STUDY PROTOCOL

Version 1.0

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A Prospective Randomized Phase II Clinical Trial of Moderately Hypofractionated Radiotherapy (70 Gy in 28 Fractions vs 60 Gy in 20 Fractions) Using Helical Tomotherapy.

The following Amendment(s) have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

TABLE OF CONTENTS

1. Introduction.
1.1 The rationale for the use of hypofractionation.
1.2 Calculation of biologically effective doses.
1.3 Randomized studies of hypofractional regimens.
1.4 Selection of patients.
2. Study objectives.
2.1 Primary objective.
2.2 Secondary objectives.
3. Eligibility
3.1 Inclusion criteria
3.2 Exclusion criteria
4. Actions before radiotherapy.
5. Radiotherapy.
5.1 Technical aspects.
5.2 Simulation and immobilization.
5.3 Treatment planning.
6. Observation after the end of radiation therapy.
7. Statistical analysis plan.
7.1 Primary Endpoint.
7.2 Secondary Endpoints.
7.3 Patient Groups.
7.4 Sample Size.
7.5 Analysis of the Primary Endpoint.
7.6 Analysis of the Secondary Endpoint.
7.7 Incidence of GU and GI Acute and Late Adverse Events.
7.8 Analysis for Endpoints Related to HRQOL.
7.9 Interim Reports.
7.10 Analysis for Reporting Initial Treatment Result

LIST OF ATTACHMENTS:

1. EPIC

2. EQ5D

3. IPSS

7. ECOG

8. TNM 8th edition.

9. Roach formula.

10. The formula for assessing the risk of lesions of the seminal vesicles.

1.0 Introduction.

1.1 The rationale for the use of hypofractionation.

The optimal radiation pattern for radical treatment of prostate cancer is currently under discussion.[1] Patients suffering from prostate cancer, as a rule, receive EXTERNAL BEAM radiation therapy (EBRT) 5 times a week for 7-8 weeks (76 Gy in 38 farctions).[2] Based on recent research, some practitioners increased the total radiation dose by adding additional fractions. In some large centers, for this cohort of patients, the standard of EBRT is treatment for 9–10 weeks.[3] Increasing the duration of the course increases the cost of treatment and is less convenient for the patient. Over the past 5 years, a large number of studies have been published confirming the comparability of shortened irradiation courses with an increase in the dose per fraction compared to the irradiation with the traditional regime. [4-7]

The death of mammalian cells from radiation is described by a linear-quadratic model. (LQE). According to this model, the survival curve of the irradiated cells depends on the total dose of radiation, a single dose of radiation and the duration of the course of treatment. In a linear-quadratic model, the reaction of a tumor and normal tissues to fractionated irradiation can be described by the alpha / beta ratio (α / β). The alpha / beta ratio determines the fractional sensitivity to irradiation of a particular cell type. The alpha / beta ratio is high enough (> 10Gy) for early responsive irradiation of normal tissues (skin, mucous membranes) and most tumors, and low (<5Gy) for late reacting normal tissues (spinal cord, bones). One consequence of the different ratio of alpha / beta of normal tissues and tumors is the possibility of using non-conventional fractionation schemes.

In 1999, Brenner and Hall published an article in which they first described the low α / β ratio in prostate cancer cells. They concluded that the α / β ratio is 1.5 Gy, which is an argument for using hypofractionation.[8] In 2001, Fowler and others updated this study with the participation of 1020 patients from 11 centers and came to the same conclusions. The same data was confirmed in the work of Miralbell and co-authors, who retrospectively analyzed data on 6000 patients stratified by risk groups and androgen deprivation.[9]

Recent years have published articles showing very low alpha / beta ratios for prostate tumors. The safety and comparability of the schemes of hypofractionated irradiation of prostate cancer (60Gy in 20 farctions; 70 Gy in 28 farctions) in comparison with the conventional radiation regime (78 Gy in 39 farctions) has been proven. However, there is not a single prospective randomized study comparing the hypofractional modes of prostate cancer among themselves. The purpose of this study is to compare the modes of hypofractional irradiation of prostate cancer.

