Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial

Anders Widmark, Adalsteinn Gunnlaugsson, Lars Beckman, Camilla Thellenberg-Karlsson, Morten Hoyer, Magnus Lagerlund, Jon Kindblom, Claes Ginman, Bengt Johansson, Kirsten Björnlinger, Mihajl Seke, Måns Agrup, Per Fransson, Björn Tavelin, David Norman, Björn Zackrisson, Harald Anderson, Elisabeth Kjellén, Lars Franzén, Per Nilsson

Summary

Background Hypofractionated radiotherapy for prostate cancer has gained increased attention due to its proposed high radiation-fraction sensitivity. Recent reports from studies comparing moderately hypofractionated and conventionally fractionated radiotherapy support the clinical use of moderate hypofractionation. To date, there are no published randomised studies on ultra-hypofractionated radiotherapy. Here, we report the outcomes of the Scandinavian HYPO-RT-PC phase 3 trial with the aim to show non-inferiority of ultra-hypofractionation compared with conventional fractionation.

Methods In this open-label, randomised, phase 3 non-inferiority trial done in 12 centres in Sweden and Denmark, we recruited men up to 75 years of age with intermediate-to-high-risk prostate cancer and a WHO performance status between 0 and 2. Patients were randomly assigned to ultra-hypofractionation (42·7 Gy in seven fractions, 3 days per week for 2·5 weeks) or conventional fractionated radiotherapy (78·0 Gy in 39 fractions, 5 days per week for 8 weeks). No androgen deprivation therapy was allowed. The primary endpoint was time to biochemical or clinical failure, analysed in the per-protocol population. The prespecified non-inferiority margin was 4% at 5 years, corresponding to a critical hazard ratio (HR) limit of 1·338. Physician-recorded toxicity was measured according to the Radiation Therapy Oncology Group (RTOG) morbidity scale and patient-reported outcome measurements with the Prostate Cancer Symptom Scale (PCSS) questionnaire. This trial is registered with the ISRCTN registry, number ISRCTN45905321.

Findings Between July 1, 2005, and Nov 4, 2015, 1200 patients were randomly assigned to conventional fractionation (n=602) or ultra-hypofractionation (n=598), of whom 1180 (591 conventional fractionation and 589 ultra-hypofractionation) constituted the per-protocol population. 1054 (89%) participants were intermediate risk and 126 (11%) were high risk. Median follow-up time was 5·0 years (IQR 3·1–7·0). The estimated failure-free survival at 5 years was 84% (95% CI 80–87) in both treatment groups, with an adjusted HR of 1·002 (95% CI 0·758–1·325; log-rank p=0·99). There was weak evidence of an increased frequency of acute physician-reported RTOG grade 2 or worse urinary toxicity in the ultra-hypofractionation group at end of radiotherapy (158 [28%] of 569 patients *vs* 132 [23%] of 578 patients; p=0·057). There were no significant differences in grade 2 or worse urinary or bowel late toxicity between the two treatment groups at any point after radiotherapy, except for an increase in urinary toxicity in the ultra-hypofractionation group compared to the conventional fractionation group at 1-year follow-up (32 [6%] of 528 patients *vs* 13 [2%] of 529 patients; (p=0·0037). We observed no differences between groups in frequencies at 5 years of RTOG grade 2 or worse urinary toxicity (11 [5%] of 243 patients for the ultra-hypofractionation group *vs* 12 [5%] of 249 for the conventional fractionation group; p=1·00) and bowel toxicity (three [1%] of 244 patients *vs* nine [4%] of 249 patients; p=0·14). Patient-reported outcomes revealed significantly higher levels of acute urinary and bowel symptoms in the ultra-hypofractionation group compared with the conventional fractionation group but no significant increases in late symptoms were found, except for increased urinary symptoms at 1-year follow-up, consistent with the physician-evaluated toxicity.

Interpretation Ultra-hypofractionated radiotherapy is non-inferior to conventionally fractionated radiotherapy for intermediate-to-high risk prostate cancer regarding failure-free survival. Early side-effects are more pronounced with ultra-hypofractionation compared with conventional fractionation whereas late toxicity is similar in both treatment groups. The results support the use of ultra-hypofractionation for radiotherapy of prostate cancer.

Funding The Nordic Cancer Union, the Swedish Cancer Society, and the Swedish Research Council.

Introduction

In 2018, the estimated number of new prostate cancer cases was 164 700 in the USA[1] and 450 000 in Europe.[2] Many of these patients were treated with external beam radiotherapy and hence they use a large part of today's radiotherapy resources.

For many years, the standard regimen for intermediate-risk and high-risk prostate cancer treated with external

Lancet 2019; 394: 385–95

Published Online June 18, 2019 http://dx.doi.org/10.1016/S0140-6736(19)31131-6

See Comment page 361

Department of Radiation Sciences, Oncology (Prof A Widmark MD, C Thellenberg-Karlsson MD, B Tavelin BSc, D Norman BSc, Prof B Zackrisson MD, Prof L Franzén MD) **and Department of Nursing** (P Fransson PhD), **Umeå University, Umeå, Sweden; Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital** (A Gunnlaugsson MD, E Kjellén MD, Per Nilsson PhD) **and Department of Clinical Sciences Lund, Cancer Epidemiology** (H Anderson PhD), **Lund University, Lund, Sweden; Department of Oncology, Sundsvall Hospital, Sundsvall, Sweden** (L Beckman MD); **Department of Oncology and Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark** (Prof M Hoyer MD); **Department of Oncology, Kalmar Hospital, Kalmar, Sweden** (M Lagerlund MD); **Department of Oncology, Institute of Clinical Sciences, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden** (J Kindblom MD); **Department of Oncology, Karlstad Central Hospital, Karlstad, Sweden** (C Ginman MD); **Department of Oncology, Örebro University Hospital, Örebro University, Örebro, Sweden** (B Johansson MD); **Department of Oncology, Ryhov Hospital, Jönköping, Sweden** (K Björnlinger MD); **Department of Oncology, Centrallasarettet, Växjö, Sweden** (M Seke MD);

and Department of Oncology,Linköping University Hospital, Linköping, Sweden
(M Agrup MD)

Correspondence to:
Prof Anders Widmark, Department of Radiation Sciences, Oncology, Umeå University, Umeå SE-90185, Sweden
anders.widmark@onkologi.umu.se

Research in context

Evidence before this study

Before the start of this trial, a search of the literature (PubMed with search terms "prostate cancer" AND "radiotherapy" AND "hypofractionation") covering Jan 1, 1990, to March 31, 2005, revealed no studies comparing ultra-hypofractionation and conventional fractionation. Since the start of the HYPO-RT-PC trial, several large randomised trials have independently and in meta-analyses shown that moderately fractionated radiotherapy is safe and shows similar tumour control to conventional fractionation. This has resulted in a rapid change of standard practice. No randomised clinical trials comparing ultra-hypofractionated radiotherapy—ie, schedules with doses per fraction greater than 5 Gy—with either moderate or conventional fractionation were retrieved in an updated search of literature (to Dec 1, 2018).

