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Review – Prostate Cancer – Editor's Choice

The Efficacy and Safety of Metastasis-directed Therapy in Patients with Prostate Cancer: A Systematic Review and Meta-analysis of Prospective Studies

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Abstract

Context: Despite the lack of level 1 evidence, metastasis-directed therapy (MDT) is used widely in the management of metastatic prostate cancer (mPCa) patients. Data are continuously emerging from well-designed prospective studies.
Objective: To summarise and report the evidence on oncological and safety outcomes of MDT in the management of mPCa patients.
Evidence acquisition: We searched the PubMed, Scopus, and Web of Science databases for prospective studies assessing progression-free survival (PFS), local control (LC), androgen deprivation therapy (ADT)-free survival (ADT-FS), overall survival (OS), and/or adverse events (AEs) in mPCa patients treated with MDT. A meta-analysis was

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performed for 1- and 2-yr PFS, LC, ADT-FS, OS, and rate of AEs. Meta-regression and sensitivity analysis were performed to account for heterogeneity and identify moderators.

Evidence synthesis: We identified 22 prospective studies (n = 1137), including two randomised controlled trials (n = 116). Two studies were excluded from the meta-analysis (n = 120). The estimated 2-yr PFS was 46% (95% confidence interval [CI]: 36–56%) or 42% (95% CI: 33–52%) after excluding studies using biochemical or ADT-related endpoints. The estimated 2-yr LC, ADT-FS, and OS were 97% (95% CI: 94–98%), 55% (95% CI: 44–65%), and 97% (95% CI: 95–98%), respectively. Rates of treatment-related grade 2 and ≥3 AEs were 2.4% (95% CI: 0.2–7%) and 0.3% (95% CI: 0–1%), respectively.

Conclusions: MDT is a promising treatment strategy associated with favourable PFS, excellent LC, and a low toxicity profile that allows oligorecurrent hormone-sensitive patients to avoid or defer ADT-related toxicity. Integration of MDT with other therapies offers a promising research direction, in particular, in conjunction with systemic treatments and as a component of definitive care for oligometastatic PCa. However, in the absence of randomised trials, using MDT for treatment intensification remains an experimental approach, and the impact on OS is uncertain.

Patient summary: Direct treatment of metastases is a promising option for selected prostate cancer patients. It can delay hormone therapy and is being investigated as a way of intensifying treatment at the expense of manageable toxicity.

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1. Introduction

The concept of oligometastatic cancer has gained significant attention in recent years thanks to better imaging and understanding of the metastatic disease state. Identification of small metastatic foci holds the promise of metastasis-directed therapy (MDT), such as stereotactic body radiotherapy (SBRT) or surgery [1]. Routine use of SBRT as an MDT became an avid subject after the SABR-COMET trial showed a significant survival benefit of MDT compared with the standard of care (SOC) in unselected oligometastatic cancer patients [2]. The recent ESTRO-ACROP Delphi consensus by Zilli et al. [3] aimed to answer several key questions regarding the inclusion criteria and therapy setting for the clinical implementation of MDT in oligometastatic prostate cancer (PCa) patients, encouraging the routine use of prostate-specific membrane antigen (PSMA) positron emission tomography (PET). However, level I evidence is still lacking, and MDT remains a promising yet investigational therapeutic approach that should only be offered to patients within a clinical trial or well-designed prospective cohort study [4].

Currently, androgen deprivation therapy (ADT) is the mainstay treatment for low-volume metastatic PCa (mPCa) in combination with an androgen receptor signalling inhibitor (ARSI) [5–8] or local treatment to the primary [9,10]. Oligometastatic cancer is a particular setting of low-volume metastatic disease on the continuum of disease states between clinically nonmetastatic and "systemic" disease [11]. Oligometastases are typically defined as the presence of up to five distant metastases, which can occur in both synchronous and metachronous hormone-sensitive (mHSPC) and castration-resistant (mCRPC) mPCa. It is hypothesised that MDT can prevent further disease progression by eliminating metastasis-to-metastasis spread and metastases to primary [12,13], therefore delaying the need for next-line systemic therapies [14], with sustainable disease control in some patients [15].

Up to now, a variety of MDT concepts have been proposed with multiple different clinical settings and disease stages in which MDT could be applied, even outside of the oligometastatic setting; however, there is no up-to-date summary of the data to allow an understanding of the current role of MDT in the treatment of mPCa patients. Therefore, the primary goal of this meta-analysis was to systematically review and synthesise the data from the recently published prospective studies analysing the effectiveness and safety of MDT in the treatment of PCa metastases in different clinical scenarios. The secondary aim was to analyse factors that could possibly influence the outcomes of MDT and identify moderators.

2. Evidence acquisition

2.1. Search strategy

The study protocol was registered in PROSPERO (registration number CRD42022337457) and conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [16]. The PRISMA 2009 checklist is included in Supplementary Table 1. The inclusion criteria were defined using the population, intervention, control outcome, and study design (PICOS) method (Supplementary Table 2).

We searched the PubMed, Web of Science, and Scopus databases to identify reports published up to January 2023 using predefined search criteria (Supplementary Table 3). Full-text publications reporting the outcomes of randomised or nonrandomised, single- or multiarm prospective trials, investigating clinical outcomes in mPCa patients treated with MDT (radiotherapy [RT] or metastasectomy) were included. Studies reporting at least one of

the outcome measures were deemed eligible. The outcomes of interest included progression-free survival (PFS), local control (LC), ADT-free survival (ADT-FS), overall survival (OS), and treatment toxicity. Three investigators performed an independent initial screening by title and abstract. Full-text publications were retrieved and evaluated for eligibility (Fig. 1). Disagreements were resolved via consensus among the coauthors.

2.2. Study selection

This meta-analysis included studies that involved patients with any setting of mPCa (population) treated with MDT (RT or metastasectomy) with or without any other concurrent therapy (intervention) in single-arm or controlled studies compared with either surveillance or SOC (comparison). The analysis focused on LC, PFS, ADT-FS, OS, and MDT-related treatment toxicity (outcome) reported in prospective studies (study design). Studies investigating symptom-oriented local treatment of metastases were excluded from the analysis (ie, low-dose RT for painful bone metastases). Studies investigating combined MDT approaches, such as combinations of MDT and ADT, immunotherapy, and/or concurrent local treatment, were included. We excluded preclinical or retrospective studies, non–English language publications, meta-analyses, reviews, letters, meeting abstracts of unpublished trials, and case reports. The references in the articles were scanned for additional records of interest. In cases of updated results of trials already included in the review or trial results described over multiple publications, the most recent data for each individual endpoint were analysed.