1.2 Calculation of biologically effective doses (BED)

To facilitate a comparison between the different fractionation regimes discussed in this protocol, biologically effective doses (BED) will be calculated and isoeffective regimes will be used according to the LQE model. The convention used in this protocol to indicate the alpha-beta relationship used in calculating the BED, will be indicated by an index; for example, BED1.5 indicates that the BED provided is calculated based on the alpha-beta ratio of 1.5.

Total Dose (Gy)	Dose per fraction (Gy)	Number of fractions	Equivalent dose of 2 Gy at alpha / beta ratio					
			1.0	1.5	2.0	3.0	5.0	10.0
70	2,5	28	81,67	80	78,75	77	75	72,92
50,4	1,8	28	47,04	47,52	47,88	48,38	68,54	49,56
60	3	20	80	77,14	75	72	68,57	65
50	2,5	20	58,33	57,14	56,25	55	53,57	52,08
44	2,2	20	46,93	46,51	46,2	45,76	45,26	44,73

Table 1

1.3 Randomized studies of hypofractional regimens.

The three largest studies, PROFIT, CHHiP and NRG Oncology 0415, demonstrate the comparability of the hypofractional irradiation regimes with those of the classical fractionation, both in local control and in toxicity, the results of which were obtained from patients after 5 years.

In the CHHiP study, 3216 men, predominantly with intermediate-risk prostate cancer, were randomized (1: 1: 1) into 3 groups. The first group is the classical

fractionation group (74 Gy in 37 fractions), the second and third groups are hypofraction modes (60 Gy in 20 fractions or 57 Gy in 19 fractions for 4 weeks) using intensively modulated radiotherapy (IMRT) and 3- 6 months of therapy for androgen deprivation (ADT). The mode of irradiation up to 60 Gy was found to be not inferior to 74 Gy with respect to biochemical or clinical disease-free survival.

In the PROFIT study, the 1206 fractions and the hypofractionation (60 Gy in the 20 fractions for 4 weeks) were randomized to the classical fractionation group (IGRT). The treatment results were also comparable.

In the NRG Oncology 0415 study, 1,115 men with low-risk prostate cancer were randomized to the traditional fractionation group (73.8 Gy in 41 fractions) and hypofractionation (70 Gy in 28 fractions). Comparable irradiation results were obtained.[10]

1.4 Selection of patients.

To participate in this study, patients with localized prostate cancer stage I-III (T1-3N0M0) will be selected, who will receive radical radiotherapy (helical-IG-IMRT) on the TomoHD.

2.0 Study objectives.

2.1 Primary objective.

Determine what regime of hypofractionation will be the best 5-10 year biochemical relapse free survival. Compare the results of hypofractional regimes (60Gy in 20 farctions; 70 Gy in 28 farctions).

2.2 Secondary objectives.

2.2.1. Determine which of the hypofractionation regimes will have the best 5-10 year survival rate without a local progression and overall survival.

2.2.2. Compare the frequency of acute and late genitourinary and gastrointestinal toxicity in patients in 2 groups using the scale ctcae v4, eortc/rtog.

2.2.3 Compare quality of life of patients in 2 groups using the scale EPIC CP (Expanded Prostate Cancer Index Composite for Clinical Practice), EQ5D (European Quality of Life Questionnaire).

