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European Association of Urology

Platinum Priority – Review – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Metastasis-directed Therapy of Regional and Distant Recurrences After Curative Treatment of Prostate Cancer: A Systematic Review of the Literature

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Article info

Article history:
Accepted September 2, 2014

Keywords:
Prostatic neoplasms
Neoplasm metastasis
Neoplasm recurrence
Radiosurgery
Lymph node excision

Abstract

Context: The introduction of novel imaging modalities has increased the detection of oligometastatic prostate cancer (PCa) recurrence, potentially justifying the use of a metastasis-directed therapy (MDT) with surgery or radiotherapy (RT) rather than a systemic approach.
Objective: To perform a systematic review of MDT for oligometastatic PCa recurrence.
Evidence acquisition: This systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. We searched the Medline and Embase databases from 1946 to February 2014 for studies reporting on biochemical or clinical progression and/or toxicity or complications of MDT (RT or surgery). Reports were excluded if these end points could not be ascertained or separately analysed, or if insufficient details were provided. Methodological quality was assessed using an 18-item validated quality appraisal tool for case series.
Evidence synthesis: Fifteen single-arm case series reporting on a total of 450 patients met the inclusion criteria. Seven studies were considered of acceptable quality. Oligometastatic PCa recurrence was diagnosed with positron emission tomography with coregistered computed tomography in most of the patients (98%). Nodal, bone, and visceral metastases were treated in 78%, 21%, and 1%, respectively. Patients were treated with either RT (66%) or lymph node dissection (LND) (34%). Adjuvant androgen deprivation was given in 61% of patients (n = 275). In the case of nodal metastases, prophylactic nodal irradiation was administered in 49% of patients (n = 172). Overall, 51% of patients were progression free 1–3 yr after salvage MDT, with most of them receiving adjuvant treatment. For RT, grade 2 toxicity was observed in 8.5% of patients, with one case of grade 3 toxicity. In the case of LND, 11% and 12% of grade 2 and grade 3 complications, respectively, were reported.
Conclusions: MDT is a promising approach for oligometastatic PCa recurrence, but the low level of evidence generated by small case series does not allow extrapolation to a standard of care.
Patient summary: We performed a systematic review to assess complications and outcomes of treating oligometastatic prostate cancer recurrence with surgery or radiotherapy. We concluded that although this approach is promising, it requires validation in randomised controlled trials.

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http://dx.doi.org/10.1016/j.eururo.2014.09.004
0302-2838/

1. Introduction

Despite continuous efforts in patient selection and advances in treatment, disease recurrence after curative treatment for prostate cancer (PCa) remains substantial in high-risk patients [1–3]. The standard treatment options and guidelines for PCa patients diagnosed with metastatic progression following primary treatment have remained unchanged over the past decade [4], with androgen-deprivation therapy (ADT) as the cornerstone of treatment [5]. Although the optimal timing and schedule of ADT is still under debate in this setting [5], the detrimental effect of ADT on general health and quality of life has resulted in a search for alternatives [6,7].

As in other solid tumours [8–12], increasing evidence indicates that patients diagnosed with a limited number of PCa metastases, so-called oligometastases, have a better prognosis compared with patients with extensive metastatic disease [13,14]. Schweizer et al. demonstrated that the survival of patients with three or fewer metastases was superior compared with patients with more than three lesions (hazard ratio [HR]: 0.5; 95% confidence interval [CI], 0.29–0.85), even though all patients received ADT [13]. In a comparable study by Ost et al., patients with a single metastasis had a 5-yr cancer-specific survival of 90% (95% CI, 71–100) compared with only 32% (95% CI, 12–52) in patients with more than one metastasis [14]. These studies demonstrate that oligometastatic PCa inherently has a favourable disease course with a median survival >6 yr [13,14]. This should be taken into account when interpreting the results of alternative treatments.

The oligometastatic state is considered an intermediate state of tumour spread with limited metastatic capacity [15]. The clinical implication of this hypothesis is that localised forms of cancer treatment, that is, metastasis-directed therapy (MDT) such as surgery or stereotactic body radiotherapy (SBRT) [8–12], may be effective in these patients [15]. These lesion-directed approaches may also have the potential to spare or to delay the toxicity associated with the use of systemic therapies. For oligometastases from various primary tumours such as colorectal cancer, sarcomas, and renal cell carcinoma, MDT is commonly offered [8–12,16–18]. Metastasectomy of lung and liver metastases results in 5-yr survival rates of 30–50% [9,16,18]. Although no randomised trials are available comparing MDT with no treatment or other therapeutic options, these treatment options are routinely offered to patients based on the promising data of large registries and case series [16–18].

The interest in MDT in PCa has certainly increased with the introduction of more accurate imaging modalities [19,20] that have led to a higher detection of oligometastatic PCa recurrence at lower prostate-specific antigen (PSA) levels [14,19]. The current systematic review synthesises the evidence to support MDT in oligometastatic PCa recurrence after curative treatment.

2. Evidence acquisition

2.1. Search strategy

The systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [21]. The Medline and Embase databases were searched for relevant articles from 1946 to February 2014 that met the study inclusion and exclusion criteria.

2.2. Inclusion and exclusion criteria

We identified articles reporting on oncologic outcome (biochemical response or progression-free survival [PFS]) and/or toxicity of PCa patients with metachronous metastases with a "controlled" primary (defined as previous curative treatment to the primary PCa) who received MDT via surgical metastasectomy or nonpalliative radiotherapy (RT). The latter was defined as a minimal 2-Gy equivalent dose of 60 Gy to the metastases with conventional fractionation. In the case of SBRT, a dose of ≥6 Gy per fraction for a total dose of >36 Gy or 5 Gy per fraction for a total dose of >45 Gy was required [12].