Added value of this study

The HYPO-RT-PC trial is, to our knowledge, the first randomised treatment study comparing ultra-hypofractionated with conventionally fractionated radiotherapy in men with intermediate-to-high-risk prostate cancer. We tested experimental ultra-hypofractionation using 6·1 Gy per fraction to a total dose of 42·7 Gy delivered every other day in 2·5 weeks compared with standard conventional fractionation using 2 Gy per fraction to a total dose of 78 Gy in 8 weeks, and found that ultra-hypofractionation is non-inferior to standard fractionated radiotherapy in terms of failure-free survival. As expected, due to the short overall treatment time for ultra-hypofractionation, both physician-recorded and patient-reported acute toxicity was more intense compared with conventional fractionation. However, late toxicity was similar in both treatment arms.

Implications of all the available evidence.

The outcomes of the HYPO-RT-PC trial are specifically relevant for patients with intermediate-risk disease because there were few high-risk patients in the trial. Our results support the use of image-guided ultra-hypofractionated radiotherapy for prostate cancer. Cohort studies suggest that extreme hypofractionation leads to promising progression-free survival and acceptable morbidity and the present study confirms these findings. There is now enough evidence from several large trials to suggest that conventional fractionation for intermediate-risk prostate cancer can be considered unconventional. Hypofractionation will benefit the health-care system by lowering treatment costs and the patients by shortening treatment time. However, sophisticated image guidance of treatment is probably a prerequisite. The same conclusion is not valid for high-risk patients owing to a lack of studies and, perhaps, a different biology. The small proportion of high-risk patients in our study does not allow any conclusions on hypofractionation for this risk group but the results motivate further studies.

beam radiotherapy has been conventional fractionation—ie, schedules delivered with 1·8–2·0 Gy fractions to a typical total dose of 74–78 Gy. Several reports have suggested that prostate cancer has a high fractionation sensitivity often expressed numerically as a low α/β ratio in the linear-quadratic formalism. The α/β ratio might potentially be even lower than for late normal tissue reactions.[3–5] If true, hypofractionation could increase the therapeutic ratio as well as reduce health-care costs and improve patient comfort.[6] Hypofractionation is generally categorised as moderate hypofractionation and ultra-hypofractionation with fraction sizes in the range of 2·4–3·4 Gy and at least 5 Gy, respectively.[7] The latter is also referred to as extreme hypofractionation, stereotactic body radiation therapy, or stereotactic ablative radiotherapy.[7]

Several recent large randomised phase 3 trials evaluating moderate hypofractionation versus conventional fractionation have shown similar efficacy and toxicity for moderate and conventional fractionation.[8–11] A pooled analysis of 1100 patients treated with ultra-hypofractionation (ie, stereotactic body radiation therapy) in eight prospective non-randomised phase 2 trials reported promising results regarding both biochemical relapse-free survival and toxicity.[12] To date, however, there are no published randomised trials that evaluate ultra-hypofractionation for localised prostate cancer. To address this, the prospective Scandinavian HYPO-RT-PC multicentre randomised phase 3 trial was initiated. This trial compares the effectiveness and tolerability of image-guided ultra-hypofractionation and conventional fractionation external beam radiotherapy without addition of androgen deprivation therapy for patients with intermediate-risk to high-risk prostate cancer. The aim of the study was to show that ultra-hypofractionation is non-inferior to conventional fractionation regarding failure-free survival without any significant differences in late normal tissue complications.

For the **study protocol** see https://www.umu.se/en/research/groups/hypo-rt-pc

Methods

Study design and participants

The HYPO-RT-PC study is an open-label, randomised, multicentre, phase 3 trial done in 12 centres in Sweden and Denmark. The study was approved in Sweden by the Ethics Committee in Umeå (03-513, 2003-12-23) and in Denmark by the Central Denmark Region Committees on Health Research Ethics (M-20090180, 2009-11-19). Trial data were collected at the study secretariat in Umeå except for radiotherapy data. The study protocol is available online.

Participants were men up to 75 years of age with histologically verified intermediate-to-high-risk prostate cancer and WHO performance status between 0 and 2. Intermediate-to-high-risk prostate cancer was categorised according to the TNM classification system as T1c–T3a

with no evidence of lymph node involvement or distant metastases with one or two of the following risk factors: stage T3a, Gleason score of at least 7, or prostate-specific antigen (PSA) of at least 10 ng/mL. The maximum PSA allowed was 20 ng/mL and no androgen deprivation therapy was permitted. All participants provided written and verbal informed consent.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to either conventional fractionation or ultra-hypofractionation. Treatment allocation could not be blinded to patients or to clinicians. However, biochemical relapse was assessed blindly. The randomisation was centralised using a minimisation algorithm balancing the factors trial centre, T stage (T1c–T2 *vs* T3a), Gleason score (2–6 *vs* 7 *vs* 8–10), and PSA (≤10 *vs* >10).

Procedures

Radiotherapy was delivered with image-guided three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, or volumetric modulated arc therapy with use of fiducial markers. The BeamCath technique[13] was initially used (10% of participants), but this technique was subsequently replaced by implanted gold fiducial markers. The clinical target volume (CTV) was defined as the prostate only; hence, seminal vesicles were not included in the target volume. The CTV delineation was done on the CT images. T2w-MRI, co-registered to the CT images with aid of the fiducials, was recommended but not mandatory. The CTV–planning target volume (PTV) margin was 6 mm (4 mm towards the rectum) with the BeamCath technique. It was used for all fractions in the ultra-hypofractionation group and for the first four fractions in the conventional fractionation group, while the remaining fractions in this group were delivered without the BeamCath but with wider (10–15 mm) margins. For patients treated with implanted gold fiducial markers an isotropic CTV–PTV margin of 7 mm was used for all fractions in both treatment groups. The rectum, anal canal, urinary bladder, penile bulb, and femoral heads were delineated as organs at risk.

Patients in the conventional fractionation group received 78·0 Gy in 39 fractions (5 days per week for 8 weeks) whereas patients in the ultra-hypofractionation arm received 42·7 Gy in seven fractions (3 days per week for 2·5 weeks inclusive of two weekends), prescribed as the mean PTV dose. The treatment schedules were designed to be equi-effective for late normal tissue complication probability under the linear-quadratic model ($\alpha/\beta=3$ Gy). The priority list of dose-volume objectives and constraints for treatment plan optimisation is shown in the appendix (p 2).

Before entering the trial, each centre did dummy runs on structure delineation and treatment planning. Treatment plans were collected in DICOM-RT format for each patient after completion of treatment and sent to the quality assurance office (Radiation Physics, Lund University Hospital, Lund) for evaluation. External monitoring of treatment planning data was done on all cases. The results were communicated to the trial centre for feedback and to ensure compliance to the protocol.