3.0 Eligibility

3.1 Inclusion criteria

3.1.1. Histologically confirmed adenocarcinoma of the prostate.

3.1.2 The presence of the following studies: TRUS of the prostate gland, pelvis MRI, OSG.

3.1.3 Histological evaluation of prostate biopsy with assignment of the Gleason index.

3.1.4 Clinical stage T1-3N0-1M0 (AJCC 7th edition).

3.1.5 ECOG performance status 0-1

3.1.6 Age limit 18 years.

3.1.7 Patient consent to participate in a clinical study.

3.2. Exclusion criteria

3.2.1. Prior or concurrent lymphomatous/hematogenous malignancy or other invasive malignancy except nonmelanomatous skin cancer or any other cancer for which the patient has been continually disease-free for ≥ 5 years (e.g., carcinoma in situ of the bladder or oral cavity)

3.2.2. Distatnt metastases.

3.2.3. Metastases in the lymph nodes of prostate cancer.

3.2.4. Radical prostatectomy or cryodestruction of the prostate gland in history.

3.2.5. Radiation of a small pelvis in the anamnesis. Bilateral orchectomy history.

3.2.6. Unstable angina and/or congestive heart failure requiring hospitalization within the past 6 months, transmural myocardial infarction within the past 6 months, acute bacterial or fungal infection requiring IV antibiotics, chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study treatment, hepatic insufficiency resulting in clinical jaundice and/or coagulation defects.

4.0 Actions before radiotherapy.

4.1. Assessment of the patient's quality of life according to the following EPIC, EQ5D scales.

4.2. Evaluation of the maximum flow rate of urine by urofluometry, assessment of urination on the IPSS scale.

5.0 **Radiotherapy.**

5.1 Technical aspects. Radiotherapy will be carried out using the iMRT method on a 6 MeV linear accelerator TomoHD.

5.2 Simulation and immobilization.

To determine the tumor, clinical and planning volumes of normal critical structures, topometric CT is required. CT scan is performed in the same position as for daily treatment. Each patient is in the supine position. Computed tomography of the pelvis should begin with the 2nd lumbar vertebra and end with the perineal region, i.e. all tissues to be irradiated must be included in the CT scan. The thickness of the sections should be no more than 0.5 cm. The bladder must be filled, and the rectum is empty. On the skin should be applied 3 marks.

5.3 Treatment planning.

The target volumes will be determined according to ICRU 83 report.

5.3.2 Gross tumor volume (GTV). GTV is a visually detectable tumor volume.

5.3.3. Clinical target volume (CTV) - is the area of microscopic spread of the tumor around GTV.

The prostate will be defined as CTV for T1-T2. At the discretion of the attending physician at T3 CTV will be a prostate or an area of about 3 mm around the prostate gland. In T3b, CTV will be a prostate with seminal vesicles.

In patients with T1-T3a with a risk of damage to the seminal vesicles of more than 15% (according to the formula for assessing the risk of damage to the seminal vesicles.), A separate CTV will be isolated, including the bases of the seminal vesicles.

In patients with a risk of lymph node damage of more than 15% (according to Roach's formula), a separate CTV will be allocated, including obstructive, external iliac, internal iliac, and general iliac lymph nodes to the level of the lumbar-cretzal joint.

5.3.4. Planning target volume (PTV) is a volume around CTV, compensating for inaccuracies arising in the treatment of the patient, the movement of internal organs. For this study, PTV indents will be 0.5 cm anteriorly, laterally, and 0.4 cm toward the rectum.

5.3.5. Planning will be carried out on the TomoProvider planning system. Treatment is carried out by the method of helical-IG-IMRT.

The treatment plan used for each patient will be based on the analysis of the volume dose, including the analysis of the volume histogram (DVH) of PTV and critical normal structures.

5.3.6 Critical normal structures

The bladder, rectum, intestine, femoral heads, penis bulbs, penis and skin should be outlined. The bladder should be contoured from the base to the dome, the rectum from the anus to the rectosigmoid bend.

