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Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): long-term results of a randomised, phase 3 trial

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Contributors

MRoa and CAFL were responsible for the initial design of RTOG 9413, while JM did the statistical analysis based on the updated data.

MRoa, CAFL, and CRT did quality assurance reviews of treatment fields for assessment of protocol compliance. All coauthors were involved in recruiting and enrolling patients and reviewing or editing this manuscript and represent investigators from the top accruing institutions.

Declaration of interests

We declare no competing interests.

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Summary

Background—The NRG/RTOG 9413 study showed that whole pelvic radiotherapy (WPRT) plus neoadjuvant hormonal therapy (NHT) improved progression-free survival in patients with intermediate-risk or high-risk localised prostate cancer compared with prostate only radiotherapy (PORT) plus NHT, WPRT plus adjuvant hormonal therapy (AHT), and PORT plus AHT. We provide a long-term update after no years of follow-up of the primary endpoint (progression-free survival) and report on the late toxicities of treatment.

Methods—The trial was designed as a 2 × 2 factorial study with hormonal sequencing as one stratification factor and radiation field as the other factor and tested whether NHT improved progression-free survival versus AHT, and NHT plus WPRT versus NHT plus PORT. Eligible patients had histologically confirmed, clinically localised adenocarcinoma of the prostate, an estimated risk of lymph node involvement of more than 15% and a Karnofsky performance status of more than 70, with no age limitations. Patients were randomly assigned (1:1:1:1) by permuted

block randomisation to receive either NHT 2 months before and during WPRT followed by a prostate boost to 70 Gy (NHT plus WPRT group), NHT 2 months before and during PORT to 70 Gy (NHT plus PORT group), WPRT followed by 4 months of AHT (WPRT plus AHT group), or PORT followed by 4 months of AHT (PORT plus AHT group). Hormonal therapy was combined androgen suppression, consisting of goserelin acetate 3·6 mg once a month subcutaneously or leuprolide acetate 7·5 mg once a month intramuscularly, and flutamide 250 mg twice a day orally for 4 months. Randomisation was stratified by T stage, Gleason Score, and prostate-specific antigen concentration. NHT was given 2 months before radiotherapy and was continued until radiotherapy completion; AHT was given at the completion of radiotherapy for 4 months. The primary endpoint progression-free survival was analysed by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00769548. The trial has been terminated to additional follow-up collection and this is the final analysis for this trial.

Findings—Between April 1, 1995, and June 1, 1999, 1322 patients were enrolled from 53 centres and randomly assigned to the four treatment groups. With a median follow-up of 8·8 years (IQR 5·07–13·84) for all patients and 14·8 years (7·18–17·4) for living patients (n=346), progression-free survival across all timepoints continued to differ significantly across the four treatment groups (p=0·002). The 10-year estimates of progression-free survival were 28·4% (95% CI 23·3–33·6) in the NHT plus WPRT group, 23·5% (18·7–28·3) in the NHT plus PORT group, 19·4% (14·9–24·0) in the WPRT plus AHT group, and 30·2% (25·0–35·4) in the PORT plus AHT group. Bladder toxicity was the most common grade 3 or worse late toxicity, affecting 18 (6%) of 316 patients in the NHT plus WPRT group, 17 (5%) of 313 in the NHT plus PORT group, 22 (7%) of 317 in the WPRT plus AHT group, and 14 (4%) of 315 in the PORT plus AHT group. Late grade 3 or worse gastrointestinal adverse events occurred in 22 (7%) of 316 patients in the NHT plus WPRT group, five (2%) of 313 in the NHT plus PORT group, ten (3%) of 317 in the WPRT plus AHT group, and seven (2%) of 315 in the PORT plus AHT group.

Interpretation—In this cohort of patients with intermediate-risk and high-risk localised prostate cancer, NHT plus WPRT improved progression-free survival compared with NHT plus PORT and WPRT plus AHT at long-term follow-up albeit increased risk of grade 3 or worse intestinal toxicity. Interactions between radiotherapy and hormonal therapy suggests that WPRT should be avoided without NHT.

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Introduction

Among the most important advances in the management of men with intermediate-risk to high-risk localised prostate cancer is the recognition of the important role of hormonal therapy combined with external beam radiotherapy. So far, at least four phase 3 trials have shown an improvement in cause-specific survival with this treatment modality and three have shown an overall survival advantage without unacceptable morbidity.[1,2] All these studies involved the administration of hormonal therapy before (neoadjuvant) and during radiotherapy (adjuvant). Before these findings, some investigators were concerned that hormonal therapy might place cancer cells into a cell cycle phase that makes them more resistant to radiotherapy and better results might be achieved if hormonal therapy was given after radiotherapy (adjuvant). However, in some in-vivo animal models, more favourable

interactions occurred with neoadjuvant hormonal therapy (NHT) combined with radiotherapy than with adjuvant hormonal therapy (AHT).[3] The NRG Oncology (NRG)/ Radiation Therapy Oncology Group (RTOG) 9413 trial (NRG/RTOG 9413) was designed to address the importance of sequence of short-term hormonal therapy when given with radiotherapy.

Another controversy in the management of men with high-risk disease is whether or not prophylactic whole pelvic radiotherapy (WPRT) of the lymph nodes results in an improvement in outcome compared with radiotherapy delivered only to the prostate and seminal vesicles (ie, prostate only radiotherapy [PORT]).[4] For many other solid tumours, prophylactic lymph nodal radiotherapy is the standard of care, but no definitive evidence of either benefit or harm was available for prostate cancer.[5] NRG/RTOG 9413 was also designed to assess the effects of WPRT compared with PORT.

When NRG/RTOG 9413 was designed (in 1993), little was known about the prognostic significance of a rising prostate-specific antigen (PSA) concentration after treatment, and no consensus had been reached on how this so-called biochemical failure should be defined. Although no studies had shown PSA failure to be predictive of survival at that time, an assumption was that it could be used as an early indicator of prognosis. Thus, in an effort to shorten the timeline to answer questions concerning the importance of interactions between the sequence of hormonal therapy combined with radiotherapy, and radiotherapy volume, the primary endpoint of the trial was chosen as progression-free survival. Progression-free survival was based primarily on biochemical or clinical failure but also included death due to any cause. Later, biochemical failure was shown to be associated with clinical failure and death, and the standard definition of biochemical failure became the so-called Phoenix definition—a rise of 2·0 ng/mL or more in PSA level above the lowest value (nadir plus 2·0 ng/mL).[6]

In this Article, we summarise the long-term results of this phase 3 trial, incorporating the biochemical PSA failure Phoenix definition into the primary and secondary endpoints.[7]

Methods

Study design and participants

The NRG/RTOG 9413 trial was designed as a 2 × 2 factorial study with hormonal sequencing as one factor and radiation field as the other factor. These factors were not expected to show any statistical interaction, so the two objectives were planned to be addressed by grouping patients across one or the other factor and comparing two large groups.

