HYPO-RT-PC

Phase III study of

HYPO-fractionated RadioTherapy

of intermediate risk localised Prostate Cancer (HYPO-RT-PC)

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Preface - general comments on study protocol version 7.0, 2015-10-15

We have during the last years had extensive discussions on an update of the protocol, particularly with respect to the change from a "superiority" design to a "noninferiority" approach and an expansion of the number of patients required for the latter. During this work, a blinded statistical update of the total number of primary events that had occurred was disclosed to the trial steering committee as well as to the safety and scientific committees for an evaluation of the number of patients required to meet the noninferiority criteria. The analysis showed that 1200 patients would be sufficient to demonstrate noninferiority. After careful consideration, based on the statistical analysis and the recommendations from the safety and scientific committees, the decision to aim for a noninferiority design was made. The statistical evaluation also showed that with another two to three years of follow-up we would be able to analyze the primary endpoint of the trial.

We expect to be able to complete enrollment during 2015. The major changes in this updated protocol compared to the previous version 6.0 are described below.

Revision of clinical follow-up plan
With the experience we now have and with the safety assessments that have been conducted, we feel confident to simplify the monitoring procedures (i.e. reduced number of visits to doctor). This will also reduce the load on the healthcare system. Mandatory visits to doctor are now:
- At 6 months after radiotherapy for evaluation of acute toxicity
- At 2 years for the evaluation of side effects
- At 5 years for the primary endpoint
- At 10 and 15 years
- At the occurrence of PSA progression (nadir + 2 ng/ml)
- At the start of a hormone therapy, where bone scan and CT should be performed
- At the time point when metastases are detected

Major protocol changes

Noninferiority Analysis
A change of the primary study design from superiority to noninferiority with 4% noninferiority margin was made. If this is met, a superiority analysis will be made. With the current relapse rate in the study the number of events (160) will be reached within two to three years. The need for fewer events than was previously advocated is due to that the patient population has fewer events than was expected according to the assumptions made in the original study protocol. The Safety Committee will regularly monitor the total number of events and advice at which time point the study can be analyzed.

Toxicity analysis
An analysis of toxicity will be made when all patients have been included and completed their radiotherapy.

All patients will be followed every six months for collection of blood samples and evaluation of side effects, until PSA progression. After blood sampling the patient will be contacted by

the doctor or research nurse for information of lab results and for a structured follow-up of adverse events.

This study has previously been approved by the EPN (Docket 05-053 / FEK03513, last revision in 2011 131-32M, latest contact Docket 12-6-32M). We have under letter 140819 expanded the study to 1200 subjects, approved by the EPN, Dnr-2015-217-32M (Addition of 05-053M).

In this revised version of the previous protocol (version 6.0 2011-12-28) text that is no longer valid has been marked with "~~strikethrough~~" while changes/additions are written in purple colour. Minor linguistic changes (which do not change the intention/content of the protocol) have not been specifically marked.

1 Table of content

2 Synopsis

Rationale
Recent publications have shown that the α/β ratio for prostate cancer is low (1.5-3.0 Gy), suggesting that HYPO-fractionated radiotherapy (HYPO-RT) could be of advantage for the treatment of localised prostate cancer, both for the outcome and for shortening of the treatment time. This hypothesis will be tested in a randomised study with HYPO-fractionated RT in comparison to conventional fractionation.

Aim of the Phase III study
Primary: ~~To demonstrate a 10 percent unit increase (70% to 80%) in freedom from failure (PSA or any clinical) in the HYPO-RT arm at 5 years after the end of treatment. Originally this required 296 patients in each arm. To compensate for the safety subgroup analysis (see 12.6.2) another 126 patients will be added. Addition of 10 % more patients to the total population will also be performed to account to lost to follow up. Totally 800 patients are required.~~

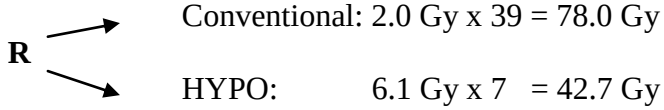
To show that HYPO-RT is non-inferior to conventional RT. If noninferiority is demonstrated, HYPO-RT will be tested for superiority. A total of 1200 patients will be randomized. For details, see Supplement 1.

Secondary: PSA response rate, time to symptoms related to local progression, time to symptoms related to distant progression, cancer specific survival, overall survival, QoL and safety.

Design
The study is an open randomised multicentre phase III study, in patients with **intermediate risk** prostate cancer. Comparison will be between conventional fractionation with 2.0 Gy x 39 to a total dose of 78.0 Gy versus the HYPO arm with 6.1 Gy x 7 to a total dose of 42.7 Gy. All fractions are given with 3D-CRT or IMRT using image guidance based on implanted markers. For detailed information on definitions of volumes and dose requirements, see section 7.

The radiobiological analysis is based on near equal rectal toxicity in both arms under the assumption that α/β=3 Gy for rectum. An independent committee will perform a safety analysis of PSA response and rectal toxicity at 1, 2 and 3 years follow up of the first 100 patients treated. PSA-response at 1 and 2 years will be defined as the percentage of patients with PSA ≤ 2.0 µg/L at 1 year and with PSA ≤ 1.0 µg/L at 2 years. The difference between the treatment arms shall not be more than 20 % units. Late rectal toxicity, evaluated by the percentage of patients with rectal bleeding, is estimated to be 13% in the conventional arm and not more than 25% in the HYPO arm. A subgroup safety analysis will be performed on the initial 126 patients with different treatment volumes.

Hormones will not be used.



A two year toxicity analysis is planned when all included patients in the study (n=1200) have completed their treatment.

Inclusion Criteria

Men with verified localised **intermediate risk** prostate cancer, T1c-T3a, PSA $\leq$ 20, with 1-2 of these risk factors; T3a or Gleason $\geq$ 7 or PSA > 10, N0/pN0, M0, $\leq$ 75 years of age. As judged by the doctor, a life expectancy of 10 years (except for cancer) at time of randomisation with performance status WHO 0-2. Patients will be stratified according to T-stage, Gleason and PSA.

3 Background (updated in Supplement 2)

In the mid 90´s institutional phase II studies suggested that dose-escalated external beam radiotherapy could improve time to treatment failure measured as a rising PSA [1-3]. In a matched study by Hanks and co-workers [4], 357 cases of "high dose" (76 Gy) radiotherapy were compared with 357 patients receiving conventional dose radiotherapy (71 Gy). The result suggested 15 percent units increase (from 56% to 71%) in disease control at five years. This improved local control transformed into a decrease in metastatic disease, an increase in cancer specific survival and even a significant increase in overall survival with about 9%. Six randomised studies have been presented with more than 2000 patients included altogether, randomised between lower doses (64-70 Gy) vs. higher dose (74-80 Gy). Of these randomised studies the MD Anderson study has been published by Pollack and co-workers [5,6]. The results showed that the PSA relapse free survival at 5 years increased by 25 percent units from about 45% to 70% in the intermediate risk group (PSA>10). A decrease in metastatic free disease of more than 10% was observed. A resent update from the large database at the Cleveland Clinic was published by Potters and co-workers showing that dose-escalated radiotherapy up to 80 Gy could show an equal outcome as surgery [7].

Patient set-up errors and prostate movements within the pelvis are major considerations when determining target margins for external beam radiotherapy of prostate cancer. If small margins are used with conventional techniques there is always a high risk of missing part of the tumour [8,9]. To ensure safe coverage of the whole prostate, the planning target volume therefore always overlaps critical surrounding tissues such as the rectum and the bladder. These organs limit the possibility to improve efficacy of treatment by dose escalation due to the increased risk of radiation injury. Even under the assumption of an optimal patient fixation and IMRT there still remains a risk that the prostate may move independently of the surrounding patient anatomy [10-14]. If the prostate localisation could be checked immediately prior to treatment and the patient position adjusted to account for external and internal movement, the margin added for uncertainty in prostate position could be decreased substantially. This would make it possible to deliver higher doses to the prostate with high accuracy without a corresponding increased risk for complications in the rectum and bladder. Different techniques have been developed to improve precision and prostate localisation. The BeamCath technique has been used since 1997 in Scandinavia to visualise the position of the prostate and the prostatic urethra before/during dose-escalation treatment [15]. Patient evaluated side effects at 3 and 5 years after dose-escalation RT with the BeamCath technique has shown no increase in toxicity. It seems therefore to be a safe way to perform dose-escalation RT of prostate cancer [16,17]. In the randomised study from MD Anderson Hospital a doubling of rectal toxicity was reported in the dose-escalation arm using shrinking field and boost technique without marker support for positioning of the prostate [18]. Gold markers have been tested in some Scandinavian centres (Göteborg, Lund, Uppsala).

Radiobiological assumptions and calculations for HYPO fractionated RT of prostate cancer

The studies by Brenner et al 1999 [19], suggesting a low α/β for prostate cancer, are based on PSA data from prostate cancer patients treated with different forms of radiotherapy regimes and are supported by in vitro data. Fowler, Chappell & Ritter [20] updated this study in 2001 with more patients and this analysis confirmed a low α/β of around 1.5 Gy for prostate cancer.

Brenner et al. (2002) [21], has also made a single institution analysis on patients treated with external beam radiotherapy + dose-escalation HDR in 2 fractions (8.25 Gy to 10.5 Gy) or 3 fractions (5.5 Gy to 6.5 Gy), confirming a low α/β (1.2 Gy) without suffering from the problems with data from different institutions. Mohan and co-workers have also reported on preliminary observations comparing short-course IMRT with 2.5 Gy per fraction to a total dose of 70 Gy, with 2.0 Gy to 78 Gy [22]. They reported a comparable biochemical relapse profile and a low late rectal toxicity profile in favour of the hypofractionated regime. Fowler et al. 2003 [23], have also discussed if the α/β for rectum could be slightly higher than 3 Gy. If the α/β value for prostate cancer is less than for late responding tissues such as the rectum, hypofractionated regimes could be designed with fewer but larger dose fractions to maintain equivalent late sequele while improving tumour outcome. Calculations and suggestions of hypofractionation schedules are given in a paper by Fowler and co-workers (2003) with the title "What hypofractionated protocol should be tested for prostate cancer?" showing that there is a high potential for therapeutic gain as well as economic and logistic advantages with hypofractionated schedules [23]. There appears to be a low risk for increased rectal and urinary toxicity as long as the overall treatment time is at least five weeks and more than 5-10 fractions are used, and total rectal doses are limited as described in this protocol. According to Dasu 2007 [24] the alpha/beta for prostate tumours is low enough to be safely used in clinical hypofractionated trials.

