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Permalink

<https://escholarship.org/uc/item/22k5b7m6>

Journal

Journal of Clinical Oncology, 41(4)

ISSN

0732-183X

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Publication Date

2023-02-01

DOI

10.1200/jco.22.00970

Peer reviewed

Sequencing of Androgen-Deprivation Therapy of Short Duration With Radiotherapy for Nonmetastatic Prostate Cancer (SANDSTORM): A Pooled Analysis of 12 Randomized Trials

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PURPOSE The sequencing of androgen-deprivation therapy (ADT) with radiotherapy (RT) may affect outcomes for prostate cancer in an RT-field size-dependent manner. Herein, we investigate the impact of ADT sequencing for men receiving ADT with prostate-only RT (PORT) or whole-pelvis RT (WPRT).

MATERIALS AND METHODS Individual patient data from 12 randomized trials that included patients receiving neoadjuvant/concurrent or concurrent/adjuvant short-term ADT (4-6 months) with RT for localized disease were obtained from the Meta-Analysis of Randomized trials in Cancer of the Prostate consortium. Inverse probability of treatment weighting (IPTW) was performed with propensity scores derived from age, initial prostate-specific antigen, Gleason score, T stage, RT dose, and mid-trial enrollment year. Metastasis-free survival (primary end point) and overall survival (OS) were assessed by IPTW-adjusted Cox regression models, analyzed independently for men receiving PORT versus WPRT. IPTW-adjusted Fine and Gray competing risk models were built to evaluate distant metastasis (DM) and prostate cancer-specific mortality.

RESULTS Overall, 7,409 patients were included (6,325 neoadjuvant/concurrent and 1,084 concurrent/adjuvant) with a median follow-up of 10.2 years (interquartile range, 7.2-14.9 years). A significant interaction between ADT sequencing and RT field size was observed for all end points (P interaction $< .02$ for all) except OS. With PORT ($n = 4,355$), compared with neoadjuvant/concurrent ADT, concurrent/adjuvant ADT was associated with improved metastasis-free survival (10-year benefit 8.0%, hazard ratio [HR], 0.65; 95% CI, 0.54 to 0.79; $P < .0001$), DM (subdistribution HR, 0.52; 95% CI, 0.33 to 0.82; $P = .0046$), prostate cancer-specific mortality (subdistribution HR, 0.30; 95% CI, 0.16 to 0.54; $P < .0001$), and OS (HR, 0.69; 95% CI, 0.57 to 0.83; $P = .0001$). However, in patients receiving WPRT ($n = 3,049$), no significant difference in any end point was observed in regard to ADT sequencing except for worse DM (HR, 1.57; 95% CI, 1.20 to 2.05; $P = .0009$) with concurrent/adjuvant ADT.

CONCLUSION ADT sequencing exhibits a significant impact on clinical outcomes with a significant interaction with field size. Concurrent/adjuvant ADT should be the standard of care where short-term ADT is indicated in combination with PORT.

J Clin Oncol 41:881-892. © 2022 by American Society of Clinical Oncology

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INTRODUCTION

The sequencing of systemic therapies with radiotherapy (RT) has been associated with differential survival benefits in multiple malignancies.^{1,2} Although androgen-deprivation therapy (ADT) has consistently been shown to improve survival when added to RT for localized prostate cancer (unfavorable intermediate-risk or

higher),³ the optimal sequencing of ADT remains controversial. Two recent studies support the notion that concurrent/adjuvant ADT sequencing may be superior to neoadjuvant/concurrent ADT sequencing. First, an individual patient data (IPD) meta-analysis of the only two randomized trials of ADT sequencing, Radiation Therapy Oncology Group (RTOG) 9413^{4,5} and Ottawa

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on August 17, 2022 and published at ascopubs.org/journal/jco on October 21, 2022; DOI <https://doi.org/10.1200/JCO.22.00970>

CONTEXT

Key Objective

The optimal sequencing of short-term androgen-deprivation therapy (ADT) when delivered with radiotherapy for prostate cancer remains controversial, with only two randomized trials attempting to investigate this. This study examined whether neoadjuvant/concurrent or concurrent/adjuvant ADT affords better outcomes. It contains individual patient data from 12 randomized trials and, to our knowledge, is the largest such analysis to date.

Knowledge Generated

There is a significant interaction between radiation field size and the impact of ADT sequencing for multiple oncologic end points. With prostate-only radiation, concurrent/adjuvant ADT was associated with significantly improved metastasis-free survival, prostate cancer–specific mortality, and overall survival; the effect of ADT sequencing with whole-pelvic radiation is less clear, with no consistent benefit with either.

Relevance

When short-term ADT is used with prostate-only radiation, concurrent/adjuvant ADT should be the standard of care. It informs clinical practice and allows rational design of ADT and radiotherapy combination in future trials.

0101,⁶ found that progression-free survival (PFS), biochemical recurrence (BCR), distant metastasis (DM), and metastasis-free survival (MFS) were all significantly improved in patients treated with adjuvant ADT.⁷ This analysis was limited to men receiving prostate-only RT (PORT) because the RTOG 9413 trial suggested a significant interaction between field size and the impact of sequencing, and combined men receiving purely adjuvant ADT with those receiving concurrent/adjuvant ADT. Second, an IPD meta-analysis of three trials of neoadjuvant ADT extension and four trials of adjuvant ADT prolongation found no benefit in any end point to the former, but MFS and overall survival (OS) benefits for the latter.⁸ This study included both patients receiving PORT and whole-pelvis RT (WPRT), but the trials investigating neoadjuvant extension used shorter overall total durations of ADT than the trials evaluating adjuvant ADT prolongation. On the basis of these two studies, we hypothesized that concurrent/adjuvant ADT sequencing would offer improved MFS compared with neoadjuvant/concurrent ADT sequencing in patients receiving short-term ADT (STADT; 4-6 months) in a RT field-size–dependent manner. To evaluate this hypothesis, we leveraged IPD from the Meta-Analysis of Randomized trials in Cancer of the Prostate (MARCAP) Consortium to perform a pooled analysis.

