The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial

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Summary

Background In men with a detectable prostate-specific antigen (PSA) level after prostatectomy for prostate cancer, salvage prostate bed radiotherapy (PBRT) results in about 70% of patients being free of progression at 5 years. A three-group randomised trial was designed to determine whether incremental gains in patient outcomes can be achieved by adding either 4–6 months of short-term androgen deprivation therapy (ADT) to PBRT, or both short-term ADT and pelvic lymph node radiotherapy (PLNRT) to PBRT.

Methods The international, multicentre, randomised, controlled SPPORT trial was done at 283 radiation oncology cancer treatment centres in the USA, Canada, and Israel. Eligible patients (aged ≥18 years) were those who after prostatectomy for adenocarcinoma of the prostate had a persistently detectable or an initially undetectable and rising PSA of between 0·1 and 2·0 ng/mL. Patients with and without lymphadenectomy (N0/Nx) were eligible if there was no clinical or pathological evidence of lymph node involvement. Other eligibility criteria included pT2 or pT3 disease, prostatectomy Gleason score of 9 or less, and a Zubrod performance status of 0–1. Eligible patients were randomly assigned to receive PBRT alone at a dose of 64·8–70·2 Gy at 1·8 Gy per fraction daily (group 1), PBRT plus short-term ADT (group 2), or PLNRT (45 Gy at 1·8 Gy per fraction, and then a volume reduction made to the planning target volume for the remaining 19·8–25 ·2 Gy) plus PBRT plus short-term ADT (group 3). The primary endpoint was freedom from progression, in which progression was defined as biochemical failure according to the Phoenix definition (PSA ≥2 ng/mL over the nadir PSA), clinical failure (local, regional, or distant), or death from any cause. A planned interim analysis of 1191 patents with minimum potential follow-up time of 5 years applied a Haybittle-Peto boundary of p<0·001 (one sided) for comparison of 5-year freedom from progression rates between the treatment groups. This trial is registered with ClinicalTrials.gov, NCT00567580. The primary objectives of the trial have been completed, although long-term follow-up is continuing.

Findings Between March 31, 2008, and March 30, 2015, 1792 eligible patients were enrolled and randomly assigned to the three treatment groups (592 to group 1 [PBRT alone], 602 to group 2 [PBRT plus short-term ADT], and 598 to group 3 [PLNRT plus PBRT plus short-term ADT]). 76 patients subsequently found to be ineligible were excluded from the analyses; thus, the evaluable patient population comprised 1716 patients. At the interim analysis (n=1191 patients; data cutoff May 23, 2018), the Haybittle-Peto boundary for 5-year freedom from progression was exceeded when group 1 was compared with group 3 (difference 17·9%, SE 2·9%; p<0·0001). The difference between groups 2 and 3 did not exceed the boundary (p=0·0063). With additional follow-up beyond the interim analysis (the final planned analysis; data cutoff May 26, 2021), at a median follow-up among survivors of 8·2 years (IQR 6·6–9·4), the 5-year freedom from progression rates in all 1716 eligible patients were 70·9% (95% CI 67·0–74·9) in group 1, 81·3% (78·0–84·6) in group 2, and 87·4% (84·7–90·2) in group 3. Per protocol criteria, freedom from progression in group 3 was superior to groups 1 and 2. Acute (≤3 months after radiotherapy) grade 2 or worse adverse events were significantly more common in group 3 (246 [44%] of 563 patients) than in group 2 (201 [36%] of 563; p=0·0034), which, in turn, were more common than in group 1 (98 [18%] of 547; p<0·0001). Similar findings were observed for grade 3 or worse adverse events. However, late toxicity (>3 months after radiotherapy) did not differ significantly between the groups, apart from more late grade 2 or worse blood or bone marrow events in group 3 versus group 2 (one-sided p=0·0060) attributable to the addition of PLNRT in this group.

Interpretation The results of this randomised trial establish the benefit of adding short-term ADT to PBRT to prevent progression in prostate cancer. To our knowledge, these are the first such findings to show that extending salvage radiotherapy to treat the pelvic lymph nodes when combined with short-term ADT results in meaningful reductions in progression after prostatectomy in patients with prostate cancer.

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Introduction

Biochemical recurrence after prostatectomy is a key clinical management issue in patients with prostate cancer, with 20–50% of men experiencing a persistently elevated or delayed rise in prostate-specific antigen (PSA) within 5–10 years after prostatectomy, depending on clinicopathological factors (including pre-prostatectomy PSA level, PSA kinetics, pathological stage, surgical margin status, and lymph node status).[1] In three randomised trials of adjuvant prostate bed radiotherapy (PBRT),[2–4] in which patients were selected mainly for adverse prostatectomy pathological risk factors (extracapsular extension, a positive surgical margin, or seminal vesicle involvement), the 10-year biochemical failure rates exceeded 60% without PBRT,[3–5] but the failure rate was reduced by about 50% with the addition of adjuvant PBRT. Although there has been an ongoing debate about the timing of radiotherapy (adjuvant versus early salvage) in such high-risk patients, based on recent reports from three randomised trials and a meta-analysis,[6–9] most patients should be recommended to have early salvage PBRT when the PSA rises after prostatectomy. The efficacy of PBRT and the preference for early salvage therapy has been established; however, the results of salvage PBRT are suboptimal and are influenced by clinicopathological factors, as well as by the intensity of treatment.[10] The three-group SPPORT trial was designed to address two key management questions in men with prostate cancer treated with salvage radiotherapy. First, whether or not an incremental benefit in freedom from progression results from the addition of short-term androgen deprivation therapy (ADT) for 4–6 months to standard PBRT and, second, whether a further benefit can be achieved from the addition of pelvic lymph node radiotherapy (PLNRT) to that combination. The benefit of adding ADT to radiotherapy is well established in men treated primarily for prostate cancer; however, much less evidence exists to support the use of ADT routinely in men treated with salvage therapy after prostatectomy[11,12] and substantial controversy remains in terms of the selection of patients for ADT.[13] The SPPORT trial aims to provide new insights into the use of short-term ADT with postoperative radiotherapy and describes, for the first time to our knowledge, the impact of adding pelvic lymph node treatment on disease progression and its associated side-effects.

Methods

Study design and participants

The SPPORT trial was an international, multicentre, randomised, controlled trial with three treatment groups: PBRT alone (group 1), PBRT plus short-term ADT (group 2), and PBRT plus PLNRT plus short-term ADT (group 3). Patients were enrolled into the trial from 283 RTOG/NRG-affiliated radiation oncology departments in the USA, Canada, and Israel.

Eligible patients were those who after prostatectomy for adenocarcinoma of the prostate had a persistently

Research in context

Evidence before this study

Salvage radiotherapy to the post-prostatectomy surgical bed in patients with a detectable prostate-specific antigen (PSA) level is a curative option for recurrent prostate cancer; however, biochemical failure occurs in more than 50% of cases, which usually leads to the need for lifelong systemic treatment. For men with high-risk prostate cancer, androgen deprivation therapy (ADT) combined with radiotherapy had been shown in randomised trials to significantly improve long-term outcomes. Pelvic lymph node radiotherapy treatment had also been shown to reduce progression when added to prostate radiotherapy plus neoadjuvant and concurrent short-term ADT (in the NRG/RTOG 94-13 trial). Before starting this trial, we did multiple searches of the published literature, using several keywords, including "prostate cancer", "radiotherapy" (with and without "salvage"), "prostatectomy", "androgen deprivation therapy" (also "hormone therapy" and "antiandrogen therapy"), and "pelvic lymph node", with a focus on clinical trials and randomised, controlled trials. At the time this trial was conceived, there were no published randomised trials evaluating the gains from the addition of ADT and pelvic lymph node treatment to salvage prostate bed radiotherapy.

Added value of this study

To our knowledge, SPPORT is the first salvage radiotherapy randomised trial to evaluate whether short-term ADT and extended radiotherapy field coverage of the pelvic lymph nodes improve patient outcomes when applied incrementally to conventional prostate bed treatment. The greatest benefit was recorded in men who received both short-term ADT and pelvic lymph node coverage. There was a minor increase in late bone marrow adverse events from the combined treatment.

Implications of all the available evidence

SPPORT is the third randomised trial to show a benefit from the addition of ADT to salvage prostate bed radiotherapy and, to our knowledge, the first to show further gains from the addition of pelvic lymph node radiotherapy to this treatment regimen. Pelvic lymph node coverage should be strongly considered in conjunction with prostate bed radiotherapy and ADT in patients with a persistently detectable or an initially undetectable and rising PSA after prostatectomy for prostate cancer.

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detectable or an initially undetectable and rising PSA of between 0·1 and 2·0 ng/mL. Patients with and without lymphadenectomy (N0/Nx) were eligible if there was no clinical or pathological evidence of lymph node involvement. Other eligibility criteria included patients with pT2 or pT3 disease, prostatectomy Gleason score of 9 or less, Zubrod performance status[14] of 0–1, age 18 years or older, adequate bone marrow function (platelet count ≥100 000 per mm³ and haemoglobin concentration ≥10·0 g/dL), aspartate aminotransferase (AST) or alanine aminotransaminase (ALT) up to 2× the upper limit of normal, serum total testosterone at least 40% of the lower limit of normal, and no evidence of distant metastasis on technetium-99m bone scan or CT scan of the abdomen and pelvis.

Exclusion criteria were: a palpable prostatic fossa mass on digital rectal examination, pN1 disease, ADT started more than 6 months before prostatectomy, ADT given for more than 3 months after prostatectomy, previous chemotherapy for prostate cancer, primary treatment of the prostate before prostatectomy, a malignancy within the previous 5 years (except non-melanomatous skin cancer or superficial bladder cancer), a history of inflammatory bowel disease, and other notable comorbidities. The full inclusion and exclusion criteria are in the appendix (pp 1–2).

See Online for appendix

Patients were consented and enrolled at institutional sites with institutional review board approval. All patients provided written consent that was obtained by participating investigators trained in Good Clinical Practice and who followed respective institutional consent procedures.