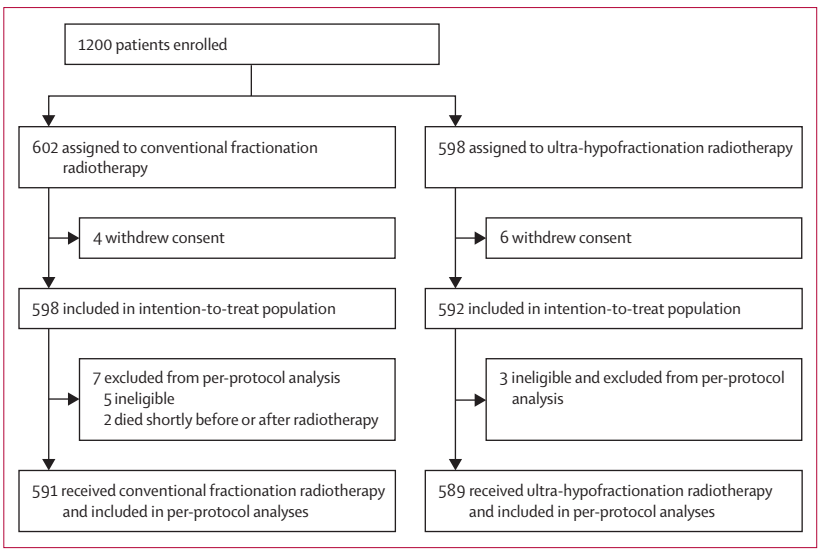

Figure 1: **Trial profile**

Pre-treatment risk assessment included PSA and a Union for International Cancer Control (UICC) staging by digital rectal examination. Patients with T1c–T2 tumours and Gleason score of 7 were considered to be node negative or non-metastasised, whereas high-risk patients (T3a or Gleason score ≥8) were recommended a CT or bone scan staging, with optional open or laparoscopic lymph node staging. The patients were followed up at the end of radiotherapy; at 3, 6, 9, and 12 months after start of treatment; and subsequently every 6 months. Patient-reported outcomes were assessed with the validated Prostate Cancer Symptom Scale (PCSS),[14–16] the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 (EORTC QLQ-C30),[17] and the International Index of Erectile Function 5 (IIEF-5)[18] with outcomes measured at baseline; at end of radiotherapy; at 3, 6, 12, and 24 months after radiotherapy; and every other year thereafter.

Outcomes

The primary endpoint was PSA relapse, clinical failure, or both. The primary outcome measure was failure-free survival—ie, time from randomisation to biochemical or clinical failure. PSA progression was defined according to the Radiation Therapy Oncology Group (RTOG) and American Society for Radiation Oncology's Phoenix definition as nadir plus 2·0 ng/mL.[19] To discriminate PSA bounce from a true PSA recurrence, endocrine therapy at progression was not recommended until PSA reached 10 ng/mL. Biochemical relapse was assessed centrally and blindly with respect to randomisation arm. Clinical

See Online for appendix

	Conventional fractionation (n=591)	Ultra-hypofractionation (n=589)
Age, years	69 (65–72)	68 (64–72)
PSA, ng/mL*		
Median (IQR)	8·6 (5·7–12·0)	8·7 (6·0–12·2)
≤10 ng/mL	356 (60%)	357 (61%)
>10 ng/mL	235 (40%)	232 (39%)
Gleason score*		
5	2 (<1%)	5 (1%)
6	106 (18%)	99 (17%)
7	444 (75%)	447 (76%)
8	37 (6%)	33 (6%)
9	2 (<1%)	5 (1%)
Clinical T stage*		
T1c	289 (49%)	313 (53%)
T2	275 (47%)	252 (43%)
T3a	27 (5%)	24 (4%)
Risk group		
Intermediate risk	527 (89%)	527 (89%)
High risk†	64 (11%)	62 (11%)
Time from randomisation to start of radiotherapy, weeks	3 (1–6)	3 (1–6)
Radiotherapy prescribed and delivered		
Total dose, Gy	78·0 (78·0–78·0)	42·7 (42·7–42·7)
Radiotherapy fractions received	39/39 (100%)	7/7 (100%)
Total radiotherapy treatment time, days	57 (55–59)	16 (15–17)
Radiotherapy technique		
3DCRT	471 (80%)	471 (80%)
VMAT/IMRT	120 (20%)	118 (20%)
Image-guided radiotherapy technique		
BeamCath	61 (10%)	61 (10%)
Fiducial markers	530 (90%)	528 (90%)

Data are n (%) or median (IQR). PSA=prostate-specific antigen. 3DCRT=three-dimensional conformal radiotherapy. VMAT/IMRT=volumetric-modulated arc therapy or intensity-modulated radiotherapy. *Stratification variables: PSA (≤10 *vs* >10), Gleason score (2–6 *vs* 7 *vs* 8–10), and T stage (T1c–T2 *vs* T3a). †T3a or Gleason ≥8.

Table: **Baseline demographics, clinical characteristics, and radiotherapy details for the per-protocol population**

failure could be either local or distant progression. Local progression was defined as a tumour-induced change in urinary symptoms (frequency, urgency, and obstructions) of such magnitude that a change of treatment was necessary (ie, transurethral resection of the prostate or castration). Distant progression was defined as detection of metastases by x-ray, bone scan, CT, or ultrasound examinations.

Secondary endpoints were biochemical disease-free survival, clinical disease-free survival, prostate cancer-specific survival, overall survival, proportion of patients achieving PSA response, time to change of treatment (ie, commencement of androgen deprivation), quality of life, and toxicity.

Physician's evaluation of urinary and bowel toxicity was done according to the RTOG morbidity scale.[20] Patient-reported urinary and bowel problems and sexual function were evaluated with the validated PCSS questionnaire.[14–16] This comprises questions with a response scale from 0 ("no problem/very good function") to 10 ("many problems/very bad function"). Here, we report data from the general PCSS questions on urinary and bowel problems and sexual function while extended results from the PCSS, EORTC QLQ-C30, and IIEF-5 questionnaires will be reported separately.

Statistical analysis

The trial was originally designed as a superiority study that aimed to show a 10% absolute increase (from 70% to 80%) in failure-free survival at 5 years for ultra-hypofractionation compared with conventional fractionation. Assuming proportional hazards, a one-sided significance level of $\alpha=0{\cdot}025$, and 80% power, 148 primary events were required.[21] To reach 148 events within a reasonable time, 800 patients were to be randomised.

In a blinded interim analysis, overall failure-free survival was estimated to be 87% at 5 years. This fact and new results from recently published studies made the initial assumptions unrealistic. Taking into consideration that ultra-hypofractionation has many advantages over conventional fractionation for patients and caregivers, it was deemed sufficient to show that ultra-hypofractionation is non-inferior to conventional fractionation, which required the extension of the sample size to 1200 participants. To conclude non-inferiority, we prespecified a margin of 4% at 5 years (from 87% in conventional fractionation to 83% in ultra-hypofractionation) corresponding to a critical hazard ratio (HR) of 1·338 (one-sided $\alpha=0{\cdot}025$). After determining the power function for different values of 5-year failure-free survival by simulation, it was decided to continue until 162 events had been reached. If the true 5-year failure-free survival is slightly better in the ultra-hypofractionation arm (ie, 88% *vs* 87%), the probability of obtaining a non-inferiority outcome then is 70%, which was judged acceptable.