Eligible patients were recruited from 53 participating hospitals in the USA and Canada and had histologically confirmed, clinically localised adenocarcinoma of the prostate, with an estimated risk of pelvic lymph node involvement exceeding 15%.[8] No formal estimate of life expectancy was required and age was not considered in the eligibility criteria of this study; however, patients were required to have a Karnofsky performance status of 70 or more and no major medical or psychiatric illnesses that would prevent completion of treatment or

interfere with follow-up. Patients were required to have a pretreatment serum PSA of 100 ng/mL or less, and no known involvement of lymph nodes or evidence of distant metastases. Pathological lymph node-positive patients were ineligible, as were those who had previous cryosurgery for prostate cancer or those with a history of previous or concurrent hormonal therapy, radiotherapy, or chemotherapy. Patients who had been previously given finasteride for prostatic hypertrophy were eligible if it was discontinued at least 60 days before randomisation, as were those who had previous testosterone administration if at least 90 days had elapsed before assessment for eligibility. Patients who were surgically staged positive for pelvic node involvement were not eligible for this study. Eligible patients had to have liver function tests up to 1·2 × the upper limit of normal and must have been ineligible for the NRG/RTOG 9408 trial (histologically confirmed, localised, adenocarcinoma of the prostate with PSA not greater than 20 ng/mL and stage T1b to T2b, with a Karnofsky performance score of at least 70, and no previous chemotherapy, radiotherapy, hormonal therapy, cryosurgery or definitive surgery), which compared external beam radiation with or without the addition of 4 months of androgen deprivation therapy (ADT). Patients received ADT, 2 months before and during the trial for a total of 4 months. Patients included on 9408 where generally lower risk.[2] Per protocol, treatment must have begun within 6 weeks after randomisation and within 60 days of surgical staging and the patient must have had no previous or concurrent cancer, other than superficial basal or squamous cell skin cancer, unless they had been disease-free for 5 years or more. This study was approved by the institutional review board at each participating RTOG institution and all patients provided written informed consent before randomisation.

Randomisation and masking

Patients were randomly assigned (1:1:1:1) to receive either NHT 2 months before and during WPRT followed by a prostate boost to 70·2 Gy (NHT plus WPRT group), NHT 2 months before and during PORT to 70·2 Gy (NHT plus PORT group), WPRT followed by prostate boost followed by 4 months of AHT (WPRT plus AHT group), or PORT followed by 4 months of AHT (PORT plus AHT group).

A stratified permuted blocked randomisation, as described by Zelen,[9] was used to account for both the specified prognostic stratification factors and institutions. Treatment assignment was centrally generated at the RTOG Statistics and Data Management Center (Philadelphia, PA, USA) and provided to the institution when the patient was entered. Treatment assignment was not masked to the participating site, the enrolling physician, or the responsible statistician, because the physician and statistician were required to be aware of the treatment group for study compliance. Stratification factors were T stage (T1c and T2a *vs* T1b and T2b *vs* T2c–T4), PSA concentration (≤30 *vs* >30 ng/mL), and Gleason Score (<7 *vs* 7–10). Although a central pathological review (of tumour samples) was performed as a quality assurance procedure to ensure that cancer was present and biopsy samples collected, the individual institutional pathology reading was used for this analysis.

Procedures

All patients received combined androgen suppression consisting of goserelin acetate 3·6 mg once a month subcutaneously or leuprolide acetate 7·5 mg once a month intramuscularly,

and flutamide 250 mg twice a day orally for 4 months. Patients receiving NHT began hormonal therapy 2 months before radiotherapy and continued to receive it during radiotherapy, whereas those receiving AHT began their treatment immediately after the completion of radiotherapy. Notably, in this study, although all patients received 4 months of hormonal therapy, patients randomly assigned to the AHT groups were started on hormonal therapy 2 months later (months 3 to 6) as measured from the date of randomisation compared with those randomly assigned to the NHT groups (months 1 to 4). Patients in the NHT plus WPRT group and in the WPRT plus AHT group had treatment to the whole pelvis with 50·4 Gy to regional lymphatics delivered at 1·8 Gy per day, five times a week, for 28 fractions followed by a boost to the prostate given at 1·8 Gy per day, five times a week, for 11 fractions to a total of 70·2 Gy in 39 fractions. The two groups given PORT (the NHT plus PORT group and the PORT plus AHT group) had treatment to only the prostate at a dose of 1·8 Gy per day, 5 days a week, to a total of 70·2 Gy in 39 fractions in 8 weeks. Megavoltage equipment was required for radiotherapy delivery with an effective photon energy of 6 MeV or more. The minimum source-to-axis distance was 100 cm and the minimum source-to-skin distance was 80 cm. Any treatment technique that was capable of producing the dose distribution specified by the protocol was allowed. For patients receiving WPRT, the minimum initial unblocked field size was 16 × 16 cm. For patients receiving PORT, the maximum initial unblocked field size was 11 × 11 cm. A urethrogram was used as part of the simulation for all patients to define the inferior portion of the field. The inferior margin of the pelvic target column was placed at least 1 cm below the highest point at which the contrast narrows to a point (termed the apex of the urethra).[10] The lateral margin required was 2 cm lateral to the pelvic brim. A four-field radiotherapy technique was recommended to adequately cover external and internal iliac node chains and extensions of the primary tumour into the seminal vesicles or perirectal tissues, or both. To achieve these goals, a major part of the rectum was included in the lateral fields. The prostate boost target volume included the prostate with margins sufficiently wide to encompass all tumour extensions into the surrounding tissues. The final boost volume did not require inclusion of the entire seminal vesicles to 70 Gy.

Hormonal therapy was permitted to be stopped if the patient had an apparent or suspected reaction to the drug or if they had signs of disease progression. Hormonal toxicities were graded with Common Toxicity Criteria version 2.0; acute radiation toxicities were graded with the Acute Radiation Morbidity Scoring Criteria; and late radiation toxicities were graded with the Late Radiation Morbidity Scoring Scheme. All patients were seen once per week by their radiation oncologist during radiotherapy to assess for toxicities. Adverse reactions to commercial hormone drugs were reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program (Bethesda, MD, USA). Follow-up schedule was every 3 months for the first year, every 4 months during the second year, every 6 months for 3–5 years, and then annually for the remainder of the patient’s life. Patients were expected to have a complete blood count drawn at each follow-up for the first 6 months and PSA testing for the duration of follow-up. Only PSA values recorded 3 months after completing hormonal therapy were assessed. A bone scan (Tc-99) was done during follow-up if clinically indicated. Patients were not removed from the study. However, data were excluded

for patients who submitted consent withdrawal forms stating that their medical information was not permitted to be used.