	Arm 2,5 Gy		Arm 3 Gy	
	Dose per fraction Gy	Total Dose Gy	Dose per fraction Gy	Total Dose Gy
Prostate	2,5	70	3	60
Seminal vesicles	2	56	2,5	50
Pelvic lymph nodes *	1,8	50,4	2,2	44

Table 2

* According to testimony

	Low risk	Intermediate risk	High risk
GTV70/60	visually detectable tumor volume	visually detectable tumor volume	visually detectable tumor volume
CTV70/60	prostate	prostate	prostate
CTV56/50	-	seminal vesicles base	seminal vesicles base /for T3b, the seminal vesicles and the area of 5 mm around them
CTV50,4/44	-	-	Pelvic lymph nodes
PTV70/60	CTV+5мм(posterior 4мм)	CTV+5мм(posterior 4мм)	CTV+5мм(posterior 4мм)
PTV56/50	-	CTV+5мм(posterior 4мм)	CTV+5мм(posterior 4мм)
PTV50,4/44	-	-	CTV+5мм

Table 3

6.0 Observation after the end of radiation therapy.

6.1 Control of PSA every 3 months within six months after the end of radiation therapy.

6.2 Control of PSA every six months for 5 years after the end of radiation therapy.

6.3. Control PSA every year after 5 years after the end of radiation therapy.

6.4 Toxicity assessment after 3 months, six months after the end of radiation therapy.

6.5 Toxicity assessment every year after the end of radiation therapy.

6.6 Assessment of the patient's quality of life on the EPIC, EQ5D scales after 3 months, six months, and then every year after the end of radiation therapy.

7.0 Statistical analysis plan.

7.1Primary Endpoint

Percentage of patients with 5-10 year biochemical relapse free survival in the groups with 3Gy/60Gy and 2,5Gy/70Gy. (PSA failure)

7.2 Secondary Endpoints

7.2.1 Local progression and overall survival

7.2.2.Acute and late GI and GU toxicity

7.2.3 EPIC QOL measurements

7.2.4 EQ-5D measurements

7.3 Patient Groups

There are two separate and independent patient groups as defined by the Hypofractionation schedule: Arm 1 patients treated with 70 Gy (28 daily fractions of 2,5 Gy over five and a half weeks) and Arm 2 patients treated with 60 Gy (2 daily fractions of 3 Gy over four weeks).

7.4 Sample Size

7.4.1 Randomization

Patients will be randomized to the two hypofractionated group 3Gy/60Gy and 2,5Gy/70Gy.

7.4.2 Sample Size

The sample size is estimated based on Schoenfeld's sample size formula.[11] This formula is used to calculate the sample size when the log rank test is used. We assume that the disease-free survival function follows an exponential distribution for each arm. Accrual to the study is assumed to be uniformly distributed. The null hypothesis (H_0) of this test is that the hazard rate of Arm 2 (λ_2) is worse than the hazard rate of Arm 1 (λ_1). The alternative hypothesis (H_A) is that the hazard rate of Arm 2 is not worse than the hazard rate of Arm 1.

$$H_0: \delta \geq \delta_0 \quad \text{vs.} \quad H_A: \delta < \delta_0$$

where $\delta = -\ln(\lambda_1/\lambda_2)$ and δ_0 is a non-inferiority margin.

the final targeted accrual for this study will be 300 patient

7.4.3 Accrual and Duration

Patient accrual is projected to be 20 cases per month. We expect to complete accrual in 1 year. The total duration of the study is expected to be 11 years from the time the first patient is entered to the final analysis.

7.5 Analysis of the Primary Endpoint.

The primary endpoint, 5 and 10-years biochemical relapse free survival, is measured from the date of randomization to the date of the biochemical failure defined by the RTOG Phoenix definition, or death from any cause. We assume that the distribution of biochemical relapse free survival for each arm is an exponential distribution. The survival distribution of biochemical relapse free survival will be estimated by the Kaplan-Meier method.

7.6 Analysis of the Secondary Endpoints

We assume that the distribution of failure times of secondary endpoints related to time to failure for each arm is an exponential distribution. In a trial of local radiation therapy, disease-specific survival, local progression provide relevant measures of the treatment effect. However, the treatment effect on other types of failure may impact the observable measures of local failure, and other competing risks may dilute the sensitivity of local failure. We will use the cause-specific hazard rate (the instantaneous rate of cause-specific failure in the presence of competing failure types as a function of time) approach to consider the competing events. Freidlin and Korn show that the cause-specific hazard rate approach is better than other approaches (e.g., the survival distribution of the time to first failure, cumulative incidence method, etc.) in most of cases. The log-rank test on times to the specific type of failure will be used to test secondary endpoints related to time to failure (local progression, disease-

specific survival the presence of competing failure types as a function of time) approach to consider the competing events [12,13].