MATERIALS AND METHODS

Study Cohorts

The MARCAP consortium has been described in detail previously.⁸ Briefly, it contains IPD from randomized clinical trials run through multiple collaborative groups including the European Organisation for Research and Treatment of Cancer (EORTC), Radiation Therapy Oncology Group (now NRG Oncology; NRG/RTOG), Medical Research Council, Institute of Cancer Research, Prostate Cancer Study Group, the Grupo de Investigación Clínica en Oncología Radioterápica, and the Ottawa trial group.

Within the MARCAP consortium, randomized trials that enrolled patients uniformly receiving neoadjuvant/concurrent or concurrent/adjuvant STADT (4-6 months) with RT on one of the arms were identified for inclusion of patients. Only trial arms that used STADT were included (eg, only the 6-month arm of EORTC 22961). Neoadjuvant/concurrent ADT was defined as ADT (luteinizing hormone-releasing hormone agonist/antagonist with or without an androgen receptor blocker) starting ≥ 2 months before the start of RT and continued throughout the RT course. Concurrent/adjuvant ADT was defined as ADT starting at the commencement of RT and given adjuvantly for ≥ 2 months after the completion of RT. The entire cohort was dichotomized into these two groups without overlap. Trial arms were excluded on the basis of the following criteria: (1) purely adjuvant STADT (eg, adjuvant ADT arms of RTOG 9413); (2) $\geq 80\%$ STADT duration being neoadjuvant with insufficient concurrent duration (eg, STADT arms of ICROG 97-01,⁹ TROG 96.01,¹⁰ and TROG 03.04/RADAR¹¹); (3) unavailability of data to compute MFS; and (4) use of nonsteroidal antiandrogen monotherapy (eg, PMH 9907¹²). For the CHHiP trial,¹³ patients receiving nonsteroidal androgen receptor blocker monotherapy were excluded, although other patients receiving STADT as defined above were included. All trials provided clear data on the receipt of WPRT except for the EORTC 22991 trial,¹⁴ in which the protocol recommended WPRT for patients with a 15% or higher risk of pelvic lymph node involvement (cT1b-T2aNOMO, Gleason score > 7 , and/or prostate-specific antigen [PSA] > 15 ng/mL) and WPRT use was imputed on the basis of this criterion. A summary of trial-specific definition of DM and imaging assessment of disease recurrence during follow-up is shown in the Data Supplement (online only).

End Points

The primary end point of this analysis was MFS, defined as the time since random assignment until metastasis or death of any cause, as it is a validated surrogate of OS.¹⁵

Secondary end points included OS, and the cumulative incidence of BCR, DM, prostate cancer–specific mortality (PCSM), and other-cause mortality (OCM). All time-to-event outcome variables were measured from the date of random assignment to the reported occurrence of the event of interest. Patients who were event-free were censored on the last date of follow-up. All analyses were conducted on an intention-to-treat basis.

Statistical Analysis

Descriptive statistics were used to characterize baseline patient and treatment characteristics, and Mann-Whitney U tests and chi-square tests were used for comparisons between the two treatment groups. Unadjusted rates of end points were estimated using the Kaplan-Meier method and the cumulative incidence function. Unadjusted subdistribution hazard ratios (HRs) for BCR, DM, PCSM, and OCM were calculated using univariable Fine-Gray competing risk models. Weighted Cox regression was used to estimate univariable average HRs for MFS and OS in the case of nonproportional hazards.¹⁶ We used inverse probability of treatment weighting (IPTW) analyses to examine the effects of ADT sequencing on clinical outcomes. The weights were calculated as the inverse of propensity scores, defined as the predicted probability of treatment conditional on age, initial PSA (iPSA), Gleason score, T stage, RT dose (< 74 Gy v ≥ 74 Gy in 2 Gy equivalent doses), and mid-trial enrollment year, using a nonparametric covariate balancing propensity score method.¹⁷ The balance of covariates at baseline between the two treatment groups was assessed by using the absolute standardized mean difference. MFS and OS were assessed by using IPTW Cox proportional hazards model. IPTW Fine and Gray competing risk regression models were used to evaluate BCR, DM, and PCSM, where deaths due to nonprostate cancer causes were competing events for PCSM, prostate cancer deaths were competing events for OCM, and deaths of any cause were competing events for DM and BCR. The above regression models included ADT sequencing, WPRT, and their interaction to account for effect modification. An a priori plan was made that should the interaction between field size and the clinical impact of ADT sequencing on MFS be statistically significant, all analyses would be repeated within cohorts receiving PORT and those receiving WPRT. The propensity scores were recalculated separately within PORT and WPRT cohorts, and same covariates were included in the models. IPTW-adjusted Kaplan-Meier analysis and cumulative incidence estimation were performed within PORT and WPRT cohorts separately, and the corresponding 10-year risk differences were calculated. As an alternative measure of the treatment effect, restricted mean time lost (RMTL, for competing risk data) was estimated using IPTW adjustment for PORT and WPRT cohorts. A sensitivity analysis was performed excluding EORTC 22991, given its imputed WPRT status. We also prespecified an analysis for an interaction between National Comprehensive Cancer Network (NCCN) risk group and impact of ADT sequencing on MFS, as well as a direct

comparison of the four subgroups defined by ADT sequencing and WPRT use. All analyses were performed by using R 4.1.1.