Outcomes

The primary endpoint of progression-free survival was defined as the time from randomisation to the first occurrence of local progression, regional or nodal failure, distant metastasis, biochemical failure (Phoenix definition), or death from any cause. Progression-free survival was based on institutional (local) reporting and was not reviewed centrally. Secondary endpoints were toxicity, Phoenix biochemical failure, overall survival, local progression, distant metastasis, regional or nodal failure, and prostate cancer-specific failure. Phoenix biochemical failure was defined a PSA level at least 2 ng/mL above current nadir (the lowest value achieved), and was measured as the time from randomisation to the first occurrence of such as a PSA level. Overall survival was defined as time from randomisation to death from any cause or the date of last follow-up (patients were censored at death or final follow-up); any unknown causes of death after a protocol biochemical failure were attributed to prostate cancer. Local progression was defined as tumour recurrence (positive repeat biopsy sample ≥2 years post-treatment, palpable tumour regrowth by 50%, or tumour that never cleared) and was measured from randomisation to the date of local progression. Distant metastasis was defined as clinical evidence of distant disease by any method, and was measured from randomisation to the date of documented metastatic disease. Regional or nodal failure was defined as clinical evidence of intrapelvic nodal progression, and measured as the time from the date of randomisation to the date of documented regional or nodal failure. Prostate cancer-specific failure was defined as death due to prostate cancer or treatment toxicity, or—for unknown causes of death—patients with local progression, distant metastasis, or Phoenix biochemical failure. Time to prostate cancer-specific failure was measured from the date of randomisation to the date of death.

Statistical analysis

We designed the study to test the hypothesis that NHT improved progression-free survival compared with AHT by at least 10%. We also designed the study to test the hypothesis that NHT plus WPRT followed by a prostate boost improved progression-free survival by at least 10% compared with NHT plus PORT. To detect these differences, we needed a sample size of 1200 patients. We used a log-rank test at a two-sided α level of 2·5%, which had 80% power for our analysis. We planned two blinded interim efficacy analyses with adjustment for multiple group sequential testing using an O'Brien-Fleming α-spending function.[11,12] We planned the interim analyses to take place when approximately 50% and 100% of the patients had been accrued. We estimated that the expected number of progression-free survival events observed by the final analysis would be 530. We estimated the expected cumulative numbers of events observed by the two interim analyses would be 60 and 200. Under this scenario, for treatment comparisons we used α levels of less than 0·0001 for the first planned interim analysis and 0·0002 for the second analysis. The data safety monitoring committee was responsible for assessing the results of the two interim analyses and the toxicity profile throughout the duration of the trial. The committee members and study investigators had no access to the data. We used an α level 0·05 for treatment comparisons in the final analysis.

We estimated progression-free survival and overall survival using the Kaplan-Meier method, comparing groups with the log-rank test.[13,14] Additionally, for these two endpoints, we used the Cox proportional hazards regression model to investigate treatment effects on survival in the presence of adjusted variables: Gleason score, PSA level, and T stage (data for overall survival not shown).[15] We estimated all other secondary time-to-event endpoints using the cumulative incidence method.[15] The cumulative incidence approach accounts for competing risks and uses Gray's K-sample test to test for differences between treatment groups.[16] We used the Fine-Gray regression model (protocol-specified) to investigate treatment effects on these secondary endpoints with competing risks in the presence of adjusted variables: Gleason score, PSA level, and T stage (data for other secondary endpoints are not shown).[17] For all regression analyses (Cox and Fine-Gray), we used a reference level variable for each adjusted analysis variable. The reference level variable is coded in such a way that if the resulting hazard ratio (HR) is greater than 1, then that implies an increased risk for that level over the reference level. Conversely, if HR is less than 1, that implies a reduced risk for the level compared with the reference level. Additionally, we did a post-hoc analysis on competing causes of death.

The primary endpoint of progression-free survival was analysed in the intention-to-treat population. The other efficacy analyses used the same population as the primary endpoint. The safety analyses used patients who received some part of protocol treatment and had toxicity information.

All analyses were conducted using SAS version 9.4. This study is registered with ClinicalTrials.gov, number NCT00769548.

Role of the funding source

The funding source had no role in the design of the study; in the collection, analysis, and interpretation of the data; or in the writing of the report. The principal investigator and corresponding author (MRoa) had full access to all the data and the final responsibility to submit for publication after review by coauthors and the publication committee.

Results

This trial opened on April 1, 1995, and closed on June 1, 1999, with a total of 1322 eligible patients enrolled from 53 participating institutions (appendix p 1). As of April 3, 2016, 42 (3%) patients were ineligible and ten (1%) patients withdrew consent (figure 1). The most common reason for ineligibility was having an estimated risk of lymph node involvement of less than 15% (n=32). Although most of the patients accrued might be considered high risk, the median PSA was 23 ng/mL (IQR 12·1–34·7) and 337 (27%) of 1270 patients had a Gleason score of less than 7; thus some patients might now be characterised as having an intermediate risk of disease according to the National Comprehensive Cancer Center Network (NCCN) guidelines. The distribution of the baseline characteristics was well balanced between groups (table 1). The median follow-up was 8·8 years (IQR 5·07–13·84) for all patients and 14·8 years (7·18–17·4) for 346 living patients. The median follow-up for living patients by group was 13·93 years (IQR 7·18–17·59) for the NHT plus WPRT group,

14·26 years (6·99–17·31) for the NHT plus PORT group, 15·56 years (6·86–17·49) for the WPRT plus AHT group, and 15·77 years (7·24–17·29) for the PORT plus AHT group.

For this analysis, progression-free survival and secondary endpoints were calculated using the Phoenix definition. Univariate Cox analysis of progression-free survival and overall survival assessing the effect of WPRT versus PORT and NHT versus AHT, and post-hoc analyses of their interactions between radiotherapy and hormonal therapy (ie, the effect of radiotherapy is dependent on whether the patient received NHT or AHT; and vice versa for the effect of hormonal therapy) making it statistically invalid to collapse the groups into WPRT versus PORT and NHT versus AHT for reporting outcomes (appendix p 2, figure 2A, B. Hence, the four groups were analysed individually.

Progression-free survival across all timepoints differed significantly across the four treatment groups (p=0·002; figure 3). The 10-year estimates of progression-free survival were 28·4% (95% CI 23·3–33·6); 274 of 318 patients had failures (ie, progression-free survival events) in the NHT plus WPRT group, 23·5% (18·7–28·3; 278 of 316 patients) in the NHT plus PORT group, 19·4% (14·9–24·0; 286 of 319 patients) in the WPRT plus AHT group, and 30·2% (25·0–35·4; 265 of 317 patients) in the PORT plus AHT group. In the multivariable Cox analysis, compared with NHT plus WPRT, NHT plus PORT had an HR of 1·21 (95% CI 1·02–1·43; p=0·027) and WPRT plus AHT had an HR of 1·21 (1·03–1·43; p=0·025), whereas PORT plus AHT had an HR of 0·93 (0·78–1·10; p=0·39; table 2). In the univariable Cox analysis, compared with NHT plus WPRT, NHT plus PORT had an HR of 1·21 (95% CI 1·02–1·43; p=0·026) and WPRT plus AHT had an HR of 1·22 (1·03–1·43; p=0·022), whereas PORT plus AHT had an HR of 0·93 (0·79–1·10; p=0·41; appendix p 3).

