Register data on long-term morbidity after prostate ultra-hypofractionation in the HYPO-RT-PC trial

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THE LANCET

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

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- Open-label, randomized, phase 3 non-inferiority trial done in 12 centers in Sweden and Denmark
- The primary endpoint- 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
- 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.

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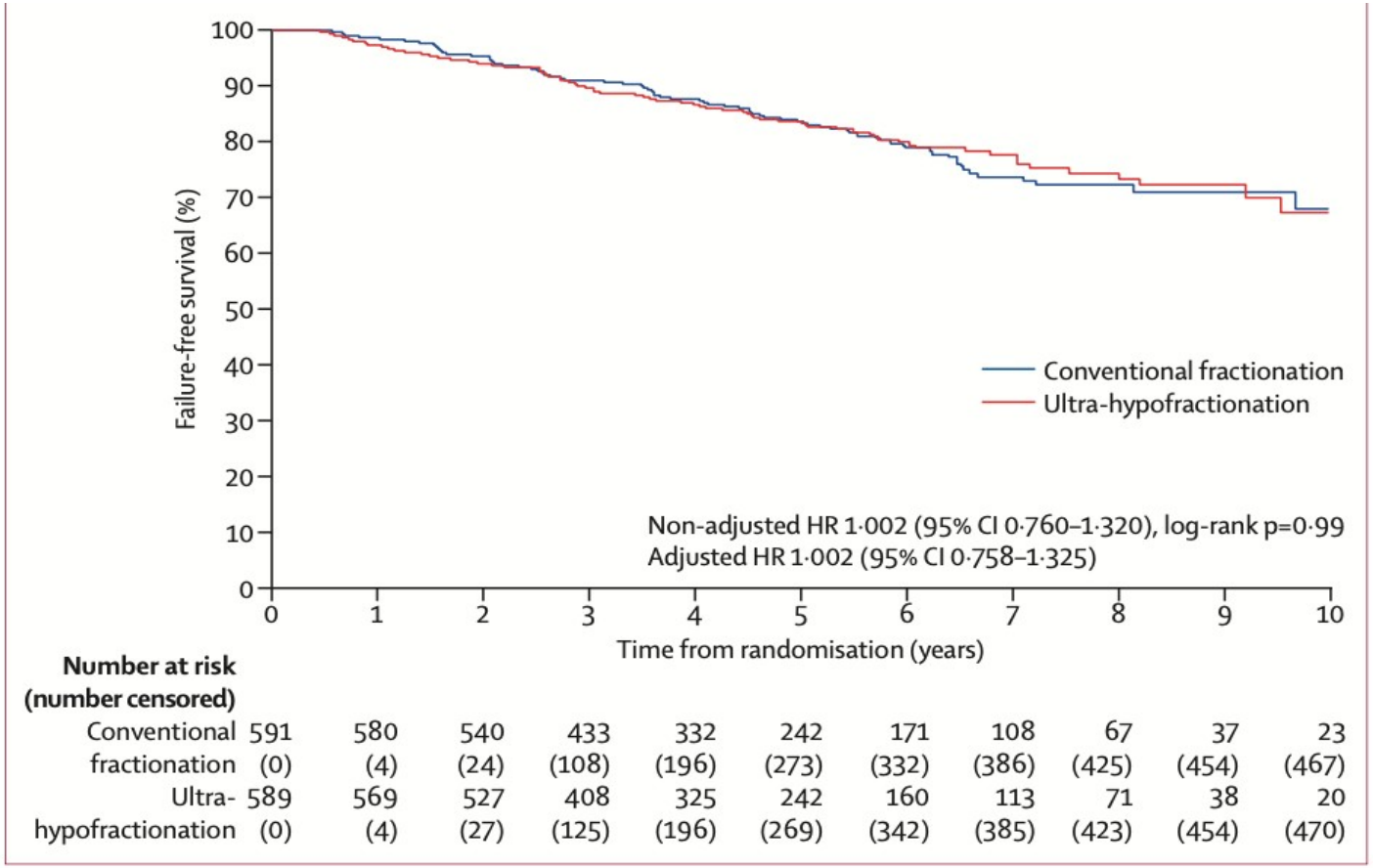
	Conventional fractionation (n=591)	Ultra-hypofractionation (n=589)
Age, years	69 (65–72)	68 (64–72)
PSA, ng/mL*		
Median (IQR)	8·6 (5·7–12·0)	8·7 (6·0–12·2)
≤10 ng/mL	356 (60%)	357 (61%)
>10 ng/mL	235 (40%)	232 (39%)
Gleason score*		
5	2 (<1%)	5 (1%)
6	106 (18%)	99 (17%)
7	444 (75%)	447 (76%)
8	37 (6%)	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%)