Potential articles were identified using the National Library of Medicine's Medical Subject Headings: "(prostatic neoplasms[mh] OR <prostat* adj5 (cancer* or carc*)[tw]>) AND (neoplasm recurrence, local[mh] OR neoplasm metastasis[mh] OR oligo-recurrence[tw] OR oligometast*[tw]) AND (salvage therapy[mh] OR reoperation[mh] OR metastasectomy[mh] lymph node excision[mh] OR lymphadenectomy[tw] OR radiosurgery[mh] OR SBRT[tw] OR SABR[tw] OR stereotactic[tw]).

Additional studies were identified by searching bibliographies of candidate articles. Relevant articles were also identified using the related citations function of PubMed.

Articles were excluded if the oncologic outcome and/or toxicity of patients could not be ascertained or separately analysed, or if insufficient detail was provided. To minimise publication and reporting bias, case series that comprised fewer than five cases were excluded. If multiple publications of the same centre were available, the most recent publication was selected (Fig. 1).

Abstracts were reviewed for relevance to the defined review question. Studies published only as abstracts and reports from meetings, review articles, and editorials were excluded from the analysis. If it was not clear from the abstract whether the article might contain relevant data, the full text was assessed. Other significant studies cited in the reference lists of the selected articles were evaluated, as were studies published after the systematic search. Two authors (P.O. and K.D.) independently selected studies for inclusion. If a title or abstract appeared to meet the eligibility criteria for inclusion or the eligibility could not be determined, the full-text version of the article was obtained and evaluated in consensus for eligibility. Discrepancies between the two authors were resolved via discussion with the other coauthors.

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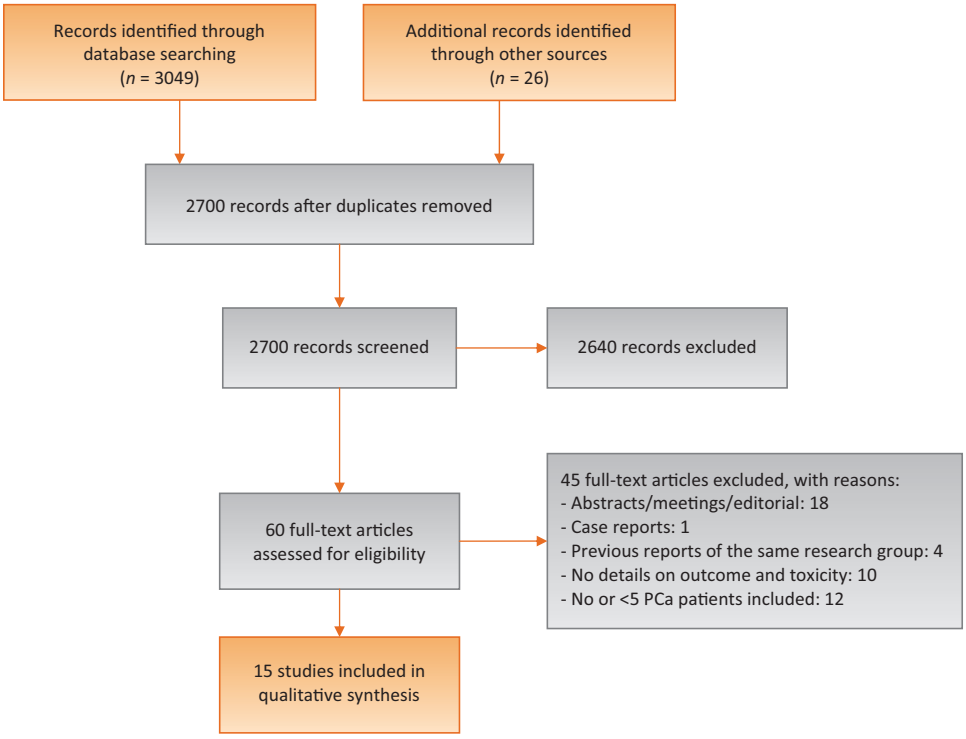

Fig. 1 – Flowchart of the systematic review.
PCa = prostate cancer.

2.3. *Data extraction*

The following information was abstracted from all primary reports: primary author, reference, year of publication, number of patients, patient population, age, study design, treatment of metastases, treatment of primary PCa, type of surgery, dose and fractionation of RT, T and N stage of the primary PCa, median follow-up, oncologic outcomes (PFS, cancer-specific survival, overall survival), local control (for RT articles), prognostic factors (univariate and multivariate), and toxicity.

Methodological quality was assessed using an 18-item validated quality appraisal tool for case series [22]. Quality appraisal judgments for each item were binary determinations of various facets of the study including study objectives, population, interventions and co-interventions, outcome measures, statistical analysis, results and conclusions, and competing interests. The number of yes responses was counted for a study and divided by 18. A study with $\geq$14 yes responses was considered of acceptable quality [22].

3. Evidence synthesis

The study selection process is outlined in the PRISMA diagram (Fig. 1). Fifteen case-series studies (12 retrospective, 3 prospective) met the inclusion criteria [23–37] (Table 1). All studies were single-arm case series. No comparative or randomised controlled trials were identified. Eight studies included patients treated with high-dose RT; seven studies included patients treated with surgery. All studies were published between 2008 and the present. Seven studies were considered of acceptable quality (Table 2).