Randomisation and masking

Patients were randomly assigned to the three treatment groups according to the permuted block scheme of Zelen[15] stratified by seminal vesicle involvement (no *vs* yes), Gleason score (≤7 *vs* 8–9), baseline PSA level (between 0·1 and ≤1·0 ng/mL *vs* between >1·0 and <2·0 ng/mL), and pathological stage (pT2 and margin negative *vs* other). Randomisation was done by RTOG/NRG headquarters. Since this was not a blinded trial, treatment assignments were generated at the time of patient registration and communicated to the enrolling site. Patients and investigators were masked to the upcoming assignment, which was revealed when registration was completed.

Procedures

Patients in all three treatment groups received PBRT. The standard PBRT consensus clinical target volume (CTVp) as defined by Michalski et al[16] was used for administration of PBRT (appendix p 3). A range of PBRT total doses to the planning target volume (PTVp; see appendix pp 3–4) were permitted, from 64·8 to 70·2 Gy at 1·8 Gy per fraction daily at five fractions per week, since emerging data from retrospective series[17,18] suggested that higher doses of PBRT might reduce progression rates. For patients in group 3 (who received PBRT plus PLNRT plus short-term ADT), the PLNRT nodal clinical target volume included the obturator, external iliac, proximal internal iliac, presacral, and common iliac nodes, estimated using the vascular structures, up to the level of L5–S1 (between the inferior aspect of the fifth lumbar and superior aspect of the first sacral vertebrae).[19] The nodal planning target volume with PLNRT was to be treated to 45 Gy at 1·8 Gy per fraction administered 5 days per week for the first 5 weeks, and then a volume reduction made to the PTVp for the remaining 19·8–25·2 Gy (appendix pp 3–4).

Short-term ADT (in groups 2 and 3), was planned to start within 6 weeks of registration and was administered to patients in these two treatment groups for a total of 4–6 months, starting 2 months before the initiation of radiotherapy. A combination of an antiandrogen, either oral flutamide 250 mg three times daily or oral bicalutamide 50 mg once daily, and injections of long-acting luteinising hormone-releasing hormone (LHRH) agonists (analogues approved by the US Food and Drug Administration or Health Canada for Canadian institutions) was used. Antiandrogen therapy was planned to begin at approximately the same time as the initial LHRH agonist injection but could be started up to 2 weeks earlier. The timing and length of ADT was based on the LHRH agonist injections and was specified at enrolment. Antiandrogen administration was planned for 4 months, ending at the completion of radiotherapy. The ADT treatments were not blinded.

Before radiotherapy, all patients underwent a complete blood count, and AST, ALT, PSA, and testosterone levels were measured. All patients also completed an American Urological Association symptom index[20] (AUASI) questionnaire at baseline. Interval assessments of quality of life and neurocognitive function were also done (at baseline; at 3, 6, and 12 months; then every 6 months through year 6, then annually) and will be reported separately. National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0[21] were used to monitor acute and late toxicity at every protocol-specified clinic visit. During radiotherapy, each patient was seen and evaluated weekly. During week 6, a complete blood count, AST, ALT, and testosterone measurements were planned, along with completion of an AUASI questionnaire. After radiotherapy, AST or ALT measurements were planned at 1·5 months, 3 months, and 6 months, while a complete blood count was to be obtained at 3 months and 6 months. PSA assessments were planned for 1·5 months and 3 months, then at 3-month intervals for the remainder of the first 2 years, and then at 6-month intervals unless the PSA was 0·2 ng per mL or higher, in which case PSA was obtained at 3-month intervals. CT or MRI scan of the pelvis and technetium-99m bone scans were done during follow-up as clinically indicated. For patients who died, two investigators (HMS and AGB) independently reviewed the cause of death and adjudication was done by a third investigator (AP).

Outcomes

The primary endpoint was freedom from progression at 5 years, in which a progression event was defined as the first occurrence of biochemical failure according to the Phoenix definition[22] (PSA ≥2 ng/mL over the nadir PSA), clinical failure (local failure, regional metastasis, or distant metastasis), or death from any cause. Local failure was defined as the development of a new palpable abnormality in the prostate bed. Regional metastasis was defined as radiographic evidence of pelvic lymphadenopathy (lymph node size ≥1·5 cm) in a patient without the diagnosis of a haematological or lymphomatous disorder associated with adenopathy. Distant metastasis was detected by imaging (ie, bone scan, CT, or MRI). Secondary endpoints were local failure, regional failure, distant metastasis, biochemical failure according to the Phoenix definition, alternative biochemical failure (PSA ≥0·4 ng/mL and a second rise above nadir or the start of second salvage therapy), castration-resistant disease (defined as three rises in PSA during second salvage ADT), cause-specific mortality (death due to prostate cancer or complications of protocol treatment [centrally reviewed] or death following clinical or biochemical progression in the absence of or after the initiation of any salvage therapy), overall survival (time from randomisation to death from any cause), adverse event rates, and time from initiation of therapy to late-grade toxicity.

Statistical analysis

The hypothesis of the SPPORT trial was that treatment intensification via the addition of neoadjuvant and concurrent short-term ADT to PBRT and then the further addition of PLNRT would result in incremental improvements in freedom from progression at 5 years. The use of the Phoenix definition of biochemical failure (PSA ≥2 ng/mL over the nadir PSA) as part of the definition of progression events was chosen based on its association with clinical failure (appendix p 1) using a large multi-institutional database.[23] The Phoenix definition is widely used in men treated primarily with radiotherapy for prostate cancer and was as good as or better than several other potential definitions in terms of sensitivity, specificity, and positive predictive value for clinical failure (appendix p 1). The anticipated freedom from biochemical failure at 5 years in the PBRT alone group of 70% was based on this multi-institutional cohort,[23] and was used to inform the sample size of the trial.

The sample size calculation was based on an assumed primary freedom from progression rate at 5 years for group 1 (PBRT alone) of 70%, a hypothesised 10% improvement in 5-year freedom from progression in patients treated in group 2 (with the addition of short-term ADT) to 80%, and a 20% improvement in patients treated in group 3 (with the addition of both short-term ADT and PLNRT) to 90%. The sample size was based on the backward elimination decision rule described by Chen and Simon[24] because the three treatments can be ordered in terms of decreasing preference from a toxicity perspective. Consequently, for evaluation of efficacy, the objective was to decide among three one-sided

	PBRT alone (group 1; n=564)	PBRT plus short-term ADT (group 2; n=578)	PLNRT plus PBRT plus short-term ADT (group 3; n=574)
Age, years			
Mean	63·8 (6·9)	63·9 (6·9)	63·9 (6·5)
Median	64 (60–69)	64 (59–69)	64 (59–69)
Range	42–84	39–80	44–80
≤49	19 (3%)	15 (3%)	8 (1%)
50–59	118 (21%)	137 (24%)	138 (24%)
60–69	307 (54%)	299 (52%)	307 (54%)
≥70	120 (21%)	127 (22%)	121 (21%)
Race			
American Indian/Alaska Native	0	0	5 (1%)
Asian	3 (1%)	6 (1%)	8 (1%)
Black or African American	74 (13%)	69 (12%)	77 (13%)
Native Hawaiian or other Pacific Islander	1 (<1%)	4 (1%)	0
White	464 (82%)	482 (83%)	474 (83%)
Mixed race	3 (1%)	0	0
Unknown or not reported	19 (3%)	17 (3%)	10 (2%)
Ethnicity			
Hispanic or Latino	21 (4%)	23 (4%)	30 (5%)
Not Hispanic or Latino	511 (91%)	527 (91%)	517 (90%)
Unknown	32 (6%)	28 (5%)	27 (5%)
Zubrod performance status			
0	522 (93%)	539 (93%)	540 (94%)
1	42 (7%)	39 (7%)	34 (6%)
Pathological seminal vesicle involvement			
No	482 (86%)	494 (86%)	488 (85%)
Yes	82 (15%)	84 (15%)	86 (15%)
Pathological tumour stage			
T2	292 (52%)	317 (55%)	304 (53%)
pT3 extraprostatic extension NOS	13 (2%)	15 (3%)	18 (3%)
pT3a extraprostatic extension	177 (31%)	162 (28%)	166 (29%)
pT3b seminal vesicle invasion	82 (15%)	84 (15%)	86 (15%)
Gleason score			
4	0	1 (<1%)	1 (<1%)
5	3 (1%)	1 (<1%)	5 (1%)
6	80 (14%)	85 (15%)	89 (16%)
7: 3+4	226 (40%)	240 (42%)	221 (39%)
7: 4+3	153 (27%)	148 (26%)	156 (27%)
7: primary or secondary not indicated	9 (2%)	5 (1%)	3 (1%)
8	57 (10%)	60 (10%)	57 (10%)
9	36 (6%)	38 (7%)	42 (7%)
Prostatectomy margins			
Positive	288 (51%)	289 (50%)	284 (50%)
Negative	267 (47%)	284 (49%)	287 (50%)
Unknown	9 (2%)	5 (1%)	3 (1%)

(Table 1 continues on next page)

	PBRT alone (group 1; n=564)	PBRT plus short-term ADT (group 2; n=578)	PLNRT plus PBRT plus short-term ADT (group 3; n=574)
(Continued from previous page)			
Pelvic lymphadenectomy			
No	189 (34%)	207 (36%)	209 (36%)
Yes	375 (67%)	371 (64%)	365 (64%)
Number of lymph nodes examined*			
Mean	7·2 (5·7)	7·8 (6·6)	7·2 (5·9)
Median	5 (3–10)	6 (3–11)	5 (3–10)
Range	0–34	1–54	1–32
Pre-radiotherapy baseline PSA (ng/mL)			
Mean	0·47 (0·38)	0·51 (0·39)	0·47 (0·37)
Median	0·32 (0·20–0·60)	0·40 (0·23–0·68)	0·32 (0·20–0·60)
Range	0·1–1·96	0·1–1·93	0·1–1·93
≥0·1 to ≤0·2 ng/mL	155 (28%)	126 (22%)	154 (27%)
>0·2 to ≤0·5 ng/mL	247 (44%)	256 (44%)	247 (43%)
>0·5 to ≤1·0 ng/mL	105 (19%)	130 (23%)	114 (20%)
>1·0 to <2·0 ng/mL	57 (10%)	66 (11%)	59 (10%)
Time from surgery to randomisation			
>0 to ≤6 months	64 (11%)	74 (13%)	69 (12%)
>6 to ≤12 months	89 (16%)	100 (17%)	81 (14%)
>12 to ≤18 months	60 (11%)	55 (10%)	71 (12%)
>18 months	351 (62%)	349 (60%)	353 (62%)
Median, years	2·3 (0·9–4·6)	2·1 (0·8–4·3)	2·1 (0·9–4·4)
Range	0·1–20·5	0·1–17·6	0·1–17·7
Postoperative PSA doubling time†			
>0 to ≤6 months	34 (22%)	32 (21%)	32 (20%)
>6 to ≤12 months	54 (35%)	55 (35%)	62 (39%)
>12 to ≤18 months	26 (17%)	33 (21%)	27 (17%)
>18 months	42 (27%)	36 (23%)	38 (24%)

ADT=androgen deprivation therapy. NOS=not otherwise specified. PBRT=prostate bed radiotherapy. PLNRT=pelvic lymph node radiotherapy. PSA=prostate-specific antigen. *Data available for n=349 patients in group 1, n=336 patients in group 2, and n=336 patients in group 3. Patients without available data were excluded from the lymph node number calculations. †The requirement to record PSA doubling time before enrollment was removed in an amendment to the protocol on March 31, 2009. Only n=471 values were available (n=156 in group 1, n=156 in group 2, and n=159 in group 3).