Log-rank tests of pairwise comparisons showed that patients in the NHT plus WPRT group had a significantly different progression-free survival across all timepoints compared with those who received NHT plus PORT (p=0·023), as did those in the NHT plus WPRT group compared with those who received WPRT plus AHT (p=0·017); the p values in both of these pairwise comparisons favoured the NHT plus WPRT group. WPRT plus AHT had a significantly different progression-free survival compared with PORT plus AHT (p=0·0024), as did NHT plus PORT compared with PORT plus AHT (p=0·0032); the p values in both of these pairwise comparisons favoured the PORT plus AHT group.

Phoenix biochemical failure across all timepoints also differed significantly between the four groups (appendix p 4) Multivariable Fine-Gray regression analysis of Phoenix biochemical failure resulted in an HR of 1·38 (95% CI 1·11–1·72) for NHT plus PORT compared with NHT plus WPRT (p=0·0045; table 2), indicating improved Phoenix biochemical failure in the NHT plus WPRT group. The Gray's tests of pairwise comparisons of Phoenix biochemical failure for the four treatment groups showed significant differences between NHT plus WPRT and NHT plus PORT (p=0·0038, in favour of NHT plus WPRT) and between NHT plus PORT and PORT plus AHT (p=0·0046, in favour of PORT plus AHT; data not shown). The four treatment groups did not differ significantly in the other secondary endpoints of overall survival, prostate cancer-specific failure (appendix pp 5–6), local progression, distant metastasis, or regional or nodal failure (appendix pp 7–9).

Early and late toxicity results have been previously reported[7] with fewer than 5 years of follow-up, and WPRT was associated with a trend for increased early and late gastrointestinal adverse events. In the current report, for patients who received radiotherapy and who had acute data, the proportion of patients with acute grade 3 or worse radiation toxicity was 9% (28 of 316 patients) in the NHT plus WPRT group, 8% (24 of 311) in the NHT plus PORT group, 7% (21 of 317) in the WPRT plus AHT group, and 5% (16 of 314) in the PORT plus AHT group (data not shown). For patients who received hormonal therapy, the proportion of patients with grade 3 or worse hormone therapy toxicity was 9% (27 of 317 patients) in the NHT plus WPRT group, 5% (17 of 315) in the NHT plus PORT group, 3% (nine of 317) in the WPRT plus AHT group, and 3% (nine of 315) in the PORT plus AHT group (data not shown). No deaths were attributable to either radiotherapy or hormonal therapy.

With additional follow-up, bladder toxicity was the most common grade 3 or worse late toxicity, affecting 18 (6%) of 316 patients in the NHT plus WPRT group, 17 (5%) of 313 in the NHT plus PORT group, 22 (7%) of 317 in the WPRT plus AHT group, and 14 (4%) of 315 in the PORT plus AHT group (table 3). Although no differences were found in late genitourinary toxicity between groups (table 3), any late gastrointestinal adverse events of grade 3 or worse occurred in 22 (7%) of 316 patients in the NHT plus WPRT group, five (2%) of 313 in the NHT plus PORT group, ten (3%) of 317 in the WPRT plus AHT group, and seven (2%) of 315 in the PORT plus AHT group (table 3).

Additionally, the cumulative incidence of time to late grade 3 or worse gastrointestinal toxicities was associated with the volume of the field and sequence of radiotherapy (p=0·001; appendix p 10); the cumulative incidence was highest for patients in the NHT plus WPRT group (6·7% [95% CI 4·3–9·8] at 10 years) and lowest for those in the NHT plus PORT group (1·3% [0·4–3·1] at 10 years). Thus, it appears that, as was the case for progression-free survival, interactions occur between radiotherapy and hormonal therapy in healthy tissues. Late grade 3 or worse haematological toxicities were also more common in men treated with WPRT (40 [6%] of 633 patients) than in those treated with PORT (20 [3%] of 628 patients; table 3).

The proportion of patients who terminated luteinising hormone-releasing hormone treatment (goserelin acetate or leuprolide acetate) early was modest, ranging from 2% (seven of 316 patients) in the NHT plus PORT group to 5% (16 of 318) in the NHT plus WPRT group (appendix p 11). The proportion of patients who terminated antiandrogens (flutamide) treatment early ranged from 12% (37 of 319) in the WPRT plus AHT group to 18% (56 of 318) in the NHT plus WPRT group (appendix p 11).

In a post-hoc exploratory analysis, we investigated the causes of death in the patients treated in this trial (appendix p 12). The most common causes of death were other causes, including cardiovascular, pneumonia, and other common conditions (data not shown). Approximately 132 (15%) of all 924 deaths were classified as due to unknown causes. There appeared to be no differences in the incidence of secondary cancers between groups, with the most common sites for secondary cancer death being the lung (58 [43%] of 136 patients), the colon and rectum (13 [10%]), the bladder (12 [9%]), and the pancreas (11 [8%]; data not shown).

Discussion

The long-term results of the NRG/RTOG 9413 study show that progression-free survival (the primary endpoint) was improved with NHT plus WPRT when compared with NHT plus PORT and was maintained with NHT plus WPRT when compared with WPRT plus AHT, but we recorded no significant difference in progression-free survival between NHT plus WPRT versus PORT plus AHT with long-term follow-up. We also found that Phoenix biochemical failure continues to be substantially improved and maintained long term with WPRT compared with PORT when accompanied by NHT. Unfortunately, this improvement in progression-free survival and biochemical failure seems to be associated with an increased risk of moderate (ie, grade 3 or worse) gastrointestinal toxicity.