2.3. Data extraction

Data on studies, patients, and treatment characteristics were extracted independently by two authors. Extracted data included the following outcome measures: survival estimates with corresponding 95% confidence intervals (CIs) for 1- and 2-yr PFS, LC, ADT-FS, and OS; rates of grade 2 and grade $\geq$3 MDT-related adverse events (AEs) according to the Common Terminology Criteria for Adverse Events (CTCAE); and descriptions of the MDT-related grade $\geq$2 AEs. Clinical characteristics of the patients were extracted, including the number of patients, castration status, synchronous oligometastases versus oligorecurrence, intervention description, inclusion criteria, percentage of patients treated for lymph node metastases only, follow-up duration, and details of the study design.

If appropriate outcome measures were not available in the text, Kaplan-Meier curves were digitised using WebPlotDigitizer software (version 4.6) to extract survival estimates with corresponding 95% CIs at 12 and 24 mo of follow-up [17,18]. In cases where available graphs did not include 95% CIs, IPDfromKM software was used to reconstruct individual patient data (IPD) based on digitised Kaplan-Meier curves and calculate estimates with corresponding 95% CI at 12 and 24 mo [19]. In the remaining cases, IPD extracted from available sources were used to calculate outcome measures in Rstudio using the package "survival".

2.4. Endpoint definition

The following criteria were used for the identification of outcomes for the purpose of a meta-analysis: PFS was defined as consisting of at least distant radiographic progression, including progression of the lesions treated with MDT. Endpoints including biochemical recurrence or initiation of ADT were considered eligible, but excluded in the sensitivity analysis under the assumption that biochemical control is less clinically important than radiographic progression, and that ADT is often prescribed upon biochemical failure. Endpoints only consisting of biochemical control and time to ADT were excluded from the PFS analysis. LC was defined as the time to local failure within the irradiation field or surgical bed. Endpoints including primary disease failure were excluded from the analysis. ADT-FS was defined as the time to ADT initiation. Endpoints that included time to other next-line therapies, such as repeated MDT or local salvage, were excluded from the analysis. OS was calculated as the time to death, either as OS or as cancer-specific survival. The toxicity was defined as the rate of grade 2 and grade $\geq$3 MDT-related AEs according to the CTCAE. The summary of endpoint definitions is shown in Supplementary Table 4.

2.5. Risk-of-bias assessment

Each study was evaluated independently by two authors using the Cochrane Collaboration's risk-of-bias (RoB) assessment tool (version. 2.0) [20] for randomised controlled trials (RCTs) and the ROBINS-I tool [21] for nonrandomised studies.

2.6. Statistical analysis

The individual study effect sizes for PFS, LC, ADT-FS, and OS were modelled as survival probabilities at 1 and 2 yr with corresponding standard error. In a toxicity analysis, individual study effect sizes were modelled as proportions. The numerator was the number of patients experiencing an event at least once, the denominator was the total number of patients for given estimation, and continuity correction was applied by adding 0.5 for studies where the event probability was 0 [22]. The restricted maximum likelihood and the Hartung-Knapp adjustment were used for the toxicity analysis.

For PFS, ADT-FS, and toxicity, the meta-analysis was performed using a random-effect model to account for the differences in study populations and designs. For LC and OS, to account for "zero-event" studies, we used a generalised linear mixed model with the logit transformation for the measure of effect size. The rma.glmm() function in the metafor package with the measure set to "PLO" (Peto's log odds ratio) was employed. The logit-transformed rates were back-transformed to probabilities for interpretation.

The statistical analysis was conducted in Rstudio using the General Package for Meta-Analysis (meta) version 6.1-0 and the Meta-analysis for R (metafor) version 3.8-1. The summary estimates with corresponding 95% CIs were depicted in forest plots. Study heterogeneity for random-effect models was assessed using Cochran's Q test. Publication bias was assessed using funnel plots for PFS and