Median follow-up time was calculated with the reverse Kaplan-Meier method. The primary outcome was analysed in the per-protocol population. A complementary analysis was to be done in the intention-to-treat (ITT) population and if non-inferiority was reached, superiority was to be tested. For the primary endpoint, the treatment groups were compared by means of a Cox proportional hazards model adjusted by stratification for the randomisation minimisation factors PSA, Gleason score, and T stage. Trial centre was adjusted for as a categorical factor. Otherwise the Cox analyses were non-adjusted. To evaluate the consistency of results, we did post-hoc tests for interaction of treatment with various clinical subgroups. All HRs were based on the whole follow-up and

proportional hazards assumptions were tested by Schoenfeld residuals tests. The Kaplan-Meier method was used to illustrate event rates and the log-rank test was used to compare treatment groups. Cumulative incidence functions for failure-free survival and prostate cancer-specific survival were estimated with non-prostate cancer death as a competing event and compared by means of Gray's test. Late side-effects were defined as those appearing more than 6 months after start of radiotherapy. Time to first late side-effect was calculated from start of radiotherapy; patients with no events were censored at last follow-up and event rates were summarised by Kaplan-Meier curves and compared by log-rank tests. Fisher's exact test was used to compare proportions. Patient-reported problems were presented as mean values with 95% CI, and the Wilcoxon rank sum test, adjusted for ties, was used to compare treatment groups. Analyses were based on the study database as of Nov 23, 2017.

Statistical calculations were done using R version 3.4.3, the IBM SPSS Statistics version 24, and Stata Statistical Software: Release 11. The HYPO-RT-PC trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN45905321.

Role of the funding source

The funders of the trial had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication. BT, PF, and PN also had full access to the data.

Results

Between July 1, 2005, and Nov 4, 2015, 1200 patients from the 12 centres were randomly assigned to either conventional fractionation (n=602) or ultra-hypofractionation (n=598; appendix p 3). Ten patients withdrew their consent, eight were found ineligible for the trial, and two died (unrelated to prostate cancer) just before or after radiotherapy (figure 1). All other patients received the prescribed radiotherapy within the allowed timeframes specified by the trial protocol. Hence these 1180 patients (591 conventional fractionation and 589 ultra-hypofractionation) constituted the per-protocol population. The ITT population differs by ten patients (1%) from the per-protocol population; because these patients also lack follow-up data, all analyses were done on the per-protocol population.

Baseline characteristics appeared well balanced between the trial groups, with the majority of patients having intermediate-risk prostate cancer (table).

After a median follow-up time of 5·0 years (IQR 3·1–7·0), 102 primary events (biochemical or clinical failure) had occurred in the conventional fractionation group and 100 in the ultra-hypofractionation group. Across both treatment groups, PSA relapse was detected in 193 patients, local recurrences in six patients, and distant metastases in three patients as a first primary event, with each event equally distributed between the groups. Failure-free survival at 5 years was 84% (95% CI 80–87) in the ultra-hypofractionation group and 84% (80–87) in the conventional fractionation group (log-rank p=0·99; figure 2). The cumulative incidence of primary events, analysed with non-prostate cancer death as competing risk, was 16% (95% CI 13–20) at 5 years in both treatment groups (Gray's test p=0·95; appendix p 7).

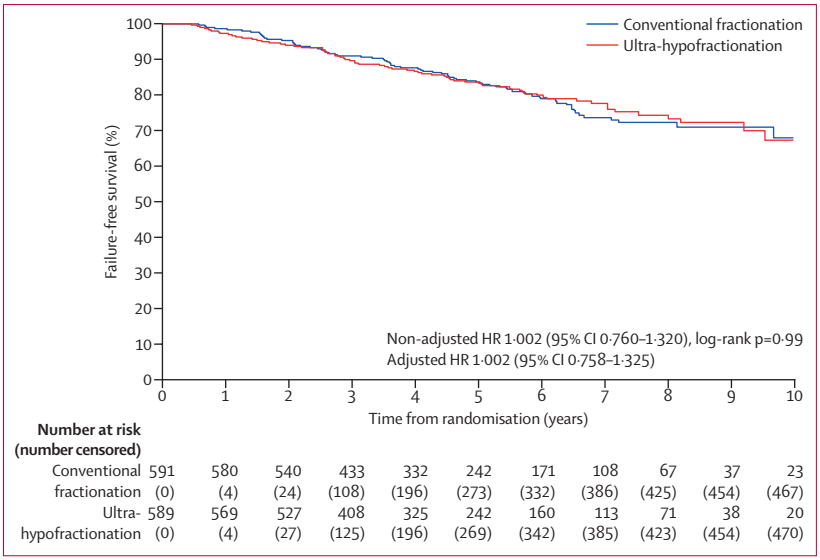

Figure 2: **Failure-free survival**
HR=hazard ratio.

Given our critical non-inferiority HR limit (1·338), ultra-hypofractionation was found to be non-inferior to conventional fractionation (adjusted HR 1·002, 95% CI 0·758–1·325). The proportional hazards conditions were fulfilled here and in all other Cox regression analyses. During the follow-up period, 19 patients (eight in the conventional fractionation group and 11 in the ultra-hypofractionation group) died due to prostate cancer and 70 patients (35 in either treatment group) died due to other causes. There was no significant difference in overall survival at 5 years between the treatment arms (94% [95% CI 92–96] in the ultra-hypofractionation group *vs* 96% [95–98] in the conventional fractionation group; HR 1·11, 95% CI 0·73–1·69; appendix p 8). The cumulative incidence of prostate cancer death at 5 years, analysed with non-prostate cancer death as competing risk, was less than 1% (95% CI 0–1) in the conventional fractionation arm and 2% (1–4) in the ultra-hypofractionation arm (Gray's test p=0·46; appendix p 9). No significant differences were found for outcomes for other survival and treatment failure endpoints (appendix p 4).

Post-hoc subgroup analyses of failure-free survival showed no significant interactions between clinical factors (age, Gleason score, T stage, PSA, and risk group) and treatment group (appendix p 10).