3.1. *Patient and tumour characteristics*

In total, 450 patients received MDT for oligometastatic recurrence after primary treatment for PCa. Most of the studies reported median age at time of oligometastatic treatment (overall median: 65 yr; median range: 63–68 yr). The overall median PSA level was 2.4 ng/ml (range: 1.5 ng/ml–8.8 ng/ml) at the time of MDT.

3.2. *Diagnostic assessments and site of metastases*

Oligometastatic disease was diagnosed with positron emission tomography with coregistered computed tomography (PET/CT) in 98% of patients, using either choline (91%) or fluorodeoxyglucose (7%) as a tracer (Table 1). A total of 353 patients (78%) were treated for nodal metastases, 93 patients (21%) for bone metastases, and 4 patients (1%) for visceral metastases (lung: 2; liver: 2).

3.3. *Type of treatment*

The type of treatment was either high-dose RT (n = 299 [66%]) or surgery (n = 151 [34%]).

3.3.1. *Radiotherapy*

The RT series included nodal (n = 202), bone metastases (n = 93), and visceral metastases (n = 4). The irradiated volume for nodal metastases included a prophylactic pelvic region in most patients (n = 128); the others received RT

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Table 1 – Full-text publications of metastasis-directed therapy for oligometastatic prostate cancer recurrence included in the systematic review

Study	No. of patients	Site of metastasis: node/bone/visceral	Median time to metastatic recurrence, mo	Median PSA at time of metastasis	Staging method	Type of MDT	Median follow-up, mo	Median PFS	Adjuvant ADT (%)	Median duration ADT	Prophylactic nodal radiotherapy (%)
Casamassima et al. [23]	25	25/0/0	11.8–36.7	5.65	Choline PET/CT	SBRT	29	24 mo	None	NA	7 (28)
Muacevic et al. [24]	40	0/40/0	NR	5.4	Choline PET/CT	SBRT	14*	NR	27 (68)	NR	NA
Würschmidt et al. [25]	15	15/0/0	NR	1.79	Choline PET/CT	NRT	28	Median not reached: 3-yr PFS: 75%	NR	NR	15 (100)
Ahmed et al. [26]	17	1/15/1	50.4	2.1	Choline PET/CT (n = 9), MRI (n = 6), CT (n = 1), and biopsy (n = 1)	SBRT	6	12 mo	15 (88)	NR	NA
Jereczek-Fossa et al. [27]	19	18/1/0	66	1.77 (pelvic nodes); 10.7 (M1)	Choline PET/CT	SBRT	17	Median not reached; 30-mo PFS: 63.5%	19 (100)	12–17 mo	None
Schick et al. [28]	50	33/15/2	15.6	6.7	Choline PET/CT and bone scintigraphy	SBRT (n = 14) NRT (n = 36)	31	Median not reached; 3-yr PFS: 58.6%	49 (98)	12 mo	25 (50)
Decaestecker et al. [29]	50	27/22/1	57.6	3.8	Choline (n = 18) or FDG (n = 32) PET/CT	SBRT	25	19 mo	35 (70)	1 mo	None
Picchio et al. [30]	83	83/0/0	NR	2.6	Choline PET/CT	HRT	22	NR	58 (70)	NR	77 (93)
Rinnab et al. [31]	15	15/0/0	NR	1.98	Choline PET/CT	LND	13.7*	NR	11 (73)	NR	1 (7)
Schilling et al. [32]	10	10/0/0	NR	8.75	Choline PET/CT	LND	11*	NR	6 (60)	NR	None
Winter et al. [33]	6	6/0/0	NR	2.04	Choline PET/CT	LND	24 mo	NR	None	NA	None
Busch et al. [37]	6	6/0/0	Mean: 79.9	37.6*	Choline (n = 3), MRI (n = 1), CT (n = 2)	LND	NR	15.5 mo	6 (100)	Lifelong ADT	None
Jilg et al. [34]	47	47/0/0	62	11.1*	Choline PET/CT	LND	35.5	27 mo**	34 (65)	NR	27 (52)
Martini et al. [35]	8	8/0/0	NR	1.62	Choline PET/CT	LND	NR	NR	None	NA	None
Suardi et al. [36]	59	59/0/0	NR	2.0	Choline PET/CT	LND	76.6	60 mo**	24 (41)	24 mo	21 (36)

ADT = androgen-deprivation therapy; CT = computed tomography; FDG = fluorodeoxyglucose; HRT = hypofractionated radiotherapy; LND = lymph node dissection; MDT = metastasis-directed therapy; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; NRT = normofractionated radiotherapy; PET/CT = positron emission tomography with coregistered computed tomography; PFS = progression-free survival; PSA = prostate-specific antigen; SBRT = stereotactic body radiotherapy.

* Mean numbers reported instead of median.

** Median estimated from curves.

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Table 2 – Quality assessment (a) for radiotherapy studies and (b) for surgical studies

a.