RESULTS

A total of 7,409 patients from 12 randomized trials were included with 6,325 treated with neoadjuvant/concurrent ADT and 1,084 treated with concurrent/adjuvant ADT (Data Supplement). Overall median follow-up was 10.2 years (interquartile range [IQR], 7.2-14.9 years). Median follow-up time was 10.3 years (IQR, 7.3-16.0 years) for the neoadjuvant/concurrent ADT group, and 9.9 years (IQR, 6.5-13.1 years) for the concurrent/adjuvant ADT group. Baseline characteristics are shown in Table 1 and the Data Supplement. In the overall cohort, the median age was 70 years (IQR, 65-74 years); 77% had cT1/T2 disease, 86% had Gleason ≤ 7 disease, and median iPSA was 11 ng/mL (IQR, 7.4-18 ng/mL). Compared with men in the neoadjuvant/concurrent ADT group, those in the concurrent/adjuvant ADT group had higher rates of cT3/T4 disease (34% v 20%), higher iPSA (median 13 v 11, $P < .001$), higher rates of NCCN high-risk disease (49% v 36%, $P < .001$), and higher rates of receiving high-dose RT (47% v 38%, $P < .001$) or WPRT (57% v 38%, $P < .001$).

Unadjusted Kaplan-Meier and cumulative incidence curves comparing concurrent/adjuvant with neoadjuvant/concurrent sequencing for BCR, DM, PCSM, OCM, MFS, and OS are shown in Figure 1A-F. In the overall cohort, concurrent/adjuvant ADT sequencing was associated with improved MFS compared with the neoadjuvant/concurrent ADT (10-year estimates: 64.9% v 61.4%; HR, 0.83; 95% CI, 0.74 to 0.93; $P = .0015$). Significant associations were also seen between concurrent/adjuvant ADT and improved BCR (27.5% v 33.7%; HR, 0.77; 95% CI, 0.68 to 0.87; $P < .0001$), PCSM (6.5% v 7.7%; HR, 0.76; 95% CI, 0.59 to 0.99; $P = .04$), and OS (68.8% v 64.7%; HR, 0.79; 95% CI, 0.70 to 0.89; $P = .0001$). No significant differences in DM were seen (12.0% v 10.2%; HR, 1.15; 95% CI, 0.95 to 1.39; $P = .14$).

Notably, a significant interaction between ADT sequencing and RT field size for all the above end points except OS was observed after IPTW adjustment (P interaction < .02 for all except $P = .2$ for OS; Data Supplement). IPTW was effective in balancing the covariate distributions (Data Supplement). Therefore, for subsequent analyses, we dichotomized the population into cohorts receiving PORT or WPRT, and performed independent analyses in each cohort. Forest plots of multivariate analyses evaluating the impact of ADT sequencing on oncologic end points in the PORT and WPRT cohorts are presented in Figure 2. IPTW-adjusted Kaplan-Meier and cumulative incidence curves for BCR, DM, PCSM, OCM, MFS, and OS in the PORT cohort are shown in Figure 3A-F. Among patients receiving PORT, MFS was significantly improved in the concurrent/adjuvant group compared with the neoadjuvant/concurrent group. Up to a 10-year truncation point, RMTL for MFS was improved by 4.0 months (95% CI, 1.2 to 6.7), corresponding to a 10-year

TABLE 1. Baseline Characteristics

Characteristic	Neoadj/conc ADT (n = 6,325)	Conc/adj ADT (n = 1,084)	P	Overall (N = 7,409)
Age, years				
Median (IQR)	70 (65-74)	70 (65-74)	.690	70 (65-74)
Missing, No. (%)	1 (0.0)	0 (0.0)		1 (0.0)
RT dose, ^a No. (%)				
Low dose	3,942 (62.0)	558 (51.0)	< .001	4,500 (61.0)
High dose	2,374 (38.0)	514 (47.0)		2,888 (39.0)
Missing	9 (0.1)	12 (1.1)		21 (0.3)
Pelvic nodal RT, No. (%)				
No	3,886 (61.0)	469 (43.0)	< .001	4,355 (59.0)
Yes	2,434 (38.0)	615 (57.0)		3,049 (41.0)
Missing	5 (0.1)	0 (0.0)		5 (0.1)
T stage, No. (%)				
T1/T2	5,009 (79.0)	715 (66.0)	< .001	5,724 (77.0)
T3/T4	1,245 (20.0)	369 (34.0)		1,614 (22.0)
Missing	71 (1.1)	0 (0.0)		71 (1.0)
Gleason score, No. (%)				
6	2,498 (39.0)	472 (44.0)	.130	2,970 (40.0)
7	2,921 (46.0)	469 (43.0)		3,390 (46.0)
8	503 (8.0)	87 (8.0)		590 (8.0)
≥ 9	256 (4.0)	40 (4.0)		296 (4.0)
Missing	147 (2.3)	16 (1.5)		163 (2.2)
iPSA				
Median (IQR)	11 (7.3-17)	13 (7.9-21)	< .001	11 (7.4-18)
Missing, No. (%)	257 (4.1)	0 (0.0)		257 (3.5)
NCCN risk group, No. (%)				
Low	701 (11.0)	61 (6.0)	< .001	762 (10.0)
Intermediate	3,310 (52.0)	491 (45.0)		3,801 (51.0)
High	2,252 (36.0)	532 (49.0)		2,784 (38.0)
Missing	62 (1.0)	0 (0.0)		62 (0.8)

Abbreviations: ADT, androgen-deprivation therapy; Conc/adj, concurrent/adjuvant; iPSA, initial prostate-specific antigen; IQR, interquartile range; NCCN, National Comprehensive Cancer Network; Neoadj/conc, neoadjuvant/concurrent; RT, radiation therapy.