Table 1: **Baseline demographic and clinical characteristics**

alternatives: group 3 is better than both groups 1 and 2; group 3 is not better than group 2 but group 2 is better than group 1; and neither groups 3 or 2 are better than group 1. In the backward elimination procedure, group 3 is first compared with group 2. If it is significantly better (Z statistic >1·6249), group 2 is eliminated and group 3 is then compared with group 1 at a critical Z value of 2·0768. If group 3 is not significantly better than group 2, group 2 is compared with group 1. The critical values for each test were chosen such that the overall alpha level (the probability of selecting either group 2 or group 3 if all three groups were equal) was maintained at the one-sided alpha 0·025 level. To detect the postulated 10% improvements in 5-year freedom from progression, 529 patients per group were required to provide 90% power using the Chen and Simon approach. The final accrual target was 1764 patients (588 per group) to allow for 10% of patients being ineligible upon review of eligibility data.

The initiation of second salvage therapy before the primary endpoint criteria being met was strongly discouraged and resulted in censoring to avoid potential bias. A sensitivity analysis was also done in which such patients were not censored.

Three interim analyses were planned to enable early stopping of the trial for efficacy or futility. For efficacy, a Haybittle-Peto (HP) boundary requiring p<0·001 was required.[25] Futility testing was based on the Freidlin and Korn method.[26] Details of the interim testing procedures are provided in the appendix (pp 4–5). The three interim analyses were planned when there were 397, 794, and 1191 eligible patients with 5 years of potential follow-up from the randomisation date. At the third interim analysis, the HP efficacy boundary was crossed for group 3 versus group 1 and the findings released. In addition to comparison of five-year freedom from progression rates, the overall freedom from progression curves were estimated using the Kaplan-Meier method[27] and compared via a log-rank test. Cox regression models[28] were fitted to estimate the hazard ratio (HR), both unadjusted and adjusted for the four stratification factors, along with age (<65 *vs* ≥65 years) and race or ethnicity (White *vs* other), as stipulated in the protocol. The secondary endpoints (except for overall survival) were analysed by estimating cumulative incidence curves, treating death as a competing risk, followed by log-rank tests and comparison of the cause-specific hazard rates.

Two post-hoc endpoints were analysed to contextualise the findings. These two endpoints were metastasis-free survival (time from randomisation to distant metastasis or death from any cause) and time from randomisation to initiation of second salvage ADT. Additional details on the secondary and post-hoc analyses are provided in the appendix (p 5). Additional post-hoc analyses were performed in which we analysed freedom from progression subdivided by the median pre-treatment PSA, as well as within subgroups defined by the stratification factors (Gleason score, pathological stage, and seminal vessel involvement). Initiation of second salvage ADT was also analysed subdivided by median pre-treatment PSA. Freedom from progression was compared in a post-hoc analysis between patients receiving 4 versus 6 months of LHRH agonist therapy.

All p values in this report are one-sided unless otherwise noted. Declarations of statistical significance for the primary endpoint (5-year freedom from progression rates) in this report are based upon the HP boundary when referring to the interim findings and the Chen and Simon critical values for the final results, while those for log-rank tests and Cox HRs for freedom from progression, as well as the secondary endpoints, are based on a one-sided p<0·0125 (to allow for multiple comparisons). The exception is toxicity, which used a per-protocol specified one-sided p<0·025. The cutoff date for the data

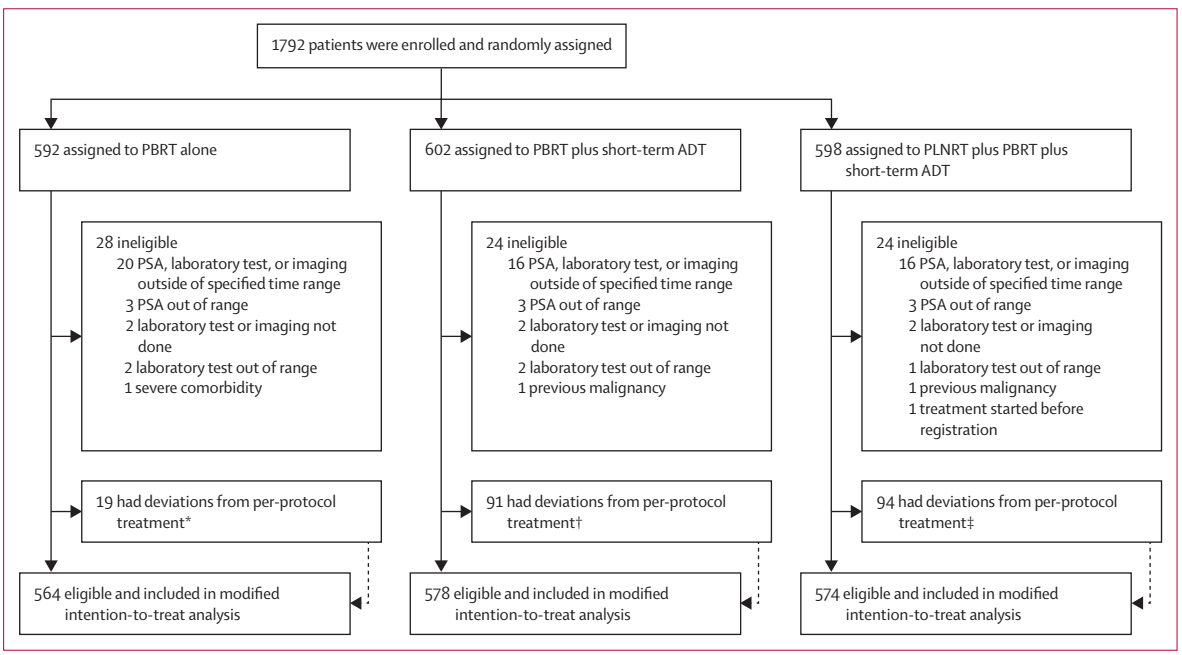


Figure 1: **Trial profile**
ADT=androgen deprivation therapy. PBRT=prostate bed radiotherapy. PLNRT=pelvic lymph node radiotherapy. PSA=prostate-specific antigen. *8 withdrew, 1 came off treatment because of other complicating disease, and 10 stopped for other or unknown reasons. †28 due to side-effects, 12 withdrew, 1 received alternative therapy, and 50 for other or unknown reasons. ‡27 due to side-effects, 1 death, 14 withdrawals, 1 alternative therapy, 2 came off treatment because of other complicating diseases, and 49 for other or unknown reasons.

included in this report was May 26, 2021. This trial is registered with ClinicalTrials.gov, NCT00567580.

Role of the funding source

This study was funded by the National Cancer Institute (NCI) Cancer Trials Support Unit. The NCI reviewed and approved the trial design and the final manuscript but had no role in data collection, analysis, interpretation of the results, or writing of the report.

Results

Between March 31, 2008, and March 30, 2015, 1792 patients were enrolled into the trial (appendix p 27). The rate of accrual was initially slower than planned because postoperative PSA doubling time calculations were required per protocol for all enrolled patients. When the requirement for PSA doubling time data was eliminated (a protocol amendment approved by the NCI and broadcast on March 31, 2009), the recruitment rate increased and the accrual goal was met ahead of schedule. In the current analysis, PSA doubling time was only available in 471 patients (table 1); however, in patients with available data, this parameter was well balanced across the three treatment groups. Of the 1792 enrolled patients, 592 were randomly assigned to PBRT alone, 602 to PBRT plus short-term ADT, and 598 to PLNRT plus PBRT plus short-term ADT. Of note, 76 patients were subsequently found to be ineligible and were excluded from the analyses; thus, the evaluable patient population comprised 1716 patients (figure 1).

Patient and tumour characteristics (table 1) were well balanced across the treatment groups. Overall, about 15% of patients had pT3b disease, 53% had pT2 disease, 50% had positive margins, and 17% had a Gleason score of 8 or higher. Pelvic lymphadenectomy was done in 65% of patients, with a median number of lymph nodes removed of 6 (IQR 3–11). The median PSA at protocol registration (pre-radiotherapy) was 0·35 ng/mL (IQR 0·20–0·60). There was no significant correlation between PSA and Gleason score (Spearman's rank correlation –0·025, p=0·30). The median time interval between surgery and randomisation was 2·3 years (IQR 0·9–4·6) in group 1, 2·1 years (0·8–4·3) in group 2, and 2·1 years (0·9–4·4) in group 3. The median age of the patients at enrollment was 64 years (IQR 59–69).

