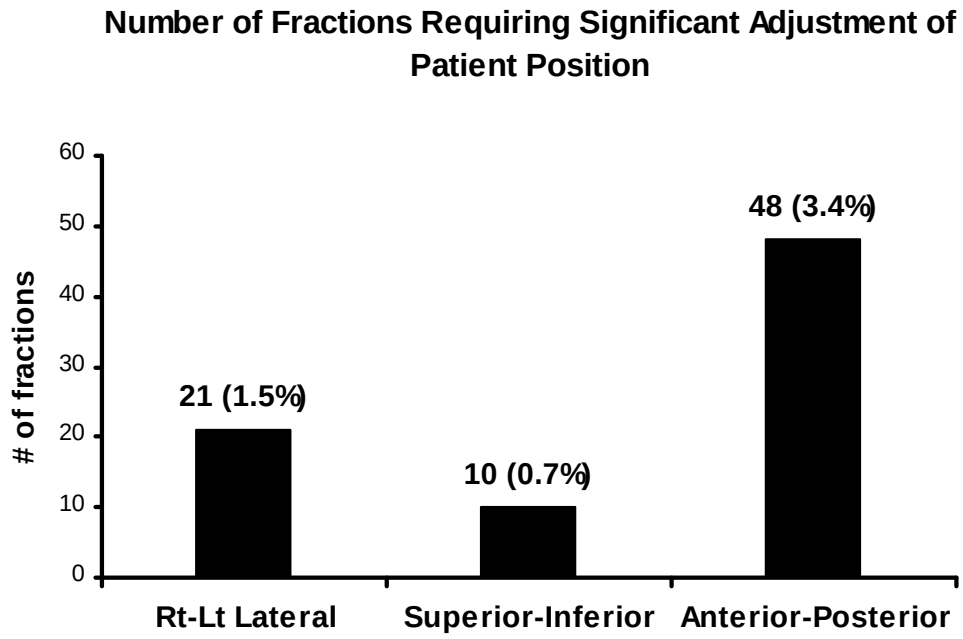


Figure 16: Significant corrective adjustments to avoid delivery of radiation beyond the targeted volume were most frequent in the anterior-posterior plane.



9.1.3. Conclusions:

Significant positional variation of the prostate and SV were observed during treatment. Daily target verification (especially in treatments utilizing hypofractionation and dose escalation) is warranted to avoid inadequate dose coverage and increased toxicity. Therefore, it is necessary to assess the prostate position daily prior to delivering treatment in order to make necessary adjustments. Results show that movement in the anterior-posterior axis is most prominent. This is likely due to daily changes in the bladder and rectum. Approximately half of the patients in this study required positional adjustments to avoid significant misses of the cancer targets.

9.2. Late effects of treatment:

The current minimum follow up period after completion of RT is 18 months. The maximum follow up is 48 months, and median follow up is 30 months. Late effect of treatment and outcome data collection is ongoing. It is reasonable to assess late effects of treatment at this time, although complete analyses will require further follow up and therefore raw data of late effects are presented here (see table 19).

Table 19: Current late GU and GI effects of treatment data

Months at follow up	Genitourinary (GU) toxicity RTOG grades			Gastrointestinal (GI) toxicity RTOG grades			Total patient Asses-sed
	G 1	G 2	≥G3	G 1	G 2	≥G3	
6	11 19%	3 5.2%	0	14 24.1%	4 6.9%	0	58
12	5 8.6%	13 22.4%	0	13 22.4%	7 12%	4* 6.9%	58
18	8 14.8%	6 11.1%	1* 1.8%	13 24%	5 9.2%	3* 5.5%	54
24	7 15.2%	5 10.8%	0	11 23.9%	2 4.3%	2 4.3%	46
30	1 2.9%	5 14.7%	1 2.9%	12 35.2%	0	0	34
36	2 9.5%	3 14.2%	0	7 33.3%	1 4.7%	0	21
42	0	1 12.5%	0	2 25%	0	0	8
48	0	0	0	0	0	0	1

Three patients have repeated Grade 3 GI toxicity during follow up at 12 and 18 months and counted at both time points. One patient has both GU and GI grade 3 toxicity at 18 month and counted under both categories. Some centres use modified version of RTOG toxicity criteria where up to 3 laser treatments considered as grade 2 GI toxicity. Using those modified version of toxicity score can downgrade some of our patient from grade 3

to grade 2 GI toxicity. Also reducing margins around prostate for PTV 68 may further decrease treatment related morbidity.

9.3. Outcomes:

To date there is no patient with evidence of loco-regional or distant metastasis. One patient is under investigation for possible biochemical failure due to PSA rise from nadir value of 0.04 to one time value of 3 ng/ml. This may be as a result of benign bounce rather than biochemical failure. Future PSA may help to differentiate benign bounce vs. biochemical failure. Early outcomes are encouraging; however, a longer follow up is required and underway for complete assessment.

9.4. Future plans:

Our experiences from this study guide us to shrink safety margins around prostate gland (CTV to PTV margin), when using daily MVCT scan prior to treatment. Decreasing safety margin will allow us increase RT doses safely due to decrease in OAR doses. This study leads us to a follow up hypofractionation study in a similar group of patients with 10% further dose escalation. This follow up study is currently accruing patients. Our aim in the follow up study is to further escalate radiation doses to targets but to reduce doses and possible side effects to organs at risk. Also, discussions are ongoing at a national level to compare this treatment regimen with standard fraction radiation in randomized fashion.