^aRT doses of 74 Gy or higher are considered high dose (presuming an α/β of 3.0 Gy).

risk benefit of 8.0% (95% CI, 3.5 to 12.5) and a HR for the concurrent/adjuvant group of 0.65 (95% CI, 0.54 to 0.79; $P < .0001$). Similarly, the cumulative incidences of BCR (10-year RMTL benefit 10.8 months, risk benefit 14.4%, HR, 0.46; 95% CI, 0.35 to 0.59; $P < .0001$) and DM (10-year RMTL benefit 2.3 months, risk benefit 3.6%, HR, 0.52; 95% CI, 0.33 to 0.82; $P = .0046$) were also improved in the concurrent/adjuvant group. Concurrent/adjuvant ADT sequencing was also associated with benefits in PCSM (10-year RMTL benefit 1.6 months, risk benefit 4.5%, HR, 0.3; 95% CI, 0.16 to 0.54; $P < .0001$) and OS (10-year RMTL benefit 2.5 months, risk benefit 6.2%, HR, 0.69; 95% CI, 0.57 to 0.83; $P = .0001$). No differences in OCM between the two ADT sequencing groups were observed (HR, 0.86; 95% CI, 0.7 to 1.05; $P = .14$).

In the WPRT cohort, ADT sequencing was not associated with differences in MFS (HR, 0.94; 95% CI, 0.79 to 1.12; $P = .48$), as shown in [Figure 4A](#). However, concurrent/adjuvant ADT was associated with a significant increase in the cumulative incidence of DM (10-year RMTL decrement of 5.5 months, risk decrement of 7.9%, HR, 1.57; 95% CI, 1.2 to 2.05; $P = .0009$). There was no statistically significant difference in BCR (HR, 0.86; 95% CI, 0.73 to 1.03; $P = .1$) or PCSM (HR, 1.09; 95% CI, 0.77 to 1.55; $P = .62$). There was a significant difference in OCM (HR, 0.59; 95% CI, 0.47 to 0.73; $P < .0001$), and a marginal, but statistically significant, difference in OS (HR, 0.82; 95% CI, 0.68 to 0.99; $P = .04$), both favoring concurrent/adjuvant ADT ([Figure 4B-F](#)).

Several prespecified analyses were performed. First, we assessed whether the effect of ADT sequencing is modified