The present study is designed to have equal late rectal toxicity in the two arms comparing conventionally fractionated treatment (2.0 Gy x 39 to 78.0 Gy) with a hypofractionation arm with 6.1 Gy x 7 to a total dose of 42.7 Gy

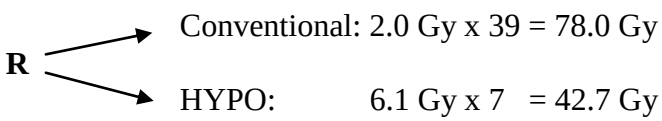
4 Rationale

Recent publications have suggested that the α/β ratio for prostate cancer is low (1.5 -3.0 Gy), suggesting that hypofractionation could be advantageous, for treatment outcome as well as regarding shortening of the treatment time. This hypothesis should be tested in a randomised study in comparison to conventional fractionation.

5 Study Objectives

5.1 Study design and outline

The study is an open randomised multicentre phase III study. The radiobiological analysis is based on equal rectal toxicity (as with 78 Gy in 2.0 Gy fractions) in both arms (α/β =3 Gy for rectum). The aim is both to test the hypothesis that α/β < 3 Gy for prostate cancer, and that hypofractionation ~~would increase outcome without~~ is non-inferior to conventional fractionation and not increasing the toxicity. If it is confirmed that HYPO-RT is non-inferior to conventional radiotherapy then superiority of HYPO-RT will be tested. See Supplement 1 for details concerning number of patients and statistical analysis. An independent data safety committee will perform comparative safety analyses throughout the study.



5.2 Aim of the study

5.2.1 Primary

~~To demonstrate a 10 % unit increase in freedom from failure (70% to 80%; PSA or any clinical) in the HYPO-RT arm at 5 years after the end of treatment. requires 296 patients in each arm (80% power, p=0.05, 2-sided test). To compensate for the safety subgroup analysis (12.6.2), similar number of patients, 126, will be added to the total patient population to get a "full population" of patients treated with the same technique and irradiation of the same volume of risk organs in both arms. Addition of 10 % more patients (72) to the total population of 800 (n=592 + 126 +72) will also be performed to account to lost to follow up.~~

To demonstrate that HYPO-RT is non-inferior to conventional radiotherapy regarding failure free survival (FFS), i.e. freedom from biochemical failure (PSA nadir + 2.0 ng/ml) or prostate cancer recurrence. If HYPO-RT is shown to be non-inferior a superiority analysis will be performed. See Supplement 1 for details concerning number of patients and statistical analysis and considerations.

5.2.2 Secondary

- PSA response rate,
- Time to symptoms related to local progression
- Time to symptoms related to distant progression
- Cancer specific survival
- Overall survival
- Quality of Life (QoL) and side effects with special focus on sexual function, urinary and gastrointestinal morbidity
- Time to change of treatment

6 Study population - selection of patients

6.1 Number of patients

~~The statistical calculation shows that totally 800 patients are needed to show a 10% increase in freedom from failure.~~

A total of 1200 patients will be randomized. See Supplement 1 for details concerning statistics.

6.2 Investigation prior to inclusion

Clinical investigation with clinical history and physical examination

Laboratory investigation: Haemoglobin, creatinine and PSA. Blood samples for later analysis ~~(Optional see 8.3.4)~~.

Biopsy: Prostatic cancer must be proved histologically.

TNM classification

T-stage: This should be determined by digital rectal examination (DRE) according to the TNM classification system UICC 2002 (see Appendix I).

N-stage (Lymph node status): Staging procedure.

- Patients with T1c-T2, PSA of ≤ 20 μg/L, Gleason ≤ 6 are considered to be node negative.
- Patients with T1c-T2, PSA of ≤ 10 μg/L, Gleason 7 are considered to be node negative.
- In other patients staging operation is recommended to be performed according to local practice with bilateral pelvic lymphadenectomy (laparoscopic or surgical technique) including obturatory nodes. Staging operation can be performed in all patients, if this is routine at the centre. In case staging operation is not performed, modern imaging technique is required (at least CT).

M-stage (Metastases): Patients should be free of bony metastases. Conventional bone scan and radiography should be performed within 2 months, if needed. Patients considered to be node-negative are also considered to be free from metastases (bone scan is not required in these patients).

6.3 Inclusion criteria

1. Men ≤ 75 years of age and, as judged by the doctor, to have a life expectancy of 10 years (except for cancer) at time of randomisation with performance status WHO 0-2 (Appendix II).

2. Patients with a histologically verified prostatic cancer.

3. Patients with intermediate risk prostatic cancer of clinical category T1c-T3a with 1 or 2 of the following risk factors; T3a or Gleason ≥ 7 or PSA > 10; (Appendix III) according to the TNM classification system UICC 2002 (Appendix I).

4. PSA ≤ 20 μg/L

5. The patients should have no evidence of metastases according to the definition above.

6. Patients should be lymph node negative according to the definition above, i.e. staging.

7. Patients should be suitable for radiotherapy.

8. Patients must have signed informed consent

6.4 Exclusion criteria

1. Patients who earlier have undergone any other treatment for prostatic cancer.

2. PSA-value at any time before inclusion > 20 µg/L, unless a temporary benign reason for the increase is likely, e.g. infection, insertion of markers.

3. Patients unable to co-operate or suffering from any other form of disease that would interfere with the planned treatment (e.g. colitis)

4. Patients with previous diagnosis of other malignant disease except ~~Exceptions could be made~~ for basal cell carcinoma of the skin or progression free survival at least 10 years after any previous tumour.

5. Previous hormone therapy (castration or anti-androgens).

6. Any condition that prevent implantation of markers, i.e. anal fissure.

7 Radiation treatment

7.1 Patient position and fixation

The patient may be treated in either supine or prone position. The position must be the same during planning, simulation and treatment.

The patient should be immobilised according to the standard procedures of each participating centre. The type of fixation device/technique shall be reported in the RTQA-report (see below).

7.2 Patient data acquisition

A CT study shall be made in the treatment position, on a flat table top and with the patient in his fixation device. CT scanning shall be performed with a slice thickness of maximum 3 mm. In patients with extremely filled rectum due to faeces or gas, a new planning CT should be performed prior to treatment planning.

7.3 Target volumes and organ-at-risk (OAR) volumes

The definition of volumes follows the recommendations made by ICRU in Report 50 and in the supplementary ICRU Report 62 for photon beam therapy [25,26].

The technique for delineation of volumes shall be the on CT, and preferably with MR support.

7.3.1 Target volumes

Gross Tumour Volume (GTV)
It is usually not possible to outline the GTV.

Clinical Target Volume (CTV)
The CTV is the prostate as outlined on CT (MR guidance is recommended).

The seminal vesicles shall not be treated.

Planning Target Volume (PTV)
The PTV includes the prostate (CTV) with a margin of 7 mm in all directions to account for delineation uncertainties, internal movements and set-up uncertainties.

Note! If automatic margin expansion is used, make sure that the margin is at least 7 mm in the cranio-caudal (cc) direction. (If needed, increase the cc figure in the TPS margin expansion tool to comply with the margin size.)

7.3.2 Organs at risk (OAR)

Rectum and anal canal

The rectal volume shall be outlined as the outer contour of the rectum, i.e. including the rectal wall. The extension of the segmentation shall, if applicable, be 5 cm in the cranial direction from the centre of the prostate and in the caudal direction down to and including the anus.

The anal canal shall be outlined as a separate volume with a default extension in the cranio-caudal direction of 4 cm.

Urinary bladder

The volume of the bladder shall be outlined on each CT image as the outer contour of the bladder, i.e. including the muscle wall.

Femoral heads

The femoral heads shall be outlined without margins.

Penile bulb (optional)

The penile bulb shall be outlined on the CT images (MR guidance is recommended).

7.3.3 Structure names in treatment planning system

For convenience the following structure names should be used:

"***CTV***", "***PTV***", "***rectum***", "***anal canal***", "***bladder***", "***penile bulb***", "***FH sin***" and "***FH dx***".

7.4 Treatment technique

The radiation treatment shall be given with external photon beam therapy with 3D-CRT and/or IMRT techniques. It is left to each centre to decide upon the optimal technique (number of beams, beam weights, beam angles, beam shaping, etc.).

The same treatment technique shall be used in both trial arms within the centre.

The position of the prostate shall be verified prior to every fraction with electronic kV or MV portal imaging or x-ray volumetric imaging (cone beam CT) using implanted markers (see Appendix IV). The treatment should start as soon as readily possible after the verification/correction.

The monitor units (dose) used for verification of position should be considered and compensated for if MV portal imaging is used.

Each centre should have treated at least two patients with their specific marker and image guidance technique before entering the study.

7.5 Treatment planning

CT-based 3D treatment planning is mandatory. Corrections for heterogeneities shall be performed.

Maximum allowed voxel size for the dose calculation grid is 3 mm in the transversal plane. A size equal to the CT slice thickness is recommended.

7.6 Photon beam quality

3D-CRT should be delivered with a minimum photon beam quality of 10 MV. In the case of IMRT, 6 MV or higher may be used.

7.7 Photon beam dose calibration

It is recommended that the participating centres take part in external dosimetry audits, in order to check the absolute dosimetry of the accelerators used in the study.

7.8 Dose specification

Dose prescription, recording and reporting

The prescribed target doses, i.e. 78.0 Gy in the conventional arm and 42.7 Gy in the hypofractionated arm, shall be equal to the mean dose in the PTV ($D_{mean,PTV}$). All relative dose values in percentage units are given in relation to the mean PTV dose.

Dose recording and reporting shall be performed as described below in the QA section (see Appendix V).

7.9 Fractionation schedule

Conventional arm

Radiotherapy is given daily (5 days/week) with 39 fractions of 2.0 Gy, i.e. total 78.0 Gy.

The total treatment time is thus 53-55 days. Maximum allowed treatment days are 65.

Hypofractionated arm

Radiotherapy is given working-days with 7 fractions of 6.1 Gy, i.e. total 42.7 Gy.

The total treatment time is 15-19 days. Treatment is given every other weekday, always including two weekends.