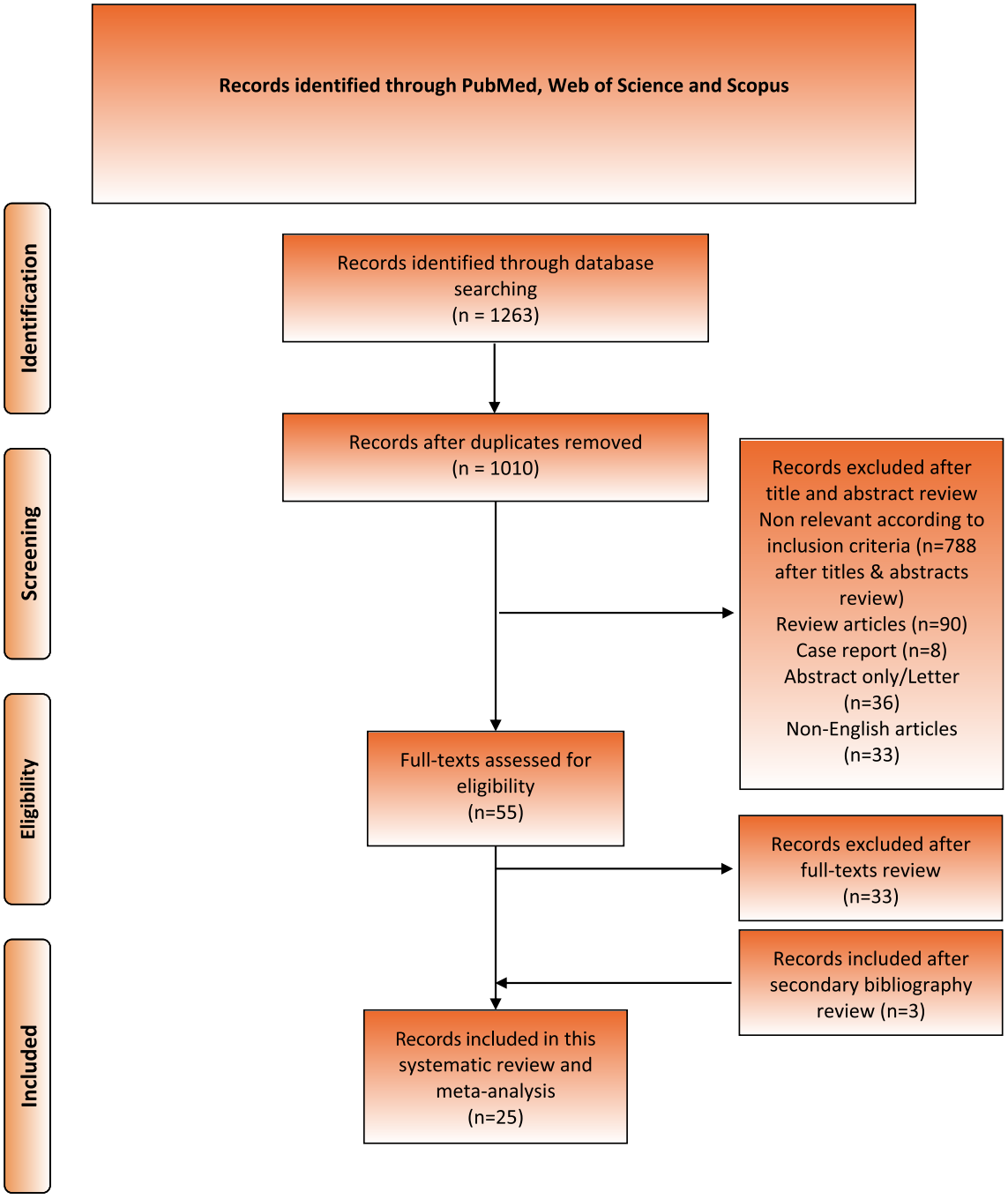


Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart of study inclusion in the systematic review.

ADT-FS, and Peters' linear regression test for funnel plot asymmetry was performed when at least ten studies were included in the meta-analysis. All tests were two sided, and $p < 0.05$ was considered significant. A meta-regression analysis was conducted for PFS by sample size, median age of included patients, fraction of patients with lymph node metastases only, fraction of patients with mHSPC, and the use of ADT in studies recruiting only mHSPC patients (allowed vs not allowed). A similar meta-regression was conducted for the occurrence of grade ≥ 3 AEs by sample size, fraction of patients with lymph node metastases only, type of MDT (RT vs RT or surgery), use of ADT (allowed vs not allowed), and use of other systemic treatments (allowed vs not allowed). Sensitivity analyses for PFS were performed to account for heterogeneity in end-point definitions, differences in castration status of patient in individual studies, and results of RoB analysis.

3. Evidence synthesis

3.1. *Study selection*

Overall, 22 prospective studies investigating the application of MDT in any mPCa setting published between 2013 and

2023 were included, comprising a total of 1137 patients (Fig. 1), with a median follow-up ranging from 6 to 118.8 mo. The majority were single-arm studies (n = 974) [23–41], including eight studies with predefined hypothesis and sample size (n = 608) [27,31–33,37–39,41]. Two studies were two-arm RCTs (n = 116) [42,43] and one was a two-arm nonrandomised study (n = 47) [44]. Most studies were conducted in North America (n = 9) or Europe (n = 8), followed by Australia (n = 4) and Asia (n = 1).

Deek et al. [45] published an updated long-term analysis of two RCTs by Ost et al. [42] and Phillips et al. [43], both of which were included due to nonoverlapping estimations for different extracted endpoints. The results of one of the trials were published in two separate publications by Hölscher et al. [39,46]. Finally, a study by Supiot et al. [32] referred to an earlier publication by Vaugier et al. [47] for the estimation of early toxicity data.

A summary of the basic study characteristics can be found in Table 1. With the exception of three trials (n = 125) [26,37,38], the initial number of metastases did not exceed 5. The most common clinical setting was metachronous mHSPC. Eight studies allowed for mCRPC patients (n = 490) [24,27,28,31,33,38,40,44], including three mCRPC-exclusive studies (n = 167) [33,38,44], two of which comprised heavily pretreated patients (n = 120) [33,38]. Synchronous oligometastases were allowed in five studies (n = 152) [26,34,35,38,41], including one study (n = 20) with synchronous oligometastases only [26]. In most studies, the intervention consisted of MDT alone (n = 408) [29,30,37,39,42–44], or MDT with or without SOC chemotherapy and/or ADT (n = 396) [23,24,27,28,31,34,45]. Several trials used combined treatment approaches, including MDT + ADT (n = 126) [33,40], MDT + immunotherapy (n = 31) [38], or a combination of MDT, local-regional treatment, ADT, and/or chemotherapy (n = 176) [26,32,35,36,41]. All studies included RT-based MDT, and six studies also allowed for surgery (n = 248) [23,26,37,41,42] or any MDT method (n = 8) [36]. Medical imaging work-up ranged from PSMA-PET, through choline, fluorodeoxyglucose, or sodium fluoride PET scans, to conventional imaging or a combination thereof. Five studies (n = 261) used PSMA-PET as the primary method of imaging [30,34,37,39,44]. The percentage of patients with only lymph node metastases ranged from 0% to 100%.

3.2. RoB assessment

The summary of RoB assessment and applicability concerns is presented in Supplementary Figure 1. According to the ROBINS-I tool, three of the nonrandomised studies were considered at a high, and 17 were at a moderate RoB. The major reasons for causing the RoB included classification of intervention (ie, systemic therapies). According to the RoB tool for randomised studies, both studies were considered at a low to moderate risk.

3.3. Oncological outcomes

In terms of oncological outcomes, there were two significant outliers (n = 120). The study by Zhang et al. [33] included patients receiving noncurative MDT doses, and in the study by Kwan et al. [38], MDT was applied only to one to two sites before the first and second doses of avelumab. In contrast to the remaining data, both studies included mCRPC patients who previously received an ARSI, chemotherapy, or a combination of both, and the MDT did not intend to be locally curative for all visible metastatic sites. Therefore, we decided to exclude them from the meta-analysis.

PFS data were available in 13 studies (n = 613). The estimated 1-yr PFS was 70% (95% CI: 59–80%), with estimates reported in individual studies ranging from 40% to 97%. The 2-yr PFS was 46% (95% CI: 36–56%) and ranged from 30% to 80% in individual studies. The estimates of 1- and 2-yr PFS rates are shown in Figures 2A and 2B. There was evidence for significant study heterogeneity for both 1- and 2-yr PFS ($p < 0.001$).