	Casamassima et al. [23]	Muacevic et al. [24]	Würschmidt et al. [25]	Ahmed et al. [26]	Jereczek-Fossa et al. [27]	Schick et al. [28]	Decaestecker et al. [29]	Picchio et al. [30]
Study Objective								
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	1	1	1	1	1	1	1	1
Study Population								
2. Are the characteristics of the participants included in the study described?	1	0	1	1	1	1	1	1
3. Were the cases collected in more than one centre?	0	0	0	0	1	1	0	0
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	1	1	0	1	1	0	1	1
5. Were participants recruited consecutively?	0	0	0	0	0	0	0	0
6. Did participants enter the study at a similar point in the disease?	1	0	0	0	0	0	1	1
Intervention and co-intervention								
7. Was the intervention clearly described in the study?	1	1	1	1	1	1	1	1
8. Were additional interventions (co-interventions) clearly reported in the study?	1	0	0	0	1	1	1	1
Outcome measures								
9. Are the outcome measures clearly defined in the introduction or methods section?	0	1	0	1	1	1	1	1
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	1	1	0	1	1	1	1	1
11. Were outcomes measured before and after intervention?	1	1	1	0	1	1	1	1
Statistical analysis								
12. Were the statistical tests used to assess the relevant outcomes appropriate?	0	1	1	1	1	1	1	1
Results and conclusions								
13. Was the length of follow-up reported?	1	1	1	1	1	1	1	1
14. Was the loss to follow-up reported?	0	1	0	0	0	0	0	0
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	0	1	0	0	1	1	1	1
16. Are adverse events reported?	1	1	1	1	1	1	1	1
17. Are the conclusions of the study supported by results?	1	1	0	1	1	1	1	1
Competing interests and sources of support								
18. Are both competing interests and sources of support for the study reported?	0	0	1	0	1	1	1	1
Total score	11	12	8	10	15	14	15	15

b.

	Rinnab et al. [31]	Schilling et al. [32]	Winter et al. [33]	Busch et al. [37]	Jilg et al. [34]	Martini et al. [35]	Suardi et al. [36]
Study Objective							
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	1	1	1	1	1	1	1
Study Population							
2. Are the characteristics of the participants included in the study described?	1	0	1	1	1	1	1
3. Were the cases collected in more than one centre?	1	0	0	0	0	0	0
4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate?	1	0	1	0	1	0	1
5. Were participants recruited consecutively?	1	0	0	0	0	1	0
6. Did participants enter the study at a similar point in the disease?	1	1	1	1	1	1	1

Table 2 (*Continued*)

b.

	Rinnab et al. [31]	Schilling et al. [32]	Winter et al. [33]	Busch et al. [37]	Jilg et al. [34]	Martini et al. [35]	Suardi et al. [36]
Intervention and co-intervention							
7. Was the intervention clearly described in the study?	1	1	1	1	1	1	1
8. Were additional interventions (co-interventions) clearly reported in the study?	0	0	1	1	1	1	1
Outcome measures							
9. Are the outcome measures clearly defined in the introduction or methods section?	1	1	0	1	1	0	1
10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	1	1	1	1	1	1	1
11. Were outcomes measured before and after intervention?	1	1	1	1	1	1	1
Statistical analysis							
12. Were the statistical tests used to assess the relevant outcomes appropriate?	1	0	1	1	1	0	1
Results and conclusions							
13. Was the length of follow-up reported?	1	1	1	0	1	0	1
14. Was the loss to follow-up reported?	0	0	0	0	0	0	0
15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	1	1	0	1	1	0	1
16. Are adverse events reported?	1	1	0	1	1	0	1
17. Are the conclusions of the study supported by results?	1	1	1	1	1	1	1
Competing interests and sources of support							
18. Are both competing interests and sources of support for the study reported?	1	1	0	0	0	0	1
Total score	16	11	11	12	14	9	15

selectively delivered only to the suspicious lymph node(s) at PET ($n = 74$). For patients with bone or visceral metastases, the dose was delivered to the suspicious region on imaging without prophylactic volumes. The fractionation patterns were heterogeneous in between studies and in the studies themselves. A conventionally fractionated (1.8–2.0 Gy per fraction) [25,28], hypofractionated (larger than standard fractions; eg, >2.5 to 4.0–5.0 Gy) [30], or SBRT (ultrahigh dose, typically >4.0–5.0 Gy per fraction) approach was used in 17%, 28%, and 55%, respectively. In case of SBRT, a single-fraction, 3-fraction, 5–6 fraction, and 10-fraction SBRT schedule was used in 32%, 38%, 9%, and 21% of the cases, respectively. The total dose varied between 18 and 24 Gy in the case of a single fraction (median: 20 Gy), between 24 and 36 Gy in the case of 3 fractions (median: 30 Gy), between 28 and 36 Gy in the case of 5–6 fractions [28], and was 50 Gy in the case of 10 fractions [29].

In the setting of nodal metastases treated with RT as MDT, 123 patients were treated with prophylactic nodal irradiation (Table 1). The median dose to the elective nodal volume ranged between 45 Gy and 52 Gy, and the enlarged nodes were boosted to a median of 52–67 Gy. Adjuvant ADT was prescribed in 203 patients (71%). The median duration of ADT was only reported in three of six studies and ranged between 1 and 17 mo (Table 1).

3.3.2. *Surgery*

All surgically treated patients underwent a salvage lymph node dissection (LND), for pelvic ($n = 78$), retroperitoneal ($n = 13$), or pelvic and retroperitoneal ($n = 65$) metastatic lymph nodes. Most patients (97%) had already undergone an LND at the time of their initial PCa treatment (data retrieved from six of seven studies). The median number of lymph nodes removed at initial LND is reported by Jilg et al. (median: 9) [34] and Suardi et al. [36] (median: 11).