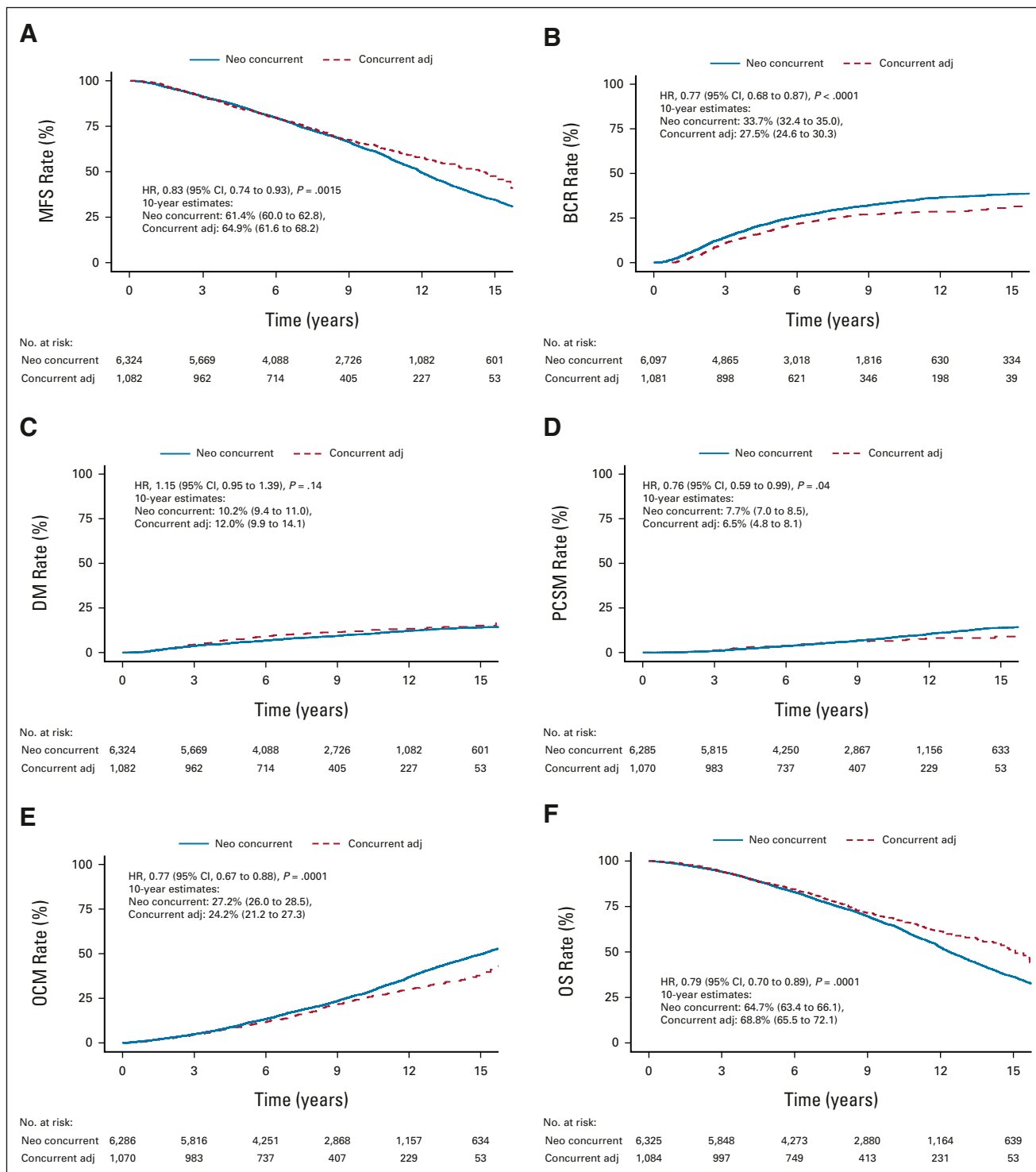


FIG 1. Unadjusted Kaplan-Meier and cumulative incidence curves evaluating the associations between concurrent/adjuvant versus neoadjuvant/concurrent ADT sequencing and oncologic outcomes in the overall cohort. Oncological outcomes included (A) metastasis-free survival, (B) biochemical recurrence, (C) distant metastasis, (D) prostate cancer-specific mortality, (E) other-cause mortality, and (F) overall survival. The neoadjuvant/concurrent ADT group was used as the reference when calculating HRs. ADT, androgen-deprivation therapy; BCR, biochemical recurrence; concurrent adj, concurrent/adjuvant; DM, distant metastasis; HR, hazard ratio; MFS, metastasis-free survival; neo concurrent, neoadjuvant/concurrent; OCM, other-cause mortality; OS, overall survival; PCSM, prostate cancer-specific mortality.

by NCCN risk groups by performing an IPTW-based interaction test and found significant interaction between the two in terms of MFS (P interaction = .0003). Additional significant interactions were found for BCR (P interaction = .034)



FIG 2. Forest plots of associations between oncologic outcomes and concurrent/adjuvant versus neoadjuvant/concurrent ADT sequencing, stratified by radiotherapy field size (PORT v WPRT). Inverse probability of treatment weighting analyses were performed on the overall cohort before multivariable analysis was conducted. The weight was calculated as the inverse of propensity score, defined as the predicted probability of treatment conditional on age, initial prostate-specific antigen, Gleason score, T stage, RT dose, and mid-trial enrollment year. ADT, androgen-deprivation therapy; BCR, biochemical recurrence; concurrent/adj, concurrent/adjuvant; DM, distant metastasis; HR, hazard ratio; MFS, metastasis-free survival; neo/concurrent, neoadjuvant/concurrent; OS, overall survival; PCSM, prostate cancer-specific mortality; PORT, prostate-only radiotherapy; RMTL, restricted mean time lost; RT, radiation therapy; WPRT, whole-pelvis radiotherapy.

and OS (P interaction = .0099). No significant interaction was observed for DM (P interaction = .13), PCSM (P interaction = .065), or OCM (P interaction = .37). The presence of the statistically significant interaction led us to stratify the population into patients with NCCN intermediate-risk and NCCN high-risk disease, with IPTW-adjusted Cox and Fine-Gray regression model performed in each separately. However, after dividing the population into these substrata defined by risk, there was not enough statistical power to ascertain the effect of ADT sequencing in each risk group. Therefore, the direction of these interactions could not be ascertained. Second, when comparing the four subgroups on the basis of ADT sequencing and use of WPRT, after IPTW, concurrent/adjuvant ADT with PORT (reference) had superior MFS compared with neoadjuvant/concurrent + PORT (HR, 1.60; 95% CI, 1.33 to 1.92; P < .0001), neoadjuvant/concurrent ADT + WPRT (HR, 1.96; 95% CI, 1.60 to 2.40; P < .0001), and concurrent/adjuvant ADT + WPRT (HR, 1.95; 95% CI, 1.51 to 2.51; P < .0001; Data Supplement). Finally, given that the WPRT status of patients in EORTC 22991 was imputed on the basis of the recommendations in the trial protocol, we performed a sensitivity analysis after excluding EORTC 22991 (n = 410) in its entirety. As shown in the Data Supplement, the outcomes are consistent with primary analyses, with concurrent/adjuvant ADT associated with superior outcomes for all end

points except OS when PORT was delivered. Neoadjuvant/concurrent ADT was significantly associated with an improved DM benefit when used with WPRT.

DISCUSSION

In this IPD pooled analysis of 12 randomized trials, a significant interaction between RT field size and STADT sequencing was found, with concurrent/adjuvant ADT sequencing being associated with improvements in multiple oncologic end points (including both MFS and OS) in men receiving PORT. In men who received WPRT, neoadjuvant/concurrent ADT sequencing was associated with improved DM, but not MFS. However, neoadjuvant/concurrent sequencing with WPRT was also associated with worse OS, driven by worse OCM than concurrent/adjuvant sequencing and most likely an artifact of the fact that trials including WPRT and concurrent/adjuvant ADT tended to be more contemporary than trials using WPRT combined with neoadjuvant/concurrent ADT. Thus, overall, the results suggest that when PORT is delivered with STADT, concurrent/adjuvant ADT sequencing should be the standard of care. If WPRT is delivered with STADT, neoadjuvant/concurrent ADT may offer an oncologically relevant benefit, albeit less consistent than the benefit provided by concurrent/adjuvant ADT with PORT.