Despite no differences between PORT plus AHT versus NHT plus WPRT with much longer follow-up, we have chosen to further investigate the potential value of WPRT and in the design of the ongoing phase 3 NRG/RTOG 0924 trial (NCT01368588) for several reasons. In the initial report of the current trial, the trends favoured NHT plus WPRT over the other three groups, despite the timing bias associated with the later use of hormonal therapy in the two AHT groups compared with the two NHT groups.[7] We believe this trend reflected the early effect of prophylactic radiotherapy on occult nodal disease. We further believe the longer-term failure pattern could be attributable to a second wave of progression due to local failures (caused by inadequate doses of radiotherapy [current recommended doses of external beam radiation from NCCN guidelines are at least 10% higher—eg, 78 Gy—based on improved prostate-specific antigen control]) and deaths from other causes negating much of the benefit of WPRT. If higher radiotherapy doses are delivered and this higher dose results in an attenuation in this second wave, the benefits of WPRT might be sustained. Another reason behind the design of the ongoing NRG/RTOG 0924 trial is that most radiation oncologists consider the standard-of-care to be NHT followed by radiotherapy, and this updated analysis continues to support NHT plus WPRT over NHT plus PORT. A formal non-inferiority study would require a larger number of patients to ultimately show that there are no differences between PORT plus AHT and NHT plus WPRT. However, we are aware of no supporting data from other randomised trials or retrospective data to justify such a trial. Finally, although chance cannot be completely excluded, given the size of this study, chance should be assumed only very cautiously to explain the findings reported here.

We believe that this large phase 3 trial provides a proof of principle that, based on PSA findings, WPRT when given under the appropriate circumstances might render better long-term outcomes than PORT when short-term NHT is used. Although WPRT did not show an improvement in overall survival compared with PORT, this result should not be surprising. If, for example, the incidence of lymph node involvement in this population was 33%, then this trial is essentially testing the value of prophylactic WPRT in 400 patients (rather than 1200 since only those with lymph node involvement can benefit from WPRT). If 10% of patients had disease beyond the superior border of the pelvic field (L5-S1) and 40% did not succeed locally because of high volume disease treated to 70 Gy, then essentially the trial is of 200 patients in four groups, with only 50 patients per group. If by 10 years follow-up, 50% of patients died of competing causes, then this trial would essentially be assessing the overall survival effect of WPRT based on 25 patients per group. Despite these limitations,

the early signal based on PSA failure is encouraging. The ongoing phase 3 NRG/RTOG 0924 trial includes a higher superior border (and thus encompasses more nodes—eg, common iliac), includes higher doses of radiation (79·2 Gy with external beam radiation therapy or including a brachytherapy boost, thus an even higher biological dose) delivered to the prostate with image guidance, and is four times as large as the two NHT groups (n=2580) in NRG/RTOG 9413, and is designed with an overall survival primary endpoint, a tighter HR, and higher statistical power.

The example above might easily explain why the only other contemporary trial addressing the role of pelvic irradiation in prostate cancer (the French GETUG-01 study)[18] is often called a negative trial. When both trials were designed, information was scarce as to what the optimal radiation field size should be to test the concept of prophylactic pelvic nodal radiotherapy. GETUG-01[18] included 446 patients, with 203 estimated to have a risk of positive lymph nodes of greater than 15%. Additionally, hormonal therapy was used selectively and the nodal volume irradiated was best described as the true pelvis or mini-pelvis, which is substantially smaller than WPRT as defined by NRG/RTOG 9413, and potentially less effective.[19] Notably, in a post-hoc subset analysis, the GETUG01 investigators suggested a potential benefit of mini-pelvic radiotherapy in patients with an estimated risk of lymph node involvement below 15%, perhaps because of the lower risk of nodal involvement beyond the true pelvis.[18] Also worth noting, in a post-hoc analysis from another phase 3 randomised trial,[20] the authors suggested that their data provided support for the potential value of WPRT, although their findings did not reach significance. In a large breast cancer trial[21] (involving patients with early-stage breast cancer), prophylactic irradiation of the regional lymph nodes seemed to increase progression-free survival, reduce breast cancer mortality, and had a small effect on overall survival.

Several interesting findings have been derived from this trial that, if supported by other studies, would add to the understanding of the effect of radiotherapy and hormonal therapy on the outcomes for men with intermediate-risk to high-risk, clinically localised prostate cancer. First, many experts consider NHT plus PORT to be the standard-of-care for men with intermediate-risk to high-risk prostate cancer.[22] This trial showed that NHT plus WPRT improved biochemical failure (Phoenix) compared with NHT plus PORT, thus providing a basis for reconsidering what the standard-of-care should be. The readers should remember, however, that progression-free survival included death due to any cause whereas biochemical failure is strictly based on the PSA level. As such, early in the study (reported by Roach and colleagues)[7] progression-free survival was driven by biochemical failure, but with long-term follow-up many of the progression-free survival events were due to death from other causes. The continued decline in progression-free survival suggests that most men of 70 years die from causes other than prostate cancer. The results from NRG/RTOG 9413 also might suggest that long-term local control was not frequently achieved with only 70 Gy radiotherapy and short-term ADT in a population of patients with a median PSA of more than 20 ng/mL; most patients staged clinically as having T2c–T4 and 70% had Gleason scores of 7–10.[23] Based on these considerations, the follow-up phase 3 trial (NRG/RTOG 0924) was launched testing WPRT versus PORT with NHT in both groups. This trial specifies higher doses of radiotherapy to minimise the confounding effect of local failure and allows long-term AHT to assist in controlling microscopic disease outside of irradiated

fields. Additionally, the size of this trial was substantially increased to allow overall survival (rather than a PSA control) to be the primary endpoint.

Several sequence-dependent and volume-dependent interactions occurred between hormonal therapy and radiotherapy. For example, with WPRT progression-free survival is improved with NHT compared with AHT (despite the timing bias favouring AHT), supporting one of our hypotheses. An unexpected sequence-dependent improvement in biochemical failure is also present with AHT rather than NHT plus PORT, with AHT being more favourable (contrary to our hypothesis). This finding is consistent with that of a small retrospective study).[24] A practical application of this observation to clinical practice might be, for patient convenience, to start radiotherapy immediately after treatment planning and start AHT when radiotherapy has been completed.

Several limitations of this study are potentially important. The so-called Roach formula is mainly based on Gleason scores and how to read this score and how to interpret it has changed overtime. Thus, the applicability of the results derived from this historical cohort to contemporary patients is questionable. However, the same can be said of most other series for which long-term follow-up is available. Our use of central pathological review and randomisation could help to attenuate this problem. Another potential limitation, is that the study was done before widespread availability of some of the newer PET imaging methods, which now might be used to guide the selection of patients for WPRT since several studies suggest that use of these agents might alter the design of treatment.[25] Additionally, whether newer systemic drugs affect the outcomes associated with pelvic nodal irradiation is unknown. Notably, however, in a post-hoc assessment of the STAMPEDE trial[26] the use of radiotherapy was associated with an improved outcome in lymph nodepositive patients. Another potential limitation of the current study is that some of the associations noted could be due to chance alone or some type of statistical bias associated with the use of factorials in the trial design.[27] Perhaps the most important limitation of NRG/RTOG 9413 is that progression-free survival is primarily a PSA-driven endpoint that might not translate into a meaningful clinical endpoint, such as overall survival. We remain hopeful that NRG/RTOG 0924 will address this question.

