REVIEW

Radiotherapy as metastasis-directed therapy for oligometastatic prostate cancer

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Purpose of review
To summarize the available literature regarding radiotherapy as a metastasis-directed therapy (MDT) in the treatment of oligometastatic prostate cancer (PCa).

Recent findings
Three different clinical scenarios of oligometastatic PCa exist in which MDT can be applied: de novo oligometastatic PCa, oligorecurrent PCa, and oligoprogressive PCa. A cut off of three to five metastatic lesions is most often used in these settings. Data from retrospective studies, treating over 1000 patients in total, have been reported. The median progression-free survival ranges between 1 and 3 years, but is influenced by a heterogeneous use of androgen deprivation therapy. For lymph node metastases, a propensity scored matched analysis suggests that cancer specific and overall survival is improved with MDT over standard of care. MDT treatment regimens vary with different radiotherapy techniques, doses, and volumes. Adverse events are limited to grade 1–2 and only rarely grade 3 events are reported.

Summary
Based on data from retrospective studies, progression-free survival following MDT for oligometastatic PCa is promising with few adverse events. Comparative prospective studies are under way and will shed light on the future of MDT.

Keywords
oligometastases, prostate cancer, stereotactic body radiotherapy, whole pelvis radiotherapy

INTRODUCTION

Oligometastases have been described for more than 20 years in different types of solid tumors [1]. It can be defined as an intermediate state of cancer situated between localized, nonmetastatic cancer, and aggressive widespread metastatic cancer [2]. Oligometastatic cancer by definition has the potential to metastasize, but its natural history is clearly different from widespread metastatic cancer [2]. In the current literature, the oligometastatic state is typically defined as less than three or five metastatic sites in the body [3,4]. The prognostic role of the number of metastases in prostate cancer (PCa) has been highlighted in recent studies [5,6], with a poorer prognosis for patients with an increasing number of metastases. Ultimately, a biologic and likely genomic definition of oligometastatic disease will prevail, but until that time these clinical and radiographic definitions are reasonable. At the recent Advanced Prostate Cancer Consensus Conference, 14% of the experts voted for a cut off of two or less metastases to define oligometastatic PCa, 66% for three or less metastases, 20% of these panelists voted for five or less metastases [7▪].

According to contemporary treatment guidelines, the basis of treatment of metastatic PCa is systemic therapy, including palliative androgen deprivation therapy (ADT) [8] with or without docetaxel [9] and more recently abiraterone acetate [10,11]. There is still some controversy, whether aggressive combinations of systemic drugs should also be applied to oligometastatic PCa taking into account the increase in adverse events of these drug combinations as compared to ADT monotherapy [12,13]. In line with the hypothesis of Hellman *et al.* [1], several groups have started investigating the potential of 'metastasis-directed therapy' (MTD) as an alternative for or in combination with

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KEY POINTS

- Radiotherapy is a well tolerated MDT.
- Progression-free survival following MDT ranges between 1 and 3 years.

systemic therapy. In PCa, this MTD usually consists of surgery or radiotherapy [14▪▪]. In the current review, we will summarize the available literature of radiotherapy as type of MDT and we will consider two important clinical scenarios for which radiotherapy has been applied: oligorecurrent and oligoprogressive PCa (Fig. 1). Oligometastatic recurrence or oligorecurrent PCa is the metachronous development of low-volume metastases following local control of the primary tumor. This state is diagnosed by a rising prostate-specific antigen in patients with testosterone levels above castration levels [15▪]. Oligometastatic progression is defined as patients with castrate levels of testosterone but with a limited number of metastases [15▪]. The treatment of the primary tumor is beyond the scope of this review.

MATERIALS AND METHODS

Studies included in this review were identified through the PubMed online database. Search terms used for the selection of articles were ['radiosurgery' (MeSH terms) OR 'radiosurgery' (all fields) or 'stereotactic' (all fields) AND 'body' (all fields) AND 'radiotherapy' (all fields) OR 'stereotactic body radiotherapy' (all fields) AND 'prostate' (MeSH Terms) OR 'prostate' (all fields)]. We concentrated on the articles focusing on the radiotherapeutic treatment of oligometastases in PCa in a recurrent or progressive state, reporting oncological results. Articles solely focusing on local prostate bed recurrence were not taken into account. Articles treating patients with polymetastases (>5) were excluded. First, screening was done on the basis of title and publication date. Abstracts were screened for usability. Studies published in a foreign language (other than English), no access to full text or reports from meetings were excluded. With the help of the suggested literature, additional articles could be included. The selected articles are all published between 2008 and the present.