Salvage LND was performed using an open approach in all studies but one, where a laparoscopic procedure was used [32]. A median number of 2 positive nodes were removed (median range: 1–4) at the time of salvage LND for a median number of 11.5 lymph nodes removed (median range: 2.5–26) as reported by five studies. The anatomic location of positive lymph nodes is described in detail in the two largest studies [34,36]. In total, 522 positive nodes were removed during salvage LND in these two studies at the following locations: obturator or internal iliac nodes in 19% ($n = 99$), external iliac nodes in 15% ($n = 77$), common iliac 21% ($n = 108$), preaortic in 9% ($n = 45$), para-aortic in 25% ($n = 129$), interaortocaval in 9% ($n = 48$), and at the aortic bifurcation in 3% ($n = 16$) [34,36]. Postoperative prophylactic nodal irradiation was administered in 49 patients (Table 1). Adjuvant ADT was prescribed in 81 patients (54%) (Table 1). The median duration of ADT was not reported in these studies, except for the study by Suardi et al., in which ADT was prescribed for a minimum of 2 yr in patients not experiencing a complete biochemical response following pelvic LND [36].

3.4. *Oncologic outcomes*

Table 3 reports the various definitions for biochemical recurrence or response and progression as well as the restaging modalities used at progression. Although treatment

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Table 3 – End points and definitions used in studies of metastasis-directed therapy for oligometastatic prostate cancer recurrence included in the systematic review

Study	Biochemical recurrence	Local progression	Progression-free survival	Restaging modality	Toxicity scale
Casamassima et al. [23]	Descriptive report of PSA evolution	Reported but not specified	The occurrence of new metastatic lesions	Choline PET/CT	EORTC/RTOG
Muacevic et al. [24]	NR	Documented tumour growth in MRI scans compared with pretreatment imaging and increased tracer uptake in choline PET/CT	Defined as the development of new metastases	Choline PET/CT and MRI	Descriptive report of toxicity
Würschmidt et al. [25]	Biochemical relapse-free survival reported but not defined	Reported but not defined	Reported but not defined	NR	CTCAE
Ahmed et al. [26]	Descriptive report of PSA evolution	Defined as tumour progression within the PTV	Defined as the absence of new metastases and/or progression of treated metastases	Not specified	CTCAE
Jereczek-Fossa et al. [27]	Defined as two increases in PSA level relative to the pre-CyberKnife SRT PSA value	Defined as progression within the CyberKnife SRT volume according to RECIST criteria	Defined as development of disease that could be in field (within the CyberKnife SRT volume) or out of field	Choline PET/CT	RTOG
Schick et al. [28]	Defined as a raising PSA value >1 ng/ml, except for the patients presenting with synchronic metastases where the Phoenix definition was used	NR	Defined as the development of new metastases	Not specified	CTCAE
Decaestecker et al. [29]	NR	Defined as tumour progression within the irradiated PTV. Each metastasis was a target lesion independently assessed for response with the RECIST criteria	Defined as the absence of new metastases and/or progression of treated metastases	FDG or choline PET/CT	CTCAE
Picchio et al. [30]	The biochemical response was classified as (1) complete response (reduction >50% of the initial PSA value); (2) partial response (reduction of between 10% and 50% of the initial PSA value; (3) stable disease (oscillation within 10% of initial values); (4) progression of disease (increase in serum PSA value >10%)	NR	Descriptive report of progression	Choline PET/CT	RTOG
Rinnab et al. [31]	Descriptive report of PSA evolution	NR	NR	NR	Descriptive report of toxicity
Schilling et al. [32]	Descriptive report of PSA evolution	NR	NR	NR	Descriptive report of perioperative toxicity
Winter et al. [33]	Descriptive report of PSA evolution	NR	NR	NR	NR
Busch et al. [37]	Descriptive report of PSA evolution	NR	Development of bone metastases	NR	Clavien-Dindo
Jilg et al. [34]	Complete biochemical response after salvage LND was defined as PSA <0.2 ng/ml, whereas incomplete response was defined as PSA >0.2 ng/ml. Biochemical recurrence after complete response was defined as increase in PSA >0.2 ng/ml on two consecutive measurements and biochemical progression after incomplete response, and lack of PSA response was defined as two consecutive PSA increases	NR	Defined as new lymph node metastases and/or bone metastases detected by imaging tests	Bone scintigraphy, CT, MRI, or choline PET/CT	Clavien-Dindo
Martini et al. 2012 [35]	Descriptive report of PSA evolution	NR	NR	NR	NR
Suardi et al. [36]	Biochemical response was defined as PSA <0.2 ng/ml at 40 d after surgery	NR	Defined as a positive choline PET/CT in the presence of a rising PSA	Choline PET/CT	Clavien-Dindo

CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organisation for Research and Treatment of Cancer; FDG = fluorodeoxyglucose; LND = lymph node dissection; MRI = magnetic resonance imaging; NR = not reported; NRT = normofractioned radiotherapy; PET/CT = positron emission tomography with coregistered computed tomography; PFS = progression-free survival; PSA = prostate-specific antigen; PTV = planning target volume; RECIST = Response Evaluation Criteria in Solid Tumours; RTOG = Radiation Therapy Oncology Group toxicity grading system; SBRT = stereotactic body radiotherapy; SRT = stereotactic radiotherapy.