7.10 Dose-volume objectives/constraints

Dose-volume objectives/constraints to target volumes and organs at risk are given in the table below.

Dose-volume objectives/constraints

Priority	Volume	Conventional arm	Hypofractionated arm	
1	CTV	D_{min} ≥ 95% D_{min} ≥ 74 Gy	D_{min} ≥ 95% D_{min} ≥ 40.6 Gy	The minimum dose to CTV shall be greater than or equal to 95% of the prescribed dose, i.e. $D_{mean,PTV}$.
2	PTV	$V_{95\%}$ ≥ 95% V_{74Gy} ≥ 95%	$V_{95\%}$ ≥ 95% $V_{40.6Gy}$ ≥ 95%	The 95% isodose shall cover at least 95% of PTV.
3	Rectum	$V_{90\%}$ ≤ 15% V_{70Gy} ≤ 15%	$V_{90\%}$ ≤ 15% $V_{38.4Gy}$ ≤ 15%	Less than 15 % of the outlined rectal volume should receive doses greater than 90% of the prescribed dose.
4	PTV	$D_{99\%}$ ≥ 90% $D_{99\%}$ ≥ 70 Gy	$D_{99\%}$ ≥ 90% $D_{99\%}$ ≥ 38.4 Gy	The “near minimum dose” to PTV should

				be greater than or equal to 90% of the prescribed dose.
5	Rectum	$V_{75\%} \leq 35\%$ $V_{59Gy} \leq 35\%$	$V_{75\%} \leq 35\%$ $V_{32Gy} \leq 35\%$	Less than 35 % of the outlined rectal volume should receive doses greater than 75% of the prescribed dose.
6	Femoral heads	$D_{max} \leq 70\%$ $D_{max} \leq 55$ Gy	$D_{max} \leq 70\%$ $D_{max} \leq 29.9$ Gy	The maximum dose to the femoral heads should be less than or equal to 70% of the prescribed dose
7	Rectum	$V_{65\%} \leq 45\%$ $V_{51Gy} \leq 45\%$	$V_{65\%} \leq 45\%$ $V_{28Gy} \leq 45\%$	Less than 45 % of the outlined rectal volume should receive doses greater than 65% of the prescribed dose.
8	Body	$D_{max} \leq 105\%$ $D_{max} \leq 82$ Gy	$D_{max} \leq 105\%$ $D_{max} \leq 45$ ~~45.7~~ Gy	The maximum global dose should be less than or equal to 105% of the prescribed dose

7.11 Quality Assurance

A working group will be assigned for collecting treatment and verification data to ensure that the physical quality of the treatments follows the study protocol.

Radiotherapy related treatment information and other relevant documentation for each patient shall be sent to the QA-group at completion of radiotherapy.

Quality audits may be performed by the QA-group during the trial.

7.11.1 Objectives

The aim of the QA protocol is to ensure uniformity of all radiotherapy data for every patient in order to answer the questions in the trial. Specifically this means:

- to establish a uniform instruction of radiotherapy details,
- to evaluate compliance for all patients with the instructions of the radiotherapy details, and
- to enable a correct evaluation of the endpoints in the trial.

7.11.2 Elements of the method of QA procedure

The QA procedure has two parts;

- dummy run, and
- individual patient evaluation checks.

Dummy run procedure
A dummy run will be performed before the start of the patient trial.

The dummy run procedure consists of two separate parts:

1. Delineation of structures (targets and organs at risk)
2. Treatment planning of predefined target volumes

The first part is dedicated to *definition of volumes*. CT images of a prostate cancer patient will be sent from RTQA-office. The target volumes (CTV and PTV) and the organs at risk (rectum, anal canal, urinary bladder, penile bulb and femoral heads) shall be delineated on the transversal CT slices according to the study protocol. The CT images and delineated structures shall be sent back to the RTQA-office for evaluation.

The second part is dedicated to *treatment planning*. Each institution shall make a treatment plan for both arms in the trial. The CT images, structures, plan, and dose data together with dose volume histograms (DVH) for all structures shall be sent back to the RTQA-office for evaluation.

The dummy run has to be performed and evaluated by the RTQA team before the centre starts to include patients.

Detailed practical information of the dummy run procedure will be sent out separately to each participating centre.

Individual patient evaluation checks of the radiotherapy treatment
A final treatment evaluation of every single patient shall be performed after completion of radiotherapy. Similar data shall be sent for the two arms in the study. The following parameters will be checked and evaluated at the RTQA-office:

- Patient immobilisation
- CT scanning (number of slices, slice thickness)
- Volumes of targets (CTV and PTV) and organs at risk (rectum, anal canal, urinary bladder, penile bulb and femoral heads)
- 3D treatment planning (beam arrangements, beam shaping, beam quality, etc.)
- Dose prescription
- Fractionation and time interval between fractions
- Total treatment time
- Dose volume histograms

A detailed description on how to prepare and process the data needed for QA is presented in Appendix V. The result of the review for each patient will be sent back to the participating institution within one month after the patient data has arrived to the RTQA-office.

8 Clinical and laboratory assessments for efficacy, tolerability and safety - Follow up

8.1 Clinical follow up (see separate flow chart)

Patients should be seen/contacted by a doctor (urologist/surgeon or oncologist or study nurse) for clinical evaluation every **6 months** (± 14 days) preferentially by an oncologist for the first year.

At 3 and 9 months after start of treatment visit to a physician is optional. These visits can be replaced by a telephone contact from the study nurse for registration of side effects.

From 12 ~~to 60~~ **months after start of treatment until PSA progression**, the patient should be ~~seen~~ contacted ~~by a doctor~~ for blood sampling and registration of side effects every six months (± 28 days) thereafter yearly until metastases are verified. Thereafter patients should be followed for verification of other treatments and death. Local modifications regarding which clinician that sees the patient might occur.

~~From visit 60 month~~ **At 5, 10 and 15 years** (±28 days) after start of treatment the patients should be seen by a doctor. At ~~six month~~ visits in between (or until PSA progression) the study nurse (or doctor) should contact the patient by telephone for registration of side effects. At each visit/telephone contact during follow-up PSA, haemoglobin, creatinine and clinical findings (side effects) should be recorded. ALP will be measured at each visit from year 2 and forwards. Further investigations should be performed if indicated for medical reasons or if signs of progression appear (pain, increase in PSA, ALP etc.). Any change of the treatment of prostate cancer should be reported. Cystoscopy, coloscopy or other surgical investigations performed because of suspected progress or side effects should be reported in the CRF.

The CRF will be completed by the responsible investigator or study nurse at each enrolling site. This means that the responsible investigator must collect source data from the clinic (urological/surgical/oncological/study nurse) where the patient performs the visits. For each patient, an individual and specified follow up schedule will be ~~sent out~~ available after randomisation. Patients should be seen/contacted every 3 months for the first year and thereafter every 6 months until PSA progression or death.

Regarding the first 200 patients it is anticipated that the CRF should be sent to Cancercentrum, Norrlands universitetssjukhus, 901 85, Umeå **within 1 month** after visit.

Mandatory visits to the doctor are

- at end of radiotherapy
- at 6 months
- at 2 years (toxicity evaluation),
- at 5 years (Primary Endpoint)
- at 10 and 15 years (long-term side effects)
- at confirmation of PSA-progress,
- at start of anti-hormonal treatment (bone scan + CT) and
- confirmation of metastatic disease.

- **From start of radiotherapy until PSA progression:** Patients should be seen/contacted by a doctor (urologist/surgeon or oncologist) or a study nurse for evaluation (symptoms and toxicity) and lab testing every 6 months (±14 days)

- **After confirmed PSA progression patients should be followed annually with PSA measurements and seen/contacted** by a doctor (urologist/surgeon or oncologist) or a study nurse for evaluation (symptoms and toxicity) and for verification of **date of change or addition of hormonal treatments and date of metastatic disease**.

- **Before start of anti-hormonal treatment, a bone scan and CT** should be performed.

- **After verified metastatic disease** patients should be followed for verification of other treatments and death.

Further investigations should be performed if indicated for medical reasons or if signs of progression appear (pain, increase in PSA, ALP etc). Any change of the treatment of prostate cancer should be reported. Cystoscopy, coloscopy or other surgical investigations performed because of suspected progress or side effects should be reported in the CRF. After verified metastatic disease, the patient should be followed for evaluation of reason for death (cancer specific or other). After metastatic disease additional treatments and their duration should be reported, but may be collected retrospectively by linkage to routinely collected data.

Blood Sampling

At each follow up, (every 6 months until PSA progression) blood samples (PSA, Hb, Creatinine) should been collected and clinical findings (side effects) should be recorded.

ALP Hb, creatinine and PSA will be measured at each follow up from year 2 and until metastasis.

Web CRF will be available at www.nscr.se

8.2 Patient's Quality of Life (QoL) questionnaire

Prostate Cancer Symptom Scale (PCSS) QoL-questionnaires, including EORTC QLQ-C30 and IIEF-5, will regularly be mailed to the patient at home (except for the first time and end of radiotherapy). He will then send the questionnaire back to the study secretary in a postage-paid, pre-addressed envelope. The questionnaires should be filled out at entrance (= start of radiotherapy), and end of radiotherapy (in the last week; given to the patient by the oncologist). Further QoL follow up is calculated from the date of start of RT and the QoL form should be filled out at 3 and 6 months, 1 year, 2, 4, 6, 8, 10 and 15 years.

8.3 Prior to Inclusion

8.3.1 Information to be provided to the patient

Before inclusion in the study each patient must be given full oral and written information about the study and its respective treatment modalities. The patients should also be informed that participation is voluntary, that he regularly will receive QoL questionnaires and that he is free to withdraw from the study at any time. Information about computerised data processing should also be given. Thereafter, each patient's written consent to participate in this study must be obtained (Appendix VI).

8.3.2 Reject Log

Each centre should keep a reject log over patients who are referred to the Oncological department, but not included in the study despite that they fulfil the inclusion criteria.

8.3.3 At the start of treatment

When the patient has agreed to participate in the study the investigator will give him the first QoL-questionnaire. Doctor's evaluation of sexual functions, urinary and intestinal problems should be recorded in the CRF before the start of treatment.