RESULTS

An overview of the selected articles using radiotherapy as a type of MDT is shown in Table 1 [4,15▪,16,17,18▪,19–33]. In total, 1025 patients have been treated with radiotherapy for oligometastatic PCa and reported in the literature. The majority of patients were treated with stereotactic body

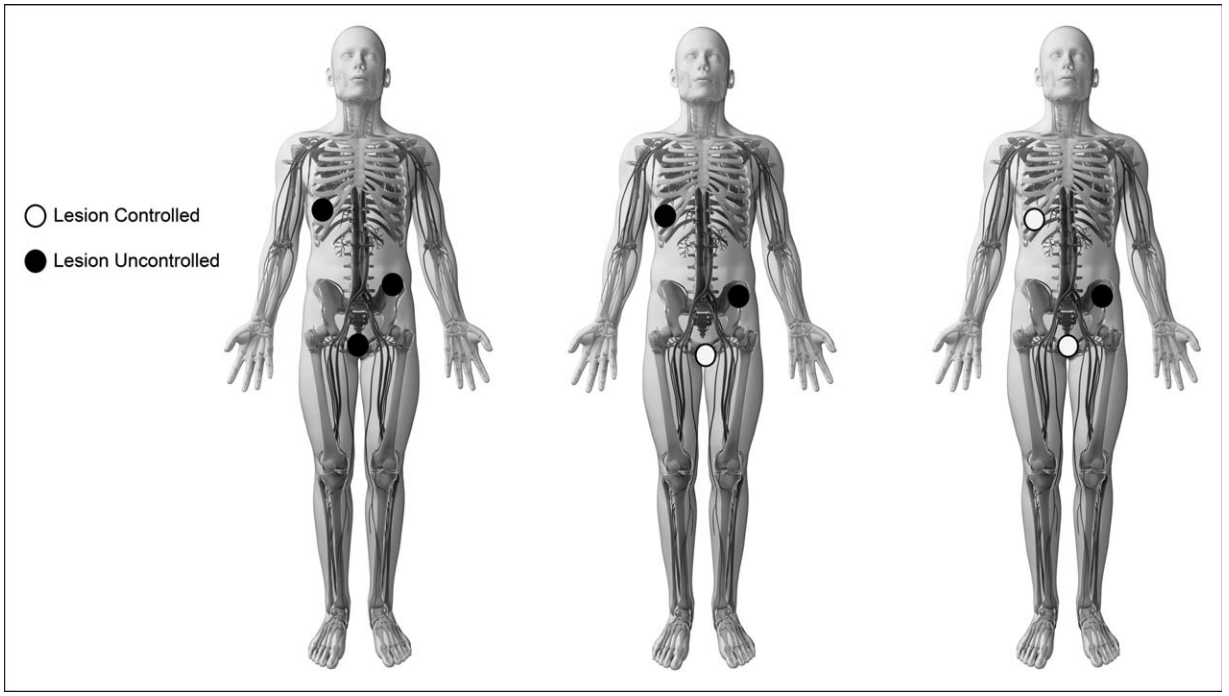

FIGURE 1. Three subsets of oligometastatic PCa. Left patient: de novo oligometastases (synchronous oligometastases). Detection of metastases at time of diagnosis of PCa. Middle patient: oligometastatic recurrence or metachronous oligometastases. Right patient: oligometastatic progression. PCa, prostate cancer.

radiotherapy (SBRT), a specific radiotherapy technique in which high dose of radiation, typically more than 5 Gy per fraction, are given in a small number of fractions to a small volume [30]. Different total doses and dose per fraction were used in the different articles, largely dependent on institutional policy. For nodal metastases, elective nodal radiotherapy (ENRT) was also used. Typically, 25–28 fractions were delivered resulting in a total dose of 45–51.8 Gy.

Diagnostic approaches in oligometastatic prostate cancer

In the majority of studies, metastases were detected by means of choline PET–computed tomography (CT; 88%) and only a minority of patients with conventional imaging or older PET–CT tracers (12%). Data using more novel tracers such as prostate-specific membrane antigen PET [34] to guide radiation MDT in oligometastatic PCa appear promising, but is too preliminary at this time and should be the focus of future reviews [35,36].