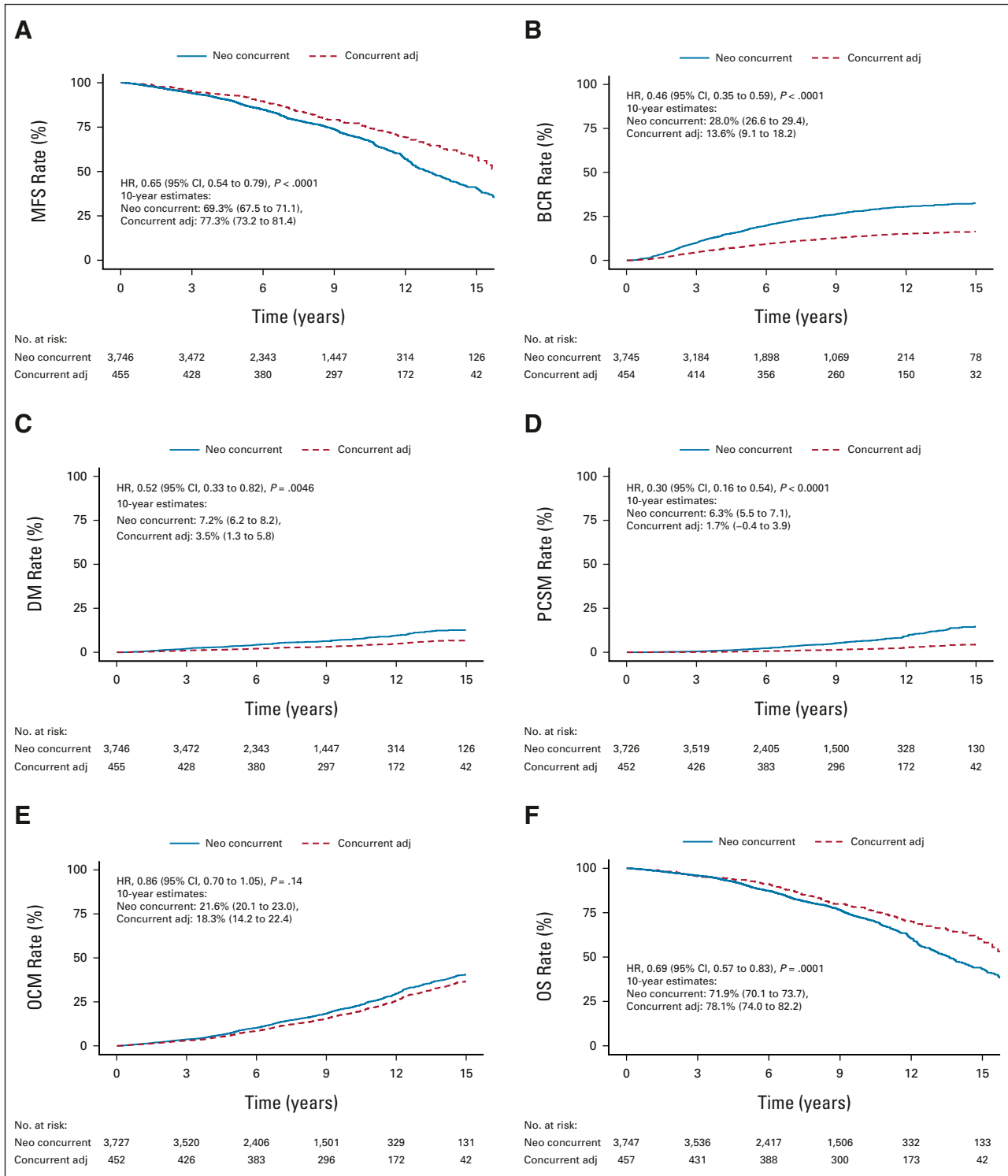


FIG 3. Inverse probability of treatment weighting–adjusted Kaplan-Meier and cumulative incidence curves evaluating the associations between concurrent/adjuvant versus neoadjuvant/concurrent ADT sequencing and oncologic outcomes in patients receiving prostate-only radiotherapy. Oncologic outcomes included (A) metastasis-free survival, (B) biochemical recurrence, (C) distant metastasis, (D) prostate cancer-specific mortality, (E) other-cause mortality, and (F) overall survival. Neoadjuvant/concurrent ADT sequencing was used as the reference when calculating the HR. ADT, androgen-deprivation therapy; BCR, biochemical recurrence; concurrent adj, concurrent/adjuvant; DM, distant metastasis; HR, hazard ratio; MFS, metastasis-free survival; neo concurrent, neoadjuvant/concurrent; OCM, other-cause mortality; OS, overall survival; PCSM, prostate cancer-specific mortality.