10. Bibliography

1. Canadian Cancer Statistics: http://cancer.ca

2. Lukka H, Canadian journal of Urology, 2002 June ; 9 suppl 1 :26-9

3. Bolla M, Collette L, Blank L et al. Long term results with immediate androgen suppression and external beam radiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomized trial. Lancet. 2002 July 13; 360 (9327):103-6 2002.

4. Hanks GE, Pajak TF, Porter A et al. Phase III trial of long term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of prostate: the Radiation Therapy Oncology Group Protocol 92-02. J. Clin. Oncol. 2003 Nov 1;21(21): 3972-8. Erratum in: J Clin Oncol. 2004 Jan 15;22(2):386.

5. Roach M 3rd, DeSilvio M, Valicenti R et al. Whole-pelvis, "mini-pelvis," or prostate-only external beam radiotherapy after neoadjuvant and concurrent hormonal therapy in patients treated in the Radiation Therapy Oncology Group 9413 trial. Int J Radiat Oncol Biol Phys. 2006 Nov 1. 66(3) pages 647-653.

6. Pollack A, Zagars GK, Starkschall G et al. Prostate cancer radiation dose response: results of the MD Anderson phase III randomized trial. MD Anderson. Int J Radiat Oncol Biol Phys. 2002 Aug1; 53(5): 1097-105.

7. Richard K. Valicenti, Kathryn Winter, James D. Cox et al. RTOG 94-06: Is the addition of neoadjuvant hormonal therapy to dose-escalated 3D conformal radiation therapy for prostate cancer associated with treatment toxicity? Int J Radiat Oncol Biol Phys volume 57 (3): 614-620 2003.

8. Bos LJ, Damen EM, de Boer RW et al. Reduction of rectal dose by integration of the boost in the large-field treatment plan for prostate irradiation. Int J Radiat Oncol Biol Phys. 2002 Jan 1; 52 (1) : 254-65.

9. Beckendorf V, Guérif S, Le Prisé E et al. The GETUG 70 Gy vs. 80 Gy randomized trial for localized prostate cancer: feasibility and acute toxicity. Int J Radiat Oncol Biol Phys. 2004 Nov 15;60(4):1056-65.

10. Brenner DJ and Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys. 1999 Mar 15;43(5):1095-101.

11. Jack A Fowler, Mark A Ritter, Rick J Chappell et al. What hypofractionated protocols should be tested for prostate cancer? Int J Radiat Oncol Biol Phys volume 56(4), 15 July 2003, Pages 1093-1104.

12. Kupelian PA, Reddy CA, Carlson TP, et al. Preliminary observations on biochemical relapse-free survival rates after short-course intensity-modulated radiotherapy (70 gy at 2.5 Gy/fraction) for localized prostate cancer. Int J Radiat Oncol Biol Phys 2002;53:904-12.

13. Pollack A, Hanlon AL, Horwitz EM, et al. Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial. Int J Radiat Oncol Biol Phys 2006;64:518-26.

14. Lim TS, Cheung PC, Loblaw DA, et al. Hypofractionated accelerated radiotherapy using concomitant intensity-modulated radiotherapy boost technique for localized high-risk prostate cancer: Acute toxicity results. Int J Radiat Oncol Biol Phys 2008 Sep 1;72(1):85-92.

15. C. N. Catton, P. Chung, T. Haycocks et al. Hypofractionated intensity modulated radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys Volume 54, Issue 2, Supplement 1, 1 October 2002, Page 188.

16. Schultheiss TE, Lee WR, Hunt MA et al. Late GI and GU complications in the treatment of prostate cancer. Int J Radiat Oncol Biol Phys 1997 Jan 1 ;37(1):3-11.

17. O'Brien PC, Franklin CI, Poulsen MG et al. Acute symptoms, not rectally administered sucralfate, predict for late radiation proctitis: longer term follow-up of a phase III trial--Trans-Tasman Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2002 Oct 1;54(2):442-449.

18. Mitchell Liu, Tom Pickles, Alexander Agranovich et al. Impact of neoadjuvant androgen ablation and other factors on late toxicity after external beam prostate radiotherapy. Int J Radiat Oncol Biol Phys 1 Jan 2004;58(1):59-67.

19. Thall PF, Simon RM, Estey EH. New statistical strategy for monitoring safety and efficacy in single-arm clinical trials. J Clin Oncol. 1996 Jan;14(1):296-303.

20. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31:1341-6.

21. Kuban D, Tucker S, Dong L, et al. 15: Long-term results of a randomized dose escalation trial for prostate cancer. International Journal of Radiation Oncology*Biology*Physics 2006;66:S8-9.

22. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs. high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial. JAMA 2005;294:1233-9.

23. Incorrect data reported in text and figure in: Comparison of conventional-dose vs. high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: A randomized controlled trial. JAMA The Journal of the American Medical Association 2008;299:899.

24. Peeters ST, Heemsbergen WD, Koper PC, et al. Dose-response in radiotherapy for localized prostate cancer: Results of the dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 gy. J Clin Oncol 2006;24:1990-6.

25. Hong TS, Tome WA, Jaradat H, et al. Pelvic nodal dose escalation with prostate hypofractionation using conformal avoidance defined (H-CAD) intensity modulated radiation therapy. Acta Oncol 2006;45:717-27.