ADT-FS was available in five studies (n = 245), including only 2-yr data in one of them. The estimated 1-yr ADT-FS was 78% (95% CI: 71–86%) and ranged from 71% to 86% in individual studies. The estimated 2-yr ADT-FS was 55% (95% CI: 44–65%) and ranged from 47% to 70% in individual studies. The estimates of 1- and 2-yr ADT-FS are shown in Supplementary Figures 2A and 2B. There was no evidence for significant study heterogeneity.

The funnel plots for PFS and ADT-FS can be found in Supplementary Figure 3. Interpretation of these plots should be approached with caution, given the significant heterogeneity in the design of the included studies.

LC data were available in ten studies (n = 421 patients). The estimated 1-yr LC was 99% (95% CI: 97–99%) and the estimates reported in individual studies ranged from 95% to 100%. The 2-yr LC was 97% (95% CI: 94–98%) and ranged from 89% to 100% in individual studies. The estimates of 1- and 2-yr LC are shown in Supplementary Figures 4A and 4B.

OS data were available in ten studies (n = 358). The estimated 1-yr OS was 99% (95% CI: 98–100%) and ranged from 97% to 100% in individual studies. The estimated 2-yr OS was 97% (95% CI: 95–98%) and ranged from 88% to 100% in individual studies, with all but one small study reporting 2-yr OS above 90%. The estimates of 1- and 2-yr OS rates are shown in Supplementary Figures 5A and 5B.

3.4. Sensitivity analysis for PFS

We conducted a sensitivity analysis for PFS, excluding studies that included either biochemical recurrence or initiation of ADT in the PFS definition [31,32,35,36,39]. The estimated 1- and 2-yr PFS were 63% (95% CI: 50–75%) and 42% (95% CI: 33–52%), respectively, as shown in Supplementary Figures 6A and 6B. The study heterogeneity was reduced for 2-yr PFS (p = 0.9), but remained significant for 1-yr PFS ($p < 0.001$).

To account for study heterogeneity, a sensitivity analysis was also conducted to estimate the PFS in studies including only mHSPC patients, as shown in Supplementary Figures 7A and 7B. The PFS was similar, with 1- and 2-yr PFS of 73% (95% CI: 58–88%) and 46% (95% CI: 29–62%), respectively. Study heterogeneity remained significant for both 1- and 2-yr PFS ($p < 0.001$), suggesting other sources of

Table 1 – Basic characteristics of 22 prospective trials reporting data on the outcomes and/or toxicity of metastasis-directed therapy in metastatic prostate cancer patients

Study	Type	Intervention	MDT radiotherapy fractionation schemes	Inclusion criteria	Imaging	*N* (study arm/control arm)	Hormonal status	Setting	N/M1a only (%)	Median FU (mo)	Evaluated clinical outcomes
Muacevic (2013) [23]	SA	SRS to all lesions ± ADT/CTx	Modal dose: 20 Gy in 1 fraction; range 16.5–22 Gy in 1 fraction	1–2 bone metastases; KPS ≥70, life expectancy >3 mo	Choline PET	40	NA	NA	0	10.2	Overall survival, local control
Ahmed (2013) [24]	SA	SRS or SBRT to all lesions ± ADT	Modal dose: 20 Gy in 1 fraction. Other schemes: 18–24 Gy in 1 fraction, 24–60 Gy in 3 fractions, 50 Gy in 5 fractions	1–5 any metastases; KPS ≥40, life expectancy >3 mo	Choline PET or conventional imaging	17	mCRPC (65%) mHSPC (35%)	Oligorecurrence (100%)	5.9	6	Freedom from distant progression, local control, cancer-specific survival
Decaestecker (2014) [25]	SA	SBRT to all lesions combined with 1-mo ADT (LHRH analogue) or SBRT alone	Modal dose: 50 Gy in 10 fractions. Other schemes: 30 Gy in 3 fractions	1–3 any metastases following biochemical recurrence after curative treatment	Choline PET or FDG PET	50	mHSPC (100%)	Oligorecurrence (100%)	54[a]	24	ADT-free survival, local control, progression-free survival
O'Shaughnessy (2017) [26]	SA	ADT, local-regional treatment (RP with (r) PLND ± RT), and SBRT in 12 out of 15 patients with bone metastases	20–30 Gy in 1–5 fractions	1–10 bone or nonpelvic lymph node metastases	Conventional imaging	20 (17 received MDT)	mHSPC (100%)	Oligometastases (100%)	25	40	Rate of undetectable PSA after testosterone recovery, clinical outcomes
STOMP; NCT01558427 Ost (2018) [42]; updated results: Deek (2022) [45]	RCT	SBRT or metastasectomy to all lesions	30 Gy in 3 fractions	1–3 extracranial metastases, asymptomatic biochemical recurrence following curative treatment (no ADT, no local relapse, serum testosterone levels >50 ng/ml); ECOG ≤1	Choline PET	31/31	mHSPC (100%)	Oligorecurrence (100%)	54.8	36	ADT-free survival, biochemical recurrence-free survival, local control
POPSTAR; U1111-1140-7563 Siva (2018) [27]	SA	SRS to all lesions ± ADT	20 Gy in 1 fraction	1–3 bone or lymph node metastases following curative treatment; ECOG ≤2	NaF-PET	33	mHSPC (82%) mCRPC (18%)	Oligorecurrence (100%)	36.4	24	Local progression–free survival, distant progression–free survival, ADT-free survival, PSA response
Evans (2019) [28]	SA	SRS or SBRT to all lesions ± ADT	Modal dose: 16 Gy in 1 fraction. Other schemes: 18 Gy in 1 fraction, 24 Gy in 1 fraction, 30 Gy in 3 fractions	1–3 extracranial metastases following biochemical recurrence after primary curative treatment; life expectancy ≥3 mo	Choline PET	37	mHSPC (68%) mCRPC (32%)	Oligorecurrence (100%)	2.7	39	Overall survival, progression-free survival, local control
Pasqualetti (2018) [29]	SA	SRS or SBRT to all lesions	Modal dose: 27 Gy in 3 fractions. Other schemes: 24 Gy in 1 fraction	1–5 lymph node or bone metastases not requiring systemic treatment (ADT/CTx)	Choline PET	51	NA	NA	NA	18.5	Local control

Table 1 (*continued*)