In addition to biochemical outcome differences, we found sequence-dependent and volume-dependent interactions between hormonal therapy and radiotherapy and toxicity. For example, in patients who received NHT, late grade 3 or worse gastrointestinal toxicity was 7% with WPRT versus 2% with PORT. Conversely, when AHT was used, the incidence of late grade 3 or worse gastrointestinal toxicity was 3% with WPRT versus 2% with PORT. The finding of a higher rate of grade 3 toxicity is an unexpected empirical observation for which we have no clear explanation. Several possibilities come to mind, including the possibility that the immune stimulatory effects of neoadjuvant ADT might sensitise normal tissues to radiation or that the immunosuppressive effects of WPRT might attenuate the toxicity of radiation.[28] Although the findings were somewhat unexpected, they seem to be internally consistent with some sort of interaction between volume of radiation and sequence of ADT. However, given the fact that 90% of the patients were given conventional radiotherapy (three-dimensional CT was not widely available), we are uncertain whether the risk of toxicity observed with WPRT is relevant to contemporary patients given intensity-

modulated radiotherapy. Hopefully NRG/RTOG 0924, which requires intensity-modulated radiotherapy to be given to all patients, will show that WPRT can be delivered with substantially less toxicity.

For the entire cohort of patients, proportion of deaths due to second cancers is similar to the proportion of deaths after radical prostatectomy, as reported by Eifler and colleagues[29] (appendix p 5). For example, in their population-based series, roughly 30% of all deaths were due to non-prostate cancer malignancies (second cancers). From our series, 21% of deaths were coded as deaths from second cancers. However, Eifler and colleagues found that only 16% of deaths were coded as due to unknown causes. If all unknown causes from NRG/RTOG 9413 were added to those coded as death due to second cancer, this diagnosis would only reach 48%, similar to the combined rate of 51% (30% plus 21%) reported by Eifler and colleagues.[29] The readers should bear in mind, however, that the standardised mortality ratio for men having radical prostatectomy to develop second malignancies was 0·45 (95% CI 0·40–0·49) compared with men in the general population, suggesting that they might not be an appropriate cohort to compare with men having radiotherapy. Our conclusions concerning the risk of second cancer in our patients is consistent with that of Abdel-Wahab and colleagues.[30] Notably, we found the rates of both colorectal and bladder cancer deaths to be approximately 1%, with a minimum follow-up of 12 years from treatment, which appears to be low for men in this age group (median 71 years). NRG/RTOG 0924 will hopefully definitively address the risk and benefits of WPRT compared with PORT in conjunction with hormonal therapy.

In this cohort of intermediate-risk and high-risk patients with localised prostate cancer, NRG/RTOG 9413 continues to show that NHT plus WPRT improved progression-free survival and biochemical failure compared with NHT plus PORT, albeit with an increased risk of grade 3 or worse gastrointestinal toxicity with the use of conventionally delivered, external beam radiotherapy. NRG/RTOG 0924 will provide evidence on whether the use of WPRT delivered with intensity-modulated radiotherapy combined with a dose-escalated prostate boost will result in an improved survival without unacceptable gastrointestinal toxicity in the setting of short-term or long-term hormonal therapy. Based on the current rate, accrual of NRG/RTOG 0924 is expected to be completed by late summer of 2019. We are hopeful that the results of this study will provide more evidence about whether or not prophylactic WPRT is beneficial to men given definitive radiotherapy and ADT for unfavourable intermediate-risk or favourable high-risk, clinically localised prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Research in context

Evidence before this study

Before launching NRG Oncology (NRG)/Radiation Therapy Oncology Group (RTOG) 9413 in 1994, we searched PubMed from Jan 1, 1982, to Dec 30, 1994. Search terms included “radiotherapy”, “localized prostate cancer”, “pelvic radiotherapy and prostate specific antigen (PSA)”, and “lymph node involvement”. Studies selected were limited to those that included an abstract in English, with long-term outcomes documenting evidence of local control after radiotherapy. A book chapter summarising the state-of-the-art of definitive radiotherapy was prepared, which identified the uncertainty surrounding the appropriate initial radiation target volume as a previously unaddressed issue. Key studies identified pointed out the controversies concerning (1) metrics for successful outcomes (including post-treatment biopsies, (2) the importance of pretreatment prostate-specific antigen (PSA) level as a predictor of the risk of biochemical failure after external beam radiotherapy and as a predictor of pathological stage (including the risk of lymph node involvement when combined with Gleason score and clinical stage), as a means of defining recurrences after external beam radiotherapy; and (3) the potential importance of regional treatment on outcomes of patients at risk for lymph node involvement. No relevant studies with high-level evidence or meta-analyses were identified based on the literature available at that time. The only other large phase 3 randomised trials assessing WPRT for prostate cancer before the launch of NRG/RTOG 9413 were NRG/RTOG 7706 and NRG/RTOG 7506. Both were launched before the availability of PSA. The focus of NRG/RTOG 7706 was to identify patients negative for lymph node involvement either pathologically or by imaging (lymphangiogram). It included only 445 patients, 90% of whom had low-grade tumours, who were randomly assigned to receive prostate radiotherapy with or without pelvic nodes. Conversely, NRG/RTOG 7506 included high-risk patients, some of whom were known to have lymph node-positive disease and were randomly assigned to either receive pelvic irradiation followed by a boost to the prostate or pelvic and periaortic irradiation followed by a boost to the prostate. A total of 448 patients were known to have received treatment per protocol. No significant differences between the treatment groups were documented for either study, and differences in treatment-related toxicity were minor.

Added value of this study

NRG/RTOG 9413 showed that compared with prostate only radiotherapy plus neoadjuvant hormonal therapy (NHT), prophylactic whole pelvic radiotherapy (WPRT) plus NHT is associated with an improvement in progression-free survival and biochemical failure, but also causes a slight increase in late grade 3 gastrointestinal toxicity.

Implications of all the available evidence

Although the surrogacy of improved PSA control as an indicator of progression-free survival (according to the Phoenix definition) has not been formally validated, improved biochemical control has been used to support all forms of dose-escalated radiotherapy and to establish disease-free status after local treatment. The results of NRG/RTOG 9413

justified the launch of NRG/RTOG 0924 (a much larger phase 3 trial), which should provide a more definitive answer concerning the use and toxicity of WPRT in men with intermediate-risk and high-risk localised prostate cancer.

