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Prostate Radiotherapy in Low-volume Metastatic Hormone-sensitive Prostate Cancer: A Network Meta-analysis

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Abstract

Background and objective: The utility of prostate radiotherapy (RT) is unclear in men with metastatic hormone-sensitive prostate cancer (mHSPC) receiving intensified systemic therapy with androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPIs). We performed a network meta-analysis of randomized controlled trials (RCTs) to investigate the role of prostate RT in low-volume mHSPC.
Methods: Bibliographic databases and conference proceedings were searched through July 2023 for RCTs evaluating the addition of ARPIs or prostate RT to standard of care (SOC) systemic therapy, defined as ADT or ADT plus docetaxel, for the initial treatment of mHSPC. We focused exclusively on aggregate data from the low-volume mHSPC subpopulation in these trials. We pooled the treatment arms into four groups: SOC, SOC plus ARPI, SOC plus RT, and SOC plus ARPI plus RT. The primary outcome was overall survival (OS). To compare treatment strategies, a fixed-effects Bayesian network meta-analysis was undertaken, while a Bayesian network meta-regression was performed to account for across-trial differences in docetaxel use as part of SOC and in proportions of patients with de novo presentation.
Key findings and limitations: Ten RCTs comprising 4423 patients were eligible. The Surface Under the Cumulative Ranking Curve scores were 0.0006, 0.45, 0.62, and 0.94 for SOC, SOC plus RT, SOC plus ARPI, and SOC plus ARPI plus RT, respectively. On a meta-regression, in a population with de novo mHSPC and no docetaxel use, we did not find sufficient evidence of a difference in OS between SOC plus ARPI plus RT versus

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SOC plus ARPI (hazard ratio [HR]: 0.76; 95% credible interval: 0.51–1.16) and SOC plus RT versus SOC plus ARPI (HR: 1.10; 95% credible interval: 0.92–1.42).
Conclusions and clinical implications: There was some evidence that SOC plus ARPI plus RT reduced mortality compared with the next best strategy of SOC plus ARPI in patients with low-volume de novo mHSPC. A meta-analysis with individual patient data or an RCT is needed to confirm these findings.

ADVANCING PRACTICE

What does this study add?
Our findings suggest but do not prove that the addition of prostate radiotherapy to systemic therapy including an androgen receptor pathway inhibitor improves survival in de novo low-volume metastatic hormone-sensitive prostate cancer. An individual patient data meta-analysis or, ideally, a large-scale randomized controlled trial addressing this question is needed for confirmation of these findings.

Clinical relevance
The treatment of oligometastatic prostate cancer is intensely debated, especially in the current era of treatment intensification and molecular imaging. In absence of high-level evidence coming from ad hoc well-powered randomized trials, the current network meta-analysis of trial-level aggregate data suggests that the most effective treatment in terms of overall survival benefit for patients with low-volume metastatic hormone-sensitive prostate cancer – as determined with conventional imaging – is a combination of intensified systemic treatment including androgen deprivation therapy and an androgen receptor pathway inhibitor, and radiation therapy delivered to the prostate. These results, while warranting confirmation through an individual patient data analysis, will inform the design of future trials where oligometastatic disease is diagnosed with positron emission tomography imaging.*
*Clinical relevance section written by *Eur Urol* Associate Editor Gianluca Giannarini, MD.

Patient summary
We synthesized the available evidence from clinical trials conducted in patients with newly diagnosed low-volume metastatic prostate cancer to compare the outcomes of four treatment approaches. A strategy that consists of androgen deprivation therapy, an androgen receptor pathway inhibitor, and prostate radiotherapy appeared to be most effective in terms of overall survival.