Intensity-modulated radiotherapy was used in 1459 (87%) of 1673 patients (478 [87%] of 548 patients in group 1, 494 [88%] of 562 patients in group 2, and 487 [86%] of 563 patients in group 3). Radiotherapy administration was assessed centrally at RTOG/NRG headquarters by AP and AGB in all patients. Total dose, fractionation, and the time window for delivery were performed per protocol in more than 95% of patients in all three treatment groups (appendix pp 6–7). The target and organs at risk volumes were acceptable in more than 90% of patients overall and within each treatment group (appendix pp 6–7). Overall, radiotherapy delivery was acceptable (per protocol or variation acceptable) in 1617 (94%) of 1716 patients (532 [94%] of 564 in group 1, 544 [94%] of 578 in group 2, and 541 [94%] of 574 in

group 3). Central review of compliance with ADT therapy was done on a random sample (drawn using computer-generated random numbers) of 258 (45%) of the 578 patients in group 2 and 255 (44%) of the 574 patients in group 3, stratified by region and period of enrollment (appendix pp 8–9). The proportion of patients who received per-protocol or acceptable ADT (those receiving 80–120% of protocol dose and without any dose delays of more than 2 weeks) was 76% (195 of 258) in group 2 and 86% (220 of 255) in group 3, for the anti-androgen component, and 86% (223 of 258) and 89% (227 of 255), respectively, for the LHRH-targeted treatment component (appendix pp 8–9). Additional details regarding radiotherapy and ADT delivery as

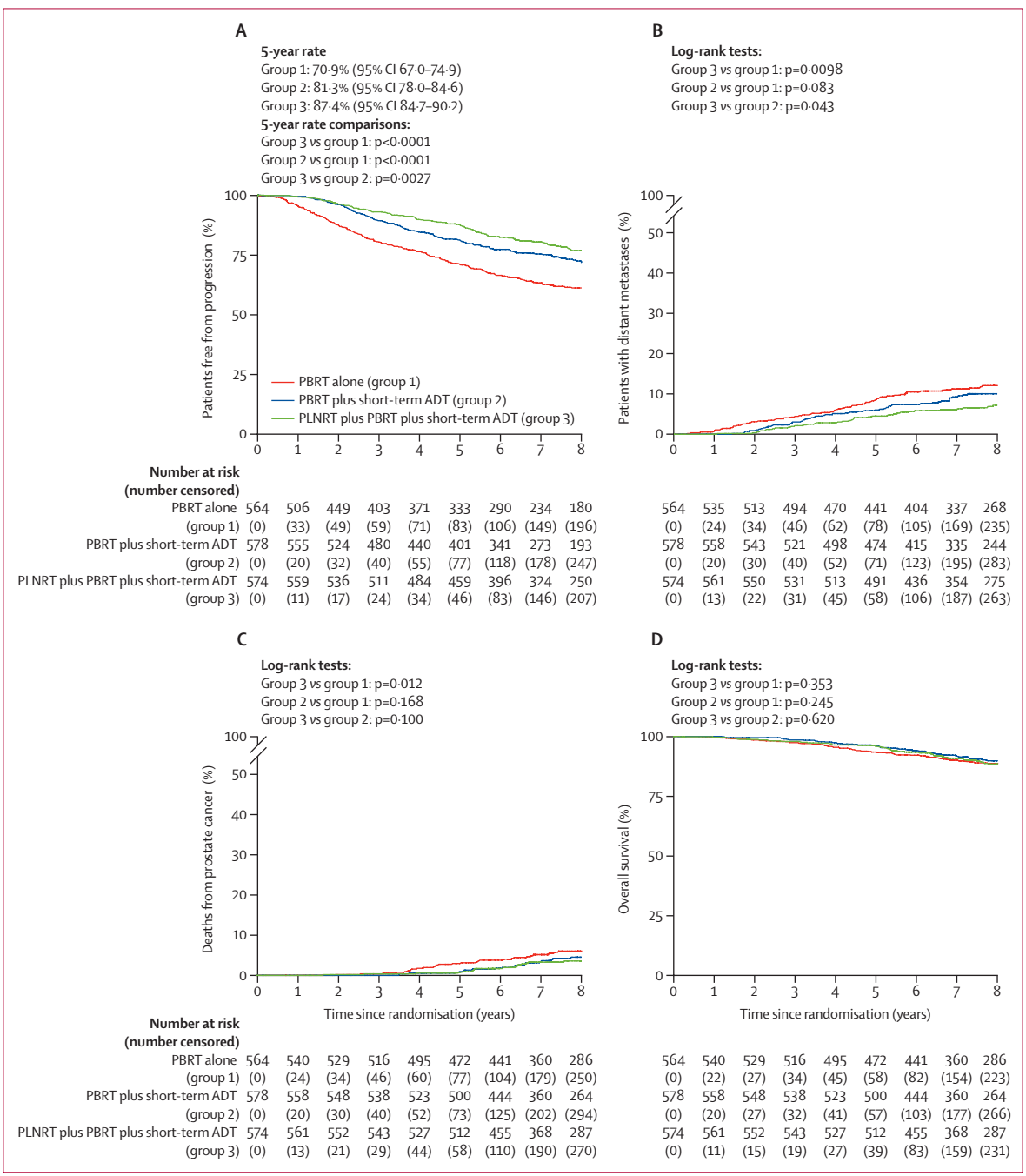


Figure 2: **Kaplan-Meier estimates and cumulative incidence curves**
(A) Freedom from progression. (B) Distant metastases. (C) Prostate cancer death. (D) Overall survival. ADT=androgen deprivation therapy. PBRT=prostate bed radiotherapy. PLNRT=pelvic lymph node radiotherapy. All p values are one-sided.

reported by the individual study sites are given in the appendix (pp 10–12). The median radiotherapy dose to the prostate bed in all evaluable patients was 68·4 Gy (IQR 66·6–70·2) and the median length of short-term ADT (LHRH component) was 6 months (IQR 4–6).

The median follow-up among surviving patients as of data cutoff on May 26, 2021 is 8·2 years (IQR 6·6–9·4). The third interim analysis of the primary endpoint was reported to the data monitoring committee on July 12, 2018. For this interim analysis, there were 1191 eligible patients with data on 5-year freedom from progression (399 in group 1, 398 in group 2, and 394 in group 3), with 5-year rates of 71·1% (95% CI 66·4–75·9) in group 1, 82·7% (78·8–86·6) in group 2, and 89·1% (85·9–92·2) in group 3 (appendix p 28). When compared with group 1, group 3 exceeded the HP efficacy stopping boundary, with a difference in 5-year freedom from progression of 17·9% (SE 2·9%; p<0·0001). Group 3 was then compared with group 2, yielding a difference in 5-year freedom from progression of 6·4% (SE 2·6%; p=0·0063), which did not cross the HP boundary. The difference between group 2 and group 1 was 11·5% (SE 3·1%; p=0·00011).

Similar results to the interim analysis were obtained for all 1716 eligible patients for this final planned analysis (figure 2A). The 5-year freedom from progression rates for all eligible patients were 70·9% (95% CI 67·0-74·9) in group 1, 81·3% (78·0–84·6) in group 2, and 87·4% (84·7–90·2) in group 3. Both group 3 (PBRT plus PLNRT plus short-term ADT) and group 2 (PBRT plus short-term ADT) were significantly different from group 1 (PBRT alone), with differences of 16·5% (SE 2·5%) for group 3 versus group 1 and 10·4% (SE 2·6%) for group 2 versus group 1, with both p<0·0001. The addition of PLNRT to PBRT plus short-term ADT (ie, group 3 *vs* group 2) resulted in an increase in 5-year freedom from progression of 6·1% (SE 2·2%), p=0·0027. Thus, according to the Chen and Simon procedure, group 3 can be declared superior to both groups 1 and 2. In a sensitivity analysis of all eligible patients, in which 22 patients who were administered salvage therapy before having an event (12 patients in group 1, 6 in group 2, and 4 in group 3) were not censored, the findings were very similar (appendix p 29).

Estimated treatment effects on freedom from progression based on univariable and multivariable Cox regression models adjusting for PSA level at baseline, pathological stage, seminal vesicle involvement, Gleason score, age, and race are shown in table 2, which also includes log-rank p values. Unadjusted and adjusted HRs were similar for all comparisons. Again, based on the Chen-Simon procedure, group 3 can be declared superior to both groups 1 and 2 (table 2). Significant (p<0·05) covariate effects obtained from the multivariate analysis of freedom from progression were pre-radiotherapy baseline PSA level (>1·0–<2·0 ng/mL *vs* 0·1–1·0 ng/mL; HR 1·83 [95% CI 1·42–2·36]), seminal vesicle involvement (yes *vs* no; HR 2·19 [95% CI 1·75–2·74]), and Gleason score (8–9 *vs* ≤7; HR 2·05 [95% CI 1·66–2·53]).