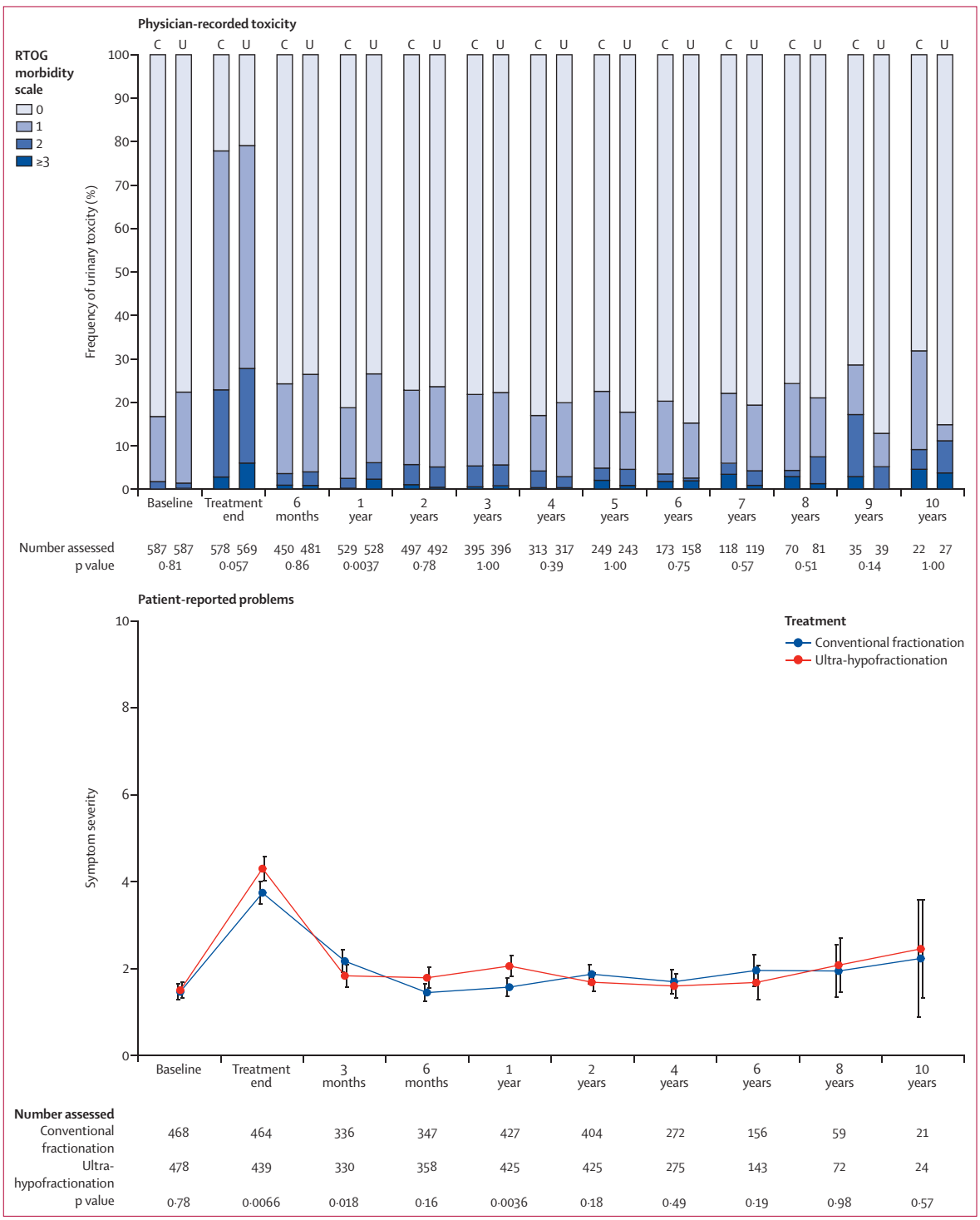

Figure 3: **Urinary toxicity and patient-reported problems**

Physician-recorded urinary toxicity was measured according to the RTOG morbidity scale; p values correspond to comparisons of grade 2 or worse toxicities by treatment group, by Fisher's exact test. The corresponding patient-reported problem was measured with the question "Do you have problems with your urinary tract?" in the PCSS questionnaire; higher values indicate more symptoms. The Wilcoxon rank sum test, adjusted for ties, was used for comparisons between treatment groups. C=conventional fractionation. U=ultra-hypofractionation. RTOG=Radiation Therapy Oncology Group. PCSS=Prostate Cancer Symptom Scale.

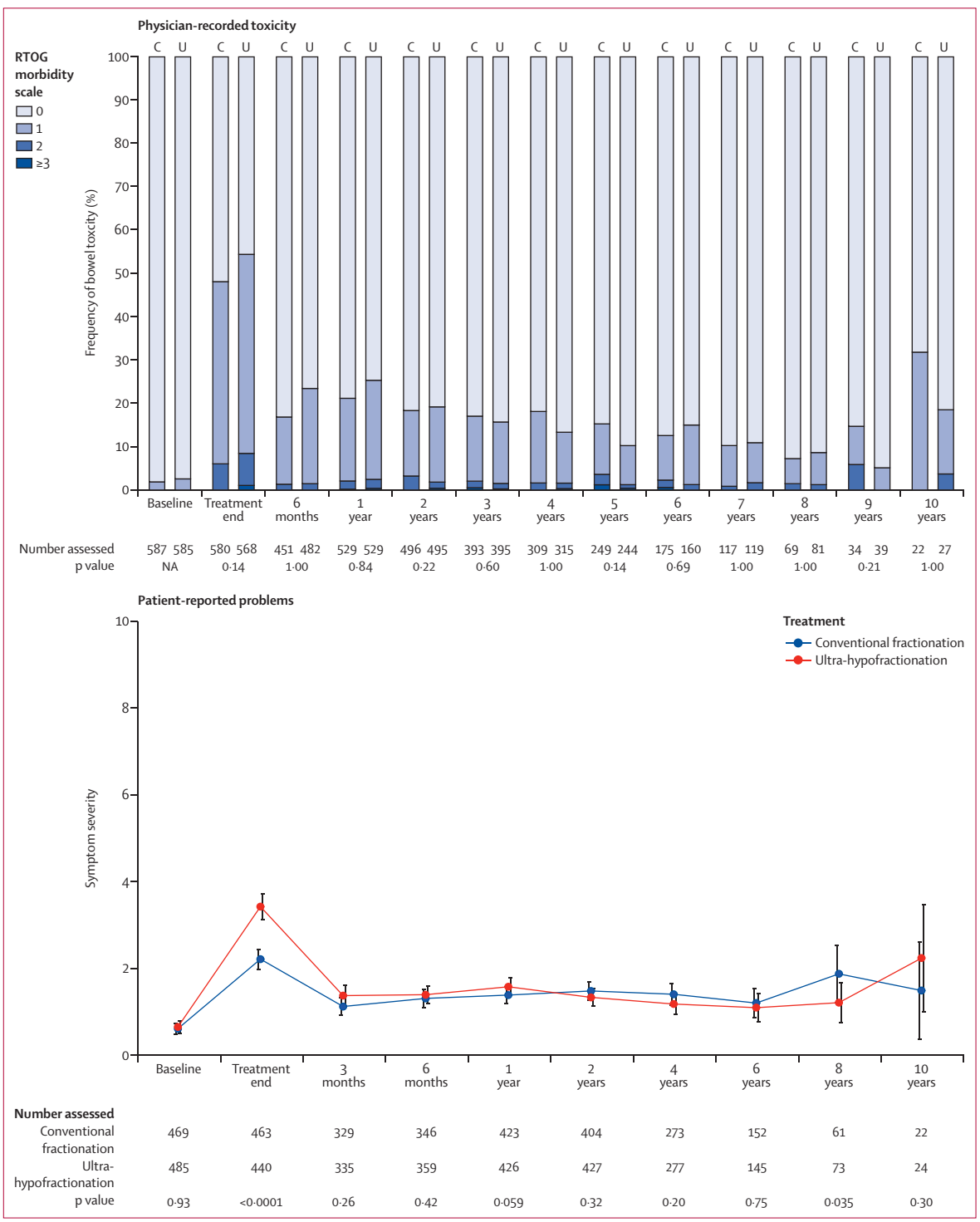

Figure 4: **Bowel toxicity and patient-reported problems**
Physician-recorded bowel toxicity was measured according to the RTOG morbidity scale; p values correspond to comparisons of grade 2 or worse toxicities by treatment group, by Fisher's exact test. The corresponding patient-reported problem was measured with the question "Do you have problems with your stool?" in the PCSS questionnaire; higher values indicate more symptoms. The Wilcoxon rank sum test, adjusted for ties, was used for comparisons between treatment groups. C=conventional fractionation. U=ultra-hypofractionation. RTOG=Radiation Therapy Oncology Group. PCSS=Prostate Cancer Symptom Scale.