1. Introduction

The combination of androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPIs), with or without docetaxel, has emerged as the current standard of care (SOC) systemic treatment strategy for men with metastatic hormone-sensitive prostate cancer (mHSPC), based on a succession of large-scale randomized controlled trials (RCTs) conducted in the last decade [1–8]. Another group of trials during the same period investigated the role of prostate radiotherapy (RT) in this patient population. The largest of this latter group was arm H of STAMPEDE, in which 2061 patients with de novo mHSPC were randomized to SOC systemic therapy with or without prostate-directed RT. Approximately one in five patients in this analysis received ADT plus docetaxel, while the remaining population received ADT alone. Prostate RT conferred a failure-free survival advantage for the entire cohort, whereas an overall survival (OS) advantage was noted with addition of prostate RT in men with low-volume metastatic disease [9]. Another contemporary RCT (HORRAD) investigated the role of prostate RT in addition to ADT in men with bone-only metastatic prostate cancer [10]. While this much smaller study itself did not identify an OS advantage with prostate RT, an individual patient meta-analysis of HORRAD and STAMPEDE arm H showed a 7% absolute improvement in 3-yr OS in men with low-volume mHSPC and fewer than five skeletal metastases [11].

A third trial in de novo mHSPC, PEACE-1, investigated the role of prostate RT with ADT (with or without docetaxel) or ADT plus abiraterone acetate (with or without docetaxel) [12]. In a recent abstract from this trial presented by Bossi et al [12], prostate RT did not improve OS significantly in de novo low-volume mHSPC but delayed serious genitourinary adverse events. In summary, while prostate RT has been shown to improve OS in men with low-volume mHSPC treated predominantly with ADT alone, it is unknown whether prostate RT retains benefit in men with low-volume mHSPC treated with intensified systemic therapy consisting of ADT plus ARPI, which has been proved to be superior to ADT plus docetaxel [13,14]. We performed a network meta-analysis (NMA) of RCTs to determine whether the addition of prostate RT confers a survival benefit in patients with low-volume mHSPC treated with intensified systemic therapy consisting of ADT plus ARPI.

2. Methods

2.1. Search strategy and selection criteria

We included parallel-design phase 3 randomized trials in mHSPC. The interventions of interest were SOC systemic therapy (defined as ADT with or without docetaxel), SOC plus ARPI, SOC plus prostate RT, and SOC plus ARPI plus RT. We excluded meta-analyses and reviews, registered trials or trials with published protocols but lacking published results or lacking results presented in abstract form, and articles not written in English. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023445641).

To identify all relevant randomized trials, a literature review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. A systematic literature search was performed using MEDLINE and Scopus from inception through July 16, 2023. In addition, proceedings of the annual meeting and Genitourinary Cancers Symposium of the American Society of Clinical Oncology, and the annual congress of the European Society for Medical Oncology were searched between 2014 and June 2023. Two investigators (S.R. and S.C.M.) independently performed the screening. Two investigators (S.R. and G.F.) independently extracted data from included trials, and two investigators (S.C.M. and C.J.D.W.) verified the extracted data. Discrepancies were resolved through consensus. Data extracted included trial design, interventions, proportion of patients with de novo mHSPC (as opposed to relapsed mHSPC after prior treatment), proportion of patients in whom docetaxel was added to ADT as part of initial SOC systemic therapy, follow-up duration, and results with respect to OS. The numbers of deaths and hazard ratios (HRs) for OS, with associated 95% confidence intervals (CIs), were collected for patients with low-volume mHSPC. For those trials with published updates, we included the most recent published analysis for the outcome of interest.

2.2. Data analysis

We pooled the treatment arms into one of four groups: SOC systemic therapy, SOC plus ARPI, SOC plus RT, and SOC plus ARPI plus RT. We applied a Bayesian fixed-effects hierarchical model with four parallel Markov chains (consisting of 150 000 samples) to compare the pooled treatment effects from the four treatment regimens. Heterogeneity was evaluated using τ^2, H, and Q-statistic values separately for the group of trials that investigated the addition of ARPI to SOC systemic therapy and for the group of trials that investigated the addition of RT to SOC systemic therapy. Treatments were ranked by the Surface Under the Cumulative Ranking Curve (SUCRA) score. A SUCRA value of 1 indicates that the treatment is certain to be the best/preferred choice and 0 indicates that it is certain to be the worst.

The trials varied with respect to the proportion of patients in whom SOC systemic therapy included docetaxel while the trials investigating the addition of ARPIs further varied with respect to the proportion of patients with de novo presentation with metastatic disease. To account for these differences, a Bayesian network meta-regression was performed for pairwise comparisons of the efficacy of the four treatment strategies after adjustment for the proportion of de novo mHSPC patients and the docetaxel utilization rate. SWOG 1216 was omitted from this meta-regression as orteronel, the ARPI investigated in this trial, has not been shown to improve survival in mHSPC and is not approved for use in this setting. Trace plots and Gelman-Rubin-Brooks plots were used to assess convergence. All statistical analyses were performed using R version 4.2.2 (2022-10-31; The R Foundation for Statistical Computing).