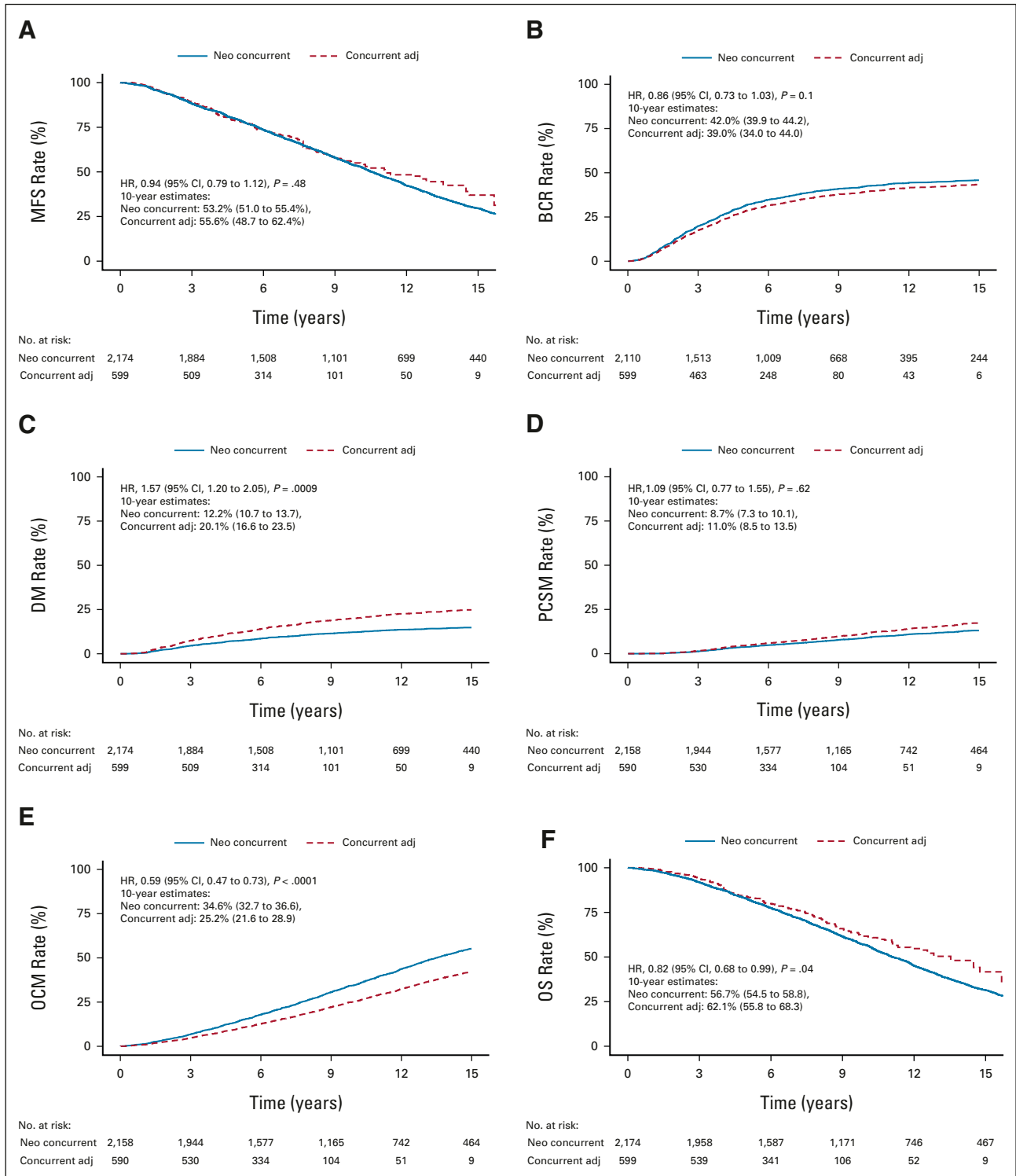


FIG 4. Inverse probability of treatment weighting–adjusted Kaplan-Meier and cumulative incidence curves evaluating the associations between concurrent/adjuvant versus neoadjuvant/concurrent ADT sequencing and oncologic outcomes in patients receiving whole-pelvis radiotherapy. Oncological outcomes included (A) metastasis-free survival, (B) biochemical recurrence, (C) distant metastasis, (D) prostate cancer-specific mortality, (E) other-cause mortality, and (F) overall survival. Neoadjuvant/concurrent ADT group was used as the reference when calculating HRs. ADT, androgen-deprivation therapy; BCR, biochemical recurrence; concurrent adj, concurrent/adjuvant; DM, distant metastasis; HR, hazard ratio; MFS, metastasis-free survival; neo concurrent, neoadjuvant/concurrent; OCM, other-cause mortality; OS, overall survival; PCSM, prostate cancer-specific mortality.

Notably, to our knowledge, this is the first time a significant association with concurrent/adjunct ADT sequencing and OS has been demonstrated. Our results are consistent with the finding of the only two randomized trials that tested the sequencing of STADT without altering the total duration, both of which were underpowered for OS. RTOG 9413 similarly found a significant interaction between RT field size and ADT sequencing with a more favorable 10-year PFS with neoadjuvant/concurrent ADT compared with adjuvant ADT when WPRT was used; the reverse was true when PORT only was delivered.⁴ Ottawa 0101 only delivered PORT and found a numerically higher 10-year biochemical relapse-free survival rate (87.4% v 80.5%) with concurrent/adjuvant ADT, although it did not reach statistical significance ($P = .1$), likely secondary to a lack of statistical power, given the lower-than-expected event rate.⁶ An IPD meta-analysis of patients receiving PORT on both of these trials showed significantly improved long-term PFS and MFS with an adjuvant ADT approach.⁷ The current pooled analysis with a much larger patient population (approximately seven-fold larger) consolidates the findings of these studies by showing robust evidence of an interaction between RT field size and the impact of ADT sequencing on multiple end points, including an OS benefit with concurrent/adjuvant sequencing in the setting of PORT.

The inferiority of neoadjuvant/concurrent sequencing is also consistent with several other lines of evidence. Three neoadjuvant ADT extension trials and a large meta-analysis of neoadjuvant extension trials did not identify an improvement in multiple key clinical outcomes, including biochemical failure-free survival.^{8,9,18,19} Although TROG 96.01 (2 v 5 months neoadjuvant) did demonstrate significantly improved event-free survival, PCSM, and OS with neoadjuvant RT prolongation, this trial compared a shorter-than-standard duration (3 months) against a standard duration (6 months) and 85% of patients had high-risk disease.¹⁰