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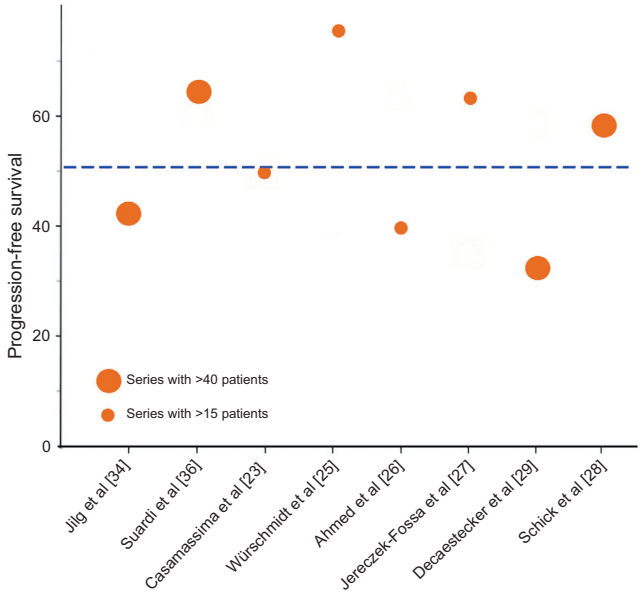

Fig. 2 – Progression-free survival in patients with oligometastatic prostate cancer recurrence at 1–3 yr of follow-up for studies with >15 patients. Dotted line represents mean proportion of patients who were progression free at the reported time point, weighted for the total number of patients.

schedules varied and no comparative studies were available, the findings indicate that approximately half of the patients were progression free 1–3 yr after MDT (Fig. 2). However, these results should be interpreted with caution in view of the nonstandardised use of adjuvant treatments after MDT. In summary, adjuvant prophylactic nodal RT was given in 49% of patients ($n = 172$) with nodal metastases, and adjuvant ADT was given in 61% of patients ($n = 275$). The benefit of MDT only without adjuvant ADT can be deducted from the articles of Casamassima et al. and Decaestecker et al. [23,29], showing a median PFS of 24 and 19 mo, respectively. In the paper of Jilg et al. [34], patients with a biochemical response (after salvage LND PSA <0.2 ng/ml) following salvage LND did not receive adjuvant ADT. This subset of patients had a median PFS of 4 yr.

3.4.1. *Radiotherapy*

Local control was reported in all but one of the RT series, with a total of 4 local relapses of the 114 patients treated (4%). All patients with bone metastases were treated with RT. Two studies observed a trend for a worse outcome for these patients compared with patients with lymph node metastases [28,29].

Although the two largest RT studies reporting PFS rates included comparable patients, the study by Decaestecker et al. [29] reported a 2-yr PFS of 35% compared with a 3-yr PFS of 59% in the study by Schick et al. [28]. Two major differences are the use of adjuvant ADT and prophylactic nodal irradiation. In the study by Decaestecker et al. [29], 70% of patients received a single injection of a 1-mo luteinising hormone-releasing hormone depot compared with 98% of patients receiving adjuvant ADT for a median duration of 1 yr in the study by Schick et al. [28]. Most of the patients (61%) with nodal recurrence in the study by Schick et al. [28] received prophylactic nodal RT, compared with none of the patients in the study by Decaestecker et al. [29]. Interestingly, the pattern of first progression was oligometastatic in 75% in the series of Decaestecker et al. [29] compared with only 10% in the series of Schick et al. [28]. A short PSA doubling time before SBRT predicted worse PFS in the study by Decaestecker et al. [29].

3.4.2. *Surgery*

The results of salvage LND are mainly based on the two largest series by Suardi et al. ($n = 59$) [36] and Jilg et al. ($n = 47$) [34] including 70% of all patients. The study by Suardi et al. [36] is the only series with a follow-up >5 yr, reporting a 5- and 8-yr PFS of 52% and 38%, respectively. Both groups examined several variables predicting PFS. Suardi et al. [36] found that patients with a lower PSA at the time of salvage LND had a better clinical outcome compared with those with higher PSA levels (HR: 1.08; 95% CI, 1.00–1.15; $p = 0.03$). Similarly, Jilg et al. [34] observed a comparable trend ($p = 0.077$). The difference in the median PSA between the two series (2.0 ng/ml in the study by Suardi et al. vs 5.2 ng/ml in that by Jilg et al.) may partially explain the discrepancy in PFS rates between the two studies (3-yr PFS rates of 64.2% vs 42.6%, respectively). Patients with a Gleason score <8 at radical prostatectomy also seemed to be better candidates for salvage LND (HR: 3.5; 95% CI, 1.07–11.7) [34]. This association was not confirmed in the study by Suardi et al. [36]. In addition, nonresponse after salvage LND and the presence of retroperitoneal lymph nodes at the time of surgery were found to be independent risk factors for clinical progression by both groups [34,36]. Interestingly, the first site of clinical recurrence after salvage LND was again nodal in most patients (47–59%) in both studies. However, it is not mentioned whether the recurrence was inside or outside the surgical template.

3.5. *Toxicity and complications*

All but one RT study reported toxicity data using either the Common Terminology Criteria for Adverse Events or Radiation Therapy Oncology Group toxicity grading system [38,39]. Six studies reported late complications ($n = 141$) with only four studies reporting them in detail (Table 4). Grade 2 toxicity, mainly gastrointestinal, was observed in 12 cases (8.5%), with one case of grade 3 toxicity (macroscopic haematuria).

Three of seven surgical series reported toxicity using the Clavien-Dindo classification, and two studies described the observed complications [40]. Table 4 provides a detailed overview. The most common complications were lymphorrhoea (13%), fever (17%), ileus (10%), and a lymphocele requiring drainage (8%). Grade 3a complications were observed in 11% of the patients. Only one case of grade 3b complication (lymphocele requiring surgical drainage) was reported.

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Table 4 – Complications associated with metastasis-directed therapy for oligometastatic prostate cancer recurrence: (a) complications associated with radiotherapy according to Common Terminology Criteria for Adverse Events; (b) complications associated with salvage lymph node dissection according to the Clavien-Dindo classification

a.