3. Results

A total of ten RCTs comprising 18 full publications and one abstract were eligible for this NMA [1–3,7–10,12,15–25]. Across these trials, a total of 4423 patients with low-volume mHSPC were included (Fig. 1). The studies have been summarized in Table 1. Overall, 2043 patients received SOC systemic therapy alone, 1629 received SOC plus ARPI, 625 received SOC plus prostate RT, and 126 received SOC plus ARPI plus RT. Among patients treated with SOC plus ARPI, 482 received enzalutamide, 465 received abiraterone, 328 received orteronel, 200 received apalutamide, and 154 received darolutamide. Among patients who received SOC plus ARPI plus RT, abiraterone was the ARPI received by all patients. RT dose-fractionation regimens used in these trials included 55 Gy in 20 fractions (n = 240, STAMPEDE arm H), 36 Gy in six fractions given weekly (n = 170, STAMPEDE arm H), 74 Gy in 37 fractions (n = 252, PEACE-1), and 70 Gy in 35 fractions (n = 89, HORRAD). Measures of between-trial heterogeneity are reported in Supplementary Table 2.

The median follow-up duration of surviving patients in all included trials is presented in Table 1. Based on the fixed-effects Bayesian NMA, compared with SOC, the addition of RT alone was associated with a 27% reduction in

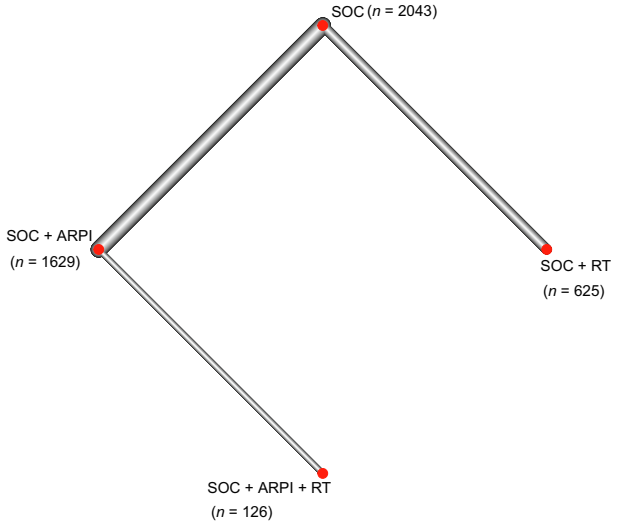


Fig. 1 – Network graph of the treatment comparisons, with nodes representing competing treatments and the sides representing RCTs for the specific pairs of treatments. ARPI = androgen receptor pathway inhibitor; RCT = randomized controlled trial; RT = radiotherapy; SOC = standard of care.

Table 1 – Summary of included randomized controlled trials

Study	Treatment	Number of patients with low metastatic burden	Proportion of patients with receipt of docetaxel [a]	Proportion of population with de novo presentation	Median follow-up duration (mo)
ARASENS (NCT02799602)	ADT + docetaxel	146	1.00	0.83	42.4
	ADT + docetaxel + ARPI (darolutamide)	154	1.00	0.82	43.7
ARCHES (NCT02677896)	ADT with/without docetaxel	203	0.18	0.63	44.6
	ADT with/without docetaxel + ARPI (enzalutamide)	220	0.18	0.70	44.6
ENZAMET (NCT02446405)	ADT with/without docetaxel	261	0.27	0.47	68.0
	ADT with/without docetaxel + ARPI (enzalutamide)	262	0.28	0.46	68.0
HORRAD (NCT00567580)	ADT	71	0.00	1.00	47.0
	ADT + RT	89	0.00	1.00	47.0
LATITUDE (NCT01715285)	ADT	110	0.00	1.00	51.8
	ADT + ARPI (abiraterone)	133	0.00	1.00	51.8
PEACE-1 (NCT01957436)	ADT with/without docetaxel	127	0.50	1.00	73.0
	ADT with/without docetaxel + ARPI (abiraterone)	126	0.50	1.00	73.0
	ADT with/without docetaxel + RT	126	0.50	1.00	73.0
	ADT with/without docetaxel + RT + ARPI (abiraterone)	126	0.50	1.00	73.0
STAMPEDE arm G (NCT00268476)	ADT	196	0.00	0.93	42.0
	ADT + ARPI (abiraterone)	206	0.00	0.93	42.0
STAMPEDE arm H (NCT00268476)	ADT with/without docetaxel	409	0.16	1.00	61.3
	ADT with/without docetaxel + RT	410	0.15	1.00	61.3
SWOG1216 (NCT01809691)	ADT	328	0.00	0.77	58.8
	ADT + ARPI (orteronel)	328	0.00	0.74	58.8
TITAN (NCT02489318)	ADT with/without docetaxel	192	0.10	0.84	44.0
	ADT with/without docetaxel + ARPI (apalutamide)	200	0.11	0.78	44.0