26. Ryu JK, Winter K, Michalski JM, et al. Interim report of toxicity from 3D conformal radiation therapy (3D-CRT) for prostate cancer on 3DOG/RTOG 9406, level III (79.2 gy). Int J Radiat Oncol Biol Phys 2002;54:1036-46.

27. Michalski J, Winter K, Purdy J, Parliament M, et al. Toxicity after three-dimensional radiotherapy for prostate cancer on RTOG 9406 dose level V. Int J Radiat Oncol Biol Phys 2005;62(3):706-713.

28. Beckendorf V, Guérif S, LePrisé E, et al. The GETUG 70 Gy vs. 80 Gy randomized trial for localized prostate cancer: Feasibility and acute toxicity. International journal of radiation oncology, biology, physics 2004;60(4):1056-65.

29. Cahlon O, Zelefsky MJ, Shippy A, et al. Ultra-high dose (86.4 gy) IMRT for localized prostate cancer: Toxicity and biochemical outcomes. Int J Radiat Oncol Biol Phys 2008;71:330-7.

30. Litwin MS, Hays RD, Fink A et al. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Med. Care. 1998; 36(7):1002-12.

31. Zeger SL, Liang KY and Albert PS. Models for longitudinal data: a generalized Estimating equation approach. Biometrics (1988) 44(4): 1049-1060.

32. Alexandra L. Hanlon, Deborah W Bruner, Ruth Peter. Quality of Life study in prostate cancer patients treated with Three-Dimensional Conformal Radiation Therapy: comparing late bowel and bladder quality

of life symptoms to that of the normal population. Int. J. Rad. Oncol. Biol. Phys., 2001; 49(1): 51-59.

33. Lips I, Dehnad H, Kruger AB, et al. Health-Related Quality of Life in Patients with Locally Advanced Prostate Cancer after 76 Gy Intensity-Modulated Radiotherapy vs. 70 Gy Conformal Radiotherapy in a Prospective and Longitudinal Study. Int. J. Radiat. Oncol. Biol. Phys 2007; 69(3):656-61.

34. Junius S, Haustermans K, Bussels B, et al. Hypofractionated intensity modulated irradiation for localized prostate cancer, results from a phase I/II feasibility study. Radiation Oncology. 2007; 2:29.

35. Namiki S, Ishidoya S, Tochigi T, et al. Health-related quality of life after intensity modulated radiation therapy for localized prostate cancer: comparison with conventional and conformal radiotherapy. Jpn. J. Clin. Oncol. 2006; 36(4):224-30.

36. Katz G, Rodriguez R. Changes in continence and health-related quality of life after curative treatment and watchful waiting of prostate cancer. Urology. 2007; 69(6): 1157- 60.

37. Smith LJ, Mulhall JP, Deveci S, Monaghan N, Reid MC . Sex after 70: A pilot study of sexual function in Older Persons. J Sex Med. 2007; 4(5):1247-53.

38. Lindau ST, Schumm LP, Laumann EO et al. A study of sexuality and health among older adults in the United States. N. Engl. J. Med. 2007; 357(8):762-74.

39. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N. Engl. J. Med. 2008; Mar 20; 358(12):1250-61.

40. Zelefsky MJ, Cowen D, Fuks Z, et al. Long term tolerance of high dose three dimensional conformal radiotherapy in patients with localized prostate carcinoma. Cancer. 1999; 85(11):2460-8.

41. Brown MW, Brooks JP, Albert PS, Poggi MM. An analysis of erectile function after intensity modulated radiation therapy for localized prostate carcinoma. Prostate Cancer Prostatic Dis. 2007; 10(2):189-93.

42. Van derWielenGJ, Van Putten WL, Incrocci L.Sexual function after three dimensional conformal radiotherapy for prostate cancer: results from a dose-escalation trial. Int. J. Radiat. Oncol. Biol. Phys. 2007; 68(2):479-84.

43. Kupelian PA, Reddy CA, Klein EA, Willoughby TR. Short-course intensity modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: preliminary results on late toxicity and quality of life. Int. J. Radiat. Oncol. Biol. Phys. 2001; 51(4):988-93.

44. Trichter R, Ennis RD. Prostate localization using transabdominal ultrasound imaging. Int J Radiation Oncol Biol Phys 2003; 56: 1225.

45. Roach M, Marquez C, You H, et al. Predicting the risk of lymph node involvement using the pre-treatment specific antigen and Gleason score in men with clinically localized prostate cancer. Int. J. Radiat. Oncol. Biol. Phys. 1993; 28:33-37.

46. Mackie TR, Holmes T, Swerdioff S et al. Tomotherapy: a new concept for the delivery of dynamic conformal radiotherapy. Med Phys. 1993 Nov-Dec;20(6): 1709-19.

Appendix 1: TNM staging for prostate cancer

From the AJCC 6th edition (2002) and UICC 6th edition.

Evaluation of the (primary) tumor ('T')

TX: cannot evaluate the primary tumor

T0: no evidence of tumor

T1: tumor present, but not detectable clinically or with imaging

T1a: tumor was incidentally found in less than 5% of prostate tissue resected (for other reasons)

T1b: tumor was incidentally found in greater than 5% of prostate tissue resected

T1c: tumor was found in a needle biopsy performed due to an elevated serum PSA

T2: the tumor can be felt (palpated) on examination, but has not spread outside the prostate

T2a: the tumor is in half or less than half of one of the prostate gland's two lobes

T2b: the tumor is in more than half of one lobe, but not both

T2c: the tumor is in both lobes

T3: the tumor has spread through the prostatic capsule (if it is only part-way through, it is still T2)

T3a: the tumor has spread through the capsule on one or both sides

T3b: the tumor has invaded one or both seminal vesicles

T4: the tumor has invaded other nearby structures

It should be stressed that the designation "T2c" implies a tumor which is palpable in both lobes of the prostate. Tumors which are found to be bilateral on biopsy only but which are not palpable bilaterally should not be staged as T2c.