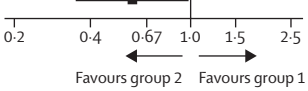
	Events, n/patients, N	Comparison	Unadjusted HR (97·5% CI)	p value*†	Adjusted HR (97·5% CI)‡	p value†§
Freedom from progression						
Group 1	202/564	Group 3 *vs* group 1	0·54 (0·42–0·69)	<0·0001	0·50 (0·39–0·64)	<0·0001
Group 2	151/578	Group 2 *vs* group 1	0·64 (0·50–0·82)	<0·0001	0·60 (0·47–0·77)	<0·0001
Group 3	140/574	Group 3 *vs* group 2	0·82 (0·63–1·07)	0·050	0·82 (0·63–1·07)	0·048
Distant metastases						
Group 1	69/564	Group 3 *vs* group 1	0·55 (0·35–0·85)	0·00098	0·52 (0·34–0·81)	0·00051
Group 2	56/578	Group 2 *vs* group 1	0·78 (0·52–1·17)	0·083	0·74 (0·49–1·11)	0·047
Group 3	41/574	Group 3 *vs* group 2	0·70 (0·44–1·11)	0·043	0·71 (0·45–1·12)	0·046
Prostate cancer death						
Group 1	36/564	Group 3 *vs* group 1	0·54 (0·29–1·00)	0·012	0·51 (0·27–0·94)	0·0070
Group 2	29/578	Group 2 *vs* group 1	0·79 (0·45–1·38)	0·168	0·73 (0·42–1·28)	0·104
Group 3	21/574	Group 3 *vs* group 2	0·69 (0·36–1·32)	0·100	0·70 (0·37–1·32)	0·104
Overall survival						
Group 1	69/564	Group 3 *vs* group 1	0·94 (0·64–1·37)	0·353	0·93 (0·63–1·36)	0·332
Group 2	63/578	Group 2 *vs* group 1	0·89 (0·60–1·31)	0·245	0·87 (0·59–1·29)	0·213
Group 3	69/574	Group 3 *vs* group 2	1·05 (0·71–1·56)	0·620	1·07 (0·72–1·58)	0·645
Biochemical failure (Phoenix definition)						
Group 1	145/564	Group 3 *vs* group 1	0·48 (0·36–0·66)	<0·0001	0·47 (0·34–0·64)	<0·0001
Group 2	104/578	Group 2 *vs* group 1	0·65 (0·49–0·87)	0·00038	0·63 (0·47–0·84)	0·00015
Group 3	83/574	Group 3 *vs* group 2	0·74 (0·53–1·03)	0·020	0·75 (0·54–1·04)	0·025
Alternative biochemical failure‖						
Group 1	245/564	Group 3 *vs* group 1	0·43 (0·34–0·55)	<0·0001	0·40 (0·31–0·51)	<0·0001
Group 2	168/578	Group 2 *vs* group 1	0·59 (0·47–0·74)	<0·0001	0·57 (0·45–0·71)	<0·0001
Group 3	133/574	Group 3 *vs* group 2	0·71 (0·55–0·93)	0·0018	0·70 (0·54–0·91)	0·0012
Time to second salvage androgen deprivation therapy (post-hoc)						
Group 1	157/564	Group 3 *vs* group 1	0·36 (0·26–0·50)	<0·0001	0·33 (0·24–0·46)	<0·0001
Group 2	109/578	Group 2 *vs* group 1	0·62 (0·47–0·82)	<0·0001	0·58 (0·44–0·77)	<0·0001
Group 3	68/574	Group 3 *vs* group 2	0·58 (0·41–0·81)	0·00015	0·58 (0·41–0·81)	0·00018
Castration-resistant disease¶						
Group 1	40/564	Group 3 *vs* group 1	0·35 (0·18–0·69)	0·00013	0·33 (0·17–0·66)	0·00015
Group 2	30/578	Group 2 *vs* group 1	0·73 (0·43–1·26)	0·100	0·68 (0·40–1·18)	0·058
Group 3	15/574	Group 3 *vs* group 2	0·47 (0·23–0·96)	0·0076	0·49 (0·24–0·99)	0·012
Local failure						
Group 1	26/564	Group 3 *vs* group 1	0·25 (0·10–0·65)	0·00023	0·26 (0·10–0·65)	0·00053
Group 2	12/578	Group 2 *vs* group 1	0·44 (0·20–0·97)	0·0085	0·43 (0·20–0·94)	0·0079
Group 3	8/574	Group 3 *vs* group 2	0·62 (0·22–1·72)	0·143	0·60 (0·21–1·68)	0·133
Regional failure						
Group 1	41/564	Group 3 *vs* group 1	0·29 (0·14–0·59)	<0·0001	0·28 (0·14–0·57)	<0·0001
Group 2	22/578	Group 2 *vs* group 1	0·51 (0·28–0·93)	0·0049	0·49 (0·27–0·89)	0·0038
Group 3	13/574	Group 3 *vs* group 2	0·57 (0·26–1·25)	0·051	0·57 (0·26–1·24)	0·052
Metastasis-free survival (post-hoc)						
Group 1	109/564	Group 3 *vs* group 1	0·81 (0·59–1·11)	0·066	0·79 (0·57–1·08)	0·042
Group 2	93/578	Group 2 *vs* group 1	0·82 (0·60–1·13)	0·082	0·80 (0·58–1·10)	0·056
Group 3	96/574	Group 3 *vs* group 2	0·98 (0·71–1·36)	0·455	0·98 (0·71–1·36)	0·454

Group 1=prostate bed radiotherapy alone; group 2=prostate bed radiotherapy plus short-term androgen deprivation therapy; group 3=pelvic lymph node radiotherapy plus prostate bed radiotherapy plus short-term androgen deprivation therapy. HR=hazard ratio. *One-sided log-rank test. †The p value required for statistical significance for the freedom from progression endpoint is based on the Chen-Simon critical values (see text). All remaining endpoints required a p value of p<0·0125. ‡Adjusted for prostate-specific antigen at baseline, stage, seminal vesical involvement, Gleason score, age, and race. §One-sided Wald test. ‖Prostate-specific antigen ≥0·4 ng/mL and a second rise above nadir or start of second salvage therapy. ¶ Three rises in prostate-specific antigen after institution of second salvage androgen deprivation therapy.

Table 2: **Univariable and multivariable Cox regression analyses**

A Freedom from progression with salvage censoring: PBRT plus short-term ADT (group 2) *vs* PBRT alone (group 1)

	Events, n/patients, N		8-year estimate (2-sided 95% CI)		p value*
	Group 1	Group 2	Group 1	Group 2	
All patients	202/564	151/578	61·2% (56·8–65·7)	71·8% (67·6–75·9)	<0·0001
Baseline PSA (ng/mL)					
≤median (0·35)	90/293	53/264	66·3% (60·4–72·3)	77·6% (71·6–83·6)	0·0083
>median (0·35)	112/271	98/314	55·7% (49·1–62·2)	66·8% (61·1–72·5)	<0·0001
≥0·1 to ≤1·0	174/507	128/512	62·6% (58·0–67·3)	73·2% (68·9–77·5)	<0·0001
>1·0 to <2·0	28/57	23/66	48·7% (34·7–62·7)	60·9% (47·7–74·1)	0·0087
Gleason score					
<8	156/471	109/480	64·4% (59·6–69·1)	76·2% (71·9–80·4)	<0·0001
8–9	46/93	42/98	44·8% (33·6–56·0)	47·3% (34·3–60·2)	0·064
Pathology					
pT2 and negative margins	54/150	40/168	61·6% (53·1–70·1)	74·8% (67·3–82·3)	0·0017
Other	148/414	111/410	61·0% (55·8–66·2)	70·5% (65·6–75·5)	0·00017
Seminal vesicle involvement					
No	160/482	115/494	64·8% (60·2–69·5)	75·2% (70·9–79·4)	<0·0001
Yes	42/82	36/84	37·2% (24·6–49·7)	50·8% (37·8–63·8)	0·010



B Freedom from progression with salvage censoring: PLNRT plus PBRT plus short-term ADT (group 3) *vs* PBRT plus short-term ADT (group 2)

	Events, n/patients, N		8-year estimate (2-sided 95% CI)		p value*
	Group 2	Group 3	Group 2	Group 3	
All patients	151/578	140/574	71·8% (67·6–75·9)	76·9% (73·1–80·6)	0·048
Baseline PSA (ng/mL)					
≤median (0·35)	53/264	67/301	77·6% (71·6–83·6)	80·0% (75·0–84·9)	0·344
>median (0·35)	98/314	73/273	66·8% (61·1–72·5)	73·5% (67·8–79·2)	0·058
≥0·1 to ≤1·0	128/512	121/515	73·2% (68·9–77·5)	77·6% (73·7–81·6)	0·054
>1·0 to <2·0	23/66	19/59	60·9% (47·7–74·1)	70·6% (58·3–82·8)	0·239
Gleason score					
<8	109/480	102/475	76·2% (71·9–80·4)	79·9% (76·0–83·8)	0·144
8–9	42/98	38/99	47·3% (34·3–60·2)	61·9% (51·2–72·7)	0·130
Pathology					
pT2 and negative margins	40/168	30/152	74·8% (67·3–82·3)	82·6% (76·0–89·2)	0·171
Other	111/410	110/422	70·5% (65·6–75·5)	75·0% (70·5–79·5)	0·074
Seminal vesicle involvement					
No	115/494	103/488	75·2% (70·9–79·4)	80·0% (76·2–83·9)	0·080
Yes	36/84	37/86	50·8% (37·8–63·8)	59·6% (48·3–71·0))	0·237

C Freedom from progression with salvage censoring: PLNRT plus PBRT plus short-term ADT (group 3) *vs* PBRT alone (group 1)

	Events, n/patients, N		8-year estimate (2-sided 95% CI)		p value*
	Group 1	Group 3	Group 1	Group 3	
All patients	202/564	140/574	61·2% (56·8–65·7)	76·9% (73·1–80·6)	<0·0001
Baseline PSA (ng/mL)					
≤median (0·35)	90/293	67/301	66·3% (60·4–72·3)	80·0% (75·0–84·9)	<0·0001
>median (0·35)	112/271	73/273	55·7% (49·1–62·2)	73·5% (67·8–79·2)	<0·0001
≥0·1 to ≤ 1·0	174/507	121/515	62·6% (58·0–67·3)	77·6% (73·7–81·6)	<0·0001
>1·0 to < 2·0	28/57	19/59	48·7% (34·7–62·7)	70·6% (58·3–82·8)	0·0015
Gleason score					
<8	156/471	102/475	64·4% (59·6–69·1)	79·9% (76·0–83·8)	<0·0001
8–9	46/93	38/99	44·8% (33·6–56·0)	61·9% (51·2–72·7)	0·0045
Pathology					
pT2 and negative margins	54/150	30/152	61·6% (53·1–70·1)	82·6% (76·0–89·2)	0·00012
Other	148/414	110/422	61·0% (55·8–66·2)	75·0% (70·5–79·5)	<0·0001
Seminal vesicle involvement					
No	160/482	103/488	64·8% (60·2–69·5)	80·0% (76·2–83·9)	<0·0001
Yes	42/82	37/86	37·2% (24·6–49·7)	59·6% (48·3–71·0)	0·0011

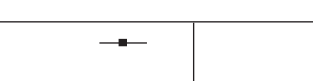


***Figure 3*: Forest plots showing freedom from progression in the three treatment groups in subgroups**

(A) Group 2 *vs* group 1. (B) Group 3 *vs* group 2. (C) Group 3 *vs* group 1. ADT=androgen deprivation therapy. PBRT=prostate bed radiotherapy. PLNRT=pelvic lymph node radiotherapy. PSA=prostate-specific antigen. *One-sided Wald test of hazard ratio from multivariable Cox proportional hazards model. In part A, p values from interaction tests were as follows: median PSA p=0·93, PSA 1·0 ng/mL cutpoint p=0·50, Gleason score p=0·44, pathology p=0·52, and seminal vesicle involvement p=0·89. In part B, p values from interaction tests were as follows: median PSA p=0·34, PSA 1·0 ng/mL cutpoint p=0·92, Gleason score p=0·55, pathology p=0·93, and seminal vesicle involvement p=0·99. In part C, p values from interaction tests were as follows: median PSA p=0·35, PSA 1·0 ng/mL cutpoint p=0·52, Gleason score p=0·95, pathology p=0·45, and seminal vesicle involvement p=0·89.