The overall survival, local progression, disease-specific survival distribution will be estimated by the Kaplan-Meier method.

7.7 Incidence of GU and GI Acute and Late Adverse Events

Adverse events are scored according to eortc/rtog, CTCAE version 4.0. An acute adverse event will be defined as an adverse event occurring less than or equal to 90 days from the completion of RT. A multivariate logistic regression will be used to model the distribution of acute adverse events for each arm. Both unadjusted and adjusted odds ratios and the respective 95% confidence interval will be computed. PSA, Gleason score, and age (as appropriate) will be adjusted for in this analysis. A late adverse event will be defined as an adverse event occurring more than 90 days from the completion of RT. The time to late adverse events will be measured from the time that protocol treatment is completed (i.e., the completion of radiation) to the time of the worst late adverse event. If no such late adverse event is observed until the time of the analysis, the patient will be censored at the time of the analysis. The distribution of time to late adverse events (observed severities of adverse events over time) will be estimated using the Kaplan-Meier method using a two-sided log-rank test with a significance level of 0.05.

A multivariate Cox regression model will be used to compare the treatment differences for time to late adverse events between the two arms. Both unadjusted and adjusted hazard ratios and the respective 95% confidence interval will be computed. PSA, Gleason score, and age (as appropriate) will be adjusted for in this analysis.

7.8 Analysis for Endpoints Related to HRQOL

We will use four instruments to measure QOL: the Expanded Prostate Cancer Index Composite (EPIC) and EQ-5D. Protocol eligible patients will be included in the QOL analysis only if they have provided baseline and at least one subsequent measurement. All QOL instruments (EPIC and EQ-5D) will be collected on all cases participating in the trial.

The EPIC and EQ-5D will be collected at pretreatment (baseline) and after 3 months, six months, and then every year after the end of radiation therapy.

Patient self-assessment of symptoms will be performed using three primary EPIC scales: urinary, bowel, and sexual symptoms. The EQ-5D is a two-part self-assessment questionnaire. The first part consists of five items covering five dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a three-point likert scale (1-no problems, 2-moderate problems and 3-extreme problems). The second part is a visual analog scale (VAS) valuing the current health state measured by a 100-point scale with a 10-point interval. (0-worst imaginable health state, 100-best imaginable health

state). We will transform the five-item index score and VAS score into a utility score between 0 (Worst health state) and 1 (Best health state) for comparative purposes.

For all QOL analyses we will conduct a comparison between the two treatment arms with a significance level of 0.05 and a two-sided test. To address the non-ignorable missing data caused by censoring survival time, the data analysis will also be done with patients who have not died.

We will describe the distributions of QOL data collection patterns over all collection points in each treatment arm. Longitudinal data analysis, specifically the general linear mixed-effect model,[15] will be performed to describe the change trend of the EPIC, and EQ-5D scores over time across the two treatments. The primary objective in the HRQOL analysis is to determine the QOL differences. The response will be the change of measurement from baseline for each measurement. z- test statistics will be used to test the null hypothesis that responses are the same across the two treatment arms versus the alternative hypothesis that they are different. To maintain the overall significance level for testing six HRQOL instruments, the Bonerroni-adjusted significance level is 0.05/6 = 0.0083. The model will include the baseline and stratification variables (Gleason score, PSA).

To examine trade-offs between the survival time and QOL, we will combine them for each patient into two single measurements: QALY and QADFSY. QALY and QADFSY are defined by the weighted sum of different time episodes added up to a total quality-adjusted survival time and a total quality-adjusted disease-free survival time, respectively.