Evaluation of the regional lymph nodes (’N’)

NX: cannot evaluate the regional lymph nodes

N0: there has been no spread to the regional lymph nodes

N1: there has been spread to the regional lymph nodes

Evaluation of distant metastasis (’M’)

MX: cannot evaluate distant metastasis

M0: there is no distant metastasis

M1: there is distant metastasis

M1a: the cancer has spread to lymph nodes beyond the regional ones

M1b: the cancer has spread to bone

M1c: the cancer has spread to other sites (regardless of bone involvement)

Appendix 2: Risk stratification for prostate cancer:

Risk category	PSA (ng/ml)	Gleason score	T stage
Low	0-10	2-6	T1a to T2a
Intermediate	>10 to 20	7	T2b and T2c
High	>20	8 to 10	T3a to T4

Appendix 3: Eligibility checklist and initial evaluation

Role of TomoTherapy (Dynamic IMRT and megavoltage CT scanning) in hypofractionated/dose escalated conformal radiation treatment and Magnetic Resonance imaging (MRI) to predict pattern of loco-regional failure for high-risk prostate cancer

Patient ID #:	Initials:	Date: - - (dd-mm-yy)	Case Number:

There will be no exceptions to the following eligibility requirements at the time of enrollment.

Please check (✓) to confirm the following:

____ Patient is 18 years or older

____ Patient has histologically proven malignancy by needle core samples or TURP with assigned Gleason score. Prostate biopsy performed within 180 days of enrollment (date of consent).

____ No clinical or radiological evidence of nodal or distant metastasis(es).

____ Patient has high risk prostate cancer (stage T3 or T4 and/or PSA ≥20 and/or Gleason score 8 or 9 or 10 or Gleason Score 7 with PSA ≥ 15)

____ In the opinion of the treating oncologist, patient is fit to undergo radical external beam radiotherapy to the prostate

____ Patient is accessible for treatment and follow up.

____ Patient does not have history of inflammatory bowel disease, anal stenosis, colorectal surgery, or repeated endoscopic examinations/interventions related to anorectal diseases

____ NO history of prostatectomy, transurethral resection of prostate on more than one occasion, or previous pelvic radiotherapy

____ NO history of androgen suppression for ≥ 6 months and willing for androgen suppression treatment

____ No contraindication to MRI

____ No hip prosthesis

____ No previous malignancy within last five years except BCC or SCC skin or highly curable malignancy

Optional Participation:

1. Did patient fill out Prostate Cancer Index Questionnaire (Form 3a)? ❑ YES ❑ NO

2. Did patient agree to participate in SNP study and give blood samples? ❑ YES ❑ NO

Investigator

Signature _____ Date _____ Name of CRA_____

Appendix 4: Patient Characteristics

Patient ID# _____ **Initials** _____ **DOB:** ____ -_____-_____ **(dd – mm – yy) Case #:** _____

Initial PSA _____ **ug/L Date of PSA** ____ **-** ____ **-** ____ **(dd – mm – yy)**

Date of Pathologic diagnosis (use procedure date) _____ - _____ - _____ (dd – mm – yy)

Gleason Score _____ + _____ = _____ / 10

Perineural invasion: ❑ Present ❑ Absent ❑ Unknown

IF core biopsy (TRUS, cystoscopy, etc):	IF TURP at any time in patient's history:
No. of Biopsy cores (+) for adenocarcinoma (of any Gleason grade or microfocus): _____ cores (+) of _____ core samples	Date of TURP ___ - ___ - ____ (ddmmyy) Total amount of Prostatic chips _____ g Percentage chips involved _____ (0-100%)

Clinical Stage: ❑ T1a ❑T1b ❑T1c ❑T2a ❑T2b ❑T2c ❑T3a ❑T3b ❑T4

CT/MRI abdomen and/or pelvis:	Bone scan:
❑ N(0) Date performed ____ - ____ - ____	❑ M(0) Date performed ____ - ____ - ____

Co-morbid Conditions (✓ if applies)
❑ Diabetes requiring medication
❑ Hypertension requiring medication
❑ Chronic bronchitis/cough (COPD) requiring any inhalers for > 3 month of the year
❑ History of hemorrhoids requiring any medication (including OTC) within the past year

Date of MRI Scan before and during radiation treatments: (Please write NA where not applicable)

Before starting hormonal treatment _____- _____ - _____ (dd-mm-yyyy)

Before starting radiation treatment _____ - _____ - _____ (dd-mm-yyyy)

During radiation treatment _____ - _____ - _____ (dd-mm-yyyy)

Date of Hormonal therapy before and during radiation treatments:

Start date _____ - _____- _____ (dd-mm-yyyy), Preparation: Monthly / 3 monthly, Timing: Pre RT/ during RT

Date: _____ - _____- _____(dd-mm-yyyy), Preparation: Monthly / 3 monthly, Timing: Pre RT/ during RT