- N-591 (78 Gy in 39 fractions in 8 weeks)
- N-589 (42.7 Gy in 7 fractions, in 2.5 weeks)
- Intermediate risk- 89%
- High risk- 11%
- Median follow-up time was 5·0 years (IQR 3·1–7·0)

FFS



Number at risk (number censored)											
Conventional fractionation	591 (0)	580 (4)	540 (24)	433 (108)	332 (196)	242 (273)	171 (332)	108 (386)	67 (425)	37 (454)	23 (467)
Ultra-hypofractionation	589 (0)	569 (4)	527 (27)	408 (125)	325 (196)	242 (269)	160 (342)	113 (385)	71 (423)	38 (454)	20 (470)

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

- 102 primary events (biochemical or clinical failure) had occurred in the CF group and 100 in UF
- 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% in both
- No significant difference in overall survival at 5 years (96% vs 94%)

Urinary Toxicity

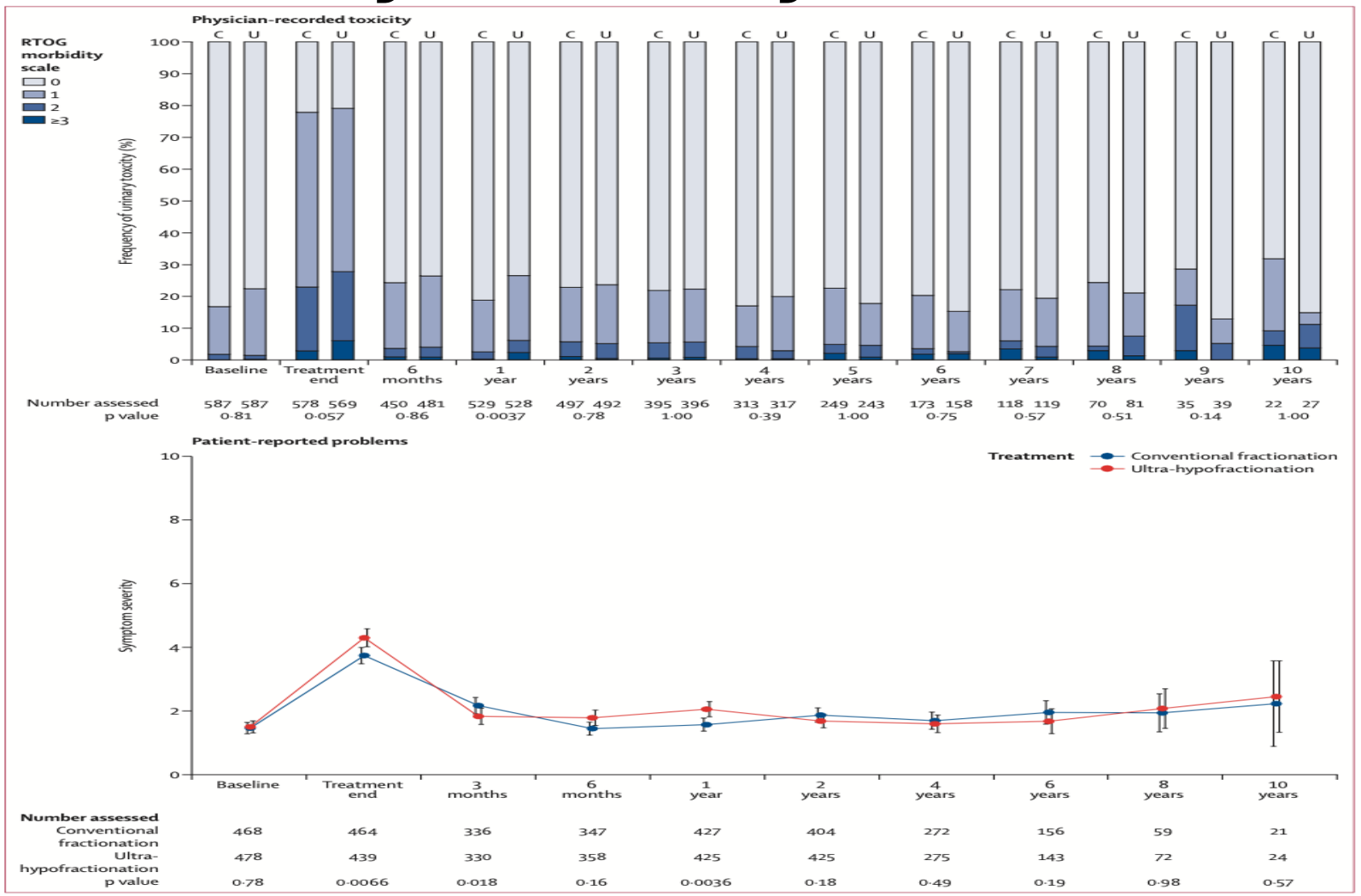


***Figure 3*: Urinary toxicity and patient-reported problems**
Physician-recorded urinary toxicity was measured according to the RTOG morbidity scale; p values correspond to comparisons of grade 2 or worse toxicities by treatment group, by Fisher's exact test. The corresponding patient-reported problem 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.

- Weak evidence of Acute Urinary Toxicity at the end of RT in UF 158 [28%] of 569 patients *vs* 132 [23%] of 578 patients
- No difference grade 2 or worse urinary or bowel toxicity in both groups at any point after radiotherapy, except for an increase in urinary toxicity at 1-year follow-up in the UF compared with CF (32 [6%] of 528 patients *vs* 13 [2%] of 529 patients
- physician-recorded cumulative late urinary grade 2 or worse toxicity