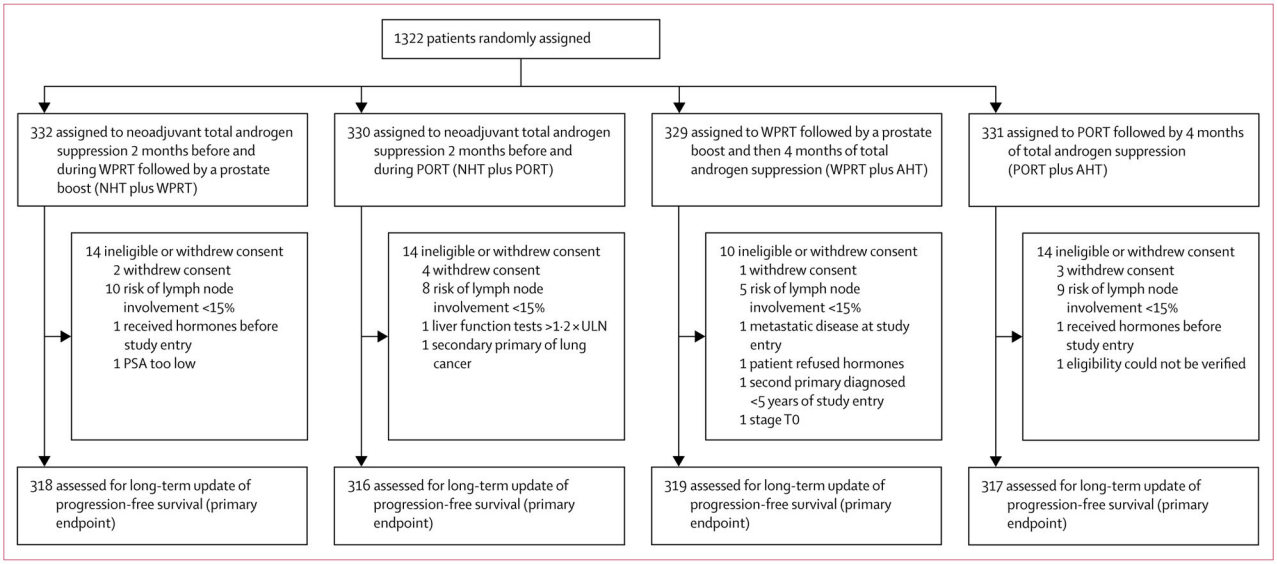


Figure 1: Trial profile

AHT=adjuvant hormonal therapy. PORT=prostate only radiotherapy. PSA=prostate-specific antigen. NHT=neoadjuvant hormonal therapy. WPRT=whole pelvic radiotherapy.

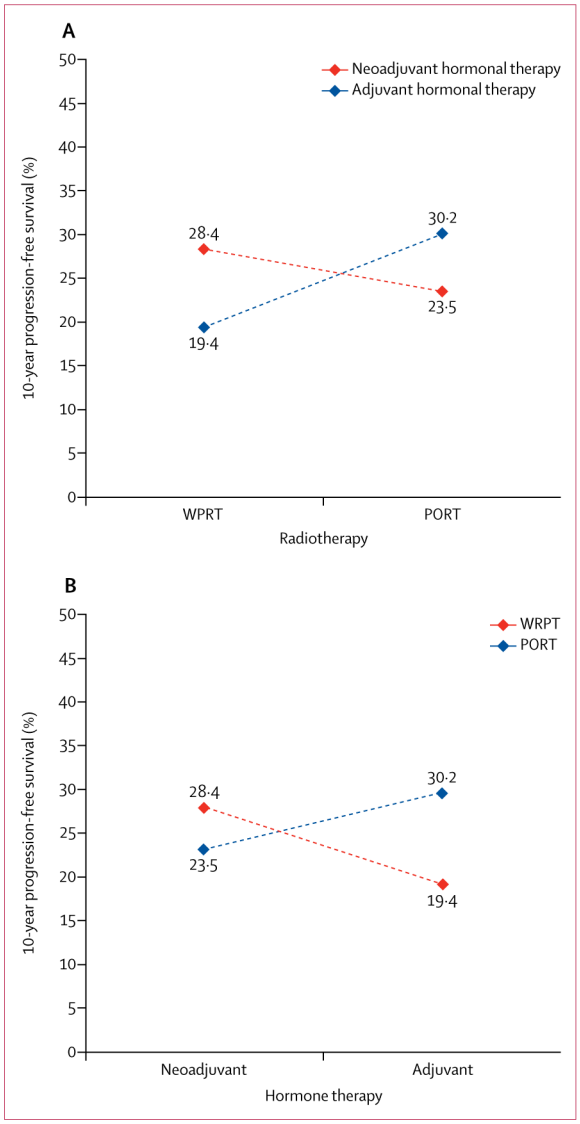
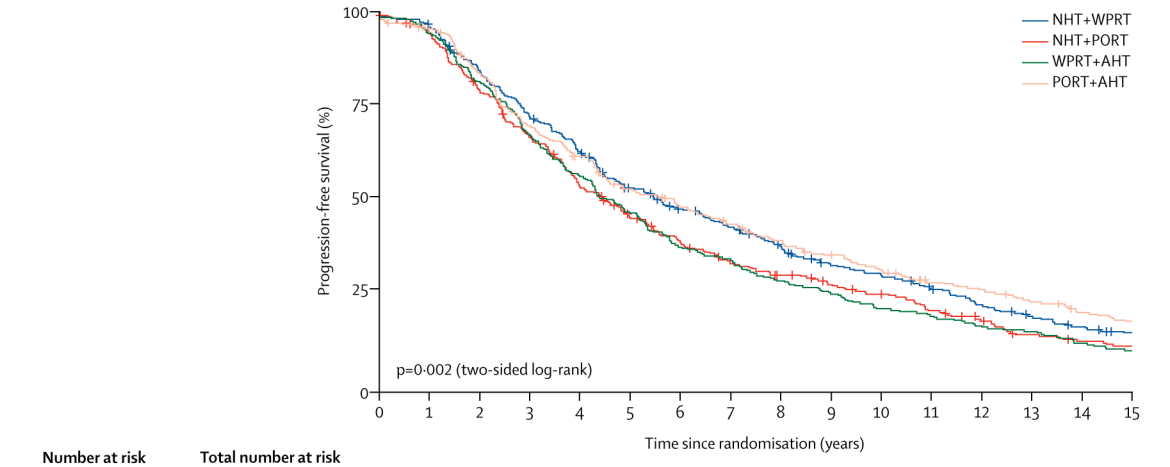


Figure 2: Interaction of radiotherapy and hormone therapy on progression-free survival

(A) By radiotherapy treatment group. (B) By hormone therapy treatment group. Progression-free survival was defined according to the Phoenix definition of biochemical failure. PORT=prostate only radiotherapy. WPRT=whole pelvic radiotherapy.



Number at risk (number censored)	Total number at risk (total number censored)			
NHT plus WPRT	318 (44)	159 (9)	78 (21)	29 (30)
NHT plus PORT	316 (38)	132 (10)	62 (21)	21 (27)
WPRT plus AHT	319 (33)	139 (9)	53 (19)	21 (22)
PORT plus AHT	317 (52)	157 (11)	86 (18)	40 (27)

Figure 3: Progression-free survival

HR=hazard ratio. AHT=adjuvant hormonal therapy. NHT=neoadjuvant hormonal therapy. PORT=prostate only radiotherapy. WPRT=whole pelvic radiotherapy.