Date: - - (dd-mm-yyyy), Preparation: Monthly / 3 monthly, Timing: Pre RT/ during RT

Patient ID:_____Initials:_____ Date:____ - ____ - _____ (dd-mm-yy) **page 1 of 4**

❑ Patient prefers not to answer questions on this page – please go to next page Case #:_____

Appendix 5: Prostate Cancer Index questionnaires (4 pages)

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? (Circle one number)
   - Every day …… 1
   - About once a week …… 2
   - Less than once a week …… 3
   - Not at all …… 4
2. Which of the following best describes your urinary control during the last 4 weeks? (Circle one number)
   - No control whatsoever …… 1
   - Frequent dribbling … … … … … … … … 2
   - Occasional dribbling …… 3
   - Total control …… 4
3. How many pads or adult diapers per day did you usually use to control leakage during the last 4 weeks? (Circle one number)
   - 3 or more pads per day …… 1
   - 1-2 pads per day …… 2
   - No pads …… 3
4. 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. Dripping urine or wetting your pants	0	1	2	3	4
b. Urine leakage interfering with your sexual activity.	0	1	2	3	4

5. Overall, how big a problem has your urinary function been for you during the last 4 weeks? (Circle one number)
   - No problem …… 1
   - Very small problem …… 2
   - Small problem …… 3
   - 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.

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

Less than once a day …… 1

About once a day …… 2 (Circle one number)

More than once a day …… 3

About once a week …… 4

Rarely or never …… 5

7. 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

8. How much distress have your bowel movements caused you during the last 4 weeks?

Severe distress …… 1

Moderate distress …… 2 (Circle one number)

Little distress …… 3

No distress …… 4

9. How often had you had crampy pain in your abdomen or pelvis during the last 4 weeks?

Several times a day …… 1

About once a day …… 2

Several times a week …… 3 (Circle one number)

About once a week …… 4

About once this month …… 5

Rarely or never …… 6

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

Big problem …… 1

Moderate problem …… 2

Small problem …… 3 (Circle one number)

Very small problem …… 4

No problem …… 5

Pt. ID# _____ Initials _____ Date ____-____-____ (dd-mm-yy) Case Number _____

Prostate Cancer Index **page 3 of 4**

❑ Patient prefers not to answer questions on this page – please go to next page

Sexual Function

The next section is about your 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, YOUR NAMES DOES NOT APPEAR ANYWHERE ON THIS SURVEY.

Please answer honestly about THE LAST 4 WEEKS ONLY

11. How would you rate each of the following during the last 4 weeks?

(Circle one number on each line.)	Very Poor	Poor	Fair	Good	Very Good
a. Your level of sexual desire. For example, feeling frisky or lustful.	1	2	3	4	5
b. Your ability of have an erection?	1	2	3	4	5
c. Your ability to reach orgasm or climax?	1	2	3	4	5

12. How would you describe the usual QUALITY OF your erections?
(Circle one number)

None at all……. 1

Not firm enough for sexual activity ……. 2

Firm enough for masturbation and foreplay only …… 3

Firm enough for intercourse …… 4

13. How would you describe the FREQUENCY OF your erections?
(Circle one number)

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

I had an erection MORE THAN HALF the time I wanted one 4

I had an erection WHENEVER I wanted one… 5

14. How often had you awakened in the morning or night with an erection?
(Circle one number)

Never ……. 1

Seldom (less than 25% of the time) …….. 2

Not often (less than half the time) ……. 3

Often (more than half the time) ……. 4

Very often (more than 75% of the time) …… 5

Pt. ID# _____ Initials _ ____Date___-___- ___(ddmmyy) Case Number _____

Prostate Cancer Index **page 4 of 4**

❑ Patient prefers not to answer questions on this page

15. During the past 4 weeks have you had sexual intercourse UNASSISTED by medical intervention (did not use medication, injections or a device such as a vacuum pump)?

No ……1

Yes ……2 (Circle one number)

Yes, more than once …… 3

16. During the past 4 weeks, have you had sexual intercourse with the ASSISTANCE of medical intervention?

No …… 1

Yes …… 2 (Circle one number)

Yes, more than once ……3

If yes, what did you use: Injection: Yes No (Circle correct responses)

Vacuum Pump: Yes No

Viagra Yes No

Other, please specify:_____

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

Very poor …… 1

Poor …… 2

Fair …… 3

Good …… 4

Very Good …… 5

(Circle one number)

18. Overall, how big a problem has your sexual function been for you during the last 4 weeks?

No problem …… 1

Very small problem …… 2

Small problem …… 3

Moderate problem …… 4

Big problem …… 5

Pt. ID# _____Initials _____Case #_____

Appendix 6: Treatment planning and delivery (page 1 of 1)

RT day	Date (dd-mm-yy)	Time in treatment room for imaging, registration and treatment (minutes)
First		
Last		

	Lateral Patient Shift (Right or Left)				Longitudinal Patient Shift (Sup or Inf)				Vertical Patient Shift (Ant. or Post.)				Rotation: Pitch, Roll, Yaw	
Fraction #	Initial X* mm	Calc. shift § mm	Appl. shift § mm	Final X*	Initial Y* mm	Calc. shift § mm	Appl. shift § mm	Final Y*	Initial Z* mm	Calc. shift § mm	Appl. shift § mm	Final Z*	Noted: P/R/Y deg	Appl.: P/R/Y deg

* Initial, final positions with respect to TomoTherapy couch home position, abs. IEC 't' coordinates

§ Shifts (calculated and applied) are given relative to reference mark

Appendix 7: RTOG acute toxicity scale (during Radiotherapy)

Pt. ID# _____ Initials _____ Case Number _____

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
G U	No change	Frequency or nocturia 2x pre-treatment habit. Dysuria,urgency not requiring medication	Frequency or nocturia less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic*	Frequency with urgency & nocturia hourly or more frequently. Dysuria, pelvic pain or bladder spasm requiring regular, frequent narcotics. Gross hematuria ± clot passage	Hematuria requiring transfusion. Acute bladder obstruction not secondary to clot passage. Ulceration or necrosis.
Day 1-7					
Day 2-14					
Day 15-21					
Day 22-28					
Day 29-35					

* Or other agents such as Flomax, ditropan, Detrol, etc.