Bowel Toxicity

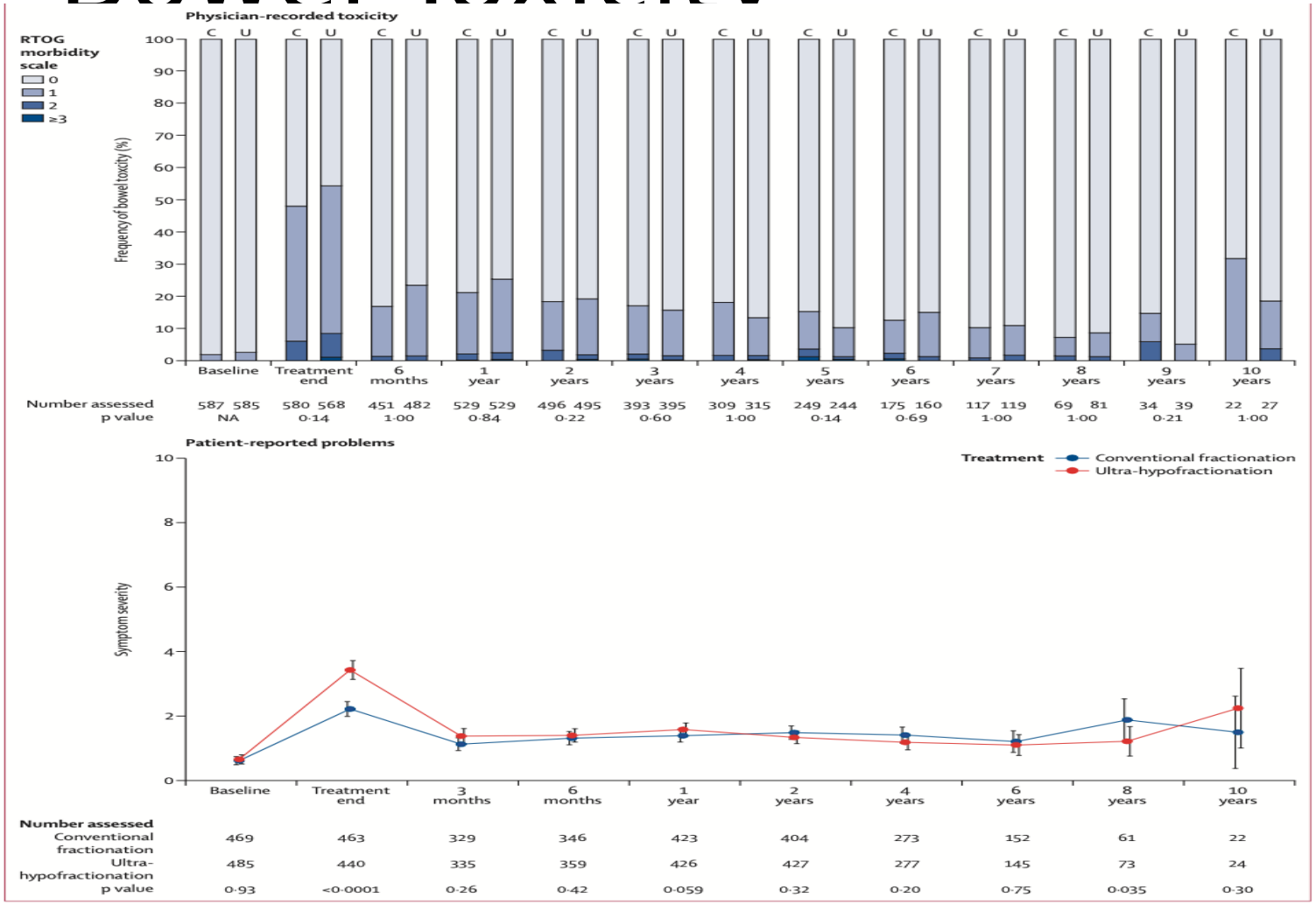


Figure 4: **Bowel toxicity and patient-reported problems**
Physician-recorded bowel toxicity was measured according to the RTOG morbidity scale; p values correspond to comparisons of grade 2 or worse toxicities by treatment group, by Fisher's exact test. The corresponding patient-reported problem was 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.

- Patients in the UF group reported significantly higher levels of acute urinary and bowel symptoms at end of radiotherapy
- No significant increases in late symptoms were found
- cumulative late bowel grade 2 or worse toxicity were 10% (7−13) in both groups at 5-year follow-up