We found weak evidence of a higher frequency of acute grade 2 or worse urinary toxicity in the ultra-hypofractionation group at end of radiotherapy compared with the conventional fractionation group (158 [28%] of 569 patients *vs* 132 [23%] of 578 patients; figure 3). There were no significant differences in grade 2 or worse

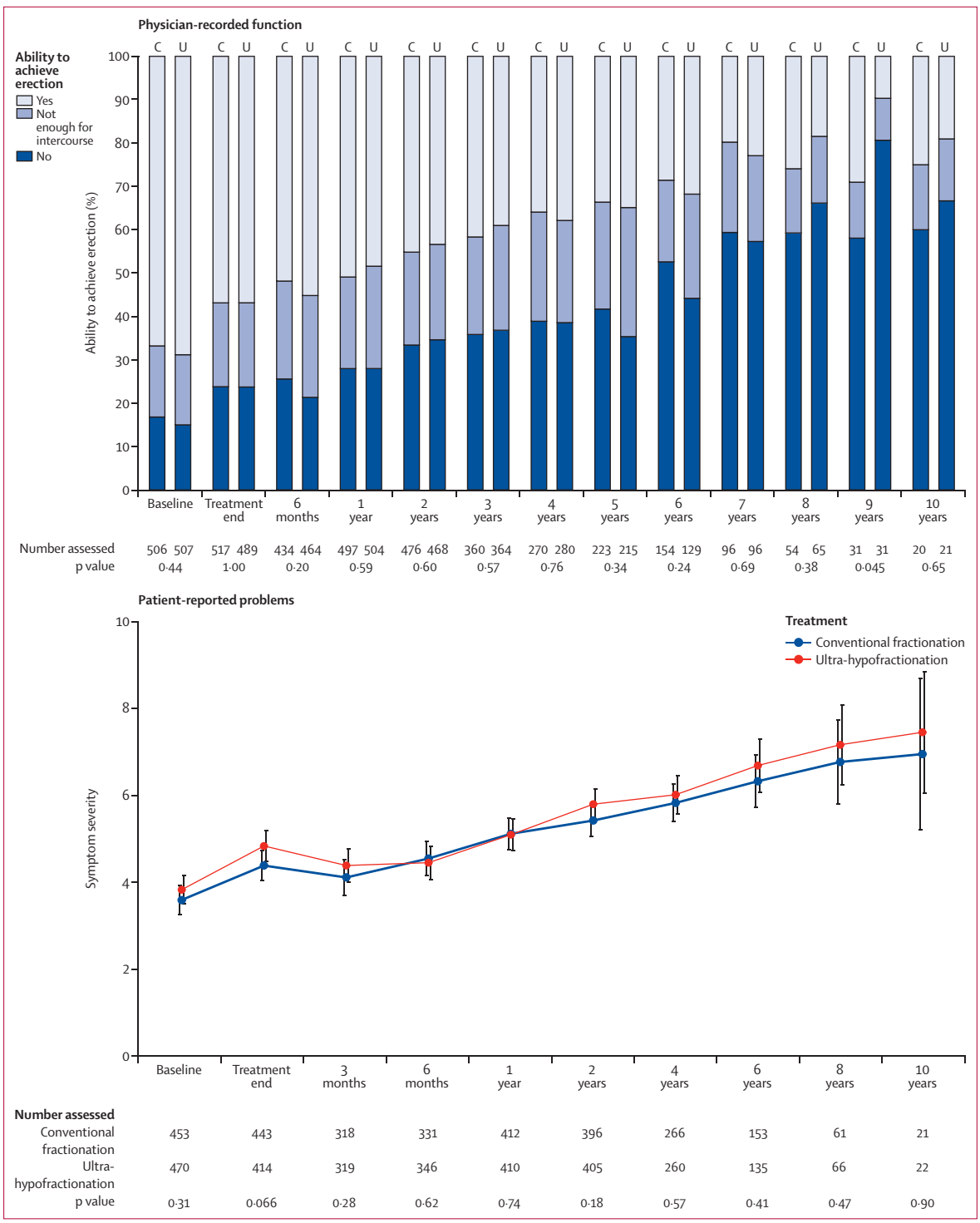

Figure 5: **Erectile function and patient-reported problems**

Physician-recorded erectile function was measured as ability to achieve erection. The corresponding patient-reported problem was measured with the question "Can you get an erection without aids?" in the PCSS questionnaire; higher values indicate worse function. The Wilcoxon rank sum test, adjusted for ties, was used for comparisons between treatment groups. C=conventional fractionation. U=ultra-hypofractionation. PCSS=Prostate Cancer Symptom Scale.

urinary or bowel toxicity between the two treatment groups at any point after radiotherapy, except for an increase in urinary toxicity at 1-year follow-up in the ultra-hypofractionation group compared with the conventional fractionation group (32 [6%] of 528 patients *vs* 13 [2%] of 529 patients; figures 3, 4). The frequency at 5-year follow-up of grade 2 or worse urinary toxicity was 5% (11/243) for ultra-hypofractionation and 5% (12/249) for conventional fractionation, whereas frequencies for bowel toxicity were 1% (3/244) and 4% (9/249), respectively (figures 3, 4). Erectile function decreased from almost 70% at start of radiotherapy to 35% at 5 years, with no significant difference between the two treatment groups (figure 5).

The estimated physician-recorded cumulative late urinary grade 2 or worse toxicity was 13% (95% CI 11–16) for ultra-hypofractionation and 9% (7–12) for conventional fractionation at 2-year follow-up and 18% (15–22) and 17% (14–20) at 5-year follow-up, respectively (figure 6). The corresponding figures for cumulative late bowel grade 2 or worse toxicity were 6% (5–9) in the ultra-hypofractionation group and 5% (4–8) in the conventional fractionation group at 2-year follow-up and 10% (7–13) in both groups at 5-year follow-up (figure 6). Further details on late urinary and bowel toxicities are presented in the appendix (pp 5–6, 11–12).

Patients in the ultra-hypofractionation group reported significantly higher levels of acute urinary and bowel symptoms (ie, at end of radiotherapy; figures 3, 4). No significant increases in late symptoms were found, except for increased urinary problems at 1-year follow-up in the ultra-hypofractionation group (mean score 2·06, 95% CI 1·82–2·30) compared with the conventional fractionation arm (1·58, 1·37–1·78), in line with the physician-evaluated toxicity. Our results show a decrease at 8-year follow-up in patient-reported bowel problems in the conventional fractionation group compared with the ultra-hypofractionation group; however, this decrease is not confirmed in the physician-reported toxicity for this same year of follow-up, nor were any significant differences in toxicities or patient-reported problems observed in the surrounding years of follow-up. No significant difference in patient-reported erectile function was observed between the treatment groups (figure 5).

