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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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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.