Metastasis-directed therapy and standard of care versus standard of care for oligometastatic prostate cancer (WOLVERINE): a systematic review and individual patient data meta-analysis from the X-MET collaboration

Chad Tang, Alex D Sherry, Hyunsoo Hwang, David P Farris, Giulio Francolini, Vanessa Di Cataldo, Lorenzo Livi, Phuoc Tran, Paul G Corn, Ana Aparicio, Gabriele Simontacchi, Ana P Kiess, Jarey H Wang, Valerie Fonteyne, Renee Bultijnck, Ryan Phillips, Matthew P Deek, Robert Olson, Stephen Harrow, Giulia Marvaso, Chiara Lorubbio, Barbara A Jereczek-Fossa, Ethan B Ludmir, Pierre Blanchard, Andrew Warner, Ryan Sun, David A Palma, Piet Ost

Summary

Background Oligometastatic disease represents the proximal end of a metastatic spectrum. Metastasis-directed therapy (MDT) is increasingly used to treat oligometastatic disease despite the absence of level 1 evidence. We amalgamated individual patient data across trials to evaluate the effectiveness of MDT for oligometastatic prostate cancer.

Methods We conducted a systematic review and individual patient data meta-analysis. We systematically searched Embase, PubMed, CENTRAL, MEDLINE, and ClinicalTrials.gov to identify randomised trials of MDT enrolling patients with oligometastatic prostate cancer. Inclusion criteria were published randomised prospective trials enrolling patients with oligometastatic (up to five metastases) prostate cancer, in which investigators recorded sufficient data to evaluate progression-free survival and overall survival. This systematic review was conducted from database creation to Nov 3, 2023, and was updated on May 4, 2025. Data appraisal was conducted using Covidence with two investigators (CT and ADS) performing independent screens. Studies were evaluated using the Cochrane Collaboration's risk-of-bias assessment (version 2.0). Individual patient data were provided by investigators. Coprimary endpoints were progression-free survival and overall survival. Secondary endpoints were radiographic progression-free survival and castration resistance-free survival. The primary analysis was conducted in the subset of studies in which patients were randomly assigned to MDT plus standard of care (SOC) versus SOC. The primary analysis included a trial-level analysis using a random effects model and a patient-level analysis stratifying by trial. This meta-analysis is registered with PROSPERO (CRD42023479078).

Findings Of 2975 studies identified for screening, seven phase 2 studies randomly assigning 574 men were included. Six trials randomly assigning 472 patients to MDT plus SOC (n=248) versus SOC (n=224) were used to evaluate MDT and had a median follow-up time of 40·7 months (IQR 25·6–53·7). MDT was associated with improved progression-free survival (trial-level hazard ratio [HR] 0·44, [95% CI 0·35–0·56], p<0·0001; patient-level HR 0·45 [0·35–0·57], p<0·0001), radiographic progression-free survival (trial-level HR 0·60 [0·42–0·85], p=0·0039; patient-level HR 0·59 [0·46–0·76], p<0·0001), and castration resistance-free survival (trial-level HR 0·58 [95% CI 0·37–0·92], p=0·019; patient-level HR 0·58 [95% CI 0·37–0·91], p=0·017). The association between MDT and overall survival showed an HR of 0·63 (95% CI 0·39–1·00, p=0·051) in trial-level analyses and 0·64 (95% CI 0·40–1·01, p=0·057) in patient-level analyses.

Interpretation WOLVERINE showed a benefit with MDT for oligometastatic prostate cancer in progression-free survival, radiological progression-free survival, and castration resistance-free survival. Overall survival benefit was not significant and further research is needed.

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Department of Genitourinary Radiation Oncology (C Tang MD, A D Sherry MD, Prof P Tran MD PhD); **Department of Biostatistics** (H Hwang PhD, R Sun PhD), **Research Medical Library** (D P Farris MSIS), **Department of Genitourinary Oncology** (Prof P G Corn MD PhD, Prof A Aparicio MD), **and Department of Gastrointestinal Radiation Oncology** (E B Ludmir MD), **The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Radiation Oncology Unit, Oncology Department, Azienda Ospedaliero Universitaria Careggi, Florence University, Firenze, Italy** (G Francolini MD, V Di Cataldo MD, L Livi MD, G Simontacchi MD); **Department of Radiation Oncology, University of Maryland, Baltimore, MD, USA** (Prof P Tran); **Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA** (Prof P Tran, A P Kiess MD PhD, J H Wang MD PhD); **Department of Human Structure and Repair, Ghent University, Belgium** (V Fonteyne MD PhD, R Bultijnck MD, P Ost MD PhD); **Department of Radiation Oncology, Mayo Clinic, Rochester, MN, USA** (A D Sherry, R Phillips MD); **Department of Radiation Oncology, Rutgers Cancer Institute, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA** (M P Deek MD); **Division of Radiation Oncology, University of British Columbia, Vancouver, BC, Canada** (Prof R Olson MD); **Department of Clinical**

Introduction

Oligometastatic disease refers to the presence of limited (≤5) metastases.[1] Metastasis-directed therapy (MDT) has emerged as a promising option for patients with oligometastatic disease from several solid tumour types.[1–5] Most of the randomised prospective data supporting MDT in this disease state are on prostate cancer, yet to date no phase 3 trials have been reported for any histology.[6–9]

Despite the absence of level 1 evidence, MDT has become standard clinical practice for oligometastatic prostate cancer on the basis of findings from randomised

Oncology, Beatson West of Scotland Cancer Center, Glasgow, UK (S Harrow MD); **Department of Oncology and Hemato-oncology, University of Milan, Milan, Italy** (G Marvaso MD, Prof B A Jereczek-Fossa MD PhD); **Department of Radiation Oncology, IEO European Institute of Oncology IRCCS, Milan, Italy** (G Marvaso, C Lorubbio MD, Prof B A Jereczek-Fossa); **Department of Radiation Oncology, Gustave Roussy Cancer Campus, INSERM 1018 CESP, University Paris-Saclay, Villejuif, France** (Prof P Blanchard MD PhD); **Division of Radiation Oncology, Department of Oncology, Western University and London Health Sciences Centre, London, ON, Canada** (A Warner MSc, Prof D A Palma MD PhD); **Department of Radiation Oncology, Iridium Network, Wilrijk, Belgium** (Prof P Ost)

Correspondence to: Dr Chad Tang, Department of Genitourinary Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030–3721, USA
ctang1@mdanderson.org