Erectile Function

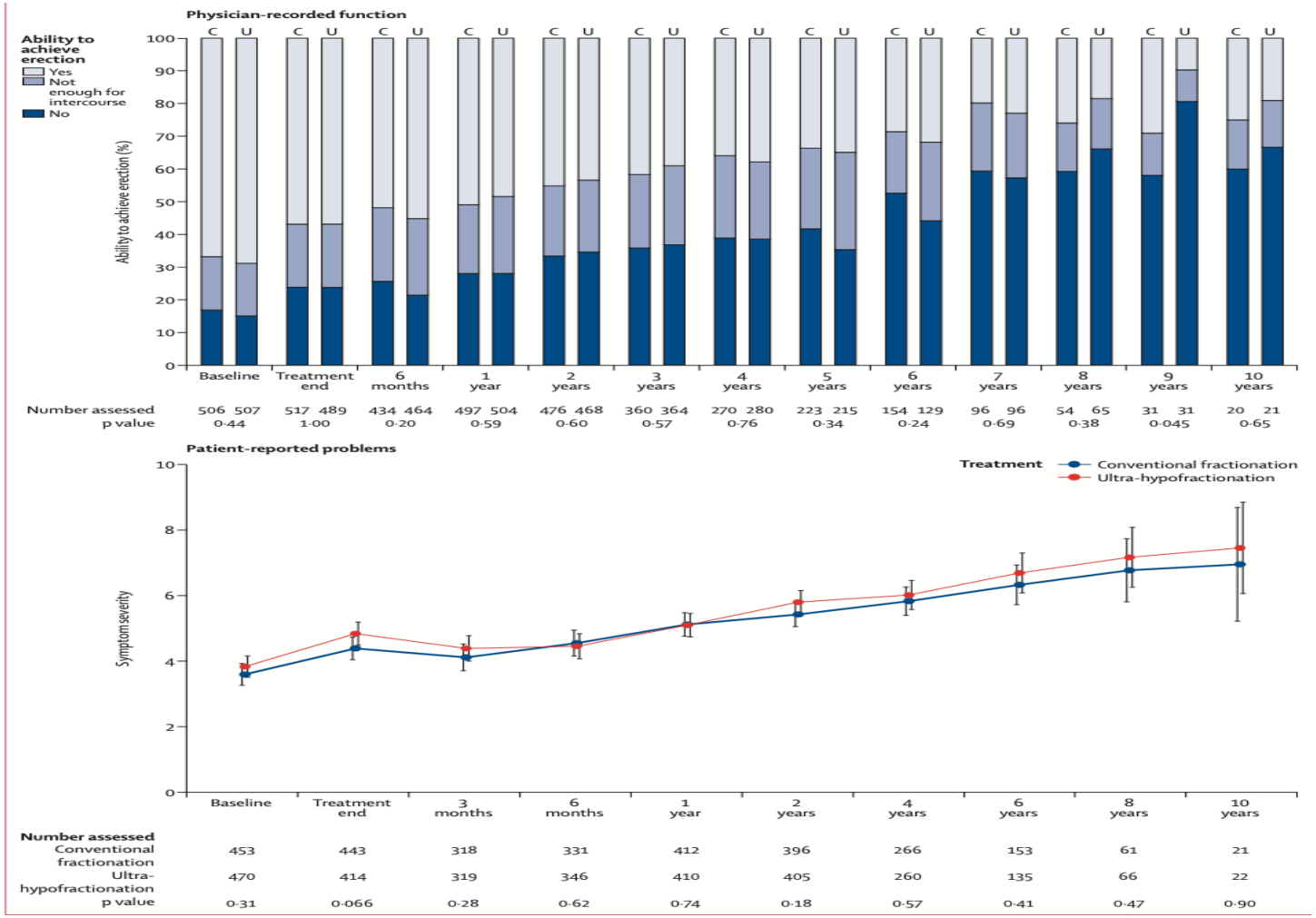


Figure 5: **Erectile function and patient-reported problems**
Physician-recorded erectile function was measured as ability to achieve erection. The corresponding patient-reported problem was measured with the question "Can you get an erection without aids?" in the PCSS questionnaire; higher values indicate 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.

- Erectile function decreased from almost 70% at start of radiotherapy to 35% at 5 years, with no significant difference between the two treatment groups

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Proffered Paper

Register data on long-term morbidity after prostate ultra-hypofractionation in the HYPO-RT-PC trial

Astrid E Persson[1,2], Elisabeth Kjellén[1,2], Hans Garmo[3,4], Gabriel Adrian[1,2], Pär Stattin[4], Anders Widmark[5], Per Nilsson[1,2], Adalsteinn Gunnlaugsson[1,2]

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Data were accessed from Prostate Cancer data Base Sweden 5.0, which links the National Prostate Cancer Register with several population-based registers, also a population-based control group of men without PCa matched 5:1 with the UHF group on birth year and county of residence.

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- Primary outcomes- medically significant GU and GI events that were considered potentially RT-related, and mortality associated with these conditions.
- Broad Code set- directly and indirectly represent any AE relevant to prostate RT (e.g., acute kidney injury)
- Narrow Code set- represent AEs strongly related to prostate RT (e.g., proctitis).
- Secondary outcomes - need for minor GU intervention equivalent to grade 2 toxicity (catheter placement, bladder irrigation, urethral dilation) and prolonged use of urinary antispasmodics and opioids assessed through filled prescriptions.
- All outcomes were analysed as time-to-first-event from start of RT with censoring at death, emigration or 31 March 2023. The control group was also censored at PCa diagnosis.
- 541 participants (approximately 90%) from each trial arm and 2705 matched men without PCa were included, with median follow-up 10.7 years (interquartile range 8.8−12.9).

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Genitourinary events using broad code set