Study	Type	Intervention	MDT radiotherapy fractionation schemes	Inclusion criteria	Imaging	*N* (study arm/control arm)	Hormonal status	Setting	N/M1a only (%)	Median FU (mo)	Evaluated clinical outcomes
Kneebone (2018) [30]	SA	SRS or SBRT to all lesions	Modal dose: 30 Gy in 3 fractions. Other schemes: 20 Gy in 1 fraction, 24 Gy in 2 fractions, 50 Gy in 5 fractions	1–3 lymph node or bone metastases following biochemical recurrence after primary curative treatment	PSMA-PET	57	mHSPC (100%)	Oligorecurrence (100%)	65	16	Biochemical failure, complete biochemical response, local failure
TRANSFORM; ACTRN12618000566235 Bowden (2020) [31]	SA	SBRT to all lesions ± ADT	50 Gy in 10 fractions. The dose was lowered in cases of overlap with previously irradiated fields	1–5 lymph node or bone metastases following distant recurrence after primary curative treatment, with no sign of active disease in prostate bed; ECOG ≤1	PSMA-PET, choline PET, or conventional imaging	199; 176 included for the analysis of the primary endpoint	mHSPC (93%) mCRPC (7%)	Oligorecurrence (100%)	63.3	35.1	Time to treatment escalation
ORIOLE; NCT02680587 Phillips (2020) [43]; updated results: Deek (2022) [45]	RCT	SBRT to all lesions	Modal dose: 30 Gy in 3 fractions or 35 Gy in 5 fractions. Other schemes: 19.5–36 Gy in 3 fractions, 44–48 Gy in 4 fractions, 25–45 Gy in 5 fractions	1–3 asymptomatic metastases after primary curative treatment, and no ADT within 6 mo of enrolment	Conventional imaging	36/18	mHSPC (100%)	Oligorecurrence (100%)	58	18.8	Progression-free survival, biochemical progression–free survival, distant metastasis-free survival
OLIGOPELVIS GETUG P07 Supiot (2021) [32]; Vaugier (2019) [47]	SA	Whole-pelvis radiotherapy combined with fractionated simultaneous boost to metastatic lymph nodes and 6-mo ADT	54 Gy in 30 fractions to the whole pelvis, with a simultaneous integrated boost of 66 Gy to pathological lymph nodes	1–5 pelvic lymph node metastases after primary curative treatment and no ADT within 6 mo of enrolment	Choline PET	67	mHSPC (100%)	Oligorecurrence (100%)	100	49.4 in survivors	Progression-free survival, biochemical relapse–free survival, overall survival, time to start of a second-line treatment, time to start palliative ADT
NCT02816983 Zhang (2021) [33]	SA	SRS or SBRT to all lesions + ADT	Modal dose: 20 Gy in 1 fraction. Range 8–50 Gy in 1–5 fractions	1–3 metastases and castration-resistant prostate cancer; ECOG ≥2, life expectancy >6 mo	Choline PET	89	mCRPC (100%)	Oligorecurrence (100%)	5.6	23	Overall survival, PSA progression–free survival, local progression-free survival, distant progression-free survival
Mazzola (2021) [34]	SA	SBRT to all lesions ± ADT	Modal dose: 35 Gy in 5 fractions. In case of retreatment, 25–30 Gy in 5 fractions	1–3 metastases; KPS >70%, ECOG ≤2	PSMA-PET and FDG-PET	20	mHSPC (100%)	Oligorecurrence (75%) Oligometastases (25%)	≥55 [a]	NA	Progression-free survival, local control

(*continued on next page*)

Table 1 (*continued*)