See Online for appendix

Research in context

Evidence before this study

Despite the lack of level 1 evidence, metastasis-directed therapy (MDT) is becoming widely used for the treatment of oligometastatic prostate cancer. Available evidence is limited to phase 2 randomised trials showing benefit from MDT plus standard of care (SOC) compared with SOC for the signal-finding endpoints (eg, progression-free survival). However, there is little evidence of improvement in later endpoints, such as radiographic progression-free survival, castration resistance-free survival, and overall survival. We conducted a systematic review to identify all randomised trials investigating MDT for patients with oligometastatic prostate cancer from Embase, PubMed, CENTRAL, MEDLINE, and ClinicalTrials.gov databases. Our search included trials evaluating multiple tumour types. General search terms were (oligometa* OR oligo-metasta* OR oligorecurrent) AND cancer AND (surgery OR radiation OR ablation) AND (randomized controlled trial OR controlled clinical trial). This systematic review was conducted from database creation to Nov 3, 2023, and updated on May 4, 2025. Seven randomised trials enrolling men with oligometastatic prostate cancer were identified, of which six randomised patients to MDT plus SOC versus SOC. Two additional trials, RAVENS (which randomised to MDT versus MDT plus Radium 223) and PEACE-V STORM (which randomised men with only lymph node oligometastases to MDT versus MDT plus elective local therapy to the uninvolved lymph nodal chain) were published after our systematic review.

Added value of this study

Our individual patient meta-analysis included seven trials randomising patients with oligometastatic prostate cancer. Six trials comparing MDT plus SOC versus SOC were included in the primary and secondary analysis examining the efficacy of MDT. To the best of our knowledge, WOLVERINE represents the first individual patient meta-analysis using more than two trials, showing that MDT was significantly associated with benefit in progression-free survival, radiographic progression-free survival, and castration resistance-free survival. The association between MDT and overall survival did not meet significance criteria. The benefit of MDT was consistent throughout most studies and in relevant patient and treatment subgroups.

Implications of all the available evidence

To the best of our knowledge, WOLVERINE includes all available clinical trials randomising men with oligometastatic prostate cancer to MDT plus SOC versus SOC during our search window. Our findings offer the highest-level evidence to date supporting the use of MDT in men with oligometastatic prostate cancer. Exploratory subgroup analyses offered additional insights into the value of MDT within relevant patient and treatment subgroups.

phase 2 trials.[6] However, these studies vary substantially in design, use of hormone therapy, imaging for initial staging, and clinical stages included. Completed phase 2 studies have shown promising benefit in early clinical endpoints (eg, prostate-specific antigen [PSA] response and progression-free survival), but their signal-finding design rendered them underpowered for investigating longer-term endpoints.[6–10] Few studies have shown benefit in longer-term endpoints, such as radiographic progression-free survival and castration resistance-free survival.[6–10]

We hypothesised that MDT improves not only progression-free survival but also the longer-term endpoints of radiographic progression-free survival, castration resistance-free survival, and overall survival in patients with oligometastatic prostate cancer. We undertook a systematic review of all randomised trials investigating oligometastatic prostate cancer. Individual patient data were then leveraged from the XRT for Metastatic Disease Individual patient Meta Analysis (X-MET) collaboration. These data were analysed in the WOLVERINE meta-analysis, which investigated the benefit of MDT plus standard of care (SOC) versus SOC.

Methods

Search strategy and selection criteria

We conducted a systematic literature review according to PRISMA guidelines to identify randomised clinical trials that enrolled patients with oligometastatic prostate cancer. Databases searched were ClinicalTrials.gov, MEDLINE, CENTRAL, PubMed, and Embase from database creation to Nov 3, 2023, and was updated on May 4, 2025. An additional manual search of ClincialTrials.gov and relevant oncology conferences was conducted. Search terms and strategies are presented in the appendix (pp 9–10). Data were requested from the principal investigators of trials published in abstract form only. The systematic review was performed in Covidence with two investigators (CT and ADS) performing independent screens. Disagreements were resolved via adjudication with a third investigator (PO). Inclusion criteria were (1) prospective trial, (2) randomised design, (3) enrolled patients with prostate cancer, (4) enrolled patients with oligometastatic (up to five metastases) disease, (5) recorded sufficient data to determine the primary outcomes for this meta-analysis (progression-free survival and overall survival), and (6) published and able to provide individual patient data. There were no specific exclusion criteria. All studies meeting inclusion criteria were evaluated independently by two authors (CT and ADS) using the Cochrane Collaboration's risk-of-bias assessment 2 (version 2.0) for randomised controlled trials.[11]

Individual patient data from selected studies were provided by trial investigators after institutional approval. The meta-analysis plan was approved by the institutional

review board of The University of Texas MD Anderson Cancer Center and registered with PROSPERO (CRD42023479078).

Data analysis

We used a structured data collection form to collect individual patient data from eligible studies, including PSA at enrolment, outcomes, age, baseline staging imaging used, number of metastases, baseline castration-resistant prostate cancer (CRPC) versus castration-sensitive prostate cancer (CSPC), and organ systems involved (appendix p 14). We confirmed the quality and completeness of provided data by generating summative baseline and outcomes for each trial to compare with the original publications.

The prespecified coprimary endpoints were progression-free survival and overall survival; prespecified secondary endpoints were radiographic progression-free survival and castration resistance-free survival. All definitions of primary and secondary endpoints were harmonised across trials. A progression-free survival event was a composite of biochemical failure (per individual trial definitions), radiographic (Response Evaluation Criteria in Solid Tumors version 1.1) progression, or death from any cause. Radiographic progression-free survival was a composite of radiographic progression or death. Castration resistance-free survival analysis was limited to patients with CSPC and was a composite of castration resistance (ie, progression with serum testosterone <50 ng/dL) or death. All time-to-event analyses were initiated from the trial enrolment.

For primary and secondary efficacy analyses, we limited our analyses to trials in which patients were randomly assigned to MDT plus SOC versus SOC, where SOC could be either hormone therapy or observation. As prespecified, two parallel analyses were conducted. In the trial-level analysis, a two-step meta-analysis was conducted in which individual trial outcomes were generated and the aggregated effect of MDT plus SOC versus SOC was analysed via a random effects model. In the patient-level analysis, Cox proportional hazards regression models analysed individual patient data stratified by trial. To estimate the absolute benefit of MDT plus SOC versus SOC, 1-year and 3-year restricted mean survival time benefit was estimated. A 3-year truncation time was the maximum whole number of years that allowed inclusion of all trials. Publication bias was visually assessed using funnel plots and the degree of asymmetry evaluated with Egger's test. Inter-trial heterogeneity and sampling error were evaluated by using Cochran's Q, I^2, and τ^2 metrics. Sensitivity patient-level and trial-level analyses were conducted excluding trials where SOC was observation.