8.3.4 Growth factors and protein pattern correlation to tumour burden (optional)

Separate vials (10 ml) of EDTA-plasma (purple) and Heparin-plasma (green) and serum should be collected from each patient before start of treatment and at year 1 and 4 for the evaluation protein pattern in serum (proteomics), basic FGF, VEGF and EGF and other potential predictive factors of response and outcome.

8.4 Treatment when progression occurs

Similar treatment routines shall be used in both arms in each centre when the patient has progressed

Biochemical progression	No change in treatment is recommended. If hormonal therapy has to be instituted it is recommended to start with anti-androgen therapy after PSA is > 10. Bone scan should always be performed before addition of hormonal therapy. Hormonal therapy will not be instituted before PSA progress has been verified. After biochemical progression treatment is optional but the patients still have to be followed up according to the protocol ~~(every 6 months)~~ annually. Follow up after biochemical (PSA) progression and local progression will continue annually to detect the date for change of treatment and metastases.
Local progression	Optional treatment. After local progression treatment is optional but the patients still have to be followed up annually. Local salvage treatment is allowed and should be reported prospectively.
Distant progression	After distant progression all patients should receive castration equivalent treatment.

The patient has to be followed for evaluation of date of death (survival) and cause of death. Details of additional treatments and their duration is optional, but may be collected retrospectively by linkage to routinely collected data.

8.5 Withdrawal from treatment

The patient can at any time withdraw from treatment. The date and reason for withdrawal

should be reported in the CRF. If a patient is lost to follow up the date and reason for this should be reported in the CRF. This does not mean that the patient leaves the study. All patients randomised should be followed until the end points have been reached - irrespective of further treatment regimens and in accordance with the intention of treatment strategy.

9 Flow Charts

Time point (from start of treatment) **Visit window**: Year 1: ± 14 days Thereafter: ± 28 days	RT-patient[b]	Patients questionnaire QoL
Entrance	Dr	X[a]
End of radiotherapy	Dr	X[a]
3 months	visit/phone call[b]	X
6 months	Dr	X
9 months	visit/phone call[b]	
1 year	Dr/phone call[b]	X
Every 6 months until ~~distant~~ PSA progression	Dr/phone call[b]	
2 years	Dr	X
4 years		X
5 years	Dr	
~~**Every 12 months until distant progression**[c, d]~~		~~X~~
6 years		
8 years	Dr/phone call[b]	X
10 years	Dr	X
15 years	Dr	X

a) QoL form is given to the patient by the doctor

~~b) The patient should be seen by a physician (oncologist/urologist/surgeon) at follow up~~

~~c~~b) Visit optional. A study nurse should call the patient for registration of side effects if visit not performed

~~d) From 5 years and forward every second visit is optional. A study nurse should call the patient for registration of side effects if visit not performed~~

PSA, Hb, creatinine at every contact. ALP start at 2 years.

Follow up after biochemical (PSA) progression and local progression will continue annually

10 Assessment

10.1 Response

10.1.1 PSA- Response

The PSA response is defined at two levels: PSA < 1.0 µg/L and PSA < 0.5 µg/L.

10.2 Progression

Time to progression of the malignant disease is calculated from randomisation to the day when progression is first suspected. This suspicion has to be verified by further deterioration, in consecutive measurements, or investigations that verify progression. On certain occasions, with very clear deterioration the statement progression may be stated at one evaluation and change of therapy may thus be initiated at once.

10.2.1 Suspicion of progression

1. Increase in PSA.
2. Increase in creatinine.
3. Increase in urinary problems or urinary retention.
4. Increase in ALP (alkaline phosphates).
5. Cancer-related decrease in haemoglobin.
7. Lymphoedema.
8. Hydronephrosis.

10.2.2 Progression

The statement "progression" is usually established when suspected progression in previous investigations is confirmed by further deterioration. In fact, it is desirable that progression as a statement is based on solid data with several parameters indicating the deterioration. If any doubt exists, it is preferred that a new check-up is arranged within a month, before the therapy is changed and "progression" is stated in the CRF.

10.2.3 PSA-progression

PSA-progression is defined according to the ~~ASTRO~~ Phoenix definition as an increase in PSA of + 2.0 ng/ml above nadir ~~(on three consecutive measurements with at least one month between each)~~. Bouncing PSA should not be considered as a progress [26].

Appropriate pages in the CRF should be filled in.

10.2.4 Clinical Progression

Local Progression
Local progression is defined as a tumour induced change in urinary problems (frequency, urgency, obstructions) of such magnitude that a change of treatment is necessary (i.e. TUR-P, castration or; if TUR-P is performed due to strictures without local progression (no tumour in TRUS-biopsy; this should be reported under side effects). Appropriate pages in the CRF should be filled in. Salvage treatment for local recurrence should be reported.

Distant Progression
Distant progression is evaluated by the retrospective sequential method. This means that cancer related pain or other signs of metastases should be verified by x-ray, bone scan, CT scan or ultrasound investigations. If needed, biopsy for histological/cytological evaluation is recommended.

Progression may, however, be stated on one occasion if

1. Use of narcotic drugs due to cancer-related pain.
2. Appearance of hot spots on bone scan or metastatic lesions on X-ray.

10.3 Side effects

Side effects should be reported according to national practice and noted in the CRF. Symptoms related to proven tumour progression should not be considered as side effects.

10.3.1 Adverse events (AE)

Side effects related to therapy during the study should be reported in the CRF. Grading will be done according to RTOG/EORTC. For events, except for bladder and small/large intestinal, use Common Terminology Criteria for Adverse Events (CTC-AE) version 3.0.

10.3.2 Serious side effects (SAE)

Serious side effects during the study should be reported to ~~Centrum för utvärdering av behandlingsnytta, CUB,~~ Cancercentrum, Norrlands universitetssjukhus, 90185 Umeå. Hospitalisation due to suspected **serious side effects related to treatment** should be reported within 10 days ~~to Centrum för utvärdering av behandlingsnytta,~~ by FAX, ~~+46 90-12 74 64~~ +46 90 12 74 64. Symptoms and death related to proven tumour progression should not be considered as serious side effects. Serious side effects are those that are life-threatening, or may give serious permanent damage or dysfunction of a magnitude that need hospital care.

Grading will be done according to RTOG/EORTC. For events, except for bladder and small/large intestinal, use Common Terminology Criteria for Adverse Events (CTC-AE) version 3.0 for definition and grading.

11 Definition of endpoints

11.1 Primary endpoint

The primary endpoint is freedom from biochemical failure (i.e. increase in PSA of 2.0 ng/ml above nadir according to the Phoenix definition) or prostate cancer recurrence. Failure Free Survival (FFS) is defined as time from randomisation until event as defined above.

11.2 Secondary endpoints

Biochemical disease-free survival: Time from randomisation until PSA progression according to the Phoenix definition.

Clinical disease-free survival: Time from randomisation with freedom from symptoms of local progression or metastases.

Cancer Specific Survival: Time from randomisation to death from prostatic cancer as defined below.

Overall survival: Time from randomisation to death from any cause.

Quality of life: Evaluation of side-effects and QoL in PROM form 2 and 4 years after start of therapy, especially sexual function, urinary and intestinal side effects.

PSA Response rate: Percent of patients in each arm receiving a PSA < 1.0 µg/L and PSA < 0.5 µg/L, respectively.

Change of treatment: Time from randomisation to commencement of androgen deprivation after ending radiotherapy.

~~1. PSA-progression according to the ASTRO definition or clinical progression~~

~~2. Biochemical disease-free survival, PSA progression has not occurred according to ASTRO definition.~~

~~3. Clinical disease-free survival analysed as time with freedom from symptoms of local progression or metastases.~~

~~4. Cause (cancer) specific survival in prostatic cancer as defined below.~~

5. ~~Quality of life 2 and 4 years after start of therapy, especially sexual function, urinary and intestinal side effects.~~

11.3 Death

CRF should be filled in.

Death should be classified as

1) death from prostatic cancer.

2) death from other disease, with the prostatic cancer as a significantly contributing factor. This means that at least signs of progression, disseminated disease or significant uraemia have been seen.

3) death solely due to other disease. It is mandatory to define the specific cause of death.

4) death from unknown cause.

12 Data management and statistical procedures

12.1 Case Record Form (CRF)

For each visit the CRF will be filled in. The investigator at the enrolling site is responsible for collection of source data if patient visits are performed at other clinics.

12.2 Quality of life

Prostate Cancer Symptom Scale (PCSS), which includes the EORTC QLQ-C30 and IIEF-5, will be used for Quality of Life evaluation. The patient will regularly (except the first and second time), by mail, receive QoL questionnaire. He will return the quality-of-life questionnaire in a postage-paid, pre-addressed envelope directly to the national data centre.

12.3 Monitoring

All monitoring functions within this study will be performed by ~~a CRO-company, Centrum för utvärdering av behandlingsnytta, CUB,~~ Cancercentrum, Norrlands universitetssjukhus, 901 85 Umeå. The monitors will work in accordance with the relevant monitoring SOPs. Monitors will establish and maintain contact between the study-coordinators and the investigators. Monitoring visits will be made to each centre at a frequency depending on included patients.

In house monitoring is required. Triggered monitoring could be an alternative when in-house monitoring identifies problems. Visits will be done to these centres.

12.4 Data management

The Department of Oncology, Umeå University Hospital will serve as Randomisation and Data Centre (Appendix VII). The signed original Case-Report Forms (CRFs) shall be faxed to ~~Centrum för utvärdering av behandlingsnytta, CUB,~~ Cancercentrum, Norrlands universitetssjukhus, Umeå (Fax: +46 90 15 49 67) within 1 month, for further work-up. Data can also be entered into the web-based e-CRF at https://www.nscr.se. The original hardcopy CRF should be kept at site until monitoring is performed. The CRFs will be edited manually.

12.5 Number of patients and power considerations

12.5.1 Determination of sample size

~~The estimated probability of freedom from failure (PSA or any clinical) for subjects receiving conventional fractionation in the same subject population as included in the study is to be 70% at five years after the end of treatment, and the expected probability of freedom from failure in subjects randomized to HYPO-fractionated radiotherapy is 80% at five years after the end of treatment. Using the log rank test the total number of events (failures) needed, with a significance level of 0.05 and a power of 80%, for testing this improvement in freedom from~~

~~failure is calculated to 148. With an estimated accrual rate of 20 subjects each month and a follow-up period of three years after the last randomized patient, a total number of 296 patients in each arm will be required. The subject recruitment will last for four years giving a total duration time (accrual + follow-up) of seven years. To compensate for the safety subgroup analysis (12.6.2), similar number of patients, 126, will be added to the total patient population to get a "full population" of patients treated with the same technique and irradiation of the same volume of risk organs in both arms. Addition of 10 % more patients (72) to the total population of 800 (n=592 + 126 +72) will also be performed to account to lost to follow up.~~

A total of 1200 patients will be randomized. See Supplement 1 for details regarding the revised statistics (noninferiority vs. superiority considerations).