Table 1:

Baseline characteristics

	NHT plus WPRT group (n=318)	NHT plus PORT group (n=316)	WPRT plus AHT group (n=319)	PORT plus AHT group (n=317)
Race				
White	228 (72%)	217 (69%)	222 (70%)	214 (68%)
Hispanic or Latino	10 (3%)	4 (1%)	12 (4%)	11 (4%)
Black or African–American	71 (22%)	86 (27%)	77 (24%)	88 (28%)
Other	8 (3%)	5 (2%)	6 (2%)	3 (1%)
Unknown	1 (<1%)	4 (1%)	2 (1%)	1 (<1%)
Karnofsky performance status				
Unable to carry on normal activity or work (70)	6 (2%)	5 (2%)	5 (2%)	6 (2%)
Normal activity with effort (80)	25 (8%)	17 (5%)	22 (7%)	19 (6%)
Minor signs or symptoms of disease (90)	136 (43%)	137 (43%)	132 (41%)	135 (43%)
Normal (100)	151 (48%)	157 (50%)	160 (50%)	157 (50%)
T stage (categorised)				
T1c, T2a	72 (23%)	75 (24%)	69 (22%)	68 (22%)
T1b, T2b	32 (10%)	34 (11%)	22 (7%)	41 (13%)
T2c-T4	214 (67%)	207 (66%)	228 (72%)	208 (66%)
N stage				
N0	16 (5%)	16 (5%)	18 (6%)	21 (7%)
N1	1 (<1%)	4 (1%)	1 (<1%)	2 (1%)
N2	0	0	2 (1%)	1 (<1%)
NX	301 (95%)	296 (94%)	298 (93%)	293 (92%)
M stage				
M0	316 (99%)	312 (99%)	317 (99%)	315 (99%)
MX	2 (1%)	4 (1%)	2 (1%)	2 (1%)
PSA level (categorised)				
≤30	213 (67%)	213 (67%)	213 (67%)	214 (68%)
>30	105 (33%)	103 (33%)	106 (33%)	103 (36%)
Gleason Score (categorised)				
<7	84 (26%)	82 (26%)	86 (27%)	85 (27%)
7–10	234 (74%)	234 (74%)	233 (73%)	232 (73%)
Intercurrent disease				
No	74 (23%)	84 (27%)	83 (26%)	75 (24%)
Yes	244 (77%)	232 (73%)	236 (74%)	242 (76%)

Data are n (%). NHT=neoadjuvant hormonal therapy. WPRT=whole pelvic radiotherapy. PORT=prostate only radiotherapy. AHT=adjuvant hormonal therapy. PSA=prostate-specific antigen.

Table 2:

Multivariable analysis

	Hazard ratio (95% CI)	p value*
Progression-free survival (Phoenix definition)		
Treatment group		
NHT plus WPRT	1 (ref)	..
NHT plus PORT	1·21 (1·02–1·43)	0·027
WPRT plus AHT	1·21 (1·03–1·43)	0·025
PORT plus AHT	0·93 (0·78–1·10)	0·39
Gleason Score		
2–6	1 (ref)	..
7–10	1·27 (1·11–1·45)	0·0006
PSA level (ng/mL)		
≤30	1 (ref)	..
>30	1·43 (1·26–1·63)	<0·0001
T stage		
T1c or T2a	1 (ref)	..
T1b or T2b	0·96 (0·76–1·20)	0·71
T2c–T4	1·05 (0·90–1·21)	0·54
Phoenix biochemical failure		
Treatment group		
NHT plus WPRT	1 (ref)	..
NHT plus PORT	1·38 (1·11–1·72)	0·0045
WPRT plus AHT	1·11 (0·89–1·40)	0·35
PORT plus AHT	1·00 (0·9–1·27)	0·97
Gleason Score		
2–6	1 (ref)	..
7–10	1·42 (1·18–1·71)	0·0002
PSA level, ng/mL		
≤30	1 (ref)	..
>30	1·59 (1·33–1·89)	<0·0001
T stage		
T1c or T2a	1 (ref)	..
T1b or T2b	1·23 (0·92–1·64)	0·15
T2c–T4	1·22 (0·998–1·49)	0·052

NHT=neoadjuvant hormonal therapy. WPRT=whole pelvic radiotherapy. PORT=prostate only radiotherapy. AHT=adjuvant hormonal therapy. PSA=prostate-specific antigen.

*χ^2 using the Cox proportional hazards model for progression-free survival and from the Fine-Gray regression model for Phoenix biochemical failure.

Table 3:

Patients with late treatment-related toxicities

	NHT plus WPRT group (n=316)			NHT plus PORT group (n=313)			WPRT plus AHT group (n=317)			PORT plus AHT group (n=315)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Bladder	185 (59%)	17 (5%)	1 (<1%)	183 (58%)	17 (5%)	0	199 (63%)	21 (7%)	1 (<1%)	178 (57%)	12 (4%)	2 (1%)
Bowel	199 (63%)	15 (5%)	4 (1%)	168 (54%)	4 (1%)	0	229 (72%)	9 (3%)	0	180 (57%)	5 (2%)	1 (<1%)
Haematological	90 (28%)	14 (4%)	7 (2%)	67 (21%)	9 (3%)	3 (1%)	80 (25%)	12 (4%)	7 (2%)	68 (22%)	7 (2%)	1 (<1%)
Liver	9 (3%)	2 (1%)	0	22 (7%)	2 (1%)	0	10 (3%)	1 (<1%)	0	15 (5%)	1 (<1%)	0
Not otherwise specified	56 (18%)	3 (1%)	0	52 (17%)	2 (1%)	0	71 (22%)	2 (1%)	0	59 (19%)	2 (1%)	0
Other gastrointestinal	60 (19%)	4 (1%)	1 (<1%)	33 (11%)	1 (<1%)	0	51 (16%)	1 (<1%)	0	48 (15%)	2 (1%)	0
Other genitourinary	60 (19%)	8 (3%)	0	52 (17%)	2 (1%)	0	73 (23%)	8 (3%)	0	55 (17%)	5 (2%)	0
Skin	90 (28%)	0	0	77 (25%)	2 (1%)	0	98 (31%)	1 (<1%)	0	87 (28%)	0	0

Data are n (%). There were no late grade 5 treatment-related events (deaths). NHT=neoadjuvant hormonal therapy. WPRT=whole pelvic radiotherapy. PORT=prostate only radiotherapy. AHT=adjuvant hormonal therapy. PSA=prostate-specific antigen.