In an exploratory analysis to assess whether the effects of MDT varied between patient and treatment subgroups, a univariable unstratified patient-level Cox regression was conducted to estimate the effect of MDT plus SOC versus SOC within each subgroup for all harmonised primary and secondary endpoints. This analysis was limited to trials comparing MDT plus SOC versus SOC. In this analysis, trial-level stratification produced uninterpretable large confidence intervals given the collinearity of inclusion criteria for individual trials with the subgroups.

A second exploratory analysis was conducted to assess the prognosis of patient subgroups after receiving MDT using patient-level data. The prognosis among

For more on **XRT for Metastatic Disease Individual Patient Meta-Analysis (X-MET)** see https://www.crd.york.ac.uk/PROSPERO/view/CRD42023479078

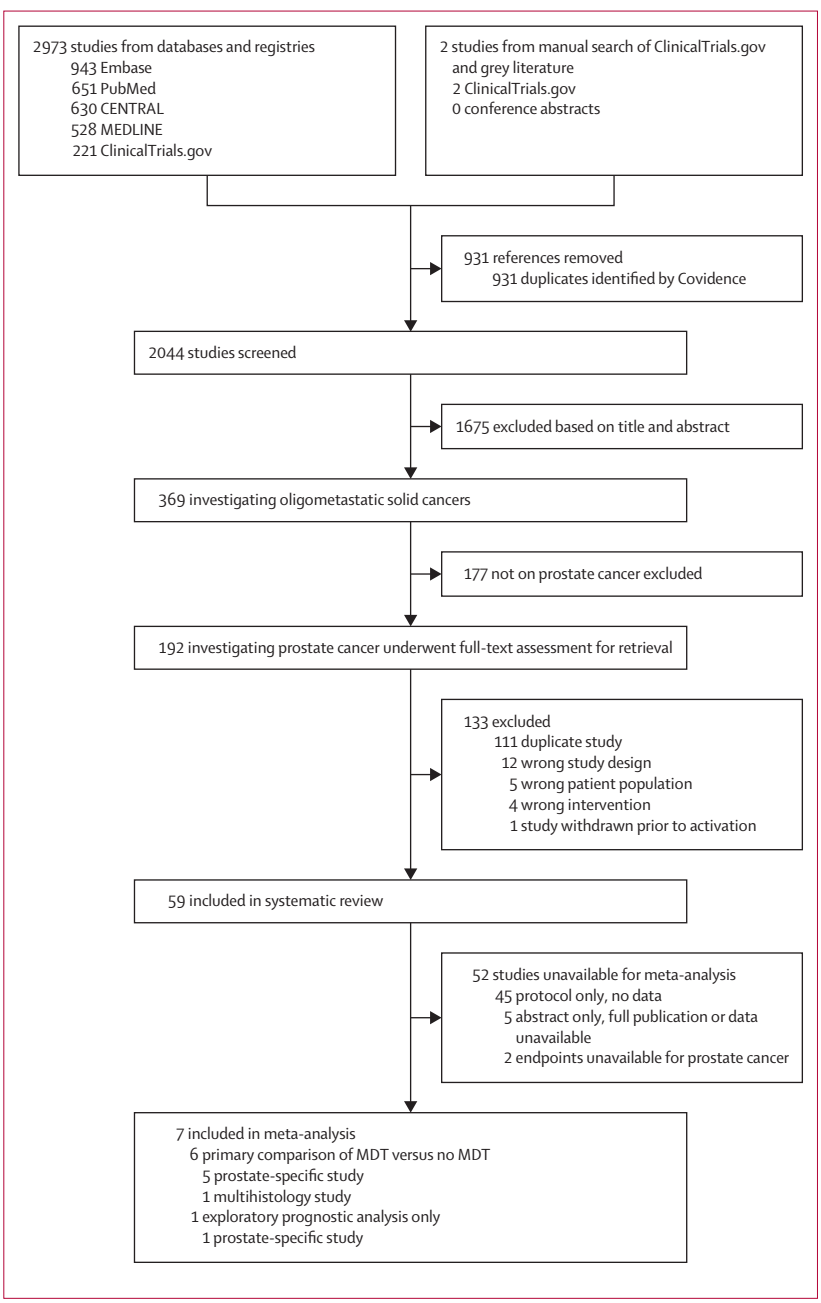

Figure 1: **PRISMA flow diagram detailing systemic review and trial selection for meta-analysis**
MDT=metastasis-directed therapy.

subgroups was compared with Cox regression analysis stratified by trial and repeated for all endpoints. The prognosis analysis included all trials regardless of randomisation but was limited to patients who received MDT on trial.

For Cox regression analyses, the Schoenfeld residual test (appendix p 22) was used to confirm the proportionality of hazards. For the primary and secondary MDT efficacy analyses, comparisons were in the intention-to-treat population. The frequency of worse adverse events experienced by an individual patient were summated. All statistical analysis was performed using R (version 4.4.1) software, using two-sided statistical testing at the 0·05 significance level.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The systematic review identified 2973 publications, with an additional two studies identified by manual search. From these publications, 931 were identified by Covidence to be duplicates (figure 1). A further 1675 studies were excluded based on title and abstract, leading to 369 publications investigating oligometastatic solid tumours, of which 177 were excluded for not enrolling patients with prostate cancer. The remaining 192 studies underwent full text assessment, of which 59 studies described randomised trials enrolling men with prostate cancer. Of these, 45 were not included because they described trials in which only the protocol was provided. Another two studies were excluded because they examined several tumour histologies and could not provide prostate-specific demographic data or data on prostate-specific endpoints including biochemical progression. Five studies presented primary analyses of protocols in abstract form only. The study team contacted