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; RT = radiotherapy.
[a] Reported as a proportion of the overall trial population.

the hazard for death (pooled HR: 0.73; 95% credible interval [CrI]: 0.62–0.87), while SOC plus ARPI was associated with a 32% reduction (pooled HR: 0.68; 95% CrI: 0.60–0.78) and SOC plus ARPI plus RT was associated with a 47% reduction (pooled HR: 0.53; 95% CrI: 0.34–0.81) in the hazard for death (Fig. 2A). SUCRA scores were 0.0006, 0.45, 0.62, and 0.94 for SOC, SOC plus RT, SOC plus ARPI, and SOC plus ARPI plus RT, respectively. A rankogram that shows the probabilities of the four treatment strategies assuming each of the possible ranks is shown in Figure 3.

The direction and magnitude of pooled treatment effects from a sensitivity analysis excluding SWOG 1216 were similar to those from the primary analysis. Compared with SOC systemic therapy, SOC plus RT was associated with a 27% reduction in the hazard for death (pooled HR: 0.73; 95% CrI: 0.62–0.87), while SOC plus ARPI was associated with a significant 36% reduction in the hazard for death (pooled HR: 0.64; 95% CrI: 0.56–0.74) and SOC plus ARPI plus RT was associated with a significant 51% reduction in the hazard for death (pooled HR: 0.49; 95% CrI: 0.32–0.76). The SUCRA scores were 0.0003, 0.40, 0.66, and 0.95 for SOC, SOC plus RT, SOC plus ARPI, and SOC plus ARPI plus RT, respectively. In the corresponding rankogram (Supplementary Fig. 1), SOC plus ARPI plus RT was most likely to be the best treatment strategy, which was consistent with the primary analysis.

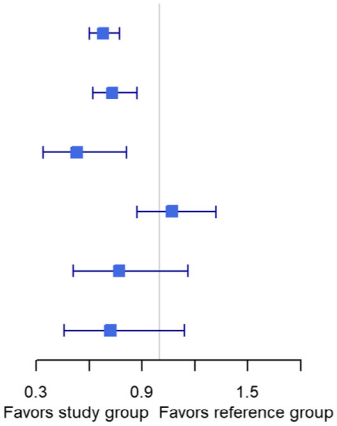
We visually explored the correlation of the proportions of trial patients who received docetaxel as part of their systemic therapy with treatment effect (Supplementary Fig. 2A) and the proportions of trial populations with de novo mHSPC (Supplementary Fig. 2B) with treatment effect in trials that investigated the addition of ARPI to the SOC systemic therapy. In the four trials that investigated the addition of prostate RT to SOC systemic therapy, we similarly explored the correlation between the proportions of trial populations receiving docetaxel with treatment effect from prostate RT (Supplementary Fig. 2C). Based on a Bayesian network meta-regression, in a population with de novo mHSPC and no use of docetaxel, SOC plus ARPI plus RT was associated with a nonsignificant 23% reduction in the hazard for death (HR: 0.77; 95% CrI: 0.51–1.16) relative to SOC plus ARPI. Similarly, there was no significant difference in treatment effect from SOC plus RT versus SOC plus ARPI (HR: 1.10; 95% CrI: 0.92–1.42; Fig. 2B).