The median pre-treatment PSA level in all patients was 0·35 (rounded from 0·3475; the true median was used in all analyses, but is referred to as 0·35). Since some evidence suggests that men with a lower PSA before salvage radiotherapy derive less benefit from the addition of ADT than those with a higher PSA,[12,29] we did an unplanned post-hoc analysis in which we examined freedom from progression subdivided by the median pre-treatment PSA. The forest plots (figure 3) and the corresponding Kaplan-Meier plots (appendix p 30) show that when PSA was less than or equal to the median there was no significant difference between group 2 and group 3 (log-rank p=0·44; p=0·34 adjusted for covariates in the Cox proportional hazards model), but both group 2 and group 3 had significantly higher freedom from progression rates than group 1 (group 2 *vs* group 1: log-rank p=0·00097, p=0·00083 adjusted for covariates; and group 3 *vs* group 1: log-rank p=0·00045, p<0·0001 adjusted for covariates). When the PSA was higher than 0·35 ng/mL (figure 3, appendix p 31), freedom from progression was higher in group 3 than group 2, although the difference was not statistically significant (log-rank p=0·038; p=0·058 adjusted for covariates), whereas freedom from progression was significantly better in both groups 2 and 3 than in group 1 (group 2 *vs* group 1 log-rank p=0·00053, p<0·0001 adjusted for covariates; and group 3 *vs* group 1 log-rank p<0·0001, p<0·0001 adjusted for covariates). In the case of pathological stage and margins, seminal vesicle involvement, and Gleason score, the treatment effects were similar across subgroups (figure 3).

Differences between the treatment groups in the cumulative incidence of time to failure according to both the Phoenix biochemical failure definition and the alternative biochemical failure definition with death as a competing event (table 2, figure 4A [alternative definition], appendix p 32 [Phoenix definition]) were concordant with the results for freedom from progression.

Distant metastasis was recorded in 69 patients in group 1, 56 patients in group 2, and 41 patients in group 3. Incidence rates were lowest in group 3 (figure 2B). Covariate-adjusted results are shown in table 2. Only the group 3 versus group 1 comparison surpassed the required significance level (p<0·0125) for distant metastasis (figure 2B, table 2). 86 prostate cancer-related deaths were recorded: 36 in group 1, 29 in group 2, and 21 in group 3 (figure 2C). These counts included 23 deaths following clinical or biochemical progression that were not classified as conclusively due to prostate cancer by the central review committee (appendix p 13). Prostate cancer deaths only differed significantly between group 3 versus group 1; all other pairwise comparisons were not significant (table 2). There were no significant differences in overall survival across all groups (figure 2D, table 2).

The results for the remaining secondary endpoints (ie, castration-resistant disease, local failure, and regional failure are displayed in table 2 and the appendix (pp 33–35). In general, these results are similar to those reported for the other secondary endpoints. Significant differences were seen between group 3 versus group 1 and between group 3 versus group 2 for the development of castration-resistant disease, and between group 3 versus group 1 and group 2 versus group 1 for local failure and regional failure (table 2).

Although not a prespecified endpoint, the initiation of second salvage therapy has substantial effects on quality of life. 157 men in group 1, 109 in group 2, and 68 in group 3

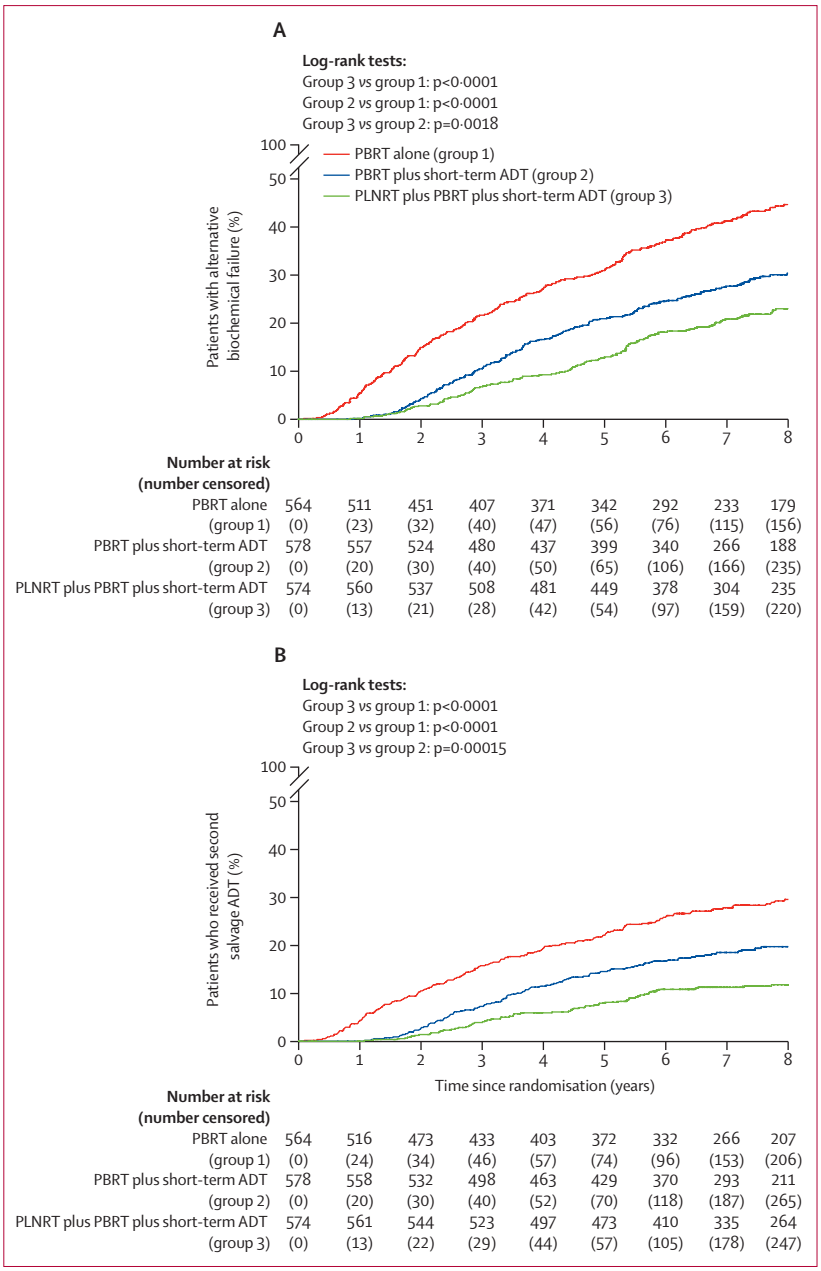


Figure 4: **Cumulative incidence curves of alternative biochemical failure (A) and second salvage ADT (B)**
ADT=androgen deprivation therapy. PBRT=prostate bed radiotherapy. PLNRT=pelvic lymph node radiotherapy. All p values are one-sided.

	Group 1 (n=547, acute; n=545, late)	Group 2 (n=563, acute; n=559, late)	Group 3 (n=563, acute; n=562, late)	p value*	Group 2 *vs* group 1		Group 3 *vs* group 2	
					OR† (95% CI)	p value‡	OR† (95% CI)	p value‡
Acute adverse events§								
All								
Grade ≥2	98 (18%)	201 (36%)	246 (44%)	<0·0001	2·55 (1·93–3·37)	<0·0001	1·39 (1·10–1·77)	0·0034
Grade ≥3	18 (3%)	41 (7%)	63 (11%)	<0·0001	2·31 (1·31–4·07)	0·0019	1·60 (1·06–2·42)	0·012
Blood or bone marrow								
Grade ≥2	12 (2%)	10 (2%)	29 (5%)	0·0016	0·80 (0·34–1·88)	0·692	3·01 (1·45–6·26)	0·0016
Grade ≥3	3 (1%)	1 (<1%)	15 (3%)	0·0012	0·32 (0·03–3·11)	0·836	15·38 (2·03–116·85)	0·0041
Gastrointestinal								
Grade ≥2	11 (2%)	22 (4%)	38 (7%)	0·00041	2·01 (0·96–4·19)	0·032	1·76 (1·03–3·03)	0·020
Grade ≥3	1 (<1%)	5 (1%)	4 (1%)	0·286	4·89 (0·57–42·01)	0·074	0·80 (0·21–2·99)	0·631
Renal or genitourinary								
Grade ≥2	49 (9%)	68 (12%)	67 (12%)	0·177	1·40 (0·95–2·06)	0·046	0·98 (0·68–1·40)	0·544
Grade ≥3	5 (1%)	5 (1%)	8 (1%)	0·622	0·97 (0·28–3·37)	0·518	1·61 (0·52–4·95)	0·203
Late adverse events‖								
All								
Grade ≥2	308 (57%)	322 (58%)	350 (62%)	0·116	1·04 (0·82–1·32)	0·367	1·22 (0·96–1·55)	0·054
Grade ≥3	65 (12%)	87 (16%)	96 (17%)	0·047	1·36 (0·96–1·92)	0·040	1·12 (0·81–1·53)	0·246
Blood or bone marrow								
Grade ≥2	20 (4%)	10 (2%)	25 (4%)	0·038	0·47 (0·22–1·01)	0·973	2·60 (1·23–5·47)	0·0060
Grade ≥3	3 (1%)	2 (<1%)	7 (1%)	0·181	0·65 (0·11–3·90)	0·682	3·51 (0·73–17·0)	0·059
Gastrointestinal								
Grade ≥2	56 (10%)	57 (10%)	51 (9%)	0·753	0·99 (0·67–1·46)	0·518	0·88 (0·59–1·31)	0·738
Grade ≥3	4 (1%)	5 (1%)	8 (1%)	0·488	1·22 (0·33–4·57)	0·384	1·60 (0·52–4·92)	0·206
Renal or genitourinary								
Grade ≥2	202 (37%)	194 (35%)	223 (40%)	0·226	0·90 (0·71–1·16)	0·793	1·24 (0·97–1·58)	0·043
Grade ≥3	29 (5%)	37 (7%)	45 (8%)	0·201	1·26 (0·76–2·08)	0·182	1·23 (0·78–1·93)	0·186

The table shows adverse events of any attribution. Data are n (%) unless stated otherwise. Group 1=prostate bed radiotherapy alone; group 2=prostate bed radiotherapy plus short-term androgen deprivation therapy; group 3=pelvic lymph node radiotherapy plus prostate bed radiotherapy plus short-term androgen deprivation therapy. OR=odds ratio. *Two degree-of-freedom χ^2 test. †The model for grade ≥2 events was adjusted for baseline prostate-specific antigen level, pathology, seminal vesicle involvement, Gleason score, age, and race; the model for grade ≥3 events was unadjusted due to the low number of events. ‡One-sided Wald test of OR. §17 patients in group 1, 15 in group 2, and 11 in group 3 who received no treatment or for whom no information on acute adverse events was provided are excluded. ‖19 patients in group 1, 19 in group 2, and 12 in group 3 who received no treatment or for whom no information on late adverse events was provided are excluded.