	Primary inclusion criteria	Enrolment period, year	SOC hormone therapy or observation	Lymph node counting method	Definition of biochemical progression	Primary endpoint
Prostate-specific trials (randomised MDT plus SOC versus SOC)						
STOMP (NCT01558427)*	Previously treated primary, CSPC, ≤3 metastases, and staged with choline-PET-CT (n=62)	2012–15	Observation	Individual lymph nodes were counted separately	≥2 ng/mL and ≥25% above nadir if PSA was ≥2 ng/mL at baseline; ≥25% above nadir if PSA was <2 ng/mL at baseline	ADT-free survival
ORIOLE (NCT02680587)*	Previously treated primary, CSPC, ≤3 metastases, and staged with conventional imaging (n=54)	2015–18	Observation	Each lymph node station was counted separately	PSA increase ≥2 ng/mL and ≥25% above nadir	Disease progression at 6 months
EXTEND intermittent HT basket (NCT03599765)*	CRPC or CSPC, ≤5 metastases, and staged with conventional imaging, fluciclovine PET-CT, or PSMA PET-CT (n=87)	2018–20	Intermittent ADT plus second-generation ARPI	Each lymph node station was counted separately	PSA increase ≥2 ng/mL and ≥25% above nadir	Progression-free survival
ARTO (NCT03449719)*	CRPC, ≤3 bone or nodal metastases, and staged with conventional imaging, flucicolvine PET-CT, PSMA PET-CT, or choline-PET-CT (n=157)	2019–22	ADT plus abiraterone acetate	Individual lymph nodes were counted separately	PSA increase ≥2 ng/mL and ≥25% above nadir	Biochemical response rate (PSA decrease ≥50% from baseline) at 6 months
EXTEND continuous HT basket (NCT03599765)*	CRPC or CSPC, ≤5 metastases, and staged with conventional imaging, flucicolvine PET-CT, or PSMA PET-CT (n=96)	2018–22	Continuous ADT plus second-generation ARPI	Each lymph node station was counted separately	PSA increase ≥2 ng/mL and ≥25% above nadir	Progression-free survival
Multihistology trials (randomised MDT plus SOC versus SOC)						
SABR-COMET (NCT01446744)*†	Previously treated primary, CSPC, ≤5 metastases, and staged with conventional imaging (n=16, prostate only)	2012–16	Observation, continuous, and intermittent ADT	Individual lymph nodes were counted separately	PSA increase ≥2 ng/mL and ≥25% above nadir	Overall survival
Prostate-specific trials (randomised MDT plus observation versus MDT plus ADT)						
RADIOSA (NCT03940235)	Previously treated primary, CSPC, ≤3 metastases limited to lymph node and bone, and staged with choline PET-CT, PSMA PET-CT, or whole-body MRI (n=102)	2019–23	Observation versus 6 months ADT	Individual lymph nodes were counted separately	PSA increase ≥20% above baseline in MDT plus observation group; PSA increase to ≥1 ng/mL in MDT plus ADT group	Clinical progression-free survival

Conventional imaging consisted of CT whole body imaging, MRI whole body imaging, and/or bone scan. ADT=androgen deprivation therapy. ARPI=androgen receptor pathway inhibitor. CRPC=castration-resistant prostate cancer. CSPC=castration-sensitive prostate cancer. MDT=metastasis-directed therapy. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. SOC=standard of care. *Six trials included in primary and secondary MDT plus SOC versus SOC analysis. †All six trials contributed to analyses of all endpoints except SABR-COMET, which did not contribute to castration resistance free survival analysis.

Table 1: **Trials included in the meta-analysis**

the principal investigators of these studies to inquire whether individual patient data would be available; however, data for only one (EXTEND-continuous HT basket) was available. Details of the randomised studies not included in the meta-analysis are provided in the appendix (pp 11–13).

WOLVERINE included seven studies, six of which randomly assigned patients with oligometastatic prostate cancer to MDT plus SOC or SOC alone and were included in the primary and secondary efficacy analyses.[3,7–9,12–14] The EXTEND intermittent-HT basket and EXTEND continuous-HT basket were conducted under the EXTEND basket trial protocol (NCT03599765) but were independently powered, randomised, and reported, and were considered separate studies for this meta-analysis. The seventh study (RADIOSA) randomly assigned patients to MDT plus observation or MDT plus intermittent hormone therapy and was included in the exploratory prognostic analyses only.[13] Overall, these seven studies included 574 patients (table 1). Most patients had CSPC (375 [65%]); however, three studies enrolled either a subset of patients with CRPC (EXTEND intermittent-HT and continuous-HT baskets) or enrolled only patients with CRPC (ARTO; NCT03449719; appendix p 15). Race and ethnicity were reported in original publications, but were not summarised in this meta-analysis. 491 patients (86%) had received previous definitive local therapy for the prostate primary tumour.

The six studies included in the primary and secondary MDT efficacy analyses included 472 patients with a median follow-up time of 40·7 months (IQR 25·6–53·7). SABR-COMET was the only multihistology study included, from which 16 men with prostate cancer were included. SABR-COMET investigators provided information on biochemical progression, which allowed harmonisation for the primary endpoint of progression-free survival, but information on the secondary endpoint of time to castration resistance-free survival was not available. Patient demographics, disease characteristics, and treatment characteristics of the six studies randomising patients to MDT plus SOC versus SOC are presented in table 2. Overall, groups were well balanced, with both groups exhibiting a median PSA of 1·9 ng/mL (SOC group IQR 0·5–6·6; MDT plus SOC group 0·6–4·5). Patients in the SOC group were slightly older and more received a second-generation androgen receptor pathway inhibitor (ARPI; table 2).

Trial-level and patient-level analyses evaluating the efficacy of MDT were conducted on the six trials that randomly assigned patients to MDT plus SOC versus SOC. 300 (64%) of 472 patients had a progression-free survival event. In the trial-level analysis, MDT was associated with improved progression-free survival in all trials individually and across trials in aggregate (hazard ratio [HR] 0·44, 95% CI 0·35–0·56; p<0·0001; figure 2A). 262 (56%) of 472 patients had a radiographic progression-free survival event. MDT was associated with improvement in radiographic progression-free survival for two trials individually (ARTO and SABR-COMET) and across all trials in aggregate (HR 0·60, 95% CI 0·42–0·85; p=0·0039; figure 2B). 76 (16%) of 472 patients died. The association between MDT and overall survival had an HR of less than 1 for each individual trial. Across