These health state-based methods of quality-adjusted survival analysis are known as Q-TWiST, the quality-adjusted time without symptoms and toxicity method.

$$\text{Q-TWiST} = \sum_{i=1}^{k} q_i \, s_i$$

where q_i is the quality (the utility coefficient) of health state i , s_i is the duration spent in each health state, and k is the number of health states. We will use Glasziou‘s multiple health-state (Q-TWiST) models[16] to use the repeated measures of EQ-5D. Because Glasziou‘s method incorporates longitudinal QOL data into an analysis of quality-adjusted survival, the health-stated model must be constructed on the following assumptions:

A1) QOL is independent from treatment

A2) A health state is independent from previous states

A3) Proportionality of quality-adjusted duration and duration of the actual state of a health state.

Assumption A1 can be checked by plotting QOL over time according to treatment, and the t-test can be used to compare the mean QOL scores of each treatment arm. Assumption A2 can be checked by comparing the QOL for patient groups in a given health state where the groups are defined by duration of previous health state experience using a regression model. Suitable checks for assumption A3 at minimum would be a simple plot. If data does not support these assumptions, we will use a method which uses the longitudinal QOL data directly.

7.9 Interim Reports

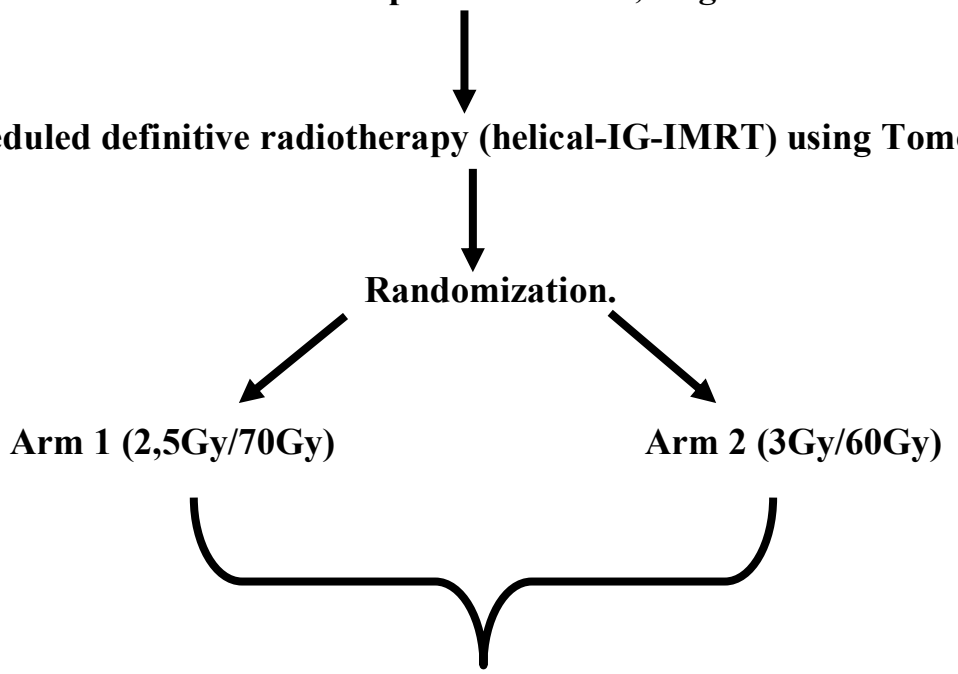
In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; data quality; compliance rate of treatment delivery with the distributions of important prognostic baseline variables; and the frequencies and severity of adverse events. The interim reports will not contain results from the treatment comparisons with respect to the primary or secondary endpoints.

7.10 Analysis for Reporting Initial Treatment Result

The final analysis will include tabulation of all cases entered and those excluded from the analyses with the reasons for such given; the distribution of the important prognostic baseline variables; and observed results with respect to the primary and secondary endpoints. All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis (intent-to-treat analysis). In addition, exploratory analyses of treatment comparisons of biochemical disease free survival, local progression, overall survival will be tested using the Cox proportional hazard model that includes age, clinical tumor stage, PSA, Gleason score/. Also, where feasible, treatment comparisons with respect to the primary endpoint (biochemical relapse free survival) and secondary endpoints (local progression and overall survival) will be compared.