In a second sensitivity analysis, we limited our Bayesian fixed-effects NMA to RCTs that enrolled only patients with de novo mHSPC. SOC plus ARPI plus RT was associated with a 48% reduction in the hazard for death (HR: 0.52; 95% CrI: 0.34–0.81) compared with SOC alone. SOC plus RT (HR: 0.73; 95% CrI: 0.62–0.87) and SOC plus ARPI (HR: 0.68; 95% CrI: 0.60–0.78) were associated with smaller improvements in OS when compared with SOC alone. Further, SOC plus ARPI plus RT was associated with a nonsignificant 23% reduction in the hazard for death compared with SOC plus ARPI (HR: 0.77; 95% CrI: 0.51–1.16).

A

Hazard ratios (95% credible intervals) from pairwise comparisons of treatment groups from Bayesian fixed-effects network meta-analysis

Pairwise Comparison	Hazard Ratio	95% Credible Interval
SOC plus ARPI versus SOC	0.68	0.60 to 0.77
SOC plus RT versus SOC	0.73	0.62 to 0.87
SOC plus ARPI plus RT versus SOC	0.53	0.34 to 0.81
SOC plus RT versus SOC plus ARPI	1.07	0.87 to 1.32
SOC plus ARPI plus RT versus SOC plus ARPI	0.77	0.51 to 1.16
SOC plus ARPI plus RT versus SOC plus RT	0.72	0.46 to 1.14



B

Hazard ratios (95% credible intervals) from Bayesian pairwise comparisons of treatment groups with adjustment for de novo population and docetaxel use

Pairwise Comparison	Hazard Ratio	95% Credible Interval
SOC plus ARPI versus SOC	0.64	0.56 to 0.73
SOC plus RT versus SOC	0.74	0.63 to 0.86
SOC plus ARPI plus RT versus SOC	0.50	0.32 to 0.76
SOC plus RT versus SOC plus ARPI	1.10	0.92 to 1.42
SOC plus ARPI plus RT versus SOC plus ARPI	0.77	0.51 to 1.15
SOC plus ARPI plus RT versus SOC plus RT	0.65	0.42 to 1.06

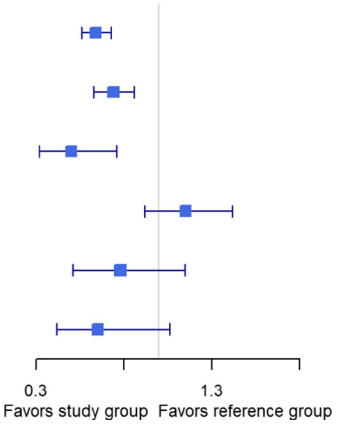


Fig. 2 – (A) Forest plot of the unadjusted fixed-effects Bayesian network meta-analysis showing hazard ratios for overall survival with associated 95% credible intervals for pairwise comparisons of the four treatment groups. Hazard ratios are reported such that the intervention listed second in the pairwise comparison is the reference group. (B) Forest plot showing hazard ratios for overall survival and associated 95% credible intervals for pairwise comparisons of treatments from a fixed-effects Bayesian network meta-regression in a population with de novo mHSPC and no use of docetaxel. Hazard ratios are reported such that the intervention listed second in the pairwise comparison is the reference group. ARPI = androgen receptor pathway inhibitor; mHSPC = metastatic hormone-sensitive prostate cancer; RT = radiotherapy; SOC = standard of care.

4. Discussion

In this NMA of patients with low-volume mHSPC, SOC plus ARPI plus RT was associated with a significant improvement in OS compared with SOC alone (ADT with or without docetaxel) and emerged as the highest ranked treatment strategy among the four considered. In a network meta-regression that considered a population with de novo mHSPC and no docetaxel use as part of SOC, there was no significant difference in the hazard of mortality between SOC plus ARPI and SOC plus RT or between SOC plus ARPI and SOC plus ARPI plus RT. Similarly, in a sensitivity analysis restricted to trials that enrolled a purely de novo mHSPC population, all three strategies (SOC plus ARPI plus RT, SOC plus ARPI, and SOC plus RT) were associated with improvements in OS compared with SOC alone. The direction of our findings, with respect to the benefit from prostate RT, is similar to that seen in the STOPCAP meta-analysis by Bur-