	SOC (n=224)	MDT+SOC (n=248)
Age, years	71 (65–76)	68 (63–75)
PSA at enrolment, ng/mL	1·9 (0·5–6·6)	1·9 (0·6–4·5)
Time from diagnosis or definitive previous primary treatment to enrolment, months*	43 (7–83)	48 (18–88)
Baseline castration sensitivity		
Castration resistant	120 (54%)	153 (62%)
Castration sensitive	104 (46%)	95 (38%)
ADT		
No	50 (22%)	69 (28%)
Yes	174 (78%)	177 (71%)
Unknown	0	2 (1%)
Second generation ARPI		
No	90 (40%)	123 (50%)
Yes	134 (60%)	125 (50%)
Primary previously treated		
No	37 (17%)	42 (17%)
Yes	185 (83%)	204 (82%)
Surgery	132/185 (71%)	162/204 (79%)
Radiation	50/185 (27%)	42/204 (21%)
Interventional radiology ablation	3/185 (2%)	0/204
Unknown	2 (1%)	2 (1%)
Baseline imaging		
PSMA PET-CT	28 (13%)	33 (13%)
Fluciclovine or choline PET-CT	117 (52%)	105 (42%)
Conventional	79 (35%)	110 (44%)
Number of metastatic lesions		
1	79 (35%)	100 (40%)
2	66 (29%)	73 (29%)
3	62 (28%)	58 (23%)
4	12 (5%)	9 (4%)
5	5 (2%)	8 (3%)
Lymph node metastasis		
No	83 (37%)	105 (42%)
Yes	141 (63%)	143 (58%)
Bone metastasis		
No	104 (46%)	104 (42%)
Yes	120 (54%)	144 (58%)
Visceral metastasis		
No	219 (98%)	244 (98%)
Yes	5 (2%)	4 (2%)

Data are median (IQR) or number (%). ADT=androgen deprivation therapy. ARPI=androgen receptor pathway inhibitor. MDT=metastasis-directed therapy. PSA=prostate-specific antigen. PSMA=prostate-specific membrane antigen. SOC=standard of care. *Time from diagnosis to enrolment was available for SABR-COMET, ARTO, ORIOLE, and STOMP, whereas time from primary treatment was available from EXTEND intermittent HT and EXTEND continuous HT baskets.

Table 2: **Baseline patient characteristics in the six trials that randomly assigned patients between MDT plus SOC versus SOC**

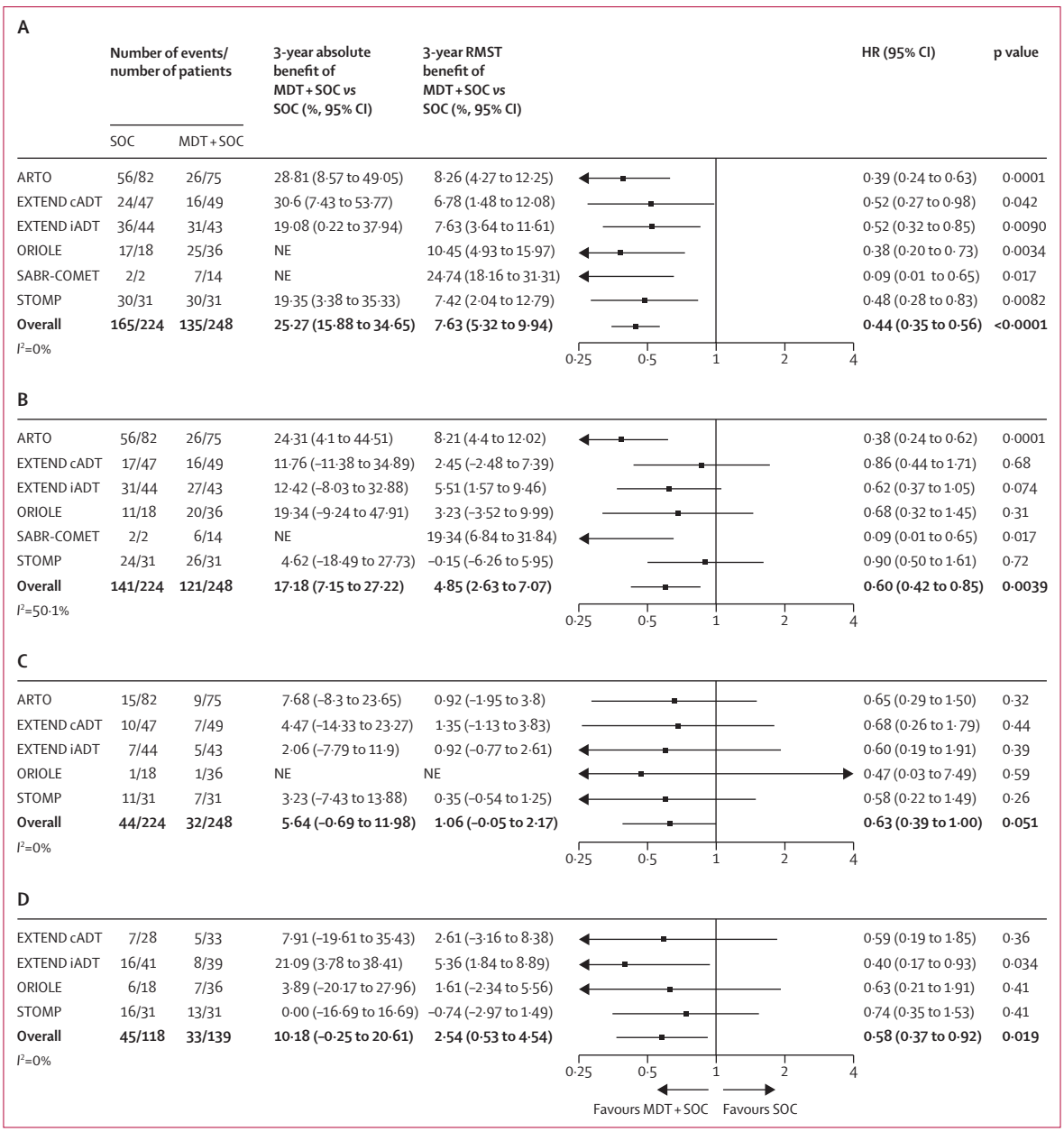

Figure 2: **Trial-level (two-step) meta-analyses investigating association of MDT plus SOC versus SOC alone with progression-free survival (A), radiographic progression-free survival (B), overall survival (C), and castration resistance-free survival (D)**

The association between MDT and castration resistance-free survival was evaluated in patients with castration-sensitive metastatic disease only. 3-year absolute benefit and RMST benefit is shown for each endpoint. Instances where either of these metrics were NE are indicated. HR=hazard ratio. MDT=metastasis-directed therapy. NE=not estimable. RMST=restricted mean survival time. SOC=standard of care.

all six trials, the aggregated association exhibited an HR of 0·63 (95% CI 0·39–1·00; p=0·051; figure 2C). 78 (30%) of 257 patients with CSPC had a castration resistance-free survival event. MDT was associated with castration resistance-free survival in only the EXTEND-intermittent HT basket and was associated with castration resistance-free survival across all trials in aggregate (HR 0·58, 95% CI 0·37–0·92; p=0·019; figure 2D). A sensitivity analysis showing 1-year restricted mean survival time is presented in the appendix (p 16). Apart from radiographic progression-free survival, which showed moderate inter-trial heterogeneity (I^2=50·1%; figure 2B), metrics of inter-trial heterogeneity and sampling error (figure 2), as well as funnel plots evaluating publication bias (appendix p 1), did not reveal substantial effects. Results from Egger's test should be interpreted with caution given the small number of studies included. Summary or risk-of-bias assessment is

present in the appendix (p 2). There were some concerns noted for most studies stemming from non-blinded randomisation. A sensitivity analysis excluding trials in which SOC was observation in all or part of the patient population (STOMP, ORIOLE, and SABR-COMET) identified results similar to the primary analysis (appendix p 3).