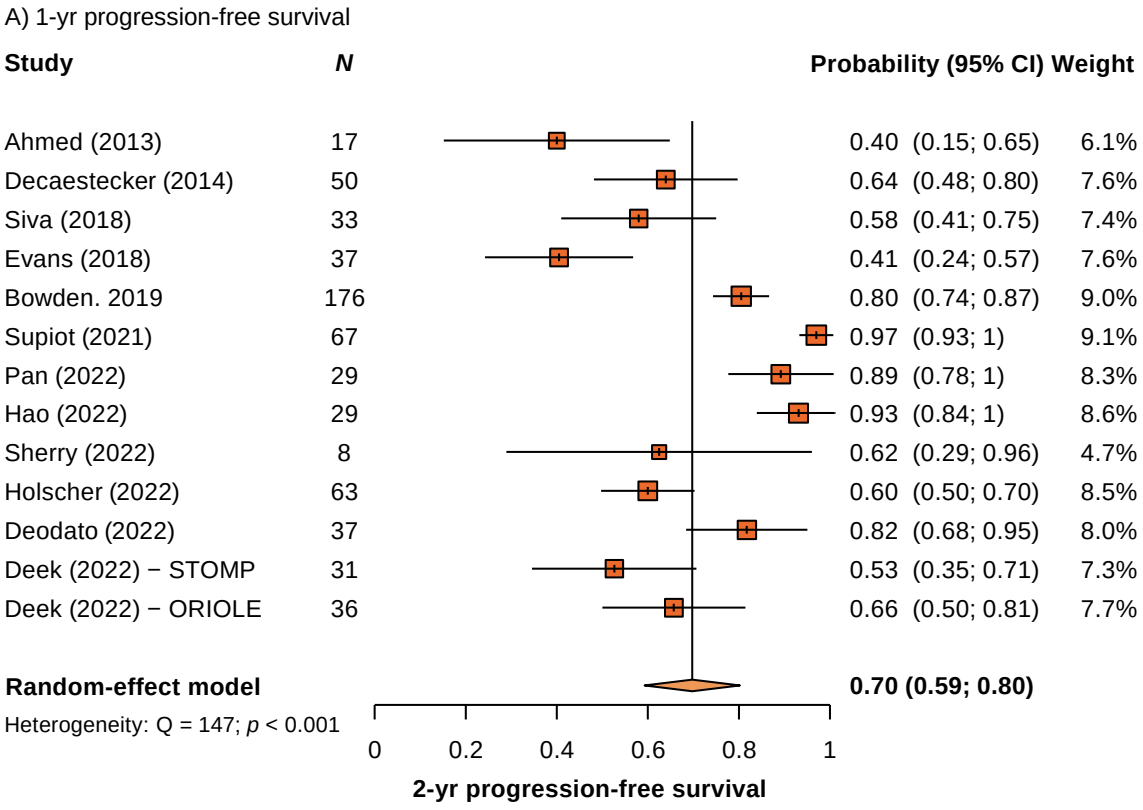
Study	Type	Intervention	MDT radiotherapy fractionation schemes	Inclusion criteria	Imaging	*N* (study arm/control arm)	Hormonal status	Setting	N/M1a only (%)	Median FU (mo)	Evaluated clinical outcomes
Pan (2022) [44]	nCT	SBRT to all lesions vs ADT in control group	Modal dose: 32 Gy in 4 fractions. Other schemes: 40 Gy in 5 fractions, 50 Gy in 5 fractions	1–5 bone or lymph node metastases and early PSA progression on ADT following curative treatment; ECOG ≤1, life expectancy >12 mo	PSMA-PET	29/18	mCRPC (100%)	Oligorecurrence (100%)	34	21.4 (20 in survivors)	Metastasis-free survival
Hao (2022) [35]	SA	36 wk of ADT followed by SABR to all visible metastases ± curative local treatment	Median dose: 45 Gy, median fraction dose: 2 Gy. Range: 37.5–55.8 Gy in 1.8–2.5 Gy fractions	1–5 metastases and hormone-sensitive prostate cancer, last ADT finished at least 2 yr before enrolment	NA	29	mHSPC (100%)	Oligometastases (51.7%) Oligorecurrence (48.3%)	27.6	118.8	Progression-free survival, overall survival, local control
EXTEND; NCT03599765 Sherry (2022) [36]	SA	SRS, SBRT, or any other MDT to all sites ± curative treatment of the primary ± ADT/CTx	Recommended schemes: 25–50 Gy in 3–5 fractions or 12–24 Gy in 1 fraction	Basket trial, described data regarding only the prostate cancer subgroup 1–5 metastases	Conventional imaging	8	NA	NA	NA	38.5 (39.6 in survivors)	Progression-free survival
NCT03160794/ NCT03718260 Glicksman (2022) [37]	SA	SABR or metastasectomy to all lesions	Dose range: 24–30 Gy in 3 fractions	1–6 metastases following biochemical recurrence after radical prostatectomy and postoperative radiotherapy ± ADT	PSMA-PET	74	mHSPC (100%)	Oligorecurrence (100%)	86.5	24	Biochemical response, PSA progression–free survival, ADT-free survival, salvage treatment–free survival, CRPC-free survival
ICE-PAC Kwan (2022) [38]	SA	24 wk of avelumab combined with SRS to 1–2 lesions before the first and second doses of immunotherapy	20 Gy in 1 fraction	Patients with any number of metastases and progressive mCRPC after at least one prior therapy with ARSI; life expectancy ≥6 mo, ECOG ≤1	Conventional imaging	31	mCRPC (100%)	Oligorecurrence (74%) Oligometastases (26%)	3.2	18 in survivors	Disease control rate, objective response rate, radiographic progression-free survival, overall survival
OLI-P, NCT02264379 Hölscher (2022) [39,46]	SA	SBRT or conventional RT to all lesions	Modal dose: 30 Gy in 3 fractions. Other scheme: 50 Gy in 25 fractions	1–5 bone or lymph node metastases following local curative therapy and PSA ≤10 ng/ml; life expectancy ≥5 yr	PSMA-PET	63	mHSPC (100%)	Oligorecurrence (100%)	68.3	37.2 (40.8 in patients without an event)	PSA progression–free time, time to start systemic therapy, progression-free survival, overall survival. local progression–free time, time to the first tumour-related clinical event
DESTROY-2 Deodato (2022) [40]	SA	SRS to all lesions + ADT	Median dose: 24 Gy in 1 fraction. Range 12–24 Gy in 1 fraction.	1–5 lymph node or bone metastases	PSMA-PET, choline PET, or conventional imaging	37	mHSPC (81.1%) mCRPC (18.9%)	Oligorecurrence (100%)	0	25	Biochemical tumour response, local control, distant metastasis–free survival, progression-free survival, time to next-line systemic treatment–free survival, overall survival

Table 1 (*continued*)

Study	Type	Intervention	MDT radiotherapy fractionation schemes	Inclusion criteria	Imaging	*N* (study arm/control arm)	Hormonal status	Setting	N/M1a only (%)	Median FU (mo)	Evaluated clinical outcomes
Reyes (2022) [41]	SA	Total eradication therapy consisting of local treatment ± adjuvant radiotherapy; combination of ADT, ARSI, and CTx; and SBRT or metastasectomy to all lesions	The dose and fractionation depended on the size and location of the lesion (not specified)	1–5 bone or lymph node metastases	PSMA-PET or conventional imaging	52	mHSPC (100%)	Oligometastases (57.7%) Oligorecurrence (42.3%)	NA	30.3	Undetectable PSA with recovered testosterone
Deek (2022) [45]	RCT		Long-term outcome analysis of STOMP (by Ost et al. [42]) and ORIOLE (by Phillips et al. [43]) trials described above							52.5	Progression-free survival, radiographic progression–free survival, time to castration-resistant prostate cancer, overall survival

ADT = androgen deprivation therapy; ARSI = androgen receptor signalling inhibitors; CRPC = castrate-resistant prostate cancer; CTx = chemotherapy; ECOG = Eastern Cooperative Oncology Group performance status scale; FDG = fluorodeoxyglucose; FU = follow-up; KPS = Karnofsky performance status scale; LHRH = luteinising hormone-releasing hormone; mCRPC = metastatic castrate-resistant prostate cancer; MDT = metastasis-directed therapy; mHSPC = metastatic hormone-sensitive prostate cancer; NA = not applicable or not available; NaF = sodium fluoride; nCT = nonrandomised controlled trial; oligometastases = oligometastatic prostate cancer (synchronous metastases); oligorecurrence = oligorecurrent prostate cancer (metachronous metastases); PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RCT = randomised controlled trial; RP = radical prostatectomy; (r)PLND = (retroperitoneal) pelvic lymph node dissection; RT = radiotherapy; SA = single-arm trial; SABR = stereotactic ablative body radiotherapy; SBRT = stereotactic body radiotherapy (usually one to five fractions); SRS = stereotactic radiosurgery (single fraction).

[a] Estimated based on the available data.