12.6 Safety and toxicity analyses

12.6.1 Sequential safety analysis

A safety analysis is planned to be conducted when the first 100 patients have been followed for ***12*** months (estimated to occur 40 months after start of treatment of the first patient). The purpose of the interim analysis is to conduct a safety analysis regarding PSA response and acute/late rectal toxicity.

Until data from this analysis is available from the first 100 patients 300 patients are allowed to be recruited.

The analysis is repeated after 200 and 300 patients followed for 12 month.

- PSA-response at 1 and 2 years will be defined as the percentage of patients with PSA ≤ 2.0 µg/L at 1 year and with PSA ≤ 1.0 µg/L at 2 years. The difference between the treatment arms shall not be more than 20 % units.

- Rectal toxicity will be evaluated by percentage of patients with rectal bleeding of 13% in the conventional arm and not more than 25% in the HYPO arm.

- Erectile dysfunction and urinary incontinence will also be evaluated at 1 and 2 years.

12.6.2 Safety Subgroup analysis

The first 126 patients in the study have been treated with different radiation volumes in the two arms. In the conventionally fractionated arm, a larger safety margin was used around the prostate than in the HYPO-fractionated arm and thereby a larger volume of the surrounding tissue was irradiated in these patients, according to the initial protocol version 2.1, 20050613. Due to technical development (Appendix IV) and the change of requirements that all patients should have implanted fiducial markers, the protocol was revised according to version 3.0, 20080114, approved by the ethical committee Dnr 05-053, 20080128. Bothe study arms are thereafter treated with the same safety margin around the prostate (7 mm).

A safety subgroup analysis on the 126 first treated patients will be performed regarding rectal toxicity and PSA response.

12.6.3 First analysis of toxicity

A first toxicity analysis is planned after complete inclusion of the study and when all patients have finished their treatment.

12.7 Statistical methods

The primary endpoint is FFS, failure free survival, i.e. time from randomisation to the first of biochemical relapse and clinical progress. Death without disease (non-prostatic cancer death) is a competing event.

The study has changed to a non-inferiority trial (see Supplement 1 for details). An absolute marginal difference of 4% in "net" 5-year FFS, from 87% in the standard arm to 83% in the HYPO arm, has been accepted to declare non-inferiority. Assuming proportional hazards, this corresponds to a hazard ratio margin of 1.338.

The non-inferiority analyses will be done for the Per Protocol population. Patients who do not fulfil the inclusion criteria or have not started radiotherapy according to the randomisation will then be excluded. As a complement, an intention to treat (ITT) analysis of the non-inferiority hypothesis will also be performed. If non-inferiority is demonstrated, analyses to show superiority for HYPO-fractionation will also be done.

Analyses of efficacy and toxicity will also be performed separately for the first 126 included patients (treated with different CTV-PTV margins in the two treatment arms) and the latter included ca 1200-126 patients (treated with the same CTV-PTV margins in the trial arms).

The primary endpoint FFS will be analysed by means of stratified Cox regression. The assumptions for proportional hazards will be checked. Non-inferiority will be declared if the upper limit of a two-sided 95% CI for the hazard ratio is less than the hazard ratio margin value 1.338, corresponding to a one-sided significance test with level 2.5%.

Other time-to-event endpoints will also be analysed using the Cox proportional hazards model.

Overall survival will be illustrated by treatment arm using Kaplan-Meier curves, and FFS will be illustrated by means of cumulative incidence curves taking the competing event "other death" into account.

~~The trial will be evaluated according to the intention-to-treat method. These patients will be evaluated in the treatment group, to which they are originally assigned at randomisation (intention to treat). In fact, only patients with major deviation from the study inclusion criteria at randomisation (i.e. patient later found to have been misdiagnosed for cancer or who already at start of treatment had another malignancy) will be excluded from the final evaluation.~~

~~Cause-specific and disease-free survival will be analysed with stratified Cox proportional hazards model. In the analysis of cause-specific survival, events will be defined as death due to prostate cancer while for the disease-free survival, local progression, distant progression or~~

~~prostate cancer death are considered as events.~~

12.8 Randomisation

Eligible patients will be assigned to treatment with one of the two therapies. When the responsible doctor has received a written informed consent from the patient, and found the patient eligible for the study, the doctor will phone +46 90-785 19 90 to the Randomisation Centre at the Oncological Centre of Umeå where randomisation lists will be generated. Questions will be asked from a checklist to verify that the patient is eligible. Then, the patients initials and birth data (in some cases, name and address) will be noted at the centre, and the patient will be given the next consecutive code number, according to the stratification category. The treatment allocated for the patient will then be given to the clinician, and after that the patient cannot be excluded from evaluation of the study. A written confirmation of the randomisation will be sent to the investigator together with a recommended follow-up schedule for the patient to be put in the CRF.

The procedure may also be performed via web page https://studies.oc.umu.se/hypo/ or by telefax communication +46 90-12 74 64.

12.8.1 Stratification

- By each centre.
- By T-stage T1c - T3a (T1c-T2;T3a)
- By Gleason score Gl. 2-6, Gl. 7, Gl 8-10
- By PSA ≤10; >10

13 Direct access to source data/documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories (1) Investigators file and (2) Subjects clinical source documents.

The investigator must keep these two categories of documents on file for at least 10 years after completion or discontinuation of the study.

The investigator shall on request supply the ~~CRO-company~~ sponsor with any required background data from the study documentation or clinical records. In case of special problems and/or governmental queries or requests for audits/inspections it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

14 Ethical consideration

The study is to be performed in accordance with the ethical recommendations of the Helsinki declaration.

15 Financing

Financial support has been granted by the Nordic Cancer Union. Application will be sent to the Local and National Cancer Foundations.

16 Report and communication of results

16.1 Ownership of the data

The data are owned by a collaborative group consisting of investigators at the participating centres.

16.2 Publication

All presentations of data from the study, in the form of lectures or publications, should only be made after agreement with the study-coordinators and a scientific committee, which will be appointed later. The results of the study will be submitted to an internationally recognized medical journal. It is the intention of the present study that analysis of the primary endpoint should not be analysed until the required number of events has been obtained. ~~if solid statistical data emerge,~~ However, if the number of events (n=162) has not been reached within xx years after the final patient is included, the primary endpoint will be analysed when the median follow-up time is five years. In case other exceptional circumstances occur the results may be published earlier after approval by the scientific committee. It is presumed that the preparation of a manuscript from the study will be done by the participants. A writing committee may be appointed. All participating clinicians and their departments should, however, be mentioned in any manuscript or poster, or shown on a slide in connection with all lectures. It is open to any participating clinician, after contact with the study-coordinators, to take part in the more extensive work that is required for the evaluation of data and preparation of manuscripts. Every participant in the study may use part of the data for more specialised analysis after consent from the study coordinators and publish it according to the above mentioned rules.

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18 Signature

I agree to conduct the study in accordance with the protocol described in this document and in compliance with ethical principles that have their origin in the Declaration of Helsinki and applicable regulatory requirements.

Study: Phase III study of HYPO-fractionated Radiotherapy of Intermediate risk Localised Prostate cancer (HYPO-RT-PC)

Name, Academic Degree: _____

Centre: _____

Function:_____

Institution:_____

Address:_____

E-mail:_____

Date:_____ Signature:_____

19 Appendices

Appendix I
TNM-CLASSIFICATION

UICC 2002 Sixth Edition (modified version)

T- Primary Tumour

TX primary tumour cannot be assessed

T0 No evidence of primary tumour

T1 - Clinically inapparent tumour not palpable or visible by imaging.

T1a – Tumour incidental histological finding in 5% or less of tissue resected
T1b - Tumour incidental finding in more than 5% of tissue resected.
T1c - Tumour identified by needle biopsy (e.g. because of elevated PSA).
T2 – Tumour confined within prostate[1]
T2a - Tumour involves ½ or less of a lobe
T2b - Tumour involves more than ½ of a lobe, but not both lobes
T2c - Tumour involves both lobes
T3 - Tumour extends through the prostatic capsule[2].
T3a - Extracapsular extension (unilateral or bilateral)
T3b - Tumour invades seminal vesicle(s)
T4 – Tumour is fixed or invades adjacent structures other than seminal vesicles; bladder neck, external sphincter, rectum, levator muscles, or pelvic wall

Notes: 1. Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.
2. Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

Appendix II

WHO GRAD – definition

Points	Performance status (WHO)
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair

Appendix III

PATIENTS POSSIBLE TO BE INCLUDED IN THE HYPO-STUDY (1-2 risk factors)

1. Patients with **intermediate risk prostatic cancer** of clinical category T1c- T3a with 1 or 2 of the following risk factors; T2c-T3a or Gleason ≥ 7 or PSA > 10; according to the TNM classification system UICC 2002 (Appendix I).

2. All patients N0, **N-stage: Lymph node status.**
Staging procedure.
– Patients with T1c-T2b, PSA of ≤ 20 µg/L, Gleason ≤ 6 are considered to be node negative.
– Patients with T1c-T2b, PSA of ≤ 10 µg/L, Gleason 7 are considered to be node negative.
– In other patients staging operation it should be performed according to local practice with bilateral pelvic lymphadenectomy (laparoscopic or surgical technique) including obturatory nodes. Staging operation can be performed in all patients, if this is routine at the centre.

3. All Patients M0

4. PSA ≤ 20 µg/L

Intermediate risk prostatic cancer (1-2 risk factors)

1 Risk factor

T-stage	Gleason	PSA
T1c-T2	2-6	***> 10***
T1c-T2	***7-10***	≤10
T3a	2-6	≤10

2 Risk factors

T1c-T2	**7-10**	***>10 ≤ 20***
T3a	**7-10**	≤10
T3a	2-6	**>10 ≤ 20**

Appendix IV

IMPLANTED MARKERS

The fiducial markers are typically made of gold, each ca 5mm long and with a diameter of ca 1mm. Usually three markers are implanted, to avoid uncertainties in case of marker migration and/or rotation of the gland. The markers are implanted under ultrasound guidance transperineally or transrectally. The implantation is recommended at least three weeks before the dose-planning-CT, to avoid post-implant oedema of the gland.
The placements of the markers are preferably one to the left in the base of the prostate, one laterally in the right lobe and one laterally to the left in the apex.