Table 3: **Adverse events of interest (grade 2 or worse severity)**

were given second salvage ADT. Figure 4B shows the time from randomisation until the initiation of second salvage ADT in each group. All pairwise comparisons between treatment groups were statistically significant (group 3 *vs* group 1 and group 2 *vs* group 1 p<0·0001; group 3 *vs* group 2 p=0·00015), and covariate-adjusted results were again very similar to the unadjusted comparisons (table 2). Additionally, a post-hoc subgroup analysis comparing time to second salvage therapy across the treatment groups remained significant for patients with baseline PSA levels below or above the median (appendix p 14).

Our post-hoc analysis of metastasis-free survival showed no significant differences between the treatment groups (table 2, appendix p 36).

A summary of the patterns of failures is shown in appendix p 15. The use of ADT in groups 2 and 3 resulted in reductions in local and regional failures; the greatest reductions were in patients in whom the pelvic lymph nodes were treated (ie, group 3), along with a concordant reduction in distant metastasis. A summary of 5-year event rates for all endpoints is provided in appendix p 16.

In groups 2 and 3 combined, 350 patients received 4 months (±0·5 months) of LHRH treatment (180 in group 2 and 170 in group 3) and 680 received 6 months (±0·5 months) of LHRH treatment (332 in group 2 and 348 in group 3), with 74 patients (43 in group 2 and 31 in group 3) not included because they did not meet these definitions (appendix p 12). The freedom from progression curves for this unplanned, post-hoc, non-randomised comparison are shown in appendix p 37. The difference in freedom from progression was not statistically significant (unadjusted HR for 6 months *vs* 4 months 0·87 [95% CI 0·65–1·16], 2-sided p=0·31; adjusted HR 0·81 [0·63–1·04], 2-sided p=0·10).

Acute and late toxicity outcomes, irrespective of relation to treatment, are summarised in table 3. In terms of acute toxicity (≤3 months after radiotherapy), 98 (18%) of the 547 evaluable patients in group 1, 201 (36%) of 563 evaluable patients in group 2, and 246 (44%) of 563 evaluable patients in group 3 had a grade 2 or worse event (p<0·0001) and 18 (3%) of 555 evaluable patients in group 1, 41 (7%) of 559 evaluable patients in group 2, and 61 (11%) of 562 evaluable patients in group 3 had a grade 3 or worse event (p<0·0001; table 3). Significant differences between group 3 versus group 2 were recorded for grade 2 or worse acute gastrointestinal and blood or bone marrow toxicities as well as grade 3 or worse acute gastrointestinal toxicities, but not for renal or genitourinary toxicities (table 3). Details of the types of acute and late events seen are provided in appendix pp 17–24. The most obvious differences in acute grade 2 or worse gastrointestinal adverse events between the groups was for diarrhoea, which was based on relatively few events for each group (4 of 11 overall grade 2 or worse acute gastrointestinal events in group 1, 11 of 22 events in group 2, and 18 of 38 events in group 3; appendix p 18). The difference in acute blood or bone marrow between groups 3 and 2 was related mostly to lymphopenia (4 of 10 overall acute grade 2 or worse blood or bone marrow events in group 2 and 27 of 29 in group 3; appendix p 17).

There were no significant differences between the groups in late (>3 months after radiotherapy) grade 2 or worse or grade 3 or worse genitourinary or gastrointestinal adverse events. An increase in late grade 2 or worse blood or bone marrow events (table 3) was observed for group 3 versus group 2 (p=0·0060), but the pattern was inconsistent, with no significant difference for the comparison between group 3 versus group 1 (p=0·26); these differences were mostly related to leukopenia and lymphopenia (appendix p 21).

Two additional comparisons of late-grade adverse events were specified in the protocol: the time from initiation of protocol therapy until the first occurrence of a late grade 2 or worse or a late grade 3 or worse adverse event. Cumulative incidence curves (with death as a competing event) are shown in appendix pp 38–39. For time to late grade 3 or worse adverse events, there was a significantly higher incidence of events in group 3 than in group 1 (p=0·011; post-hoc comparison). Overall rates of toxicity (acute or late) in the three treatment groups by system organ class are provided in appendix pp 25–26.

Discussion

The consensus recommendation for post-prostatectomy radiotherapy is treatment of the prostate surgical bed or PBRT. Based on randomised adjuvant post-prostatectomy radiotherapy trials involving patients with adverse pathological features,[2–4] more than 60% of patients left untreated will develop a rising PSA within 10 years of PBRT. Additional recent level I evidence shows that at least during the first 65 months of follow-up, early salvage radiotherapy is as effective as adjuvant radiotherapy, indicating that early salvage therapy will be the treatment pathway selected for most patients post-prostatectomy.[6–8] Randomised trials of salvage radiotherapy involving men with a rising PSA after prostatectomy[11,12] show biochemical failure rates in excess of 35% at 5 years and 50% at 10 years, following PBRT alone.

Based on the results of several randomised trials,[30] primary prostate radiotherapy in men with intermediate-to-high-risk prostate cancer typically includes the addition of ADT. Compelling data from two randomised trials for men treated postoperatively with salvage radiotherapy indicate that combining androgen signalling mitigation via short-term ADT for 6 months[11] or long term anti-androgen therapy for 2 years[12] reduces progression, prolongs metastasis-free survival, and, in the case of long-term anti-androgen therapy, improves survival. The SPPORT trial is complimentary to, and distinguished from, these salvage radiotherapy trials in several ways.

The freedom from progression endpoint in the SPPORT trial is driven in large part by the Phoenix definition of biochemical failure (PSA ≥2 ng/mL over the nadir PSA)[22] because of stronger associations with clinical failure, as compared with the American Urological Association definition of biochemical failure (PSA ≥0·2 ng/mL and a confirmatory PSA of ≥0·2 ng/mL) and similar definitions using PSA cutpoints of ≥0·4 and ≥0·5 ng/mL.[11] The Phoenix definition has been associated with clinical failure, distant metastasis, and overall survival in men treated primarily with radiotherapy.[31] Based on the freedom from progression definition in the SPPORT trial, a failure event would be based on a PSA level of 2 ng/mL or higher, which is a notable level post-prostatectomy that often triggers further intervention. The implementation of second salvage ADT in the SPPORT trial reflected the incremental differences in freedom from progression between the three treatment groups, with all comparisons being highly significant in post-hoc analyses.

The two key clinical questions addressed by the SPPORT trial are central to current salvage radiotherapy management considerations: the potential benefit of adding short-term ADT to standard PBRT, and the further potential benefit from the addition of PLNRT to this combination. The SPPORT trial results are concordant with the hypotheses that there would be statistically significant incremental gains in freedom from progression with intensification of treatment, including the addition of short-term ADT in group 2 and the further addition of PLNRT in group 3. Concerning the impact of short-term ADT on failure, the SPPORT trial is consistent with the findings of the GETUG-AFU 16 trial,[11,29] showing a significant improvement in

biochemical failure from PBRT plus short-term ADT over that of PBRT alone. The 5-year biochemical failure rates for the SPPORT trial (alternative biochemical failure with a 0·4 ng/mL PSA cutpoint) and the GETUG-AFU 16 trial (0·5 ng/mL PSA from nadir) trials were 31% and 38%, respectively, for PBRT alone and 21% and 20%, respectively, for PBRT plus short-term ADT.

There are some methodological differences between the SPPORT and GETUG-AFU 16 trials that should be mentioned. Intensity-modulated radiotherapy was used in 87% of the patients in the SPPORT trial and conformal radiotherapy was used in 96% of those in the GETUG-AFU 16 trial. Furthermore, 6 months of ADT was used in the GETUG-AFU 16 trial, whereas 4–6 months was allowed in the SPPORT trial. In a post-hoc analysis of 4 months versus 6 months of ADT in the SPPORT trial, there was no significant difference in freedom from progression; however, this comparison was not randomised and lacks sufficient power to be conclusive. Patients enrolled in the SPPORT and GETUG-AFU 16 trials had relatively similar risk features; median PSAs at entry were 0·35 and 0·30 ng/mL, respectively, and most patients had a Gleason score of up to 7 disease (83% and 89%, respectively). By contrast, the median PSA level in the RTOG 96-01 trial was 0·6 ng/mL, indicating a higher risk cohort.

The SPPORT trial is the first post-prostatectomy trial to test the benefit of increasing radiotherapy field size to treat the pelvic lymph nodes. The decision to limit the study to three groups, without a PBRT plus PLNRT alone (without ADT) group, was based in part on the early results of NRG/RTOG 94-13,[32] wherein a 2×2 design with four primary prostate cancer treatments were studied. The treatments included prostate radiotherapy with neoadjuvant and concurrent short-term ADT versus adjuvant short-term ADT and prostate radiotherapy alone versus prostate radiotherapy plus PLNRT. In NRG/RTOG 94-13 there was an early reduction in progression-free survival when PLNRT and neoadjuvant and concurrent short-term ADT were added to prostate radiotherapy. The SPPORT trial was designed to take advantage of the perceived interplay between neoadjuvant and concurrent short-term ADT and PLNRT. With longer follow-up, there remains some evidence of an interactive effect between PLNRT and neoadjuvant and concurrent short-term ADT in RTOG 94-13;[33] however, a clear advantage over the other combinations was not evidenced, most probably because the dose to the prostate was low, allowing for local persistence of disease to impact the lasting effect from PLNRT. In a recent report by Murthy and colleagues[34] on the randomised POP-RT trial in which a higher biologically equivalent radiation dose at 2 Gy was administered to the prostate primarily, in combination with long-term ADT (for ≥2 years), significant improvements in biochemical failure-free survival (the primary endpoint), disease-free survival, and metastasis-free survival were recorded with the addition of whole pelvis radiotherapy at 6·8 years of follow-up.