Study design

Patients with localized prostate cancer, stage cT1-3N0M0.



Simulation and immobilization

Evaluation of the rectum, bladder.

Radiotherapy

Evaluation of acute toxicity (at the end of EBRT).

Evaluation of PSA after 1.5 months completion of EBRT.

Observation after treatment.

Estimation of PSA level every six months.

Evaluation of late toxicity.

Assessment of relapse-free survival.

Study objectives

- **Oncological results (5th, 10th summer)**

Biochemical relapse free survival rate

Survival rate without a local progression

Overall survival.

- **Negative effects**

Early and late genitourinary (GU) toxicity

Early and late gastrointestinal (GI) toxicity

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ATTACHMENTS.

1. EPIC.

Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP)
Prostate Cancer Quality of Life (QOL)

Patient Name: _____ Date of Birth: _____

Physician: _____ Date of Visit: _____

Patients: Please answer the following questions by circling the appropriate answer. All questions are about
your health and symptoms in the **LAST FOUR WEEKS.**

Select ONE answer for each question:

B **Overall, how much of a problem has your urinary function been for you?**				
No Problem	Very small problem	Small problem	Moderate problem	Big problem

2. Which of the following best describes your urinary control?				
0-Total control	1-Occasional dribbling	2-Frequent dribbling	4- No urinary control	
3. How many pads or adult diapers per day have you been using for urinary leakage?				
0-None	1-One pad per Day	2-Two pads per Day	4- Three or more pads	
4. How big a problem, if any has urinary dripping or leakage been for you?				
0-No problem	1-Very small problem	2-Small problem	3-Moderate problem	4-Big problem
***CLINICIANS**: Add the answers from questions **2-4** to calculate the **Urinary Incontinence Symptom Score** (out of 12)*				

5. How big a problem, if any, has each of the following been for you?						
	No problem	Very small problem	Small problem	Moderate problem	Big problem	
a. Pain or burning with urination	0	1	2	3	4	
b. Weak urine stream/incomplete bladder emptying	0	1	2	3	4	
c. Need to urinate frequently	0	1	2	3	4	
***CLINICIANS: ADD** the answers from questions **5a-5c** to calculate the **Urinary Irritation/Obstructive Symptom Score** (out of 12)*						

6. How big a problem, if any, has each of the following been for you?						
	No problem	Very small problem	Small problem	Moderate problem	Big problem	
a. Rectal pain or urgency of bowel movements	0	1	2	3	4	
b. Increased frequency of your bowel movements	0	1	2	3	4	
c. Overall problems with your bowel movements	0	1	2	3	4	
d. Bloody stools	0	1	2	3	4	
***CLINICIANS: ADD** the answers from questions **6a-6d** to calculate the **Bowel Symptom Score** (out of 16)*						

7. How do you rate your ability to reach orgasm (climax)?					
0- Very good	1-Good	2-Fair	3-Poor	4-Very poor to none	

8. How would you describe the usual quality of your erections?				
0- Firm enough for intercourse	1-firm enough for masturbation and foreplay	2-Not firm enough for any sexual activity	4-None at all	

9. Overall, how much of a problem has your sexual function or lack of sexual function been for you?

0-No problem	1-Very small problem	2-Small problem	3-Moderate problem	4-Big problem	

10. How big a problem, if any, has each of the following been for you?

	No problem	Very small problem	Small problem	Moderate problem	Big problem	
a. Hot flashes or breast tenderness/enlargement	0	1	2	3	4	
b. Feeling depressed	0	1	2	3	4	
c. Lack of energy	0	1	2	3	4	
***CLINICIANS: ADD** the answers from question s**10a-10c** to calculate the **Vitality/Hormonal Symptom Score**(out of 12)*						