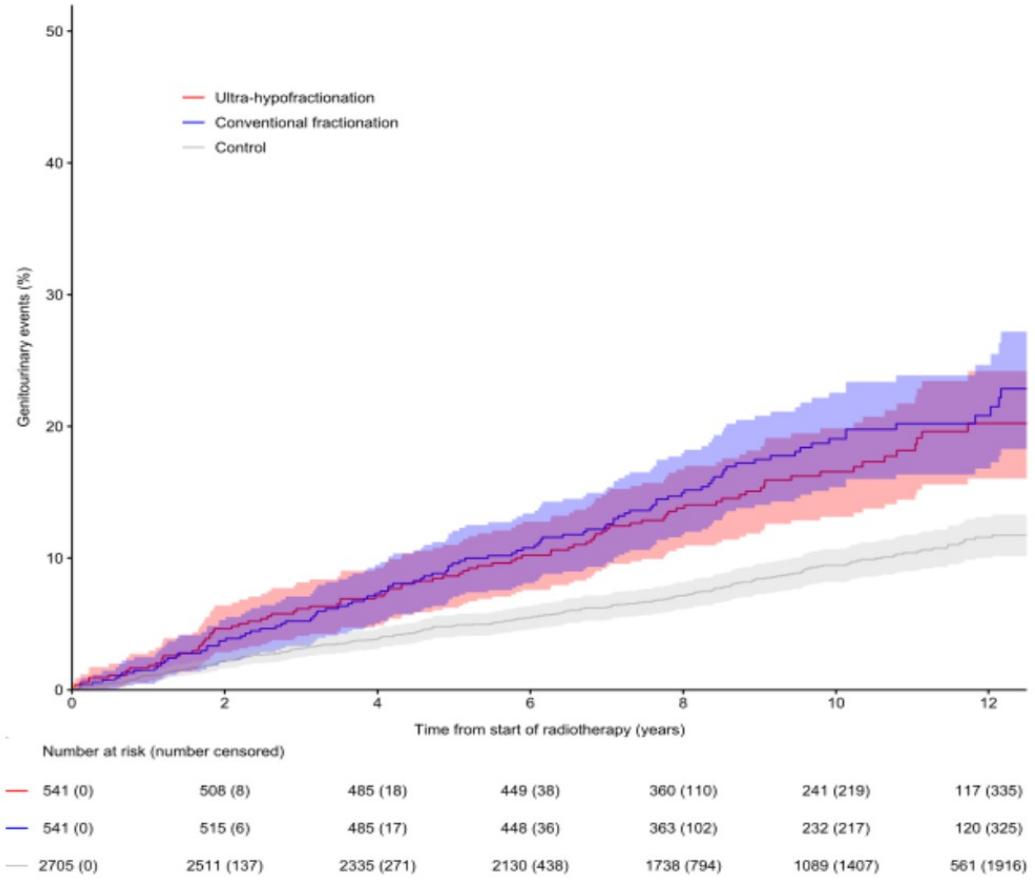

Table: Cumulative incidences of genitourinary and gastrointestinal events

	Ultra-hypofractionation (n=541)	Conventional fractionation (n=541)	Control (n=2705)
Genitourinary events (years)			
Broad code set			
1	2% (0.6–3)	1% (0.5–2)	1% (0.7–1)
5	9% (6–11)	10% (7–12)	5% (4–6)
10	17% (13–20)	19% (15–23)	9% (8–11)
Narrow code set			
1	0.7% (0.0–1)	0.9% (0.1–2)	0.3% (0.1–0.6)
5	4% (2–6)	4% (2–6)	2% (1–2)
10	9% (6–11)	9% (6–11)	4% (3–5)