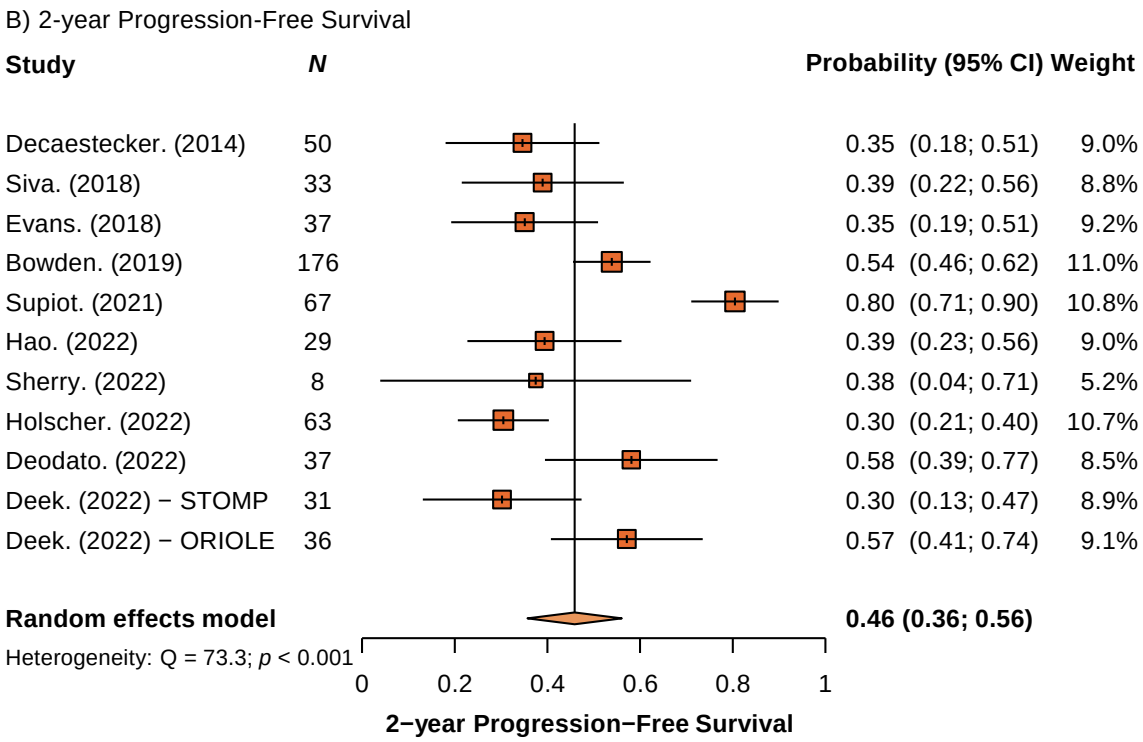


Fig. 2 – Estimations for (A) 1-yr and (B) 2-yr progression-free survival in patients treated for metastatic prostate cancer with metastases-directed therapy. CI = confidence interval.

study heterogeneity besides differences in castration status of included patients.

A sensitivity analysis was also performed to address the results of the RoB analysis. The results did not change substantially after excluding studies with a high RoB (n = 41) [27,36]. The 1- and 2-yr PFS were 71% (95% CI: 59–83%) and 47% (95% CI: 35–59%), respectively, and the study heterogeneity remained significant for both (p < 0.001), as shown in Supplementary Figures 8A and 8B.

3.5. MDT-related AEs

The majority of the trials provided data on AEs, which are summarised in Supplementary Table 5, along with the description of individual AEs below. In general, MDT-related AEs were sparse, and toxicity mostly occurred in trials that used combined-modality therapies, such as concurrent systemic therapy or local treatment. Three trials did not report on the adverse effects of MDT [23,28,35], and the side effects in the STOMP [42] and ORIOLE [43] trials were described in the initial articles rather than the long-term updated pooled analysis [45].

The rates of grade ≥3 AEs were reported in 17 studies (n = 846), and the pooled estimated rate was 0.3% (95% CI: 0–1%), as shown in Supplementary Figure 9A. Eleven trials reported no grade ≥3 AEs (n = 552) [24,25,30,31,34,36,39,40,42–44], and the rates ranged from 0% to 5.9% in individual studies. There was no evidence for significant study heterogeneity.

The rates of grade 2 AEs were reported in 16 trials, and the pooled estimated rate was 2.4% (95% CI: 0.2–7%), as shown in Supplementary Figure 9B. Four trials reported no grade 2 toxicity (n = 156) [34,39,40,42]. The rates ranged from 0% to 15.2% in individual studies, and there was evidence for significant study heterogeneity (p < 0.001).

3.6. Moderator analysis

We considered the potential prognostic roles of variables using meta-regression and meta-analysis of variance models for PFS and treatment toxicity, as shown in Supplementary Table 6. We found no statistically significant moderators.

3.7. Discussion

We present the most up-to-date and largest comprehensive systematic review and meta-analysis of prospective studies evaluating the outcomes of MDT in mPCa patients, the majority of which were performed in the oligometastatic setting. There are several important findings in our study. First, we found that the overall PFS rates were promisingly high, and MDT was associated with excellent LC. Second, MDT allowed for a clinically relevant delay of definitive ADT in a large proportion of oligorecurrent mHSPC patients, which is crucial for patients seeking to avoid or postpone ADT-related side effects. Third, MDT was found to be associated with a low rate of MDT-related grade ≥3 and grade 2 AEs, facilitating the use in both combined-modality treatment intensification and systemic treatment de-escalation.

Owing to the fact that the majority of included studies lacked a comparator, it is not possible to accurately compare the obtained results with available treatment modalities for mPCa patients, especially considering that ADT alone can be associated with as high 2-yr PFS as 35–52% in mHSPC patients [5–7]. The results are significantly worse in mCRPC patients [48], often presenting with polymetastatic, high-burden disease. Two single-arm trials investigated the addition of MDT to systemic treatment following progression on ARSI or chemotherapy in mCRPC patients and found 1-yr PFS rates as low as 13–18% [33,38]. On the contrary, Pan et al. [44] found excellent 1-yr PFS of 89% in clinically oligometastatic patients receiving MDT at the diagnosis of CRPC following local curative treatment. Consistently with the results of the moderator analysis, this suggests a possible application of MDT in selected, early diagnosed oligometastatic mCRPC patients. In the mHSPC setting, MDT was investigated as a mean to both postpone systemic treatment and avoid related toxicity, or to intensify treatment through eradication of clinically visible metastatic lesions, possibly improving the systemic response. However, the majority of available data on MDT supporting these concepts come from relatively small heterogeneous single-arm studies, and there is an urgent need for prospective, controlled data. Notably, while there are multiple on-going trials analysing the application of MDT in mHSPC, including phase 3 studies investigating the impact of MDT on PFS, time to mCRPC, and/or time to polymetastatic disease, there is only one phase 2/3 trial in the mCRPC setting [49].