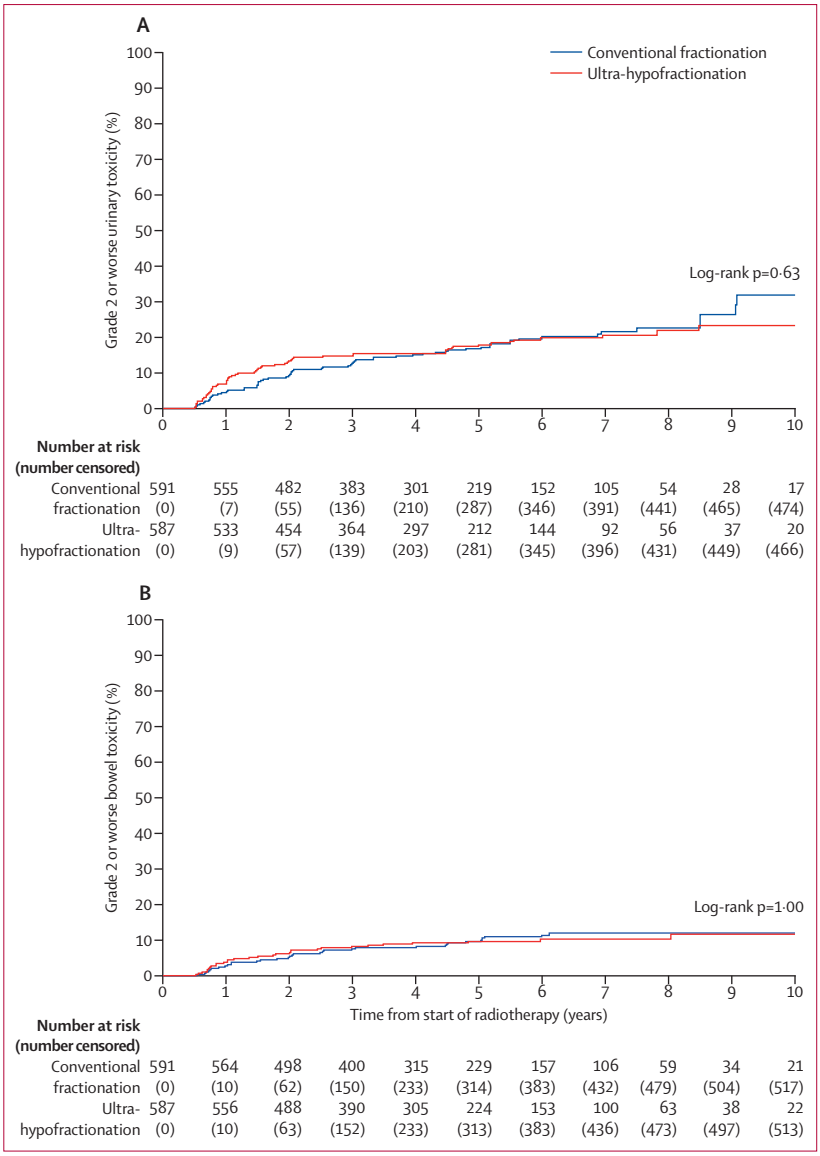

Figure 6: **Cumulative incidence of physician-reported late urinary and bowel toxicity of grade 2 or worse**
Urinary (A) and bowel (B) toxicities were measured according to the RTOG morbidity scale. RTOG=Radiation Therapy Oncology Group.

Discussion

To our knowledge, the present study is the first randomised trial to report on the efficacy and side-effects of ultra-hypofractionation compared with conventional fractionation for prostate cancer. In this adequately powered clinical trial, we found that the ultra-hypofractionation radiotherapy schedule of 42·7 Gy in seven fractions (3 days per week for 2·5 weeks inclusive of two weekends) was non-inferior (4% margin in failure-free survival at 5 years) to a standard regimen of 78·0 Gy in 39 fractions (5 days per week for 8 weeks) in regards to failure-free survival for intermediate-to-high-risk prostate cancer.

Four published randomised trials, comprising three non-inferiority studies (CHHiP,[8] NRG Oncology RTOG 0415,[10] and PROFIT[11]) and one superiority study (HYPRO[9]), have compared conventional fractionation and moderate hypofractionation radiotherapy for prostate cancer.[8–11] Overall, they show that moderate hypofractionation is safe and results in disease control that is comparable to that achieved with conventional fractionation radiotherapy; these studies have changed clinical practice in many American and European centres. Two relatively large prospective non-randomised studies[22,23] comparing conventional fractionation and ultra-hypofractionation

(five fractions) found high biochemical control and low toxicities in these exclusively low-risk prostate cancer populations. A 2018 evidence-based guideline[7] from the American Society for Radiation Oncology, the American Society for Clinical Oncology, and the American Urological Association now recommends that moderate hypofractionation should be offered to all patients who choose external beam radiotherapy for treatment of localised prostate cancer, independent of risk group. Their recommendation for ultra-hypofractionation is graded as "conditional" until evidence is available from randomised studies.

The 5-year failure-free survival of our trial, which was comprised of 89% intermediate-risk patients and 11% high-risk patients, was almost identical in the treatment groups (84% in both groups; adjusted HR 1·002, 95% CI 0·758–1·325; log-rank p=0·99) and was comparable to the outcome of the moderate hypofractionation trials.

We found a strong correlation between physician-evaluated toxicity and patient-reported problems. Early side-effects were more pronounced in ultra-hypofractionation than in conventional fractionation. This is probably mainly due to the accelerated ultra-hypofractionation schedule, with its total dose delivered in 2·5 weeks compared with 8 weeks in the conventional fractionation group. The CHHiP,[8] PROFIT,[11] and HYPRO[9] trials also reported increased acute gastrointestinal toxicity with moderate hypofractionation compared to conventional fractionation.

The HYPO-RT-PC trial showed low and similar frequencies of physician-recorded toxicity and patient-reported late bowel and urinary problems in the ultra-hypofractionation and conventional fractionation groups, with the exception of a second significant increase in urinary side effects for ultra-hypofractionation at 1 year after start of radiotherapy. In comparison, the 2-year patient-reported data from the CHHiP trial[8] showed a small decline in patient-reported urinary function at 18 months. In a prospective stereotactic body radiation therapy study, delivering 35·00–36·25 Gy in five fractions, Katz and Kang[24] found a median time to development of late urinary problems of 18 months and return to baseline at 2 years, remaining stable thereafter. In the present study, the cumulative incidence of grade 2 or worse urinary and bowel toxicities at 5 years (appendix pp 5–6) was similar to the data in the PROFIT trial[11] but lower than in the HYPRO[9] and NRG Oncology 0415[10] trials. Sexual dysfunction increased over time but was similar in both treatment schedules.

Given that the linear-quadratic concept is valid at ultra-hypofractionation fraction sizes,[25] the outcome of the HYPO-RT-PC study indicates an α/β ratio close to 3 Gy for both tumour and late normal tissue effects. As mentioned previously, the trial was designed to be equi-effective for this α/β value, disregarding any effects due to difference in total treatment time between the fractionation schedules. However, the equi-effectiveness is strictly valid only for the prescribed doses. A more detailed evaluation of the α/β ratio should consider the complete dose distribution. More information about the α/β ratio will hopefully be available when results from other ongoing randomised ultra-hypofractionation trials are completed—eg, the PACE trial (ISRCTN17627211), the HEAT trial (NCT01794403), and NRG GU005 trial (NCT03367702), which all compare 36·25 Gy in five fractions over 1–2 weeks with conventional fractionation or moderate hypofractionation.

There are a number of practical issues in the radiotherapy workflow that might negatively affect tumour control. The image guidance radiotherapy technique used in this study as well as in the moderate hypofractionation studies mentioned does not allow for position control during the fraction, which might lead to partial target misses due to internal motion. This risk is potentially more pronounced in the ultra-hypofractionation group due to its longer beam-on time per fraction. Additionally, a partial target miss is more severe in ultra-hypofractionation due to the reduced number of fractions delivered compared with conventional fractionation. These facts taken together might overestimate the apparent tumour α/β ratio.