De novo or synchronous metastases

To our knowledge, there are no studies reported adding MDT to completely consolidate disease in these patients. Sometimes patients treated in this comprehensive fashion are included as a small subset of larger retrospective studies [26,29], making it hard to draw any meaningful conclusions on the value of MDT for this patient group.

Oligorecurrent or metachronous metastases

Most of the literature focuses on recurrent or metachronous oligometastatic PCa. Analysis of the relapse patterns following primary PCa treatment suggests that the majority of patients relapse with three or fewer metastases [37–39] and recurrences are most often located in the nodes, followed by bone and visceral locations.

Lymph node recurrence

We identified nine articles focusing on metastatic spread in the lymph nodes only. The majority of studies include both pelvic and extrapelvic nodes. The type of MDT was SBRT for 55% of cases, whereas 45% were treated with ENRT to a lymph node region or to the whole pelvis using whole pelvis radiotherapy (WPRT) with or without extrapelvic lymph node regions (Table 1). There are no comparative studies of SBRT with ENRT. Radiation doses as well as fractionation schedules used were also very heterogeneous between and within the studies.

SBRT is a pure lesion-based technique, targeted at the identified lesion on imaging. The success rate depends on the sensitivity of the imaging modality used as other regional lymph nodes are not irradiated. The 3-year progression-free survival (PFS) in the largest SBRT series ranges between 26 and 33% [15▪,18▪,20] with excellent local control of targeted lymph node metastases in cases were a sufficiently high SBRT dose is used. Ost *et al.* [18▪] suggested using a biological equivalent SBRT dose of more than 100 Gy ($\alpha/\beta = 10$), resulting in a local control rate of 99%. Adverse events are often absent, with around 2–3% grade 2 events and rare grade 3 events (<1%; Table 2).

At the 2017 annual meeting of the American Urology Association, the first comparative study of standard of care (SOC) versus MTD [SBRT or salvage lymph node dissection, (sLND)] for oligorecurrent PCa was presented [40▪▪]. All included patients were treated with prostatectomy and postoperative radiotherapy at diagnosis and developed a subsequent biochemical recurrence. The patients were matched for patient age, year of primary treatment, prostate-specific antigen, tumor stage, margin status, and pathological Gleason score. A 10-year cancer-specific survival of 84.8% [95% confidence interval (CI): 79.5–89.0] and 95.6% (95% CI: 88.0–98.5) for SOC and MDT was shown ($P = 0.002$), respectively, corresponding to a hazard ratio of 0.29 (95% CI: 0.14–0.55) in favor of MDT.

In the study by Ost *et al.* [18▪], a detailed pattern of relapse was conducted revealing that 68% of recurrences were located in nearby nonirradiated lymph node regions. These data show that microscopic disease is missed by choline PET–CT. This was confirmed in the study by Decaestecker *et al.* [4], suggesting repeat SBRT in cases where the recurrence was again oligometastatic, which occurred in 88% of cases [18▪]. These repeated courses of SBRT were well tolerated [4]. This treatment paradigm is comparable to that of repeated stereotactic radiosurgery for brain metastases as an alternative to whole brain radiotherapy; reducing the toxicity by reducing the volume of normal brain tissue treated, but at a cost of a higher regional recurrence rate.

As an alternative for SBRT, ENRT has been used to a lesser extent [23,29]. This approach presumes that the sensitivity of the imaging modality to stage patients is insufficient for a pure lesion-targeted approach and includes elective regional lymph node regions in the radiotherapy treatment field. As the majority of patients in the reported studies are staged with choline PET–CT, an ENRT approach seems logical as data have shown that choline PET–CT has a low sensitivity on a lesion-based level [41]. This approach is also used commonly for

Table 1. Overview of the selected articles reporting metastasis-directed radiotherapy for oligometastatic prostate cancer