Complication type	Muacevic et al. [24] (*n* = 40), no. (%)	Würschmidt et al.* [25] (*n* = 15), no. (%)	Ahmed et al. [26] (*n* = 17), no. (%)	Jereczek-Fossa et al. [27] (*n* = 19), no. (%)	Decaestecker et al. [29] (*n* = 50), no. (%)	Total (*n* = 141), no. (%)
Grade 1						
Bone pain	0 (0)	0 (0)	0 (0)	0 (0)	3 (6)	3 (2)
Asymptomatic fracture	1 (2.5)	0 (0)	0 (0)	0 (0)	1 (2)	2 (1.4)
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (0.7)
Rectal toxicity	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)	2 (1.4)
Urinary toxicity	0 (0)	0 (0)	0 (0)	2 (11)	0 (0)	2 (1.4)
Grade 2						
Nausea requiring antiemetics	5 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	5 (3.5)
Rectal toxicity	0 (0)	2 (13.3)	0 (0)	1 (5)	2 (4)	5 (3.5)
Urinary toxicity	0 (0)	0 (0)	0 (0)	1 (5)	1 (2)	2 (1.4)
Grade 3						
Urinary toxicity	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)	1 (0.7)

b.

Complication type	Rinnab et al. [31] (*n* = 15), no. (%)	Busch et al. [37] (*n* = 6), no. (%)	Jilg et al. [34] (*n* = 47), no. (%)	Suardi et al. [36] (*n* = 59), no. (%)	Total (*n* = 127), no. (%)
Grade 1					
Lymphorrhea	0 (0)	0 (0)	4 (7.7)	12 (20.3)	16 (12.5)
Fever	0 (0)	0 (0)	3 (5.8)	18 (30.5)	21 (16.5)
Temporary weakness of the hip flexor	0 (0)	0 (0)	1 (1.9)	0 (0)	1 (0.8)
Wound dehiscence	0 (0)	0 (0)	3 (5.8)	0 (0)	3 (2.3)
Grade 2					
Deep vein thrombosis	0 (0)	0 (0)	0 (0)	1 (1.7)	1 (0.8)
Ileus	1 (7)	0 (0)	0 (0)	12 (20.3)	13 (10.2)
Grade 3a					
Lymphocele requiring drainage	1 (7)	0 (0)	2 (3.9)	7 (11.2)	10 (7.8)
Wound dehiscence	0 (0)	0 (0)	0 (0)	3 (5.1)	3 (2.3)
Hydronephrosis requiring stenting	1 (7)	0 (0)	0 (0)	0 (0)	1 (0.8)
Grade 3b					
Lymphocele requiring surgical drainage	0 (0)	0 (0)	0 (0)	1 (1.7)	1 (0.8)

* One patient experienced a grade 4 toxicity: bladder shrinkage requiring cystectomy with urinary derivation. This patient received radiotherapy to the prostate gland and metastatic nodes for a recurrence in the seminal vesicle and iliac nodes after previous brachytherapy to the prostate.

3.6. *Ongoing randomised clinical trials including patients with metachronous oligometastatic prostate cancer*

Three prospective registered trials are currently recruiting patients with oligometastatic PCa. The first trial (NCT01558427) is a randomised phase 2 trial comparing MDT (surgery or SBRT) with active surveillance followed by ADT at progression for oligometastatic recurrence (three or fewer metastases). This trial includes only patients who are not castrated at the time of oligometastasis with a controlled primary tumour. The primary end point is the time to the start of palliative ADT. The underlying hypothesis is that patients under active surveillance will progress faster compared with those treated with MDT. No adjuvant ADT will be administered.

The second trial (NCT01777802) is an observational study for patients with oligometastatic PCa (three or fewer metastases) both with untreated and treated primary tumours undergoing SBRT. The primary outcome measure is the induction of anti-PCa immunity. The hypothesis is that SBRT is able to induce a robust antitumoural immune response, as recently suggested [41].

The third trial (NCT01859221) is a single-arm phase 2 trial hypothesising that SBRT for oligometastatic PCa improves median PFS compared with historical controls. This trial includes patients regardless of prior systemic treatments or castration status. If primary PCa is active and has not previously been treated with RT, conventional RT (6–8 wk of daily treatment) is recommended. The metastatic tumour will be treated at the same time. Hormone therapy will be administered to all patients.

3.7. *Discussion and limitations*

In the field of PCa, MDT for oligometastatic recurrence is a fairly novel approach. For MDT to be successful, three main prerequisites should be fulfilled: (1) accurate imaging to detect early metastases, (2) complete eradication of all oligometastatic sites, and (3) acceptable toxicity.

In recurrent PCa, choline PET/CT is the restaging method of choice, used in 91% of patients in this review. A pooled sensitivity and specificity >85% was reported on a per patient basis in this setting [42,43]. Unfortunately, on a per lesion basis, these numbers are probably lower for nodal metastases

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[42–44]. This was recently highlighted by several authors [44–46], showing a low sensitivity at a lesion-based level, demonstrating that choline PET/CT misses micro-metastatic disease. This was confirmed by the relapse pattern reported in the study of Decaestecker et al. Apparently, 67% of the patients treated with SBRT only to the lymph nodes relapsed in the pelvis or retroperitoneal nodes, suggesting under-treatment if SBRT is used as a sole treatment modality. However, even extended salvage LND might be insufficient because it appears that the first site of clinical recurrence is again nodal in 47–59% [34,36]. Consequently, the inclusion of prophylactic nodal irradiation in the management of nodal recurrences seems reasonable in this setting.