Using electronic portal image device, EPID, two orthogonal pictures (frontal and lateral) are taken with a few monitor units. Registration of the markers is performed against reference images (the reference image could be a simulator image or a digitally reconstructed radiograph, DRR). The position of the treatment couch is then corrected for optimal matching of the markers.

Alternatively the verification of the marker positions can be performed with kV planar imaging or kV/MV x-ray volumetric imaging (cone beam CT).

The verification and correction procedure shall be performed prior to each treatment fraction in both treatment arms.

The radiation treatment shall start as soon as possible after the registration/correction to minimize additional movement of the prostate.

Appendix V

INSTRUCTIONS FOR REPORTING RADIOTHERAPY QA-DATA IN THE HYPO-RT PROSTATE STUDY

Radiotherapy related data shall be collected and reported by the hospital for every patient.

All data shall be copied to a CD. Create a directory on the CD named "xxx", where xxx is the patient randomization number (always three digits; start with zeros, if necessary)

- Export from the TPS all CT-images, structures (CTV, PTV, rectum, anal canal, urinary bladder, penile bulb, femoral heads, and body outline), plan and dose distribution in DICOM-RT format. Include the number of fractions and the dose/fraction (in Gy) when performing the DICOM-export.
  Save all DICOM-files in a subdirectory named "Dicom" under the directory "xxx".
- Export DVHs in differential form and in cumulative form for all delineated structures including the body outline in ASCII-format. The DVHs should be exported with the dose preferably given in relative values (%) with a dose bin width ≤ 0.5%. Corresponding volumes should be given in percent of the total structure volume. Name the differential and the cumulative DVH files xxx_dif.txt and xxx_cum.txt, respectively and save them in a subdirectory named "DVH".
- Fill in the "Radiotherapy QA" report form. Name the file xxx_QAform.doc.
  Save the completed form on the CD-R under the directory xxx.

Data to RT-QA office

Please mark the CD-R with "HYPO-RT-PC", the randomization number of the patient and the hospital name. Send the CD to:

Eva Englund
Radiofysik
Klinikgatan 7
Universitetssjukhuset i Lund
SE-221 85 Lund

Appendix VI

PATIENTINFORMATION

Studie jämförande konventionell (=vanlig) strålbehandling mot hypofraktionerad (= högre dos per tillfälle vid färre tillfällen) strålbehandling av patienter med prostatacancer.

Allmänt om Din sjukdom

Du har tidigare av Din behandlande läkare fått information om Din prostatacancer och tillsammans har ni valt att Du ska få strålbehandling mot Din sjukdom. Eftersom prostata kan röra sig används markörer placerade direkt i prostata för att säkrare kunna verifiera prostatas läge i samband med behandling.

Det har nu kommit nya data som tyder på att prostatacancer skulle kunna vara särskilt känslig för behandling med större dagsdoser än man vanligen han använt. Denna studie avser att studera om så är fallet och om biverkningarna skiljer sig från den nu vanligaste tekniken.

Studiens syfte

Syftet med studien är att undersöka om effekten av färre, men större stråldoser per dag kan vara bättre än att som hittills ge behandling med lägre dagsdoser under en längre period. I båda behandlingsgrupperna ges strålbehandling mot prostata med tillägg av lika säkerhetsmarginal. Total behandlingstid för konventionell strålbehandling (=vanlig) är ca 8 veckor. Hos den grupp som får högre stråldos vid varje behandling kommer behandlingstiden att vara 2 -3 veckor.
Studien är upplagd så att det bedöms vara likvärdig risk för eventuella biverkningar från tarm- och urinvägar. Studien ska undersöka om det finns någon skillnad i tid till eventuellt återfall av sjukdomen i de båda grupperna.

Hur går studien till?

I samband med att Du ska få strålbehandling markeras prostatas läge med särskild teknik. Ett par markörer av små guldkorn införes i prostata med hjälp av en ultraljudstav via ändtarmen eller via bäcken botten ett par veckor före strålstart. Vilket alternativ som blir aktuellt just för dig beror på vid vilken klinik du kommer att få din behandling. Du kommer att få särskild information angående hur den teknik som används på denna klinik går till. Metoderna med markörer innebär att vi med hjälp av ett bildavläsningssystem i strålfältet kan registrera läget för markörerna i prostata och sedan exakt rikta strålen mot prostata under behandlingen och då minimerar bestrålningen av känsliga organ som blåsa och ändtarm.

För att genomföra undersökningar av det här slaget på ett tillförlitligt sätt krävs många patienter, ungefär ~~800~~ 1200 stycken. Flera sjukhus i Norden samarbetar för att genomföra studien och arbetet leds av en studiegrupp med Professor Anders Widmark, Onkologen i Umeå och Prof. Lars Franzén, Onkologen, Sundsvall, som huvudansvariga.

Vi kommer också att be Dig fylla i livskvalitetsformulär för att registrera Dina biverkningar. Det kan vara ett visst obehag att få markörer insatta med nålar i prostata. Detta görs dock av erfaren personal som utfört detta som ett rutinmässigt arbete under de senaste åren

Efter avslutad strålbehandling kommer Du att följas upp på ett rutinmässigt sätt och få ett

återbesök ca var sjätte månad då bl.a. rutinmässiga blodprov kommer att tas.

Prover för forskningsändamål

Om det är praktiskt möjligt och om Du medger det, kommer blodprover, ca 30 ml, att samlas in vid tre tillfällen, innan behandlingen, efter ett och efter fyra år. Analys kommer att ske av bl.a. s.k. proteinmönster och andra faktorer som närmare kan bestämma hur Din prostatacancer ser ut. Proverna kommer också att analyseras för att studera Din känslighet för strålbehandlingen när vi har sett vilka eventuella biverkningar som Du eventuellt har drabbats av. Det är känt att några enstaka patienter har ökad känslighet för strålbehandling och vi avser att studera detta. Du kommer inte att få ta del av något analysresultat som rör Dig personligen. Syftet med analysen är att man i framtiden ska kunna ta prover för att förutsäga vilka individer som kan ha en högre känslighet för strålbehandling

Prover kommer inte att användas för andra ändamål än det som beskrivits. Proverna förvaras i frys, i s.k. Biobank, vid Onkologiska kliniken i Umeå och hanteras enligt biobankslagen. Enligt lagen har du rätt att när som helst begära att proverna ska kasseras. Din kontaktperson är Din läkare i studien

Dina rättigheter
Ditt deltagande i studien är helt frivilligt. Under studiens gång kan du när som helst och utan närmare förklaring avsluta Ditt deltagande utan att det påverkar Din fortsatta behandling här vid kliniken. Data som samlas in under studiens gång kommer att jämföras med anteckningar i Din patientjournal. Detta arbete utförs av representant från oberoende monitoreringsföretag. Data kommer att hanteras av och statistiskt bearbetas vid Onkologiskt Centrum i Umeå. Du betecknas endast med kodnummer och initialer. Alla personliga data är sekretesskyddade och Du kommer inte att kunna identifieras i rapporterna av resultaten

Under studieperioden omfattas Du av det skydd som finns i Patientskadeförsäkringen.

Har Du några speciella frågor angående studien eller Din prostatasjukdom kan Du vända Dig till behandlande läkare som gett Dig denna information eller till någon annan på kliniken.

Läkare: ……Tfn: …….

Sjuksköterska: ……. Tfn: …….

Om Du vill delta ber vi Dig signera bladet ”Patientens samtycke till att deltaga i klinisk prövning”.

Patientens samtycke till att deltaga i klinisk prövning:

Studie jämförande konventionell strålbehandling (vanlig behandling) mot hypofraktionerad (= högre dos per tillfälle vid färre tillfällen) strålbehandling av patienter med prostatacancer.

Information om studien har jag fått dels av min läkare och genom skriftlig patientinformation.

Jag känner till att mitt deltagande är helt frivilligt och att jag när som helst utan närmare förklaring kan avbryta mitt deltagande. Detta kommer inte att påverka mitt framtida omhändertagande.

Jag lämnar också mitt medgivande till blodprovstagning för forskningsändamål som beskrivits här ovan.

Jag samtycker även till att representant för monitoreringsföretag och eventuell myndighet får jämföra de i studien rapporterade uppgifterna med de data som finns i min patientjournal. Detta får endast ske efter godkännande av journalansvarig läkare och under förbehåll om sekretess.

Jag har fått en kopia av detta medgivande

Härmed samtycker jag till att deltaga i studien av konventionell strålbehandling jämfört med hypo-fraktionerad strålbehandling av prostatacancer.

…….. ……..
Datum Namnteckning (patient)

……..
Namnförtydligande

Intygar härmed att informationen angående studien givits både muntligt och skriftligt och att patienten samtycker till deltagande.

…….. ……. .
Datum Namnteckning (läkare)

……..
Namnförtydligande

Appendix VII

ADMINISTRATION

Organization

This is a co-operative multicentre study.

Principal investigators	**Address**	**Phone/Fax**
Anders Widmark	Department of Oncology University Hospital S-901 85 UMEÅ Sweden	Tel: +46 90-785 28 57 Fax: +46 90-77 46 46
Lars Franzén	Department of Oncology Sundsvall Hospital S-851 86 SUNDSVALL Sweden	Tel: +46 60 181000 Fax: +46 60 182726

Study Services:

Randomisation and Data centre	Oncological Centre	
	University Hospital S-901 85 UMEÅ Sweden	Tel: +46 90-785 19 90 Fax: +46 90-12 74 64
Monitoring	Cancercentrum Norrlands universitets-sjukhus S-901 85 UMEÅ Sweden	Tel: +46 90 785 8591 Fax +46 90 12 74 64
Radiotherapy QA		
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Statisticians		
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Harald Anderson

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Sweden

20 Supplement 1: Statistical amendment

Background and number of patients (superiority trial)

The trial was originally designed as a superiority study. The aim was to demonstrate a 10% absolute increase (70% to 80%) in failure free survival (PSA or any clinical), FFS, in the HYPO-RT arm at five years after end of treatment. Assuming proportional hazards, a one-sided significance level of 0.025, and power 0.80, D=148 primary events were required. To reach this number of events within a reasonable time, initially 600 patients were to be randomized. To compensate for the safety subgroup analyses (see section 12.6.2) and to account for loss to follow up, this figure was increased to 800 patients in 2012. Discussions were started in 2013 with the CHHiP trial group from the UK with the aim to redesign the HYPO-RT-PC study to a noninferiority trial. The ethical committee approved 2013 05 - an additional 200 patients to be included in order to still recruit patients while these discussions were ongoing. During the extensive discussions with UK, a request was sent to EPN 2014-08-20 for inclusion of additional 200 patients to a total of 1200 patients, which was approved by EPN 2014-09-09.