Results from the trial-level analyses were replicated in the patient-level analyses, which revealed similar associations of MDT with progression-free survival (HR 0·45, 95% CI 0·35–0·57; p<0·0001; figure 3A), radiographic progression-free survival (0·59, 0·46–0·76; p<0·0001), overall survival (0·64, 0·40–1·01; p=0·057; figure 3C), and castration resistance-free survival (0·58 0·37–0·91; p=0·017; figure 3D). Similar results were observed in a patient-level sensitivity analysis excluding patients from trials in which SOC was observation (appendix p 4). Evaluation of Schoenfeld residuals tests did not indicate violation of the proportional hazards assumptions (appendix p 25).

An exploratory analysis of MDT within subgroups was conducted in the six trials that randomly assigned patients to MDT plus SOC versus SOC. Given the importance of castration sensitivity, the analysis was conducted in the full cohort and separately in CSPC and CRPC subgroups (appendix pp 5–8). For progression-free survival, MDT was associated with improvement compared with SOC alone across most patient subgroups, and no significant interactions were observed (appendix p 5). Among patients with CSPC for whom SOC was known (n=271) the benefit of MDT was similar, irrespective of SOC, with no significant interaction detected based on the choice of SOC: observation (n=119 [44%]; HR 0·42, 95% CI 0·28–0·63), androgen deprivation therapy only (ADT; n=79 [29%]; HR 0·40, 95% CI 0·22–0·70; $p_{interaction}$=0·66 *vs* observation), and ADT with a second generation ARPI (n=73 [27%]; HR 0·60, 95% CI 0·30–1·20; $p_{interaction}$=0·13 *vs* observation). For radiographic progression-free survival and castration resistance-free survival, MDT was associated with improvements across most subgroups (appendix pp 6, 8); however, significant interactions were noted between MDT and baseline PSA (median PSA on hormone therapy 0·12 ng/mL [IQR 0–0·8], p=0.04; off hormone therapy 5 ng/mL [1·8–11·5], p=0.01) within the CSPC cohort for radiographic progression-free survival. MDT was associated with improved radiographic progression-free survival in patients with baseline PSA lower than the

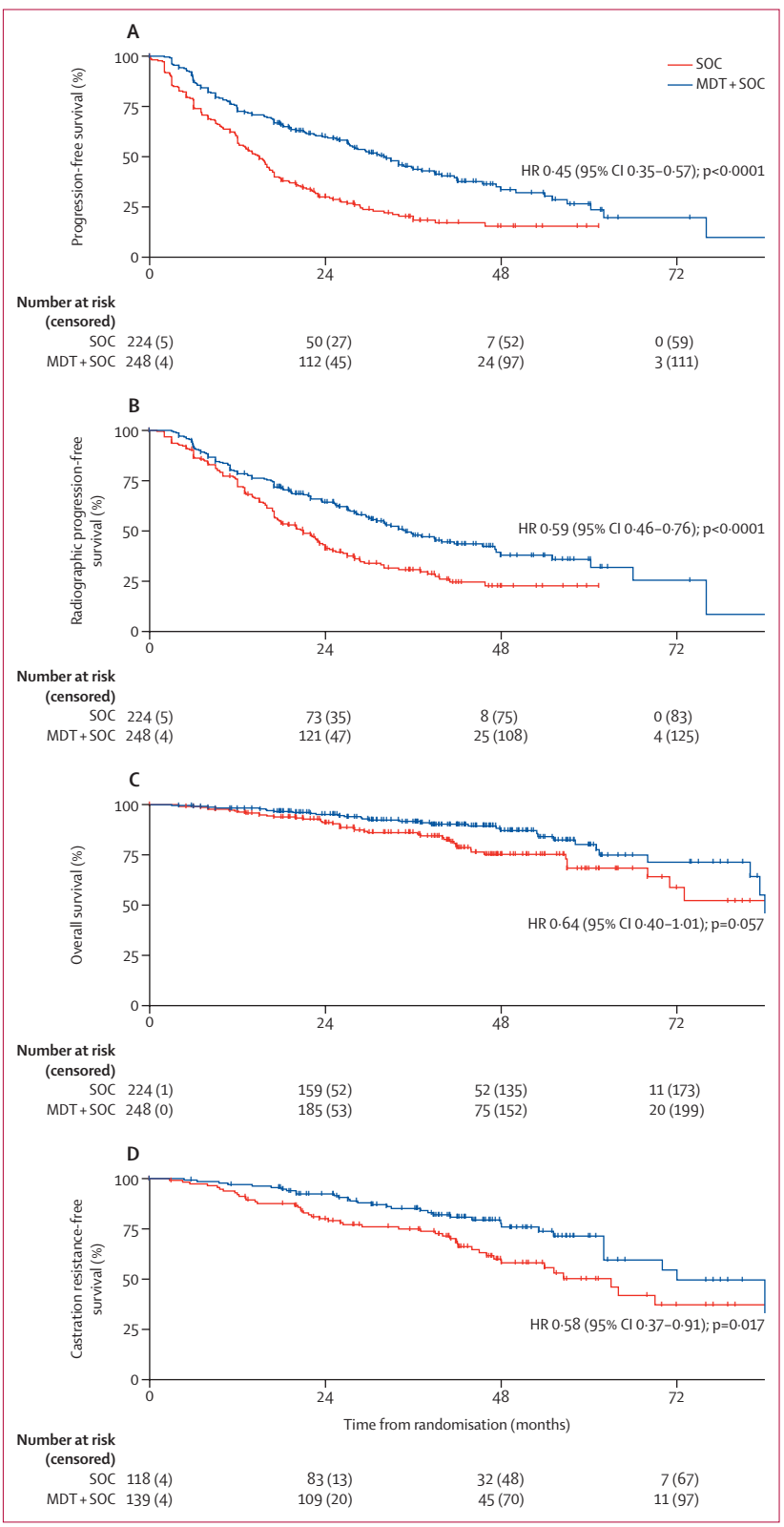

***Figure 3*: Kaplan-Meier curves showing patient-level analyses investigating association of MDT plus SOC versus SOC with progression-free survival (A), radiographic progression-free survival (B), overall survival (C), and castration resistance-free survival (D)**

The association between MDT and castration resistance-free survival was evaluated in patients with castration-sensitive metastatic disease only. HR=hazard ratio. MDT=metastasis-directed therapy. SOC=standard of care.

median but not in patients with PSA higher than the median. The 95% CI intervals for the association between MDT and overall survival crossed 1 for most patient subgroups (appendix p 7).