Study	Number of patients	Median age at diagnosis (year)	Staging method	Site of metastasis: Node/bone/ visceral/mixed	Number of metastases	Median time to metastatic recurrence (month)	Median PSA at time of metastases (ng/ml)	Type of MDT	Adjuvant ADT N (%)	Median Duration ADT (month)	Adjuvant chemother-apy (%)	Median FU (month)	Median PFS[a] (month)
Lymph node metastases only													
Detti *et al.* [16]	30	64	Choline PET/CT	30/0/0/0	NR	75.6	4.99	SBRT	14 (47)	NR	No	12	NR
Ponti *et al.* [17]	16	71.5	Choline PET/CT	16/0/0/0	1–2	25.9	6.65	SBRT	10 (63)	NR	No	29.38	NR
Ost *et al.* [18▪],[b]	72	NR	FDG ($n=17$), Choline PET/CT ($n=54$), MRI ($n=1$)	72/0/0/0	≤3	44.4	3.4	SBRT	41 (57)	1	No	36	21 Estimated 3-year PFS: 33%
Ingrosso *et al.* [19]	40	74	Choline PET/CT	40/0/0/0	NR	37.45	4.2	SBRT	19 (48)	NR	No	23.8	NR
Jereczek-Fossa *et al.* [20]	94	70.7	Choline PET/CT ($n=90$), normal CT Thorax/ abdmen ($n=1$),MRI ($n=3$)	94/0/0/0	≤5	49.6	3.5	SBRT	34 (36)	14.5	3 (3)	18.5	2-year RFS: 33.3%
Casamassima *et al.* [21]	25	63–68	Choline PET/CT	25/0/0/0	NR	11.8–36.7	5.65	SBRT ($n=18$; 72%), WPRT ($n=7$; 28%)	No	NA	No	29	24
Rischke *et al.* [22]	47	65	Choline PET/CT	47/0/0/0	NR	53	3	Salvage LND and Adjuvant WPRT (IMRT/ 3D-conformal RT)	No	NA	No	28.7	Median not reached 3-year and 5-year RFS[c] in treated region: 70.7%. Time to next relapse outside treated region: 27 month. 3-year RFS outside treated region 45.7%
Fodor *et al.* [23]	81	68	Choline PET/CT	81/0/0/0	NR	63	2.59	ENRT	58[d] (72)	12	7 (9)	36	Median not reached 3-year cRFS: 61.8%[c]
Bone metastases only													
Muacevic *et al.* [24]	40	66	Choline PET/CT	0/40/0/0	1–2	NR	5.4	SBRT	19 (48)	NR	8 (20)	10.2	NR
Wu *et al.* [25]	30	78	Bone scan and Choline PET/CT	0/30/0/0	≤3	NR	NR	SBRT	30 (100)	≤12	5 (17)	32.5	3-year RFS: 22.8%
Mixed metastatic sites													
Würschmidt *et al.* [26]	16	65	Choline PET/CT	15/1/0/0	NR	NR	1.79	ENRT	NR	NR	No	28	Median not reached 3-year PFS: 75%
Ahmed *et al.* [27]	17	65	Choline PET/CT ($n=7$), MRI ($n=6$), both ($n=2$), biopsy ($n=1$), CT ($n=1$)	1/15/1/0	≤5	50.4	2.1	SBRT	15 (88)	NR	No	6	12

Table 1 (*Continued*)

Study	Number of patients	Median age at diagnosis (year)	Staging method	Site of metastasis: Node/bone/ visceral/mixed	Number of metastases	Median time to metastatic recurrence (month)	Median PSA at time of metastases (ng/ml)	Type of MDT	Adjuvant ADT N (%)	Median Duration ADT (month)	Adjuvant chemother-apy (%)	Median FU (month)	Median PFS[a] (month)
Jereczek-Fossa *et al.* [28]	19	68	Choline PET/CT	18/1/0/0	1	66	1.77 (pelvic LN) 10.7 (Bone)	SBRT	14 (74)	12.3–17.5	No	17	LN rec.: Median not reached 30-month PFS: 63.5% (Median > 30 month) Bone rec. Median: 11 month
Schick *et al.* [29]	50	63	Choline/C-acetaat PET/CT and bone scan	33/15/1/1	<5	13	6.7	SBRT ($n=14$; 28%), ENRT ($n=36$; 72%)	49 (98)	12	No	31	Median not reached 3-year PFS: 58.6%
Decaestecker *et al.* [4]	50	59	FDG ($n=32$), Choline PET/CT ($n=18$), MRI ($n=11$)[e]	27/22/1/0	≤3	57.6	5.1	SBRT	35 (70)	1	No	24	19 Estimated 3-year PFS: 15%
Ost *et al.* [30]	119	61	FDG ($n=24$), Choline PET/CT ($n=92$), MRI ($n=3$)	72/43/2/2	≤3	56.4	4.0	SBRT	60 (50)	2	No	36	21 Estimated 3-year PFS: 32%
Pasqualetti *et al.* [31]	29	71.2	Choline PET/CT	15/12/0/0	≤3	11.5	3.43 (Mean)	SBRT	No	NA	No	11.53	NR
Muldermans *et al.* [32]	66	61.4	Choline PET/CT ($n=46$), MRI ($n=8$), CT ($n=2$), bone scan ($n=10$)	5/60/1/0	<5	NR	NR	SBRT	42 (64)	NR	6 (9) (As primary treatment)	16	2-year PFS: 45%
Bouman-Wammes *et al.* [33]	43	68 (mean)	Choline PET/CT	33/9/0/1	≤4	87.6	4.5	SBRT	No	NA	No	31.2	31.5 month[f]
Triggiani *et al.* [15[b]]	OR: $n=100$ OP: $n=41$	OR: 67 OP: 65	OR: Choline PET ($n=96$), CT and bone scan ($n=4$) OP: Choline PET ($n=38$), CT/ scintigraphy ($n=3$)	OR: LN and bone, specific number of patients NR PR: LN and bone, specific number of patients NR	≤3	OR: 43.9 OP: 37 (= time from start of ADT to the onset of clinical metastases)	OR: 2.4 OP: 4	OR: SBRT ($n=93$; 93%) WPRT ($n=7$; 7%)] OP: SBRT	OR: 24 (24) OP: DNA	OR: 11 OP: NA	No	OR: 20.4 OP: 24	OR: 17.7. 3-year PFS: 26.6% OP: 11, 3-year PFS: 11.9%