Fewer data are available for magnetic resonance imaging (MRI) as a restaging tool for the detection of distant recurrences [47]. It was suggested that whole-body MRI outperforms bone scintigraphy and CT for the detection of bone metastases [48]. However, no comparison has been made between whole-body MRI and PET/CT in the recurrent setting. For nodal recurrence, MRI has to rely on size criteria, and even with the use of diffusion-weighted MRI the results have been contradictory [47].

The treatment results reported in this review are mostly based on retrospective studies. Despite this, both patient characteristics and selection criteria were fairly homogeneous with approximately 50% of patients remaining disease free at 1–3 yr of follow-up (Fig. 2). However, the rather random use of a multimodality approach with adjuvant ADT and prophylactic nodal irradiation in 61% and 49% of patients, respectively, makes it difficult to compare PFS between series. The use of immediate adjuvant or concomitant ADT in this setting might be questioned because the oligometastatic state is hypothesised to be an intermediate state between local disease and widespread metastases. The clinical implication is that localised forms of cancer treatment might be sufficient in these patients and that systemic treatments might be postponed until progression to widespread metastases [49]. The current European Association of Urology guidelines also suggest postponing palliative ADT in well-informed asymptomatic men with metastatic PCa because of the lack of a clear survival benefit [5]. This strategy may partially decrease the negative effects of ADT on general health and quality of life [6,7], and it might also have an economic benefit because ADT seems to be more cost effective when initiated in symptomatic stages [5]. In the study by Decaestecker et al. [29], palliative ADT was postponed for a period of 25 mo (95% CI, 20–30 mo). Suardi et al. [36] reported that 56% and 37% of the patients were free from palliative ADT at 1- and 5-yr follow-up, respectively. The potential to postpone palliative systemic treatment is being investigated in a randomised trial comparing MDT with active surveillance followed by ADT at progression (NCT01558427).

Finally, both salvage LND and RT appear to be safe treatments for oligometastatic PCa recurrence, with grade 2 and 3 toxicity observed in 20% and 13% of the cases, respectively. RT has fewer grade 2 events and only a single case of grade 3 complications (Table 4). However, such a comparison may be biased by its retrospective nature, differences in patient selection, and follow-up schedules. Moreover, no life-threatening complications were reported for LND. Lymphorrhoea (13%), fever (17%), ileus (10%), and a lymphocele requiring drainage (8%) were the most common reported side effects.

Although MDT for PCa recurrences appears promising and might entail an important paradigm shift, its impact should be considered unproven due to the lack of results from prospective randomised controlled trials as well as to differences in the administration of posttreatment multimodal therapies, patient selection, and the lack of use of validated standardised end points. The limited follow-up of most case series is also insufficient to estimate the potential benefit of MDT, and the results might be representative of the population of patients on adjuvant ADT. Only case series without control groups were identified, with only 7 of 15 studies classified as acceptable quality. The rigorous search for systemic recurrence in this patient population with PET/CT might also introduce a lead-time bias. For example, in the study by Schweizer et al. [13] in which conventional CT and bone scintigraphy were used, the PSA level of patients with three or fewer metastases was 25 ng/ml compared with 2 ng/ml in this systematic review, where 98% of patients were evaluated with PET/CT. Future studies should incorporate well-defined end points for PFS and cancer-specific survival, with predefined indications for the use of adjuvant ADT and prophylactic nodal irradiation. Meanwhile, MDT might be offered to selected patients, but the low level of evidence generated by case series does not allow extrapolation to the standard of care. The best candidates for salvage LND are those men with a low PSA, as well as moderately differentiated primary tumour (Gleason score <8) and nodal involvement limited to the pelvis. As for RT, patients with a shorter PSA doubling time progressed earlier compared with patients with slower PSA kinetics. Although patients with bone metastases may potentially gain less benefit from MDT, they still seem to be potential candidates for this type of treatment.

4. Conclusions

MDT is a promising approach for oligometastatic PCa recurrence. However, due to the absence of comparative or randomised trials, the overall low number of patients treated, the limited follow-up, the heterogeneity of patients treated, and the nonstandardised use of sequential treatments, MDT should not be considered the standard of care.

Author contributions: Piet Ost had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ost, Decaestecker, Giannarini, Briganti.
Acquisition of data: Ost, Decaestecker, Giannarini, Briganti.
Analysis and interpretation of data: Ost, Decaestecker, Giannarini, Briganti.
Drafting of the manuscript: Ost, Bossi, Decaestecker, De Meerleer, Giannarini, Karnes, Roach, Briganti.
Critical revision of the manuscript for important intellectual content: Ost, Bossi, Decaestecker, De Meerleer, Giannarini, Karnes, Roach, Briganti.
Statistical analysis: Ost, Decaestecker.

Please cite this article in press as: Ost P, et al. Metastasis-directed Therapy of Regional and Distant Recurrences After Curative Treatment of Prostate Cancer: A Systematic Review of the Literature. Eur Urol (2014), http://dx.doi.org/10.1016/j.eururo.2014.09.004

Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Ost, Giannarini, Briganti.
Other (specify): None.

Financial disclosures: Piet Ost certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Acknowledgement statement: Piet Ost, Gianluca Giannarini, and Alberto Briganti are members of the Prostate Cancer Working Group of the European Association of Urology Young Academic Urologists. Piet Ost is a senior clinical investigator of the Research Foundation – Flanders (Belgium) (FWO).

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