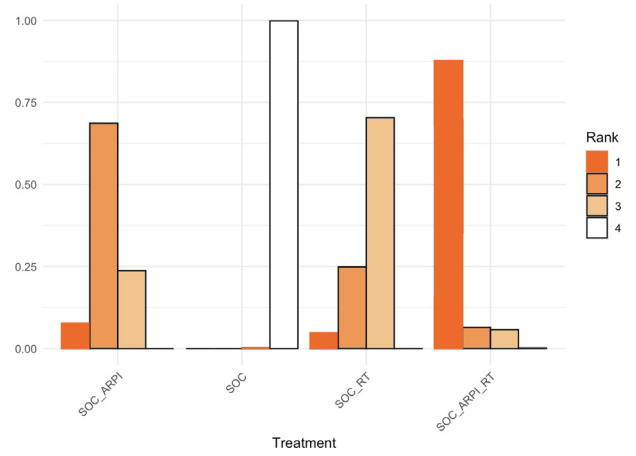


Fig. 3 – Rankogram showing the probabilities of the four treatment strategies assuming each of the possible ranks based on a fixed-effects Bayesian network meta-analysis. ARPI = androgen receptor pathway inhibitor; RT = radiotherapy; SOC = standard of care.

dett et al [11], which included results only from HORRAD and STAMPEDE arm H and did not consider trials investigating ARPIs. The lack of statistical significance in our NMA might be due to limited power, as relatively few patients, for example, received SOC plus ARPI plus RT. Further, our comparator group included ADT with or without docetaxel, while ADT alone was the comparator in the STOPCAP meta-analysis. Subsequently, when we undertook a network meta-regression, SOC plus RT had a significantly better predicted treatment effect over SOC systemic therapy alone in a population that consisted of patients with de novo mHSPC and no docetaxel use. While our findings would be best validated in an individual patient data-based meta-analysis or a new RCT, overall these results suggest that in patients with de novo low-volume mHSPC, a treatment approach that includes ADT, ARPI, and prostate RT confers outcomes superior to one in which RT is omitted. Further, in settings where access to ARPIs is limited [26,27], or in clinical scenarios where comorbidity considerations or patient preferences preclude the use of an ARPI, ADT plus prostate RT represents an alternative with similar efficacy [28].

Beyond its effect on OS, the addition of prostate RT has been shown to improve a number of other oncologic endpoints. In PEACE-1, the addition of prostate RT significantly prolonged radiographic progression-free survival (HR: 0.65; 99% CI: 0.36–1.19; $p = 0.02$), time to emergence of castration resistance (HR: 0.62; 95% CI: 0.44–0.82), and time to serious genitourinary adverse events [12]. Similarly, the addition of prostate RT to SOC systemic therapy in STAMPEDE arm H significantly improved failure-free survival (HR: 0.59; 95% CI: 0.49–0.72), which is an outcome that closely parallels castration resistance–free survival [25]. In a recently presented secondary analysis of STAMPEDE arm H, there was a significant reduction in the 5-yr incidence of upper urinary tract obstruction requiring intervention in the SOC plus RT arm (3% vs 5%; subdistribution HR = 0.57, 95% CI: 0.35–0.91) [29]. These findings point to a multifaceted oncologic benefit from prostate RT and warrant consideration in clinical decision-making for men with low-volume de novo mHSPC.

A pooled analysis of toxicity across the included trials could not be done robustly and reliably with the aggregate data that are available currently. In many of the included trials, toxicity was not reported separately in the de novo low-volume subgroup of interest. Further, where toxicity was reported, there was significant heterogeneity in how it was documented across the trials, with variation in scales, grade cut points, and the frequency and time periods over which toxicity data were collected. Notably, the nature of reporting of toxicity in the STAMPEDE trial was significantly different from that of other trials. The lack of reporting of toxicity in some cases and heterogeneity of reporting elsewhere precluded a reliable pooled analysis. However, to summarize, in LATITUDE, grade 3 or 4 adverse events were observed in 63% of patients treated with ADT plus abiraterone, while in STAMPEDE arm G, which used a different analytical and reporting methodology, only 16% had grade $\geq$3 toxicity at 4 yr [1,23]. In ARCHES, the rate of grade 3 or 4 treatment-emergent adverse events was 39% in patients treated with ADT plus enzalutamide, while in ENZAMET, the rate of grade $\geq$3 adverse events was 69% in patients treated with the same combination [15,16]. Finally, in TITAN, the rate of grade $\geq$3 adverse events was 42% in patients treated with a combination of ADT plus apalutamide [7].