[a]If available, 3-year PFS was estimated using Kaplan–Meier curve.
[b]The 72 patients discussed in this study, the same patients with lymph node recurrence research.
[c]cRFS, clinical relapse-free survival.
[d]Seven of these patients recieved ADT in combination with another systemic therapy (Estramustine, docetaxel, ketoconazol).
[e]11 patients of the 18 that where staged with PET–CT, recieved an MRI because of ambiguous findings.
[f]PFS once ADT had been started.
Choline PET/CT, Choline positron emitting tomography with co-registered computed tomography; NA, not applicable; ENRT, elective nodal radiotherapy; FDG, fluorodeoxyglucose; HRT, hypofractionated radiotherapy; IMRT, intensity-modulated radiation therapy; LN, lymph nodes; MRI, magnetic resonance imaging; NR, not reported; NRT, normofractionated radiotherapy; OP, oligoprogressive prostate cancer, metastatic progression defined as a rise of PSA using ADT, in which the prostate cancer cells have become castration resistant; OR, oligorecurrent prostate cancer, the manifestation of metastatic lesions after biochemical recurrence, in ADT naïve patients, thus endocrine responsiveness; PSMA ligand PET/CT, 68Ga-prostate-specific membrane antigen ligand positron emitting tomography with coregistered computed tomography; Rec., recurrence; WPRT, whole pelvis radiotherapy.
Adapted with permission from [16] and [26].

Table 2. Overview of observed toxicity in studies reporting on metastasis-directed therapy of oligometastatic prostate cancer