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
G I	No change	Increased frequency or change in quality of bowel habits not requiring medication. Rectal discomfort not requiring analgesics.	Diarrhea requiring parasympatholytic drugs (e.g. Lomotil). Mucous discharge not necessitating sanitary pads. Rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support. Severe mucous or blood discharge necessitating sanitary pads. Abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation. GI bleeding requiring transfusion. Abdominal pain or tenesmus requiring tube decompression or bowel diversion.
Day 1-7					
Day 2-14					
Day 15-21					
Day 22-28					
Day 29-35					

- including prescription rectal suppository/ointment/foam/enema

OTHER TOXICITY (e.g. skin, fatigue)	Grade (use RTOG grades)	Radiotherapy Week (1 – 5)

Comments/Other Pertinent Findings:_____

_____

Please immediately (within 24 hours) report PI in event of Grade 3 or 4 toxicity

Appendix 8: RTOG acute toxicity scale (follow up to 3 months)

Pt. ID#. _____ Initials _____ Case Number _____

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
G U Date eval'd	No change	Frequency or nocturia 2x pre-treatment habit. Dysuria,urgency not requiring medication	Frequency or nocturia less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic*	Frequency with urgency & nocturia hourly or more frequently. Dysuria, pelvic pain or bladder spasm requiring regular, frequent narcotics. Gross hematuria ± clot passage	Hematuria requiring transfusion. Acute bladder obstruction not secondary to clot passage. Ulceration or necrosis.

* Or other agents such as Flomax, Ditropan, Detrol, etc.

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
G I Date eval'd	No change	Increased frequency or change in quality of bowel habits not requiring medication. Rectal discomfort not requiring analgesics.	Diarrhea requiring parasympatholytic drugs (e.g. Lomotil). Mucous discharge not necessitating sanitary pads. Rectal or abdominal pain requiring analgesics*	Diarrhea requiring parenteral support. Severe mucous or blood discharge necessitating sanitary pads. Abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation. GI bleeding requiring transfusion. Abdominal pain or tenesmus requiring tube decompression or bowel diversion.

* including prescription rectal suppository/ointment/foam/enema

OTHER TOXICITY (e.g. skin, fatigue)	GRADE (use RTOG grades)	Date Evaluated (dd-mm-yy)

Comments/Other Pertinent Findings:_____

_____

Please immediately (within 24 hours) report PI in event of Grade 3 or 4 toxicity

Appendix 9: Late toxicity (6 monthly post RT)

Pt. ID# _____ Initials _____ Case Number _____

Date of Last Radiotherapy treatment: ____ - ____ - ____ (dd – mm – yy)

Please check/circle one:

G U	❑ Grade 0 None	❑ Grade 1 Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	❑ Grade 2 Moderate frequency. Generalized telangiectasia. Intermittent macroscopic hematuria	❑ Grade 3 Severe frequency & dysuria. Severe generalized telangiectasia (often with petechiae). Frequent hematuria. Reduction in bladder capacity (< 150cc)	❑ Grade 4 Necrosis/contracted bladder (capacity <100cc). Severe hemorrhagic cystitis

G I	❑ Grade 0 None	❑ Grade 1 Mild diarrhea, mild cramping. Bowel movement 5 times daily. Slight rectal discharge or bleeding.	❑ Grade 2 Moderate diarrhea and colic. Bowel movement > 5 times daily. Excessive rectal mucus or intermittent bleeding	❑ Grade 3 Obstruction or bleeding requiring surgery*	❑ Grade 4 Necrosis, perforation, or fistula

* including endoscopic cauterization of bleeding

Comments/Other Pertinent Findings:_____

_____

Please immediately (within 24 hours) report PI in event of Grade 3 or 4 toxicity

Appendix 10: PSA, DRE, Other events

Pt. ID# _____ Initials _____ Case Number _____

Date of Last Radiotherapy treatment: ____ - ____ - ____ (dd – mm – yy)

Date of Follow Up for this form: ____ - ____ - ____ (dd – mm – yy)

Please check or circle one:

<table>
<tr><td>Digital Rectal Exam</td><td>❑ Not done</td><td>❑ No palpable abnormality; benign gland</td><td>❑ Residual palpable nodule, not suggestive of local recurrence or progression</td><td>❑ Palpable nodule or mass indicative of local recurrence or progression</td></tr>
<tr><td>Other Clinical Signs of Disease progression</td><td colspan="3">Please describe:</td><td>❑ Presence of distant metastases
Date ____ - ____ - ____
(dd – mm – yy)</td></tr>
<tr><td colspan="2">PSA Date ___ - ____ - ____ (dd – mm – yy)</td><td colspan="3">Level: _____ ug/L</td></tr>
<tr><td colspan="2">Hormonal treatment: ❑ Continue ❑Discontinue</td><td colspan="3">Reason & date if discontinue ___-___-___</td></tr>
<tr><td colspan="2">Prostate Cancer Index