Blinded interim analysis

In a blinded interim analysis, performed in March 2015, the overall FFS was estimated to 86.6% at 5 years. This result is much better than anticipated when the study was originally designed. To detect a 10% absolute improvement in 5 year FFS, fewer primary events are needed than with the original assumptions.

Non-inferiority considerations

Taking into consideration that hypofractionated treatment has many clinical advantages, it was deemed sufficient to show that its efficacy is noninferior to that of standard treatment. The trial was therefore changed to a noninferiority study based on recommendations from the Trial Steering Committee (TSC) and approval given by the independent safety and scientific committees. Similar RT studies have also been designed as noninferiority studies. A noninferiority margin of 4% in 5-year FFS was suggested to be adequate, considering the estimated overall 5-year FFS.

The difference in "net" FFS (censoring at non-prostate death) has stabilized after 5 years. First, we assume that a marginal delta=0.06 for noninferiority is acceptable, i.e. HYPO treatment is adequate as long as 5-year FFS is at most 6 percentage units worse compared to standard treatment. In the final dimensioning this marginal will be changed to 4%; see below.

Let 5-year FFS equal p_0 in the control group and p_1 in the HYPO group, and consider the hypotheses

$$H_0: p_0 - p_1 \geq 0.06$$

$$H_1: p_0 - p_1 < 0.06$$

If H_0 is rejected it is shown that H_1 holds and thus that HYPO is non-inferior to control treatment.

In the dimensioning we assume proportional hazards for prostate events (PSA or clinical relapse) with constant hazard ratio HR between the HYPO arm and the control arm. Using the definitions above $p1=(p0)^{HR}$ in the HYPO group. For different values of p_0 this corresponds to different values of HR according to the equation

$$p_0 - (p_0)^{HR} = 0.06$$

yielding the corresponding marginal hazard ratio

$$HR_0 = \ln(p_0 - 0.06)/\ln(p_0)$$

The null and alternative hypotheses may then be expressed in terms of HR:

H_0: $HR >= HR_0$

H_1: $HR < HR_0$

To reject H_0 thus means to demonstrate that HYPO is non-inferior to standard treatment.
The test of H_0 vs. H_1 is done by comparing the upper level of a two-sided 95% CI for the HR with HR_0.

The study is event-driven. With one-sided significance level of 2.5%, power 80% for the specific case of HR=1 (i.e. no difference between the treatment arms) and 1:1 randomization, the necessary number of events is determined by equation (4) in Jung et al. (2005) with reference to Chow et al. (2003)

$$D = 4*(z_{0.025} + z_{0.20})^2/(\ln(HR_0))^2 = 4*(1.96 + 0.84)^2/(\ln(HR_0))^2$$

Below is a table where HR_0, D and $p_{mean}=(p_0+p_1)/2$ are determined for various values of p_0 and $p_1=p_0-0.06$.

p_mean	p0	p1	HR0	D
0.73	0.76	0.70	1.30	456
0.74	0.77	0.71	1.31	429
0.75	0.78	0.72	1.32	402
0.76	0.79	0.73	1.34	375
0.77	0.80	0.74	1.35	349
0.78	0.81	0.75	1.37	324
0.79	0.82	0.76	1.38	298
0.80	0.83	0.77	1.40	274
0.81	0.84	0.78	1.43	250
0.82	0.85	0.79	1.45	227
0.83	0.86	0.80	1.48	204
0.84	0.87	0.81	1.51	183
0.85	**0.88**	**0.82**	**1.55**	**162**
0.86	0.89	0.83	1.60	142
0.87	0.90	0.84	1.65	124
0.88	0.91	0.85	1.72	106
0.89	0.92	0.86	1.81	89
0.90	0.93	0.87	1.92	74
0.91	0.94	0.88	2.07	60
0.92	0.95	0.89	2.27	47

In the blinded interim analysis (see above) the average event rate was 0.0271 per person year and p_mean was estimated to 0.866. To allow for some uncertainty in the determination of average event rate, p_mean is chosen to 0.85 corresponding to $p_0=0.88$ and $p_1=p_0-0.06=0.82$ and yielding the marginal hazard ratio $HR_0=1.55$. The study will then have 80% power to show noninferiority when **162 patients have had a failure**. Note, that the power has been determined to 80% for the situation when the HYPO and standard arms are equal. If the HYPO arm is better the power will increase.

Radiobiological considerations

The HYPO-RT-PC trial is based on equal late toxicity (at the prescription dose levels) in the trial arms given that the α/β=3 Gy, i.e. the equieffective dose EQD2(3)=78 Gy. As described in Supplement 2 the literature points fairly unanimously towards an even lower α/β value for prostate cancer.

Stronger evidence for this assumption was recently presented when the results from the UK randomized phase III CHHip trial were revealed (Dearnaley et al 2015). In this trial, results from standard treatment (74 Gy/37 fx) and two experimental hypofractionated schedules (60Gy/20 fx and 57Gy/19 fx, respectively) were compared. The 5-year progression free survival (biochemical failure or prostate cancer recurrence) in the three treatment arms indicates that the fractionation sensitivity for prostate cancer corresponds to an α/β value in the range ≈1.5−2.5 Gy. Applying the upper conservative value α/β=2.5 Gy to the HYPO-RT-PC trial results in EQD2(2.5)=82 Gy for the hypofractionated arm. Converting this dose to an estimate of tumour control probability (TCP) for intermediate risk prostate cancer, using input data from published reviews (e.g. Dasu and Toma-Dasu 2014), suggests a few percentage units better progression-free survival in the hypofractionated arm compared to the control arm (EQD2(2.5)=78 Gy) in the HYPO-RT-PC study. Note that a prerequisite for these estimations is that the α/β ratio is not only valid for fraction doses of 3.0 Gy as in CHHiP, but also for 6.1 Gy as in HYPO-RT-PC.

Non-inferiority considerations, continued

A 6% noninferiority margin around a control rate of 85-90% can clinically seem to be wide. The number of events needed increases drastically if smaller margins are applied, and hence a considerable increase in the number of patients is needed to get 80% power when the outcome in the treatment arms are exactly equal (HR=1). However, following the radiobiological considerations above, and assuming that the hypofractionated arm is somewhat better than the standard arm, will yield good power to show non-inferiority, also for 162 primary events and smaller margins.

Let 5-year FFS for standard treatment be 87% and choose a margin of 3% or 4% instead of 6%. This leads to the marginal Hazard Ratios HR_0=1.252 and HR_0=1.338, respectively. Non-inferiority is thus obtained if the upper level of a two sided 95% CI is smaller than respectively 1.252 and 1.338. With 162 primary events the following power functions are obtained by simulation of 1000 Cox regression analyses per parameter combination:

5-yr FFS prob		**Power**	
HYPO	Standard	3% marg.	4% marg.
0.83	0.87	1.1%	2.4%
0.84	0.87	1.9%	5.9%
0.85	0.87	6.6%	14.4%
0.86	0.87	15.7%	27.6%
0.87	0.87	31.9%	50.0%
0.88	0.87	52.4%	69.8%
0.89	0.87	72.9%	86.6%
0.90	0.87	91.5%	95.6%

Assume that the true values of 5-yr FFS are 0.83 and 0.87 in the HYPO and standard arms, respectively. Then the probability (the risk) to get a noninferiority outcome is 1.1% and 2.4% using margins of 3% and 4%, respectively. If the true 5-yr FFS values are 0.89 for HYPO and 0.87 for standard RT, the probability (power) to obtain a noninferiority outcome is 72.9% and 86.6% with margins of 3% and 4%, respectively.

With n=1200 randomized patients at the end of 2015, and with the overall event rate estimated in the blinded interim analysis, 162 primary events will be obtained within 2-3 extra years of follow-up. A

margin of 4% when 5 yr FFS is 87% with standard RT corresponds to a marginal HR_0=1.338, and this is considered clinically acceptable.

Conclusion

Based on the reasoning and statistical analyses above, a total of 1200 patients will be randomised. The outcome (primary endpoint) of the trial will be analysed after 162 events. This number of events seems feasible to reach within a reasonable time frame without the study being outdated. With 30 expected events per year, another two to three years of follow-up will be needed. This time point will approximately coincide with 5 year median follow up of all patients in the study. In case the event rate will be significantly lower than expected, the trial will be analysed at 5 years median follow up, independent of the number of events.

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21 Supplement 2: Revised and updated background

Dose Escalation

In the mid 90´s institutional phase II studies suggested that dose-escalated external beam radiotherapy could improve time to treatment failure measured as a rising PSA [1-3]. In a matched study by Hanks and co-workers [4], 357 cases of "high dose" (76 Gy) radiotherapy were compared with 357 patients receiving conventional dose radiotherapy (71 Gy). The result suggested 15 percent units increase (from 56% to 71%) in disease control at five years. This improved local control transformed into a decrease in metastatic disease, an increase in cancer specific survival and even a significant increase in overall survival with about 9%. Six randomised studies have been presented with more than 2000 patients included altogether, randomised between lower doses (64-70 Gy) vs. higher dose (74-80 Gy). Of these randomised studies the MD Anderson study has been published by Pollack and co-workers [5,6]. The results showed that the PSA relapse free survival at 5 years increased by 25 percent units from about 45% to 70% in the intermediate risk group (PSA>10). A decrease in metastatic free disease of more than 10% was observed. A report from the large database at the Cleveland Clinic was published by Potters and co-workers showing that dose-escalated radiotherapy up to 80 Gy could show an equal outcome as surgery [7]. Longer term follow up from the phase 3 trials of dose escalation has confirmed the improvement in PSA control using higher doses but emphasise that this comes at a cost of increased rectal toxicity [75-78].