Study	Number of patients	Toxicity scale	Grade 1		Grade 2		Grade 3	
			Acute ($n=847$)[a]	Late ($n=847$)[a]	Acute ($n=922$)[a]	Late ($n=922$)[a]	Acute ($n=969$)[a]	Late ($n=969$)[a]
Detti *et al.* [16]	30	CTCAE 4.0	0	1 (3%)	1 (3%)	0	0	0
Ponti *et al.* [17]	16	RTOG	0	0	1 (6%)	0	0	1 (6%)
Ost *et al.* [18▪][b]	72	CTCAE 4.0	10 (14%)	12 (17%)	3 (4%)	3 (4%)	0	0
Ingrosso *et al.* [19]	40	RTOG/EORTC	0	0	1 (3%)	0	0	1 (3%)
Jereczek-Fossa *et al.* [20]	94	NR	7 (7%)	2 (2%)	1 (1%)	3 (3%)	0	0
Casamassima *et al.* [21]	25	RTOG	NR	NR	0	0	0	0
Rischke *et al.* [22]	47	CTCAE 4.0	NR	NR	NR	NR	0	0
Fodor *et al.* [23]	81	CTCAE 3.0	57 (70%)	4 (5%)	10 (12%)	0	2 (2%)	1 (1%)
Muacevic *et al.* [24]	40	NR	NR	NR	NR	NR	NR	NR
Wu *et al.* [25]	30	CTCAE 3.0	2 (7%)	0	1 (3%)	0	0	0
Würschmidt *et al.* [26]	16	NR	NR	NR	NR	NR	NR	NR
Ahmed *et al.* [27]	17	CTCAE 3.0	2 (12%)	0	2 (12%)	0	0	0
Jereczek-Fossa *et al.* [28]	19	RTOG	0	3 (16%)	0	1 (5%)	1 (5%)	1 (5%)
Schick *et al.* [29]	50	CTCAE 3.0	NR	NR	0	0	0	0
Decaestecker *et al.* [4]	50	CTCAE 3.0	7 (14%)	0	3 (6%)	1 (2%)	0	0
Ost *et al.* [30]	119	CTCAE 4.0	0	17 (14%)	0	3 (3%)	0	0
Pasqualetti *et al.* [31]	29	CTCAE 4.0	0	0	0	0	0	0
Muldermans *et al.* [32]	66	CTCAE 4.0	6 (9%)	0	2 (3%)	0	0	0
Bouman- Wammes *et al.* [33]	43	NR	2 (5%)	0	2 (5%)	0	0	0
Triggiani *et al.* [15▪]	OR: 100	CTCAE 4.0	OR: 5 (5%)	OR: 0	OR: 2 (2%)	OR: 2 (2%)	OR: 0	OR: 0
	OP: 41		OP: 0	OP: 1 (2%)	OP: 0	OP: 0	OP: 0	OP: 0
Total	1.025		98 (12%)[c]	40 (5%)[c]	29 (3%)[c]	13 (1%)[c]	3 (0.3%)[c]	4 (0.4%)[c]

The numbers in this table correspond to the observed toxicity; it is possible that the same patient experienced more than one complication.
[a]Number of patients of which toxicity was reported. Articles not reporting toxicity where not taken into account.
[b]The 72 patients discussed in this study [18▪], are the same patients with lymph node recurrence treated in the study by Ost *et al.* [30].
[c]Percentages calculated from the total number of patients of which toxicity was reported (see[a]).
CTCAE, common terminology criteria for adverse events; EORTC, European organization for research and treatment of cancer; NR, not reported; OP, oligoprogression; OR, oligorecurrence; RTOG, radiation therapy oncology group.
Adapted with permission from [16] and [26].

primary PCa radiotherapy treatment with men who have a high risk for pelvic lymph node involvement [13].

In the study by Fodor *et al.* [23] and Schick *et al.* [29], the 3-year PFS is approximately 60%, which compares favorably to the data by Ost *et al.* [18▪], Jereczek-Fossa *et al.* [20], and Triggiani *et al.* [15▪], reporting a 3-year PFS of around 30% [15▪,18▪,20]. In the study by Rischke *et al.* [22], a sLND was performed in case of nodal recurrences with or without the addition of ENRT. The relapse pattern following sLND alone was remarkably comparable to the SBRT data by Ost *et al.*, with the majority of patients relapsing in adjacent nodal regions. The addition of ENRT, improved the relapse-free survival from 26.3 for sLND alone to 70.7% for the combination ($P < 0.0001$).

However, increasing the radiotherapy treatment volume, also potentially increases acute toxicity [19,23,42]. Fortunately, late grade 2 or 3 adverse events were not observed in the studies by Fodor *et al.* [23] and Schick *et al.* [29]. This might be an underreporting of adverse events, as postoperative WPRT does increase late gastrointestinal toxicity as compared with prostate bed only radiotherapy, with approximately 30% late grade 2 complaints [43].

Bone metastases

Studies focusing solely on bone oligometastases are rare [24,25]. Muacevic *et al.* [24] treated 40 patients with SBRT and Wu *et al.* [25] treated 18 patients with short-course radiation therapy and 12 with long-course radiation therapy. The use of adjuvant ADT in these 2 studies was high (81%) and five patients even received adjuvant chemotherapy [24,25].

Visceral metastases

Visceral metastases in hormone-sensitive PCa are rare and account for less than 5% of sites of recurrence [37–39]. Consequently, literature on MDT in PCa focusing on visceral metastases only is nonexistent [44]. In this review five articles are included that treated visceral metastases in nine patients (0.8%) [4,27,29,30,32]. Four patients were treated for liver metastasis (44%), two patients had lung metastasis (22%), and one patient suffered from one bone and one lung metastasis (11%). Of two patients the specific organ is not specified (22%) [30]. Because of the limited patient data involving visceral metastases in PCa, it is impossible to draw conclusions if MDT is useful in this context.