(Appendix 5)</td><td colspan="3">❑ Completed (at each follow up visit)
❑ Not Required at this visit
❑ Not performed at baseline</td></tr>
<tr><td>MRI
On follow up (6, 12, 18, 24 months then yearly)
or at PSA failure</td><td colspan="2">❑ Not required at this visit
❑ Booked or Performed date
____ - ____ - ____
(dd-mm-yyyy)</td><td colspan="2">❑ Performed for follow up
❑ Performed due to PSA failure</td></tr>
</table>

Comments/Other Pertinent Findings: _____

_____

_____

Appendix 11: Study exit, early termination, or drop out

Pt ID# _____ Initials _____ Case Number _____

Date of this form: ____ - ____ - ____ (dd – mm – yy)

Reasons for Study termination (please check whichever applies):

❑ Patient-initiated request

❑ Due to radiation complication

❑ Due to inability to continue follow up (e.g. move out of country, refusal of medical care)

❑ Other reasons (please briefly describe) _____
_____

❑ Patient Died Date of Death ____ - _____ - _____ (dd – mm – yy)

Cause of death (must be determined):

❑ Death due to prostate cancer

❑ Death due to treatment complication

❑ Death due to other causes

❑ Patient lost to follow up, moved without forwarding address or contact information

❑ Other reasons for termination: _____
_____
_____

Return completed form immediately to PI Date_____

Appendix 12
Consent Version Date: February 23, 2005
(Modified for thesis purposes)

Role of tomotherapy (dynamic IMRT and megavoltage CT scanning) in hypofractionated/dose escalated conformal radiation treatment using magnetic resonance Imaging (MRI) scans.

(Tomotherapy treatment machine may be able to deliver a larger dose of radiation treatment in a short period of time with less side effects and better tumor control. Magnetic Resonance Imaging may be helpful to delineate targets)

CONSENT FORM

This form is part of the process of informed consent. It is designed to explain this research study and what will happen to you if you choose to be in the study.

If you would like to know more about something mentioned in this consent form, or have any questions at anytime regarding this research study, please be sure to ask your doctor or nurse. Read this consent form carefully to make sure you understand all the information it provides. You will get a copy of this consent form to keep. You do not have to take part in this study and your care does not depend on whether or not you take part.

This study is being conducted by the genito-urinary cancer group at the Cross Cancer Institute.

Your doctor has given us permission to ask you to be in this study.

Your participation in this study is entirely voluntary. Please take your time to make your decision. It is recommended that you discuss with your friends and/or family about whether to participate in this study.

This study may or may not help you directly, but we hope that it will teach us something that will help others in the future.

"WHY IS THIS STUDY BEING DONE?"

You are being asked to take part in this study because you have prostate cancer, and have decided to undergo radiation and hormonal treatment, which is a standard treatment. Patients generally receive seven or eight weeks of radiation treatment. Recent evidence suggests that higher dose each fraction (hypofractionation) with a shorter duration of treatment may have at least the same cancer control with less side effects and be more convenient for patients due to shorter treatment duration. Tomotherapy is a new treatment system available at the Cross Cancer Institute and is expected to deliver radiation treatment to cancer more accurately which may further reduce side effects.

Magnetic Resonance Imaging (MRI) is a new kind of scan that has been recently acquired at Cross Cancer Institute. We believe the MRI scan may help us better target delineation.

“WHAT DO WE HOPE TO LEARN?”

We hope to learn whether the accurate delivery of higher dose per day radiation treatment to cancer is feasible using tomotherapy and whether it reduces side effects which are at least equal to or better than cancer control for conventional treatment. We also hope to learn whether the changes seen on MRI scans during and after radiation treatment can predict how well the treatment will work and may detect cancer recurrence earlier on follow-up. These may help us to plan radiation treatment more accurately in future.

“WHAT IS INVOLVED IN THIS STUDY?”

If you take part in this study, you will have an MRI scans of the pelvis taken before starting hormonal and radiation treatments. These scans are performed in addition to the standard tests ordered by your physician. It will take about one hour to perform this scan. There will be no delay in starting treatment due to this additional scan and this will not alter treatment planning.

Your treatment planning will be performed and delivered on Tomotherapy over five weeks time (compared to conventional seven or eight weeks) with larger dose each fraction (hypofractionation). All patients on this study will undergo the MRS scans and treatment delivery on Tomotherapy. There is no ‘randomization’.

“HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?”

About fifty people will take part in this study

“WHAT WILL MY PARTICIPATION INVOLVE?”

If you take part in this study, you will have MRI scan before, during and after radiation/hormonal treatment on follow up. Follow up MRI scans will be done twice yearly for two years and yearly thereafter. You will receive your treatment on tomotherapy treatment machine over five weeks.

“HOW LONG WILL I BE INVOLVED IN THE STUDY?”

You may be involved in this study up to three years or more to observe treatment related late effects.

“WHAT ARE THE SIDE EFFECTS?”