The strengths of the HYPO-RT-PC trial include its large patient population (1200 patients recruited from 12 centres), the pure radiotherapy fractionation trial design without addition of hormonal therapy, and a very good compliance to allocated treatment. Comparing the outcome in the moderate hypofractionation studies using 6 months of castration treatment, with non-hormone trials such as the PROFIT[11] and HYPO-RT-PC trials, a 3–5% improvement in 5-year progression-free survival could be seen. Use of castration treatment induced poor (10%) recovery of potency.[8] A limitation of the HYPO-RT-PC study is the relatively short follow-up of 5 years; further follow-up is required to assess 10-year and 15-year outcomes and rule out any late emerging differences. Another limitation is that the high-risk subgroup only comprises 11% of the study population. These men would receive neoadjuvant and adjuvant androgen deprivation therapy under current recommendations and the outcome of this study might thus not be generalisable for the high-risk population. More research is needed in the high-risk group and the role of anti-hormone therapy remains to be elucidated in this treatment paradigm. We do not yet know what benefit, if any, exists with androgen deprivation therapy in the setting of ultra-hypofractionation. As this study has not addressed the issue of treatment duration, we also do not know the optimal fractionation scheduling of ultra-hypofractionation (eg, daily versus every other day), although it has been reported that three fractions per week versus daily fractions could decrease toxicity.[26] Furthermore, the use of the PCSS questionnaire has not been used in similar trials outside Scandinavia. It is not standardised and might not be comparable to other instruments. The questionnaire is, however, validated

for detecting quality of life among men with prostate cancer.[16]

In conclusion, we present the first randomised trial comparing ultra-hypofractionation to conventional fractionation in men with intermediate-to-high-risk prostate cancer. With a median follow-up of 5 years, we found that ultra-hypofractionation is non-inferior to conventional fractionation radiotherapy regarding failure-free survival. As expected, acute side-effects were more pronounced with ultra-hypofractionation while our results show that both physician-recorded and patient-reported bowel and urinary treatment-related late side-effects of ultra-hypofractionation are similar to those of conventional fractionation. The results are specifically relevant for patients with intermediate risk disease as there were few high-risk patients in the trial and no androgen deprivation therapy was used. Introduction of ultra-hypofractionation with image-guided radiotherapy techniques would offer added patient convenience and significantly reduced radiotherapy department workloads.

Contributors

AW was the principal investigator of the study. The concepts and design of the trial were done by AW, BZ, EK, LF and PN. The study was coordinated by AW, AG, LF, and PN, who also were members of the trial steering committee together with MH and ML. PN and EK were responsible for radiotherapy quality assurance and PF was responsible for patient-reported outcome measurements. BT, DN, PN, and HA did the statistical analyses. AW, AG, LB, CT-K, MH, ML, JK, CG, BJ, KB, MS, MA, BZ, EK, and LF were involved in patient recruitment and data collection. Data analysis and interpretation were done by PN, HA, BT, AG, and AW. AW wrote the first draft of the report with input from PN, PF, AG, JK, MH, ML, and LB. All authors reviewed the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Patient data will not be available because this was not a concern when the trial was conducted and the patients were not informed.

Acknowledgments

We acknowledge support of the Nordic Cancer Union, the Swedish Cancer Society and the Swedish Research Council. We thank the clinical staff and research nurses at the trial centres with special thanks to Kerstin Granberg for monitoring and Eva Englund for collecting radiotherapy data. We would also like to thank the Safety Committee (Anders Ask, Roger Henriksson, and Björn Tavelin) and the Scientific Advisory Committee (Jonas Bergh and Lars Holmberg).

References

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; **68:** 7–30.

2 Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer* 2018; **103:** 356–87.

3 Brenner DJ. Fractionation and late rectal toxicity. *Int J Radiat Oncol Biol Phys* 2004; **60:** 1013–15.

4 Dasu A, Toma-Dasu I. Prostate alpha/beta revisited—an analysis of clinical results from 14168 patients. *Acta Oncol* 2012; **51:** 963–74.

5 Vogelius IR, Bentzen SM. Dose response and fractionation sensitivity of prostate cancer after external beam radiation therapy: a meta-analysis of randomized trials. *Int J Radiat Oncol Biol Phys* 2018; **100:** 858–65.

6 Zietman AL. Making radiation therapy for prostate cancer more economical and more convenient. *J Clin Oncol* 2016; **34:** 2323–24.

7 Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated radiation therapy for localized prostate cancer: an ASTRO, ASCO, and AUA evidence-based guideline. *J Clin Oncol* 2018; published online Oct 11. DOI:10.1200/JCO.18.01097.

8 Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016; **17:** 1047–60.

9 Incrocci L, Wortel RC, Alemayehu WG, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 2016; **17:** 1061–69.

10 Lee WR, Dignam JJ, Amin MB, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. *J Clin Oncol* 2016; **34:** 2325–32.

11 Catton CN, Lukka H, Gu CS, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. *J Clin Oncol* 2017; **35:** 1884–90.

12 King CR, Freeman D, Kaplan I, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol* 2013; **109:** 217–21.

13 Bergstrom P, Lofroth PO, Widmark A. High-precision conformal radiotherapy (HPCRT) of prostate cancer—a new technique for exact positioning of the prostate at the time of treatment. *Int J Radiat Oncol Biol Phys* 1998; **42:** 305–11.

14 Fransson P, Tavelin B, Widmark A. Reliability and responsiveness of a prostate cancer questionnaire for radiotherapy-induced side effects. *Support Care Cancer* 2001; **9:** 187–98.

15 Reidunsdatter RJ, Lund JA, Fransson P, Widmark A, Fossa SD, Kaasa S. Validation of the intestinal part of the prostate cancer questionnaire "QUFW94": psychometric properties, responsiveness, and content validity. *Int J Radiat Oncol Biol Phys* 2010; **77:** 793–804.

16 Hamoen EH, De Rooij M, Witjes JA, Barentsz JO, Rovers MM. Measuring health-related quality of life in men with prostate cancer: a systematic review of the most used questionnaires and their validity. *Urol Oncol* 2015; **33:** 69.e19–28.

17 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365–76.

18 Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 1999; **11:** 319–26.

19 Roach M 3rd, Hanks G, Thames H Jr, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006; **65:** 965–74.

20 Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995; **31:** 1341–46.

21 Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. *Stat Med* 1982; **1:** 121–29.

22 Musunuru HB, Quon H, Davidson M, et al. Dose-escalation of five-fraction SABR in prostate cancer: Toxicity comparison of two prospective trials. *Radiother Oncol* 2016; **118:** 112–17.

23 Loblaw A, Pickles T, Crook J, et al. Stereotactic ablative radiotherapy versus low dose rate brachytherapy or external beam radiotherapy: propensity score matched analyses of Canadian data. *Clin Oncol (R Coll Radiol)* 2017; **29:** 161–70.

24 Katz AJ, Kang J. Quality of life and toxicity after SBRT for organ-confined prostate cancer, a 7-year study. *Front Oncol* 2014; **4:** 301.

25 McMahon SJ. The linear quadratic model: usage, interpretation and challenges. *Phys Med Biol* 2018; **64:** 01TR.

26 King CR, Brooks JD, Gill H, Presti JC Jr. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; **82:** 877–82.