According to our meta-analysis, MDT can delay definitive ADT by at least 2 yr in more than half of the oligorecurrent mHSPC patients. ADT is associated with relatively common AEs in the long term, many of which can be serious and/or difficult to mitigate [50]. For example, 7.6% of patients receiving ADT combined with a new antiandrogen, and 2.7% of patients receiving ADT plus placebo experienced grade 3–4 treatment-emergent AEs, including fractures and ischaemic heart and/or cerebrovascular disease [51]. Considering that the estimated risk of grade 2 and ≥3 AEs is substantially lower for MDT than for ADT, MDT could be offered to patients with oligorecurrent mHSPC who wish to avoid or delay toxicity associated with definitive ADT. We have also found that the 1- and 2-yr OS is excellent; however, this should be attributed to or used as an argument in favour of MDT as short-term survival is likely to be high in mHSPC patients regardless of treatment (eg, 100% 2-yr survival was reported for both the control and the study group in the ORIOLE and STOMP trials [45]).

MDT was also studied in combination with systemic treatment as a form of treatment intensification, including a combination with immunotherapy in the ICE-PAC trial [38]. The OLIGOPELVIS GETUG P07 trial combined MDT with 6 mo of ADT. The reported low rate of adverse effects suggests that MDT combined with short-term ADT might be a well-tolerated alternative to definitive ADT [47]. While there are no data supporting the use of MDT to delay ADT in patients with synchronous oligometastases, three studies investigated the possibility of combining ADT with local curative treatment and MDT [26,35,41]. Considering that RT to the prostate is a viable option in selected low-volume mPCa patients [9,10], MDT could be the next step

towards treatment intensification. Future clinical trials need to investigate the optimal imaging methods for reducing the risk of occult metastases. Early detection of progression and retreatment could also become a viable MDT concept.

The estimated rate of grade ≥3 AEs was low, and the majority of the grade ≥3 AEs were not associated with SBRT. Considering the excellent LC, SBRT should be considered a preferable method of MDT in most cases. Surgical metastasectomy has mostly been studied in the context of salvage lymph node dissection, and there are little data on the role of surgery for bone and visceral metastases [1]. In general, the toxicity profile is associated with the location and size of the metastases, and the choice of MDT method. A high volume of irradiation or vicinity of organs at risk can be associated with a considerably higher risk of AEs, or even preclude the use of MDT. Similarly, reirradiation in the pelvis or proximity to previously irradiated lesions can be associated with an increased risk of treatment-related toxicity. Ultimately, the decision should remain patient tailored.

Medical imaging ranged from conventional imaging consisting of computed tomography and bone scans to different types of PET, including PSMA-PET as the main method of imaging in five studies [30,34,37,39,44]. Hofman et al. have shown that the latter has better accuracy for the detection of distant metastases [52]. The routine use of PSMA-PET could improve the results of MDT by stage migration towards less extended disease through identification of lesions undetected on conventional imaging [53]. For example, in the ORIOLE trial, the investigators were blinded to the data on PSMA-PET performed at baseline. As a result, 16 out of 36 participants in the study arm had baseline PSMA-PET avid lesions that were not targeted with MDT. Only one of 19 remaining patients assessed at 6 mo had disease progression, compared with six out of 16 participants with untreated lesions (5% vs 38%, p = 0.03) [43]. At the same time, it is possible that the initially undetected lesions could be treated successfully with repeated MDT at progression, and the importance of treating lesions undetected on conventional imaging remains a matter of discussion. We chose not to include the use of PSMA-PET in the meta-regression analysis due to the lack of a single comparator. Several trials used other types of PET scans, including NaF-PET for patients with bone metastases only, and in some cases the medical imaging was not explicit in the study protocol. Nevertheless, according to the most recent ESTRO-ACROP Delphi consensus recommendations, PSMA-PET is the preferred imaging method for guiding MDT [3].

3.8. Limitations

The study has several limitations. First, the available data come from numerous early-phase trials, leading to differences in the characteristics of the study populations such as castration status, disease volume, and concurrent and previous systemic treatments. There is significant study heterogeneity, and the wide CIs of the meta-analytic averages should be considered while interpreting the results. Second, only two RCTs were found eligible for the meta-analysis. Owing to the single-arm design of the vast majority of the studies, there was no reliable comparator. Indirect comparisons are prone to a selection bias and do not account for differences such as variability in concurrent treatments. Third, there were differences in definitions of endpoints between studies, in particular with regard to the inclusion of biochemical endpoints in PFS. Fourth, in some cases, the trial results were published over more than one publication, possibly reducing the quality of extracted data. Fifth, MDT is not a uniform concept. While in the majority of cases SBRT was used, several studies included conventional RT or surgery. MDT was sometimes combined with local and/or elective nodal RT and systemic therapies. The treatment of mPCa remains a complex issue, comprising several significantly different clinical scenarios and different combinations of multiple treatment modalities. There is no consensus on optimal multimodality strategies, and focus on MDT alone might lead to overlooking equally or more important issues, such as the timing and choice of systemic therapy. Further RCTs are necessary to assess the clinical benefit of MDT in particular clinical scenarios.

4. Conclusions

We found that MDT offers favourable PFS and a low toxicity profile. The application of MDT allows for the delay in the initiation of ADT in a significant subset of oligorecurrent mHSPC patients, helping them to avoid or defer ADT-related toxicity.

Combining other therapies with MDT is an emerging concept for treatment intensification, and the excellent LC of MDT suggests potential as a component of definitive treatment in oligometastatic patients. However, most of the prospective data come from small phase 1/2 studies. Until the results of ongoing randomised phase 3 studies are published, MDT in the setting of treatment intensification should be considered a promising yet investigational treatment modality with an uncertain impact on OS.

Author contributions: Shahrokh F. Shariat 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.

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Acquisition of data: Miszczyk, Rajwa, Nowicka.
Analysis and interpretation of data: Miszczyk, Rajwa, Yanagisawa, Nowicka, Kawada, Shariat.
Drafting of the manuscript: Miszczyk, Rajwa.
Critical revision of the manuscript for important intellectual content: Yanagisawa, Laukhtina, von Deimling, Pradere, Rivas, Gandaglia, van den Bergh, Goldner, Supiot, Zilli, Trinh, Nguyen, Briganti, Ost, Ploussard, Shariat.
Statistical analysis: Miszczyk, Rajwa, Nowicka, Shim.
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