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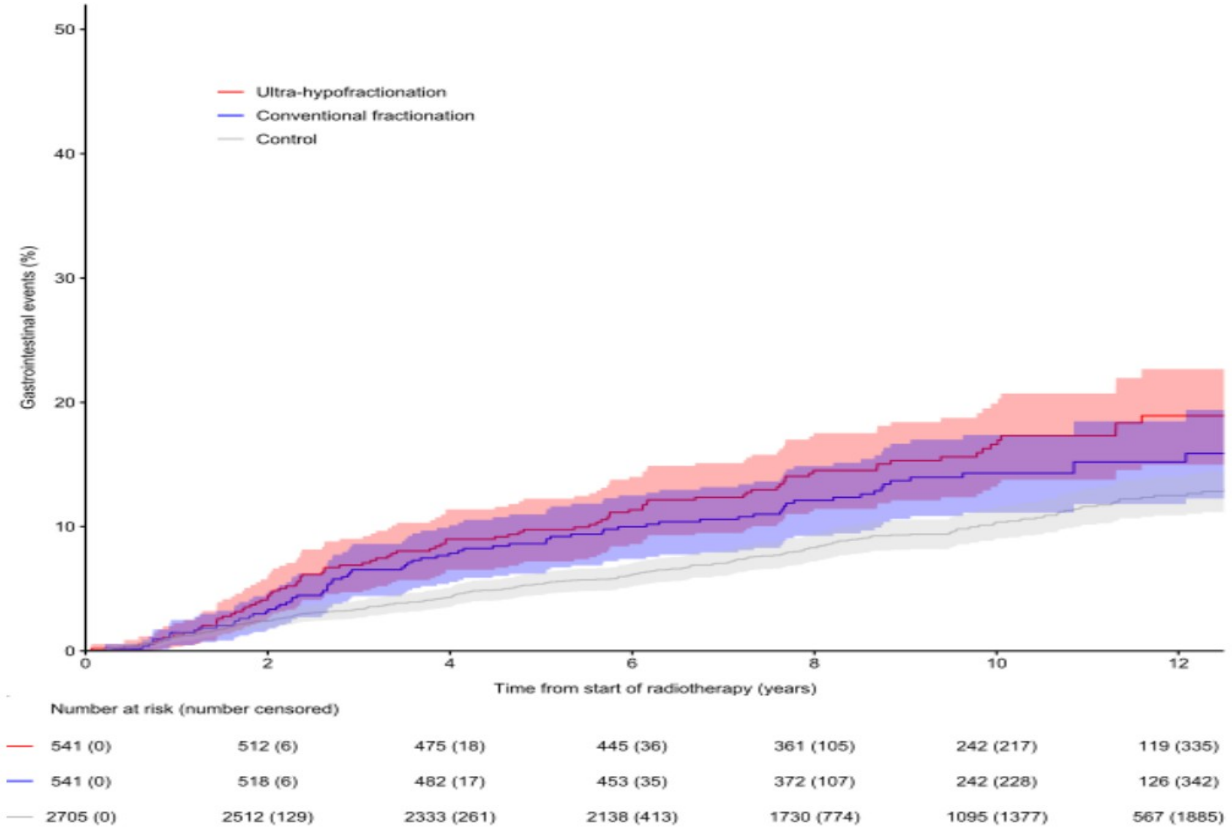
Gastrointestinal events using broad code set



Gastrointestinal events	UF	CF	Control
Broad code set			
1	1% (0.3–2)	1% (0.5–2)	1% (0.7–2)
5	10% (7–12)	9% (6–11)	5% (4–6)
10	17% (13–20)	14% (11–17)	10% (9–12)
Narrow code set			
1	0.4% (0.0–0.9)	0.2% (0.0–0.5)	0.0% (0.0–0.1)
5	5% (3–7)	3% (2–5)	0.4% (0.2–0.7)
10	6% (4–8)	4% (2–6)	0.8% (0.4–1)

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- There were no significant differences in cumulative incidences between the UHF and CF groups for any of the primary and secondary outcomes (log-rank p>0.128)
- Excess GU and GI events at 10 years was 4–10% for the broad code sets and 3–5% for the narrow code sets.
- Mortality from the GU or GI conditions at 10 years was low (broad: 1.3%, narrow: 0.1%) and similar to the control group without PCa (1.8%, 0%).
- Routinely-collected health data support the trial findings of similar long-term GU and GI morbidity after UHF and CF RT in localised PCa.
- Excess GU and GI morbidity related to prostate RT as defined in our study ranged between 3% and 10% at 10 years compared to a matched group without PCa.
- No excess mortality from the GU or GI conditions.

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Two-Week Radiotherapy Proven as Safe and Effective as Eight-Week Course for Prostate Cancer, After 10-Year Follow-Up in Phase III Trial

Key outcomes after 10 years:

- Failure-free survival (no return of cancer or need for additional treatment): 72% in the short-course group vs 65% in the standard group
- Overall survival: 81% for short-course vs 79% for standard
- Prostate cancer-specific mortality: 4% in both groups
- Side effects: Urinary and bowel symptoms were similar in both groups, and most were mild to moderate.

Conclusion

- For many patients, radiotherapy is a standard treatment option that offers outcomes comparable to surgery, particularly for localized disease
- A significantly shorter course of radiotherapy for localised prostate cancer is just as safe and effective as the traditional eight-week schedule even10 years after treatment.
- For patients, this means less disruption to daily life and potentially lower healthcare costs without compromising outcomes and safety
- These results demonstrate how modern radiotherapy approaches can make treatment more efficient, accessible, and patient-friendly without sacrificing effectiveness or safety.