Mixed literature

The majority of studies include patients treated with MDT for a mixture of node, bone, and visceral metastases. In the study of Ost *et al.* [30] and Triggiani *et al.* [15▪], a subgroup analysis did not show a difference in time to progression for node versus bone metastases [30]. It might be that these studies are underpowered to detect a difference in PFS or that follow-up is too short to detect a difference.

Oligoprogressive castration-resistant prostate cancer

Patients progressing on palliative ADT or 2nd-line systemic therapy often have widespread metastatic disease, however, 34% of patients have less than three metastases [45]. Instead of initiating additional lines of systemic treatment, some authors have argued that MDT can postpone the need for these drugs and their associated toxicity [15▪]. The biological rationale is that the progressing visible lesions contain clonogens resistant to the current systemic therapy and thus having the potential to form new resistant macroscopic metastases as seen in lethal PCa [46,47]. We found two articles that included 52 patients with hormone resistant, progressive PCa [15▪,27]. Triggiani *et al.* [15▪] treated 49 lymph node and 21 bone metastases in 41 patients. After a median follow-up of 24 months, 1 and 2-year distant PFS were 43.2–21.6%, respectively. The median time to the start of 2nd-line systemic treatment was 22 months.

Adjuvant androgen deprivation therapy

In this large cohort of 1025 patients, 522 of them (51%) were treated with adjuvant ADT and 23 patients (2%) received adjuvant chemotherapy. Adjuvant ADT was mostly given at the discretion of the treating physician and duration ranges between a single depot injection of 1 month of an Luteinizing-hormone-releasing hormone agonist to lifelong ADT. The addition of ADT influences the time to progression, making it more challenging to compare studies. Standardization of the indication and duration of ADT in oligometastatic PCa is indicated for future studies.

Toxicity

Table 2 gives an overview of the observed toxicity. Overall, in 87% of patients treated with MDT no acute toxicity was observed. In 94% of cases no late toxicity was observed. Acute and late grade 2 toxicity was observed in 3 and 1% of patients, respectively. Grade 3, acute or late, toxicity was rare and only seen in 0.3 and 0.4% of patients, respectively. Given the heterogeneity and limitations of these retrospective studies, the incidence of MDT toxicity

is most certainly underreported, but given the highly favorable reported results, radiation MDT is most likely safe and generally well tolerated.

Future trials

In the coming years, choline PET–CT will probably be replaced by other next generation imaging methods. These imaging advances will further improve the sensitivity of metastatic lesion detection and as such improve oligometastatic patient selection for MDT. The Advanced Prostate Cancer Consensus Conference panel agreed, with 78% of the panelists voting for one of the next generation imaging methods to restage biochemically recurrent PCa (PET–CT and/or whole body - MRI), with 76% preferring prostate-specific membrane antigen over fluciclovine (10%) or choline (6%) [7▪].

For oligorecurrent PCa, the SOC is ill-defined and both initial observation with delayed ADT or immediate ADT are established treatment options. Consequently, the option of MDT followed by initial observation could be compared with observation with delayed ADT or immediate ADT. This will be addressed by two different prospective phase II trials [48,49]. Oligopelvis is a randomized phase II trial comparing SOC (intermittent ADT) with WPRT with a short course of ADT for nodal oligorecurrent PCa. The UK-LED CORE Conventional Care Versus Radioablation (Stereotactic Body Radiotherapy) for Extracranial Oligometastases phase II/III trial will randomize patients with oligometastatic prostate, breast, or nonsmall cell lung cancer to standard therapy with or without SBRT to all lesions. The Movember Foundation is set to launch their Global Action Plan 6 initiative on oligometastatic PCa with one major goal set to tackle understanding the biological differences between hormone-sensitive oligometastatic and polymetastatic PCa at the genetic and transcriptomic level (https://gap6.fluidreview.com/).

CONCLUSION

Only retrospective data support the use of MDT, and few of these studies provide an appropriate control group for comparison. Existing data suggests that MDT carries a low risk of adverse events and provides excellent local control, but long-term data are not reported. As such, MDT should still be considered investigational. Efforts should be made to support inclusion in prospective trials [50].

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

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