MRI:

The MRI scanning is a painless way to examine the body without X-ray exposure. Instead, it uses a large magnet, radio-waves, and a computer to scan your body and give us information about your tumor. The scan itself does not have any side effects. Some medical devices, such as cardiac pacemakers and other metallic implants can interfere with the study or be hazardous. We will discuss this matter with you in detail prior to scanning to ensure you do not have any of these medical devices. Those who suffer from claustrophobia may feel anxiety with the scan as it is taken with the patient in a relatively small space.

Radiotherapy:

As with other forms of radiotherapy for prostate cancer, there may be side effects in the areas around the prostate. These side effects are the result of “good cells” being damaged by radiation. However, in the majority of times, such damage is temporary, though there may be a few symptoms that linger for months to possibly years.

It may cause reddening or tanning of the skin, hair loss in the treatment area, temporary fatigue, nausea, diarrhea, abdominal cramps, bladder irritation, rectal irritation and in some patients permanent impotence. There is also a small possibility of late injury to the bladder, urethra, bowel and other tissues in the pelvis or abdomen.

"WHAT ARE THE REPRODUCTIVE RISKS?"

There are no known reproductive risks associated with MRI scanning. Hormonal or radiation treatment will affect potency and hence reproductive capability.

“WHAT ARE MY ALTERNATIVES?”

You may choose not to participate in this study. Not participating in the study will not affect the treatment of your cancer of the prostate in any way. You will be offered conventional treatment with three years of hormone treatment and seven to eight weeks of radiation.

“ARE THERE ANY BENEFITS TO PARTICIPATING IN THIS STUDY?”

Participation in this study may or may not be of personal benefit to you. However, based on the results of this study, it is hoped that, in the long-term, patient care can be improved.

“CAN I WITHDRAW FROM THIS STUDY?”

Participation in this study is voluntary. You are free to withdraw your consent to participate in this study at any time without prejudice to subsequent care. Refusal to participate will involve no penalty, or loss of benefits. You are free to seek care from a physician of your choice at any time. If you do not take part or withdraw from this study, you will continue to receive care.

“ARE THERE COSTS TO ME FOR TAKING PART IN THIS STUDY?”

You will not have to pay for the MRI scans or radiation treatment you receive in this study. You will need to come to the Cross Cancer Institute more than if you were not part of this study for pre-treatment and follow-up scans. There will be 12 less visits for radiation treatment. There may be additional costs for taking part in this study due to additional time required such as:

- parking
- meals
- babysitting, etc.

“WHAT ARE MY RIGHTS AS A PARTICIPANT?”

If you suffer an injury or become ill as a result of participating in this research, you will receive all medical treatments (or services) recommended by your doctors that are not covered by health insurance. No compensation will be provided beyond this point.

However, it is important to note that nothing said in this consent form alters your legal rights to recover damages.

“WILL MY PERSONAL INFORMATION BE KEPT CONFIDENTIAL?”

Identifying health information will be collected during this study. This information may be used by the researchers who are carrying out this study, and may be disclosed to others as described below. Any research proposal to use information that identifies you for a purpose other then this study must be approved in advance by the ACB Research Ethics Board.

Direct access to your identifiable health information collected for this study will be restricted to the researchers who are directly involved in this study except in the following circumstances.

Your identifiable health information may need to be inspected or copied from time to time for quality assurance (to make sure the information being used in the study is accurate) and for data analysis (to do statistical analysis that will not identify you). The following organization may do this inspection:

- ACB Research Ethics Board, the institutional review board at this centre
- Health Canada
- Office of the Information and Privacy Commissioner

Any disclosure of your identifiable health information will be in accordance with the Alberta Health Information Act. As well, any person from the organizations looking at your records on-site at the Cross Cancer Institute will follow the relevant ACB policies and procedures that control these actions. Any disclosure of your identifiable health information to another individual or organization not listed here will need the approval of the ACB Research Ethics Board.

The researchers who are directly involved in your study may share information about you with other researchers, but you will not be identified in that shared information except by a number. The key that indicates what number you have been assigned will be kept secure by the researchers directly involved with you study and will not be released.

Although absolute confidentiality can never be guaranteed, the ACB will make every effort to keep your identifiable health information confidential, and to follow the ethical and legal rules about collecting, using and disclosing this information in accordance with the Health Information Act and other regulatory requirements.

"WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?"

For information about your disease and/or research related injury/illness, you may contact the Principal Investigator, page him through the Cross Cancer Institute Switchboard to answer any questions you have about this study.

If you feel, at any time, that you have not been informed to your satisfaction about the risks, benefits, or alternatives of this study, or that you have been encouraged to continue in this study after you wanted to withdraw, you can call the Patient Representative.

UNDERSTANDING OF PARTICIPANTS

I can refuse to take part or withdraw from this study at any time without jeopardizing my health care. If I continue to take part in the study, I will be kept informed of any important new developments and information learned after the time I gave my original consent.

I also give consent for the Principal Investigator and the Alberta Cancer Board (the Custodian) to disclose identifiable health information, as per the Health Information Act, to the organization mentioned on the previous page.

I have read and understood all of the information in this consent form. I have asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review and discussion. My consent has not been forced or influenced in

any way. I consent to participate in this research study. Upon signing this form I will receive a signed copy of the consent.

(PRINT NAMES CLEARLY)

_____	_____
Name of Patient Date &Time	Signature of Patient
_____	_____
Name of Witness Date & Time	Signature of Witness
_____	_____
Name of Person Obtaining Consent Date &Time Obtaining Consent	Signature of Person
_____	_____
Name of Investigator Date & Time	Signature of Investigator