The exploratory prognosis analysis was conducted in all seven trials and limited to patients who received MDT (n=350). The prognostic association of baseline clinical and treatment-related factors was analysed for the overall, CPSC, and CRPC cohorts (appendix pp 17–20). Patients with metastases limited to bone had worse progression-free survival than did those with metastases limited to lymph nodes within the entire cohort (HR 1·45, 95% CI 1·05–2·00) and CSPC subgroup (1·61, 1·13–2·17). Within the CSPC subgroup, hormone therapy use and lower baseline PSA (median PSA on hormone therapy 0·6 ng/mL [IQR 0·1–2·2]; off hormone therapy 2·8 ng/mL [1·4–7·8]) were consistently associated with improved prognosis. Use of ADT was associated with improved progression-free survival (HR 0·45, 95% CI 0·29–0·72) and radiographic progression-free survival (0·43, 0·25–0·76) compared with observation, as was use of combined ADT and second-generation ARPI (progression-free survival HR 0·38, 95% CI 0·16–0·88; radiographic progression-free survival 0·38, 0·15–0·97; appendix pp 17–18). Baseline PSA higher than the median was associated with worse progression-free survival, radiographic progression-free survival, and castration resistance-free survival within the CSPC subgroup, and with worse progression-free survival and radiographic progression-free survival in the CRPC subgroup (appendix pp 17–18, 20).

The frequency of worst adverse events experienced by an individual patient on trial was similar among patients receiving MDT plus SOC versus SOC in the six trials that randomly assigned patients between these treatments (appendix p 21). No grade 5 toxic effects were observed in either group, and grade 2 or worse adverse events were observed in 34 (15%) of 224 of patients receiving SOC and 42 (17%) of 248 receiving MDT plus SOC.

Discussion

The WOLVERINE individual patient meta-analysis showed a robust association between MDT and improved progression-free survival both within individual trials and across all trials in aggregate. MDT was also associated with improvement in the longer-term endpoints of radiographic progression-free survival and castration resistance-free survival, which has rarely been shown in randomised trials. MDT was not significantly associated with overall survival. In lieu of phase 3 randomised trials, to the best of knowledge, these data provide the most compelling evidence to date of benefit from MDT across endpoints. All associations were consistent across two prespecified methods: a two-step trial-level analysis using a mixed effect model and a patient-level analysis using a trial-stratified Cox proportional hazards regression model. The fact that all trials allowed patient crossover from the SOC group to receive MDT after progression strengthens these findings. Exploratory analyses identified a significant interaction between MDT and baseline PSA: specifically, patients who had lower baseline PSA exhibited an association between receipt of MDT and longer radiographic progression-free survival, whereas patients with higher baseline PSA did not. Following completion of our systemic therapy review, two additional randomised trials investigating oligometastatic prostate cancer were published: RAVENS, which randomised patients to Radium223 versus observation following MDT, and PEACE-V Storm, which randomised patients with lymph-node-only metastases to MDT versus MDT plus elective local therapy to uninvolved LN chain.[15,16]

Individual randomised trials have shown improvements in progression-free survival but generally have not shown improvement in later endpoints such as radiographic progression-free survival or castration resistance-free survival. To the best of our knowledge, only two analyses combining individual patient data from separate randomised trials have been conducted, both aggregating data from two trials. Deek and colleagues[10] combined patients from the ORIOLE and STOMP trials and showed improvements with MDT for progression-free survival but no benefit for radiographic progression-free survival, castration resistance-free survival, or overall survival. The EXTEND basket protocol included a prespecified analysis combining the prostate intermittent-HT and continuous-HT baskets and found improvement in progression-free survival in addition to radiographic progression-free survival and castration resistance-free survival.[14] Two meta-analyses restricted to trial-level data and larger observational registries have been conducted with similar outcomes.[17–19]

Although several prognostic factors have been established for metastatic prostate cancer, whether these factors modify outcomes after MDT in oligometastatic prostate cancer is unclear. In our exploratory analysis of MDT within subgroups, a consistent benefit from MDT was apparent across subgroups. For radiographic progression-free survival, higher baseline PSA modified the effect of MDT; specifically, patients with higher baseline PSA derived less benefit ($p_{interaction}$ values <0·05). One explanation is that higher PSA might reflect greater microscopic disease burden. This notion is further supported by our finding that among patients who received MDT, a higher baseline PSA was also an adverse prognostic marker across several endpoints.

Several notable subgroups did not exhibit an interaction with MDT. Disease and therapy factors underlying these subgroups are active areas of investigation for ongoing trials. These factors include number of metastases, systemic therapy use, CRPC status, and the presence of an untreated primary tumour. Several ongoing randomised studies are investigating the benefit of MDT for patients with increasing numbers of metastases.

These studies include SABR-COMET 10 (NCT03721341) and SABR-SYNC (NCT05717166), which are enrolling patients with up to ten metastases, whereas ARREST-2 (NCT05508464) is enrolling patients with polymetastatic disease (>ten metastases). The current analysis identified similar benefit for MDT regardless of metastasis number and that metastasis number was not prognostic for outcomes after MDT; however, the number of patients with higher (three to five) metastases was low (n=85). More trials will be needed to define the upper limit of metastases in patients who derive benefit from MDT.