The underlying mechanisms behind superior outcomes with concurrent/adjuvant compared with neoadjuvant/concurrent ADT coupled with PORT, but not with WPRT, remain to be elucidated. The adjuvant component of ADT may be beneficial regardless of radiation field size. The benefit of adjuvant ADT could be related to protracted RT-induced tumor cell death²⁰; so, continued blockade of androgen receptor-regulated DNA repair genes²¹ and RT-induced neoangiogenesis²² may be needed to optimize outcomes. Given that testosterone levels may be suppressed for several months after cessation of ADT, an adjuvant component of castration will exist even if neoadjuvant/concurrent ADT is given, and would simply be longer in duration with concurrent/adjuvant ADT. In terms of potential mechanisms for field size interaction, the immunologic effects of ADT may be important. ADT has been shown to increase interferon- γ production,²³ decrease regulatory T-cell activation,²⁴ and increase naive T-cell infiltration into the prostate.^{25,26} WPRT may eliminate

proinflammatory lymphocytes in the pelvic nodal system and periphery,²⁷ such that these presumptive oncologic benefits of ADT would only occur if the ADT were given neoadjuvantly. Alternatively, the doses used for WPRT are low, and hypoxia induced by neoadjuvant ADT may be required to potentiate cytotoxic effects against occult cancer cells in the lymphatic system.²⁸ Notably, this analysis does not rule out any utility to neoadjuvant ADT; a neoadjuvant/concurrent/adjuvant approach may be more efficacious than concurrent/adjuvant sequencing, which will need prospective validation. Similarly, the analysis was not designed to evaluate the oncologic benefit of WPRT. The interim analysis of NRG/RTOG 0924 (ClinicalTrials.gov identifier: [NCT01368588](https://clinicaltrials.gov/ct2/show/study/NCT01368588)), a phase III randomized trial of PORT versus WPRT in patients receiving neoadjuvant/concurrent ADT, is expected to be performed in October 2023 (Roach personal communication). The PIVOTALboost trial (ISRCTN80146950) will also evaluate WPRT in this context.

Toxicity data were not available. It is theoretically possible that the prostate downsizing offered by neoadjuvant/concurrent ADT might lead to less toxicity than a concurrent/adjuvant approach. However, in the context of PORT, no differences in GI, genitourinary, or sexual toxicity between the two sequencing approaches that would support this hypothesis have been shown in either RTOG 9413⁴ or Ottawa 0101.²⁹ There was also no difference in time to full testosterone recovery³⁰ and rates of early ADT termination.⁴ Toxicity differences have not been rigorously studied in the setting of WPRT.

The current study has several limitations. First, given the nonrandomized nature of this study, there was considerable heterogeneity in baseline characteristics between groups. Despite the use of IPTW, residual confounding factors in clinical practice such as follow-up pattern, imaging, and salvage treatment still exist, and could not be accounted for. For instance, if certain trials and/or certain enrollment centers within trials more frequently evaluated patients for recurrences with more frequent PSA checks or lower thresholds for triggering systemic imaging, this might have led to higher rates of BCR or DM detection in a fashion independent of ADT sequencing. Second, heterogeneities exist across trials regarding how DM was ascertained. Advanced imaging, such as prostate-specific membrane antigen positron emission tomography, was neither required nor recommended in the trials included; and how routine inclusion of such imaging modalities may alter the conclusion is uncertain. Third, neoadjuvant/concurrent ADT provides a period of adjuvant androgen suppression, and its duration will be influenced by the duration of the neoadjuvant component (and so the total duration) of ADT. Similarly, concurrent ADT may take up to 1 month into the RT course to suppress testosterone to castration level.³¹ Thus, these results may not pertain to the use of novel ADT agents that have altered kinetics of testosterone reduction and recovery.³² Furthermore, GnRH agonists and depot

doses may not be equivalent in terms of their kinetics and proportions of patients achieving castration level³³⁻³⁵; however, the difference is likely small. Fourth, this analysis was restricted to patients receiving STADT (≤ 6 months). An interaction between sequencing and risk group was seen, but stratification by both risk group and RT field size resulted in sample sizes that were too small to detect meaningful differences on the basis of ADT sequencing. Although the presented results thus correspond to patients with intermediate-risk and high-risk disease, the findings should not be extrapolated to patients receiving longer durations of ADT, as would be standard for patients with high-risk disease.

In conclusion, ADT sequencing exhibits a significant interaction with RT field size, such that concurrent/adjuvant

STADT sequencing is associated with optimal oncologic outcomes with PORT. The effects are not as clear for patients receiving WPRT, although neoadjuvant/concurrent STADT sequencing may be preferred, given its DM benefit. These data strongly suggest that when PORT is being delivered with STADT—as is recommended for men with intermediate-risk disease—concurrent/adjuvant ADT sequencing should be the standard of care. The findings also support, albeit to a lesser degree, the recommendation that if WPRT were to be used, neoadjuvant/concurrent sequencing should be the standard of care. Future trials, such as RTOG 0924 and PIVOTALboost, will provide level I evidence evaluating the benefit of WPRT with neoadjuvant/concurrent ADT sequencing in selected patients with intermediate-risk and high-risk disease.

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DISCLAIMER

The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. N.G.Z. is supported by the National Institutes of Health Grant LRP 1 L30 CA231572-01 (2018-2022).

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SUPPORT

Funding support for this study comes from the Prostate Cancer Foundation and ASTRO to AUK. AUK also thanks generous donations from the DeSilva, McCarrick, and Bershad families. A.T. acknowledges support from Cancer Research UK (C33589/A28284 and C7224/A28724) the National Institute for Health Research (NIHR) Cancer Research Network. This project represents independent research supported by the National Institute for Health research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London. N.G.Z. is supported by the American Cancer Society – Tri State CEOs Against Cancer Clinician Scientist Development Grant, CSDG-20-013-01-CCE (2020).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO.22.00970>.

DATA SHARING STATEMENT

Data for these analyses were made available to the authors through agreement with individual contributing institutions. As such, the authors cannot make these data publicly available because of data use agreement.

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ACKNOWLEDGMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Sequencing of Androgen-Deprivation Therapy of Short Duration With Radiotherapy for Nonmetastatic Prostate Cancer (SANDSTORM): A Pooled Analysis of 12 Randomized Trials**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

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No other potential conflicts of interest were reported.