***CLINICIANS: ADD** the five domain summary scores to calculate the Overall Prostate Cancer QOL Score (out of 60)*

2. EQ 5D.

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ☐

I have slight problems in walking about ☐

I have moderate problems in walking about ☐

I have severe problems in walking about ☐

I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐

I have slight problems washing or dressing myself ☐

I have moderate problems washing or dressing myself ☐

I have severe problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐

I have slight problems doing my usual activities ☐

I have moderate problems doing my usual activities ☐

I have severe problems doing my usual activities ☐

I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfor ☐

I have slight pain or discomfort ☐

I have moderate pain or discomfort ☐

I have severe pain or discomfort ☐

I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐

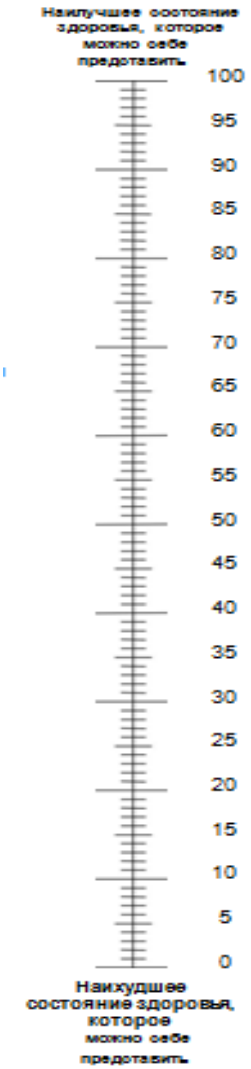
I am slightly anxious or depressed ☐

I am moderately anxious or depressed ☐

I am severely anxious or depressed ☐

I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
- **0** means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.



Now, please write the number you marked on the scale in the box below
YOUR HEALTH TODAY

3. IPSS

International Prostate Symptom Score (IPSS)

Patient Name: _____ Date of birth: _____ Date completed _____

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: *Mild* 8-19: *Moderate* 20-35: *Severe*

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

4. ECOG.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

5. TNM 8th edition

Definitions of AJCC TNM

Definition of Primary Tumor (T)

Clinical T (cT)

T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as the external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

PATHOLOGICAL T (PT)

T category	T criteria
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of the bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as the external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Note: There is no pathological Tl classification
Note: Positive surgical margin should be indicated by an Rl descriptor, indicating residual microscopic disease

DEFINITION OF REGIONAL LYMPH NODE (N)

N category	N criteria
NX	Regional nodes were not assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)

DEFINITION OF DISTANT METASTASIS (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Note: When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced

DEFINITION OF PROSTATE-SPECIFIC ANTIGEN (PSA)

PSA values
<10
≥10<20
<20
≥20
Any value

DEFINITION OF HISTOLOGIE GRADE GROUP (G)

Grade group	Gleason score	Gleason pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4
5	9 or 10	4+5, 5+4, or 5+5

AJCC PROGNOSTIC STAGE GROUPS

When T is...	And N is...	And M is...	And PSA is...	And grade group is...	Then the stage group is...
cT1a–c, cT2a	N0	M0	<10	1	I
pT2	N0	M0	<10	1	I
cT1a–c, cT2a	N0	M0	≥10<20	1	IIA
cT2b–c	N0	M0	<20	1	IIA
T1–2	N0	M0	<20	2	IIB
T1–2	N0	M0	<20	3	IIC
T1–2	N0	M0	<20	4	IIC
T1–2	N0	M0	≥20	1–4	IIIA
T3–4	N0	M0	Any	1–4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	N0	M1	Any	Any	IVB

Note: When either the PSA or grade group is not available, grouping should be determined by T category and/or either the PSA or grade group is available

6. Roach Formula = [(2/3) (*) PSA + (Gleason score - 6) (*) 10]

7. Evaluation formula for involvement of the seminal vesicles = PSA + (Gleason score - 6) (*) 10]