In contrast to the substantial tumour burden for men treated primarily for high-risk prostate cancer in the NRG/RTOG 94-13 and POP-RT trials, patients treated postoperatively in the SPPORT trial had relatively low-volume microscopic disease in the prostate bed at the time of radiotherapy (patients with palpable tumours on digital rectal examination were ineligible). The significant freedom from progression benefit from PLNRT in the SPPORT trial was achieved with standard radiotherapy doses and short-term ADT. Nevertheless, some newer evidence indicates that there is a radiotherapy dose response with PBRT,[35] suggesting that further improvements with more aggressive dose-escalated radiotherapy might, among other potential mechanisms, add to the gains seen with short-term ADT. Alternatively, our results showing a reduction in local failure with short-term ADT suggest that a higher radiation dose might not be needed with the use of short-term ADT, potentially by reducing the tumour burden or through supra-additive or radiosensitising effects.[36,37]

Pre-radiotherapy PSA level is a strong predictor of outcome after salvage radiotherapy. To examine its association with the treatments tested, the median PSA at protocol entry (0·35 ng/mL) was used as a cutpoint in exploratory post-hoc analyses. Two observations are of particular importance. First, all patients benefited from short-term ADT in terms of freedom from progression, including those with entry PSAs of up to 0·35 ng/mL, which is consistent with the GETUG-AFU 16 post-hoc analysis of those with entry PSAs of up to 0·5 ng/mL.[29] However, when a similar post-hoc analysis in NRG/RTOG 96-01 was done for those with entry PSAs of up to 0·7 ng/mL, there was no apparent benefit on overall survival from 2 years of anti-androgen therapy added to PBRT. Long-term anti-androgen therapy with bicalutamide at 150 mg per day has been shown to increase cardiovascular events and mortality, which would be expected to counterbalance potential gains in survival in patients with low PSAs before PBRT, as indicated in NRG/RTOG 96-01.[38] Moreover, overall survival as an endpoint should not be used as the sole criterion for considering the use of ADT in combination with salvage radiotherapy in men with low pre-radiotherapy PSA levels. In the SPPORT trial, a post-hoc analysis showed that short-term ADT in both groups 2 and 3 was associated with significantly lower rates of second salvage ADT in men with entry PSAs at or below the median of 0·35 ng/mL, as compared with PBRT alone. In clinical practice, second salvage ADT is typically a lifelong management approach, whether it is given intermittently or continuously.

The subgroup analysis of baseline PSA also indicated that the freedom from progression benefit of PLNRT was greatest in patients with PSAs above the median of 0·35 ng/mL. The lack of statistical significance in baseline PSA subgroup comparisons of group 2 versus group 3 should be interpreted with caution, however,

since the study was not powered to analyse these subgroups independently. Follow-up might be too short, especially for the more favourable subgroup (patients with PSAs below the median), and second salvage therapy was used significantly less frequently in group 3 than in both groups 2 and 1, even when the entry PSA was low.

The freedom from progression endpoint was chosen for the SPPORT trial because of its association with clinical failure, which is concordant with the finding that the combination of PBRT plus PLNRT plus short-term ADT resulted in the lowest rate of distant metastasis and greatest improvement in metastasis-free survival (although differences in metastasis-free survival across the groups were not significant by protocol criteria). The follow-up period is relatively short for the distant metastasis and survival secondary endpoints. The GETUG-AFP 16 trial did not show an improvement in metastasis-free survival from the addition of short-term ADT until an analysis at a median follow-up of 112 months was done.[11] As the NRG/RTOG 96-01 trial has demonstrated,[12] the overall survival endpoint requires follow-up of longer than 10 years because it is affected to a greater degree by both advances in the management of recurrent prostate cancer and advances in medicine overall that reduce the risk of death from all causes. Our post-hoc analysis finding that the use of second salvage ADT was highest in patients in group 1 and lowest in group 3 with all cross-comparisons being highly significant, indicates that the slight, but significant, increased side-effects with treatment intensification are offset by a reduction in the morbidity that is anticipated from second salvage ADT.

Limitations of the SPPORT trial include that longer follow-up is needed to better define the influence of PLNRT on the distant metastasis and survival endpoints and that newer developments in more prostate-specific PET imaging tracers that are becoming a major part of clinical practice will probably affect recommendations on how PLNRT is applied. The new PET tracers confirm that recurrence after primary or salvage treatment is often in the lymph nodes[39] and, based on lymph node recurrence distribution studies[40,41] also suggest that further extending lymph node treatment volumes superiorly might result in additional reductions in progression.

In conclusion, extension of the standard post-prostatectomy salvage prostate bed radiotherapy fields to include the pelvic lymph nodes, when used in combination with short-term ADT, was found to result in the greatest impact on outcomes in the SPPORT trial.

Contributors

AP participated in study design (at all levels: endpoints, stratification, and eligibility), monitoring of accrual, data consistency and verification (including quality assurance assessment during and after accrual, and cause of death attribution), data interpretation, construction and formatting of the tables and figures, and manuscript writing, editing, and approval. TGK participated in data compilation, data integrity assessment, statistical oversight, data analysis, data interpretation, and writing, editing, and approval of the manuscript. AGB was the study co-principal investigator and was involved in patient accrual, quality assurance of contouring for half of all cases, cause of death attribution, and manuscript writing, editing, and final approval. LGG was the urology co-principal investigator on the protocol and was involved in protocol design, protocol updates, quality assurance reviews, interpretation of data, and writing and approval of the manuscript. DAL was the medical physicist on the NRG/RTOG 0534 trial and provided medical physics input, and was involved in data interpretation, writing, and approval of the final manuscript. DWB participated in the design of the trial and all aspects of the manuscript. JSW participated in data collection, data analysis, data interpretation, writing, and approval of the final manuscript. AG-M, JMM, and HMS, as members of the genitourinary steering committee of RTOG/NRG Oncology, were involved in trial group design, endpoints, and treatment approach. They also enrolled patients onto the trial from their local institutions and were involved with data interpretation and manuscript writing and approval. SJA participated in patient accrual to the study, manuscript editing, and manuscript approval. HL participated in the design of the study, interpretation of data, accrual, and writing of the manuscript. SLF participated in data collection, data interpretation, manuscript editing, and manuscript approval. GBR participated in the local accrual and data collection of patients, as well as data interpretation, manuscript editing, and approval of this work. M-CB participated in data collection, manuscript editing, and manuscript approval. RJL participated in enrolling patients, patient management, and manuscript review, editing, and approval. SAS was involved in data collection, patient management, and manuscript writing, editing, and final approval. AMA was involved in the recruitment of patients, and review, editing, and final approval of the manuscript. DCM was involved in patient accrual, and manuscript review, editing, and final approval. WS was involved in programming data analysis, construction of tables and figures, and manuscript review, editing, and final approval. OS was the medical oncologist lead on the trial and provided input on systemic management considerations during the conduct of the trial and was involved in data interpretation, manuscript editing, and manuscript approval. FF is the current NRG genitourinary section chair and participated in data interpretation, and manuscript writing, editing, and final approval. HMS was the NRG Oncology genitourinary section chair during the implementation and enrollment period, and was involved in the cause of death attribution review. AP, TGK, and WS had access to the raw data and were responsible for the decision to submit the manuscript for publication. TGK and WS verified the underlying data.

Declaration of interests

FF reports personal fees from Janssen Oncology, Sanofi, Bayer, Celgene, Blue Earth Diagnostics, Genentech, Myovant Sciences, Riovant Sciences, and Astellas Pharma; grants from Zenith Epigenetics; and is a scientific adviser for and owns stock options in PFS Genomics and Serimmune, outside the submitted work. AP reports grant support from an NCI P30 grant and from a University of Miami Sylvester Professorship, during the conduct of the study. M-CB reports personal fees from AbbVie and Tersera, outside the submitted work. LGG reports grants from NCI, during the conduct of the study; and advisory boards from Astellas/Pfizer, Astra Zeneca, Bayer, and Abbvie, outside the submitted work. HMS reports personal fees from Janssen and Caribou Publishing, and stock from a non-active advisory board from Radiogel, outside the submitted work; and is a member of the ASTRO Board of Directors. JSW reports personal fees from AbbVie, Bayer, Blueprint Medicines, and Vanquish Oncology; and grants from Angiochem, Juno, and Roche, outside the submitted work. HL reports per-case funding for accrued patients from Juravinski Cancer Centre, during the conduct of the study; and personal fees from Astra Zeneca, Sanofi, Abbvie, Tersera, and Ferring, outside the submitted work. OS reports grants or contracts from Advanced Accelerator Applications, Amgen, AstraZeneca, Bayer, Constellation, Endocyte, Invitae, Janssen, Lantheus, Merck, Progenics, and Tenebio; and consulting fees from Advanced Accelerator Applications, Astellas, AstraZeneca, Bayer, Blue Earth Diagnostics, Bavarian Nordic, Bristol Myers Squibb, Clarity Pharmaceuticals, Clovis, Constellation, Dendreon, EMD Serono, Fusion, Isotopen Technologien Meunchen, Janssen, Merck, Moyvant, Myriad, Noria Therapeutics,

Novartis, Noxopharm, Progenics, POINT Biopharma, Pfizer, Sanofi, Tenebio, Telix, and Theragnostics, outside the submitted work. All other authors declare no competing interests.

Data sharing

According to National Cancer Institute (NCI) requirements, the data from this Article will be submitted to the NCI National Clinical Trials Network NCI Community Oncology Research Program (NCORP) data archive (https://nctn-data-archive.nci.nih.gov) no later than 6 months after publication. After the required NCI reviews are completed, it will be released and available in the data archive for data-sharing proposals. The study protocol is available on the ClinicalTrials.gov website.

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