The toxicity profile of radical-dose prostate RT, when given with ADT, is very well characterized in the localized prostate cancer literature and is generally mild [30–34]. It is noted further that the doses used in the completed RCTs were slightly subradical, and the overall rates of grade $\geq$3 toxicity were limited compared with a combination of ADT plus ARPI. In STAMPEDE arm H, over the entire reported follow-up period, at least one grade 3–5 adverse event was reported for 45% of the patients receiving SOC plus RT. However, the toxicities attributable to RT were very low: 0.5% grade $\geq$3 urinary adverse events and 1% grade $\geq$3 bowel adverse events at 2 yr [9]. In PEACE-1, only 4% of patients had grade $\geq$3 toxicities that were attributable to RT.

Our meta-analysis is subject to several limitations. The chief among them is that this meta-analysis, similar to those published previously on mHSPC [13], is based on aggregate data rather than individual patient data. As a result, the pooled estimates of treatment effect apply to the overall populations studied. Although a network meta-regression was undertaken to adjust for docetaxel utilization and the proportion of patients with de novo disease in the overall trial populations, the results should be interpreted considering the loss of power inherent in such pairwise comparisons. Therefore, an analysis based on patient-level data would have had significant advantages. First, it would have permitted the efficacy of the various treatment approaches to be explored precisely in the subgroup of interest, namely, the low-volume synchronous metastatic population. Further, while we have adjusted for docetaxel utilization for the entire trial population, individual patient data would have enabled us to determine the docetaxel utilization rate specific to the low-volume de novo mHSPC population. Further, a lack of individual patient data precluded a robust determination of the interaction or hetero-

geneity of effect of prostate RT with ADT alone, ADT plus docetaxel, ADT plus ARPI, or ADT plus docetaxel plus ARPI. Thus, we could not identify subgroups that would derive greater or lesser benefit from the addition of RT to these systemic therapy strategies. Finally, there was heterogeneity across the included trials in several respects. The length of median follow-up was variable among the included trials, although we employed a time-to-event analysis and did not observe significant between-study heterogeneity in our analysis. The trials also varied in the approach taken for integrating docetaxel into triplet therapy. In the ARCHES and TITAN trials, docetaxel was used in a sequential fashion, while in the ARASENS, ENZAMET, and PEACE-1 trials, docetaxel was given concurrently with the ARPI.

5. Conclusions

To conclude, in this trial-level aggregate data-based NMA, the addition of RT to a combination of ARPI and ADT (with or without docetaxel) conferred a significant OS improvement relative to ADT with or without docetaxel in low-volume mHSPC, and was the highest ranked strategy among the four treatment strategies that were investigated. After adjustment for the proportion of patients with de novo presentation and docetaxel utilization, SOC plus ARPI plus RT was again the highest ranked strategy among the four treatment strategies investigated. This latter analysis best reflects contemporary real-world practice in which patients with low-volume de novo mHSPC rarely receive docetaxel as part of their initial treatment. There was some evidence that the addition of prostate RT to ADT plus an ARPI in these patients reduced mortality, although this did not reach statistical significance. A large-scale RCT addressing this question or a meta-analysis of the existing trials with individual patient data is necessary to confirm this finding. Finally, our results suggest that in settings where access to ARPIs is limited or where use of an ARPI is precluded by toxicity or comorbidity considerations, the addition of prostate RT to ADT alone remains a reasonable alternative in patients with de novo mHSPC and a low metastatic burden.

***Author contributions*:** Scott C. Morgan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Roy, Morgan.
Acquisition of data: Roy, Fervaha, Morgan, Wallis.
Analysis and interpretation of data: Roy, Morgan, Sun, Spratt.
Drafting of the manuscript: Roy, Morgan, Wallis, Sun, Spratt.
Critical revision of the manuscript for important intellectual content: All authors.
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Supplementary data

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