Image Guided Radiotherapy (IGRT)

Patient set-up errors and prostate movements within the pelvis are major considerations when determining target margins for external beam radiotherapy of prostate cancer. If small margins are used with conventional techniques there is always a high risk of missing part of the tumour [8,9]. To ensure safe coverage of the whole prostate, the planning target volume therefore always overlaps critical surrounding tissues such as the rectum and the bladder. These organs limit the possibility to improve efficacy of treatment by dose escalation due to the increased risk of radiation injury. Even under the assumption of an optimal patient fixation and IMRT there still remains a risk that the prostate may move independently of the surrounding patient anatomy [10-14]. If the prostate localisation could be checked immediately prior to treatment and the patient position adjusted to account for external and internal movement, the margin added for uncertainty in prostate position could be decreased substantially. This would make it possible to deliver higher doses to the prostate with high accuracy without a corresponding increased risk for complications in the rectum and bladder. Different techniques have been developed to improve precision and prostate localisation. The BeamCath technique has been used since 1997 in Scandinavia to visualise the position of the prostate and the prostatic urethra before/during dose-escalation treatment [15]. Patient evaluated side effects at 3 and 5 years after dose-escalation RT with the BeamCath technique has shown no increase in toxicity. It seems therefore to be a safe way to perform dose-escalation RT of prostate cancer [16,17]. In the randomised study from MD Anderson Hospital a doubling of rectal toxicity was reported in the dose-escalation arm using shrinking field and boost technique without marker support for positioning of the prostate [18]. Gold markers have been tested in some Scandinavian centres (Göteborg, Lund, Uppsala) and in the UK at the Royal Marsden Hospital [66] and additionally in 18 further centres who contributed to the image guided radiotherapy (IGRT) sub-study of the CHHiP trial [67, 53]. A literature review [59, 60-66] and work from RMH and Clatterbridge Centre for Oncology (CCO) have been used to calculate margins to incorporate residual set up errors and infra fraction motion,

using the van Herk formula [59]: RL 1.4 to 3.3 mm; SI 2.3 to 3.4 mm and AP 3.6 to 3.9 mm [68]. The margins include possible microscopic spread of tumour outside the prostate capsule (CTV), which is estimated to be small in good risk prostate cancer. Modelling works suggests that this level of margin reduction can lead to a 30% to 40% reduction in PTV volume and 30 to 50% reduction in volume of rectum irradiated to critical dose levels (dependent on planning technique and dose level assessed), which we believe is sufficient to expect a clinically significant reduction in toxicity.

Radiobiological assumptions and calculations for HYPO fractionated RT of prostate cancer

The studies by Brenner et al 1999 [19], suggesting a low α/β for prostate cancer, are based on PSA data from prostate cancer patients treated with different forms of radiotherapy regimes and are supported by in vitro data. Fowler, Chappell & Ritter [20] updated this study in 2001 with more patients and this analysis confirmed a low α/β of around 1.5 Gy for prostate cancer. Brenner et al. (2002) [21], has also made a single institution analysis on patients treated with external beam radiotherapy + dose-escalation HDR in 2 fractions (8.25 Gy to 10.5 Gy) or 3 fractions (5.5 Gy to 6.5 Gy), reaffirming a low α/β (1.2 Gy) without suffering from the problems with data from different institutions. Recently several large analyses and meta-analyses of clinical radiotherapy data have sought to define an alpha-beta ratio with greater confidence [24, 39, 41, 43, 44, 45]**.** Vogelius and Bentzen reviewed the data from 5 studies of conventional versus altered fractionation, totalling 1965 patients which gave a best estimate for the α/β ratio of 1.93 Gy (95% CI -0.27-4.14) [44]. Dasu and Toma-Dasu reviewed the largest sample to date of clinical EBRT only studies, analysing 14,168 patients and reporting an α/β value of 1.7 (95% CI 1.2-2.2) [45]. Details of these reports are summarised in appendix 1. Initial clinical studies by Mohan and co-workers reported on preliminary observations comparing short-course IMRT with 2.5 Gy per fraction to a total dose of 70 Gy, with 2.0 Gy to 78 Gy [22]. They reported a comparable biochemical relapse profile and a low late rectal toxicity profile in favour of the hypofractionated regime. Other investigators of international studies of hypofractionated radiotherapy have also reported favourable toxicity. A small Italian phase 3 trial [56] included 168 men and was designed to establish whether a high-dose hypofractionation schedule (62 Gy in 3·1 Gy daily fractions) was associated with lower radiation-related toxicity than was a high-dose conventional schedule (80 Gy in 2 Gy daily fractions). Frequency of side-effects after 3 years of follow-up and PSA control was reported to be at least as good in the hypofractionated cohort as in the control group (PSA control 87% *vs* 79%, p=0·04) [56]. Additionally, reports from phase 1 or 2 trials of high-dose hypofractionated radiotherapy treatments in prostate cancer are encouraging. Three reports [71,72] and [49] document schedules of 3 Gy per fraction to give total doses of 57–60 Gy. Late bowel side-effects (RTOG grade 2 or worse) have been reported in 4%, 5·5%, and 6·3% and late bladder side-effects in 4·2%, 5·6%, and 4·3% of men after 2–5 years of follow-up. [71, 72] and [49]. A preliminary report [70] of a dose-fractionation escalation study in 210 men (2·94 Gy in 22 fractions to 4·3 Gy in 12 fractions) reported rectal bleeding in 8·8% of patients. In a large phase 2 study including 770 men treated with 2·5 Gy fractions to a total of 70 Gy in 5·5 weeks, [47] rates of late grade 2 or worse rectal and bladder toxicity were 4·5% and 5·2%.

Preliminary estimates of PSA control rates in these studies [56, 71, 72, 49 and 47] are comparable to those in standard fractionation schedules. A large single-institute series of 705 men in Manchester, UK, is valuable, because it suggests that a schedule of 50 Gy in 16 fractions (3·125 Gy per fraction) was equivalent to a contemporaneously treated series with 65–70 Gy in 1·8–2·0 Gy fractions [73]. Previously reported randomised controlled trials of hypofractionation have used only modest radiation doses by present standards. A phase 3 trial

[46] in 936 men has compared 52·5 Gy in 20 fractions to 66 Gy in 33 fractions. Results show a 7% reduction in PSA control rate (52·95% *vs* 59·95%) in the 20 fraction group with HR for failure of 1·18 (95% CI 0·99–1·41). Late grade 3 or 4 toxicity was roughly 3% in the two groups. A second randomised controlled trial [69] of 120 men compared a dose of 64 Gy in 32 fractions with 55 Gy in 20 fractions. After median follow-up of 44 months, 4 year PSA control rates were alike (86·2% for hypofractionation *vs* 85·4% for standard fractionation); rectal bleeding was more frequent in the hypofractionated group. All these studies are compatible with an α-β ratio for prostate cancer of 1·5–3·0 Gy [74].

A compilation of recent clinical studies of hypofractionation is given in appendix 2. In particular there are now 3 randomised controlled trials of modest hypofractionation. The largest of these is the UK CHHiP trial which randomised 3216 men to receive either 74Gy in 2GY fractions or 57Gy or 60 Gy in 3Gy fractions [67] and reported preliminary results showing similar bowel and bladder toxicity rates after 2 years follow up ***(Dearnaley ref 61).*** In Canada, investigators are comparing 60 Gy in 20 fractions with 78 Gy in 39 fractions in a planned cohort of 1204 patients (ISRCTN 43853433); and in the Netherlands, researchers are comparing 64·6 Gy in 19 fractions with 78 Gy in 39 fractions, with a planned cohort of 800 patients (ISRCTN 85138529). The Dutch study regimen treats in 7 weeks rather than 4 weeks to keep the total treatment time constant, avoiding the possible time-related increase in damage.

Fowler et al. 2003 [23], have also discussed if the α/β for rectum could be slightly higher than 3 Gy. If the α/β value for prostate cancer is less than for late responding tissues such as the rectum, hypofractionated regimes could be designed with fewer but larger dose fractions to maintain equivalent late sequele while improving tumour outcome. Calculations and suggestions of hypofractionation schedules are given in a paper by Fowler and co-workers (2003) with the title "What hypofractionated protocol should be tested for prostate cancer?" showing that there is a high potential for therapeutic gain as well as economic and logistic advantages with hypofractionated schedules [23]. There appears to be a low risk for increased rectal and urinary toxicity as long as the overall treatment time is at least five weeks and more than 5-10 fractions are used, and total rectal doses are limited as described in this protocol. According to Dasu 2007 [24] the alpha/beta for prostate tumours is low enough to be safely used in clinical hypofractionated trials.

The present study is designed to have equal late rectal toxicity in the two arms comparing conventionally fractionated treatment (2.0 Gy x 39 to 78.0 Gy) with a hypofractionation arm with 6.1 Gy x 7 to a total dose of 42.7 Gy

Hormonal therapy

Phase III studies assessing the addition of neoadjuvant hormonal therapy (NAD) to radical prostate radiotherapy have shown clear evidence of improved overall and cause specific survival in meta-analysis (Bria [26], Shelley [27]). Review of additional recent trial results (Denham [28], D'Amico [29], Roach [30], Jones [31]) confirms the benefit on survival. Trials of AD have been in patients treated with modest doses of radiotherapy by today's standards (≤70Gy equivalent) and predominantly with locally advanced and high risk disease. However a recent large single centre series from the Memorial Sloan-Kettering Cancer Centre in 710 patients with intermediate risk disease who received ≥81Gy either with or without short term HT showed improvements in bPFS,and PCa specific mortality (Zumsteg [32], Zumsteg [33]). Ongoing trials are evaluating the role of high dose radiotherapy with NAD in patients with intermediate risk disease which will more completely define the role of combined modality therapy in this group of patients. However there is persuasive evidence that both dose

escalation and short course HT are appropriate for men with intermediate risk disease with adverse features or higher risk disease. In the proposed expansion of this study 6 months NAD may be offered to men with either high risk prostate cancer or intermediate disease with high risk factors (Gleason primary grade 4 or ≥ 50% of biosy core involvement) (Zumsteg [32]). Use of NAD was mandated for men with intermediate or high risk disease in the UK for both MRC RT01 and ICR CHHiP Trials.

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