Whether the benefit of MDT is enhanced by hormone therapy is an active area of investigation. Although some ongoing and planned phase 3 trials (eg, PSMA-DC [NCT05939414]) are using MDT plus observation as the control group, most incorporate MDT and ADT with or without second-generation ARPI (eg, STAMPEDE 2 [NCT06320067], INDICATE [NCT04423211], and OLIGO-PRESTO [NCT04115007]). The question of whether hormone therapy enhances the benefit of MDT is the subject of several ongoing trials, including ADOPT (NCT04302454), DART (NCT04641078), and PROMETHEAN (NCT05053152). The only published randomised trial investigating this question is the RADIOSA trial (included in WOLVERINE), which randomly assigned patients with CSPC to MDT versus MDT and 6 months of ADT.[13] RADIOSA found that the addition of ADT improved clinical progression-free survival (similar to radiographic progression-free survival) and progression-free survival; however, later endpoints such as castration resistance-free survival or overall survival were not improved. Although hormone therapy use did not modify the effect of MDT plus SOC versus SOC in the current analysis, hormone therapy use was associated with improved prognosis for progression-free survival and radiographic progression-free survival among patients who received MDT.

Treatment of oligometastatic CRPC remains an active area of investigation since most completed randomised trials have been limited to patients with CSPC. Although CRPC status is a clear indication of hormone sensitivity, no studies have shown that CRPC status modifies the benefit of MDT. Two trials exclusively enrolling patients with CRPC have been reported: ARTO, included in WOLVERINE, and GROUQ-PCS9 (NCT02685397), reported as an abstract in the 2025 American Society of Clinical Oncology Genitourinary Cancers Symposium, which randomly assigned patients with oligometastatic CRPC to ADT plus second-generation ARPI versus MDT plus ADT plus second-generation ARPI and showed a benefit from MDT.[12,20] These results are similar to the benefit from MDT observed for the CRPC and CSPC subgroups in WOLVERINE. Ongoing studies such as DECREASE (NCT04319783) and PEACE8 (NCT06276465) are further investigating the benefit of MDT for patients with oligometastatic CRPC.

Several limitations of the current study deserve mention. First, not all trials defined progression-free survival and biochemical progression-free survival similarly. Across trials, the most common definition of progression-free survival was a composite of biochemical and radiographic progression. Thus, WOLVERINE also applied a composite progression-free survival definition after data harmonisation across studies. Second, given the widespread availability of salvage therapies and the relatively favourable prognosis of metastatic prostate cancer compared with metastatic disease from other solid malignancies of patients with oligometastatic prostate cancer compared with oligometastatic disease from other solid malignancies, signals for later endpoints such as overall survival are difficult to interpret. Third, SOC regimes used were heterogeneous, reflecting the era in which each trial was run. Observation and single-agent ADT arguably do not reflect current practice for metastatic prostate cancer. Fourth, initial clinical staging was subject to variability, and counting systems for lymph nodes were heterogeneous. As PSMA PET represents arguably the most sensitive form of imaging and is commonly used in many countries, including the USA, caution should be taken in extrapolating results from patients staged with conventional imaging. Fifth, this meta-analysis contained a limited number of studies and thus results from Egger's test should be interpreted with caution. Finally, there were several efficacy endpoints and multiple comparisons were conducted for exploratory subgroup analyses without adjustment for multiple testing.

To better address the important questions raised by the subgroup analyses, future meta-analyses from X-MET will incorporate ongoing trials to explore specific subgroups and treatment scenarios. Additional biomarkers should also be developed, including genomic alterations, PSMA-avid tumour volume, and circulating tumour DNA. Several strengths of the current study deserve mention. Our systematic review was comprehensive and included not only prostate cancer-specific trials, but also multihistology trials enrolling patients with oligometastatic prostate cancer. To the best of our knowledge, the WOLVERINE meta-analysis included all available published trials randomly assigning men with oligometastatic prostate cancer to MDT plus SOC versus SOC and this meta-analysis represents the first individual patient meta-analysis investigating MDT for oligometastatic prostate cancer that includes more than two clinical trials.

In conclusion, the WOLVERINE meta-analysis provides the strongest evidence to date that MDT improves progression-free survival, radiographic progression-free survival, and castration resistance-free survival, findings that were consistent across individual studies and most patient and treatment subgroups. The association between MDT and overall survival warrants further investigation due to a relative lack of events for this endpoint.

Contributors

CT contributed to funding acquisition, project administration, and study supervision. CT, ADS, and PO contributed to conceptualisation and study design. CT, ADS, DPF, GF, VDC, LL, PT, PC, AA, GS, APK, JHW, VF, RB, RP, MPD, RO, SH, GM, CL, BAJ, AW, DAP, and PO contributed to data collection. HH, RS, EBL, and AW contributed to statistical analysis. CT, ADS, HH, EBL, DAP, PB, and PO contributed to quality assurance. CT, ADS, HH, DAP, PB, and PO contributed to data interpretation. CT, ADS, HH, PB, and PO contributed to writing of the original draft. CT, HH, and RS had direct data access and verified underlying data. All authors had access to all data reported in the study and provided critical academic review including reviewing and editing of the submitted draft.

Declaration of interests

CT has served on a scientific advisory board for Bayer, Lantheus, Telix and Molli Surgical; received honoraria from Elekta; support for attending meetings from Vision RT; consulting fees from Boston Scientific; royalties from Wolter Kluwer; and research support from Myriad Genetics, Merck, and Guardant Health. PGC has received research support from Janssen. VF has received consulting fees from Janssen, Merck Sharp & Dohme, and Astellas; and support for attending meetings from Janssen and Ipsen. APK has received grants or contracts from Novartis, Lantheus, Bayer, Convergent, Adenoid Cystic Cancer Research Foundation, Prostate Cancer Foundation, US Department of Defence, and National Cancer Institute; received honoraria from Physicians' Education Resource; participated in advisory boards for Novartis and AstraZeneca; and served in a leadership role in ASTRO. EBL has received consulting fees from Xerient and served on an advisory board for Nanobiotix. RO has received a grant from Varian Medical Systems and consulting fees from Need. PO has received consulting fees from AstraZeneca, Bayer, Janssen, and Novaritis; received honoraria from Curium and Micropos; participated in advisory board for Telix, AstraZeneca, and several Institute of Cancer Research trials in the UK; and served in a leadership role as an ESTRO board member. ADS has received honoraria from Sermo. PT has received grants and contracts from the National Institutes of Health; has a patent licensed with royalties from Natsar Pharmaceuticals; has received consulting fees from Regeneron, Dendreon, Noxopharm, Myovant Sciences, AstraZeneca, Lantheus, Bayer, Johnson & Johnson (J&J), Pfizer, and Novartis; has received honoraria from MJH Life Sciences; and has received meeting and/or travel support from Bayer and J&J. All other authors declare no competing interests.

Data sharing

Individual patient data obtained via data sharing agreements were used in this manuscript. Academic researchers interested in obtaining de-identified patient data can request from the corresponding author via email. All data sharing requires appropriate regulatory approval and signed data access agreements.

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