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Review

A Review of Stereotactic Body Radiation Therapy in the Management of Oligometastatic Prostate Cancer

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Abstract. *Background/Aim: Management strategies such as surgery and systemic therapy (androgen-deprivation therapy and chemotherapy) are considered a standard of care for patients with oligometastatic prostate cancer and have shown some positive results in many patients. However, they are often accompanied by side-effects that can negatively affect patients. The aim of this study is to review the potential of stereotactic body radiation therapy (SBRT) in the management of oligometastatic prostate cancer and to compare treatment outcomes with SBRT to those under standard of care management regarding progression-free survival (PFS), androgen-deprivation therapy (ADT)-free survival and local control rate (LCR) as well as a comparison of toxicity profiles. Materials and Methods: MEDLINE (PubMed), EMBASE, and Clinicaltrials.gov databases were searched to identify prospective randomised controlled trials as well as retrospective studies investigating SBRT and standard of care management for oligometastatic prostate cancer. Data on treatment outcomes and toxicity profiles were extracted. Results: A total of 18 studies were included: 14 reported on the use of SBRT and four reported on the use of standard of care management. For SBRT, median PFS was 7.36-24 months. Median ADT-free survival was 12.3-39.7 months. The LCR varied, with some reports of 100% at 6 months and others of 92% at 5 years. No significant grade 3 toxicity was reported, with only five grade 3 events reported in two studies. For standard of care management, most of the studies reported 3-year PFS of 46.9-58.6%, with one study reporting a median PFS of 38.6 months. No standard of care study reported on LCR and ADT-free survival. Although different toxicity grading systems were used depending on the treatment modality, there were some reports of grade 3 events using standard of care management. Conclusion: SBRT appears to be a safe and effective modality for treating oligometastatic prostate cancer, having the potential to defer palliative ADT. Although LCR is excellent compared to conventional therapies, the PFS rate is reportedly inferior to standard of care therapies. No significant grade 3 toxicity was observed with SBRT.*

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In 1995, researchers proposed the existence of a clinical state termed 'oligometastatic disease' as an intermediate step in cancer progression from a localised confined process to a disseminated state, at which point metastases are limited in number and location (1). Management strategies such as systemic therapy, surgery and active surveillance are considered valuable options in metastatic cancer patients (2). Androgen-deprivation therapy (ADT) is still the gold standard treatment option to alleviate cancer-related symptoms and delay cancer progression for non-castrated patients with prostate cancer diagnosed with metastases (3). Although ADT is efficient, this monotherapy can lead to a significant deterioration in quality of life, especially loss of libido, erectile dysfunction, fatigue, depression and loss of muscle strength (4, 5). In addition, prostate cancer subsequently may become castration-resistant and ADT therefore loses its efficacy (6). The long-term negative impact of ADT on general health, quality of life and progression of the disease has resulted in the search for other therapies (7).

There are several studies showing that patients with a limited number of metastases have a better prognosis compared to those with extensive metastatic disease (8, 9). Therefore, for patients with oligometastatic prostate cancer, metastatic-directed therapy such as stereotactic body radiation therapy (SBRT) may have the potential to prevent additional metastatic spread and improve survival.

Table I. *Search strategy for the identification of studies*.

Database	Search/MeSH terms	Studies retrieved
Medline (PubMed)	"Radiosurgery"[Mesh] AND "Prostatic Neoplasms"[Mesh] AND ("oligometastatic prostate" OR "prostate oligometastases")	50
	("Prostatic Neoplasms"[Mesh]) AND ("oligometastatic prostate" OR "prostate oligometastases") AND ("Radiotherapy"[Mesh] OR "Hormone Replacement Therapy"[Mesh] OR "Lymph Node Excision"[Mesh] OR "Prostatectomy"[Mesh] OR "Disease Management"[Mesh])	93
Embase	('stereotactic body radiation therapy'/exp OR 'SBRT' OR 'stereotactic' OR 'SRS' OR 'SRT') AND ('oligometastatic prostate cancer' OR 'prostate oligometastases')	95
Clinicaltrials.gov	"oligometastatic prostate cancer" AND ("stereotactic" OR "SBRT")	19

MeSH: Medical Subject Headings.

SBRT uses highly conformal and precisely targeted radiation delivered in a very dose-intensive pattern (10) and is emerging as a low-toxicity treatment option for prostatic oligometastases that can potentially eliminate all macroscopic cancer foci; thereby prolonging the progression-free interval and postponing ADT. The concept of ADT-free survival (ADT-FS) is defined as the time to the delayed start of ADT, and is a method to spare the known negative side-effects of systemic therapy in patients with metastatic cancer, such as increased occurrence of cardiovascular events and metabolic syndrome (11).

Confirming the benefits of SBRT in oligometastatic prostate cancer might shift the treatment paradigm from palliative to a potentially curable disease in a subset of patients. However, to date, there is a paucity of randomised studies in which SBRT is compared with standard of care management.

The aim of this review was to evaluate the efficacy of SBRT among patients with oligometastatic prostate cancer, and to ascertain if the treatment outcome was improved by using SBRT in terms of ADT-FS, progression-free survival (PFS) rate, and local control rate (LCR) and to compare the toxicity profile of SBRT to that of standard of care management.

Materials and Methods

Search strategy for identification of studies. A literature search of the electronic databases MEDLINE (PubMed), EMBASE, and Clinicaltrials.gov was performed. Search terms related to SBRT and oligometastatic prostate cancer were used alone or in combination including, "SBRT", "SRT", "stereotactic body radiation therapy", "oligometastatic prostate cancer", "prostate neoplasm" and "management". A conclusive list of search words/MeSH terms and number of studies found are described in Table I. The reference lists of potentially eligible studies were subsequently manually searched to identify additional studies.

After identification of articles through database searching, duplicate articles were removed. The remaining articles were screened using the following criteria.

Inclusion criteria: Published prospective or retrospective studies; case–control and randomised-controlled trials; in English and published in the past 10 years; demonstrated and evaluated at least one treatment option with reported outcomes; for studies reporting on SBRT, SBRT should have been the main treatment following recurrence; minimum of 10 patients; patients must have had 1-5 metastatic lesions of the bone or soft tissue; SBRT was used solely or as part of combination therapy with the intent of managing oligometastatic prostate cancer; SBRT dose of 5-60 Gy in 10 fractions; surgery or systemic therapy or conventional radiation therapy were used as the management of oligometastatic prostate cancer. Exclusion criteria: Review articles and studies published in abstract form only.

Type of outcomes. Eligible studies reported the treatment outcome of SBRT and current standard of care therapies in the management of oligometastatic prostate cancer. Primary outcome: PFS, defined as the absence of new metastases or lack of progression of untreated metastases. Secondary outcome: ADT-FS, defined as the time between start of the treatment for metastatic disease and the initiation of palliative ADT. Local control: Lack of tumour progression within the irradiated field.

Toxicity profile: Common Terminology Criteria for Adverse Events version (CTCAE) 3.0/4.0 (38), or according to Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) (39) for those who received RT. The Clavien–Dindo classification (40) was used for patients who underwent surgery.

Results

The initial search yielded 257 studies. Studies were initially screened and reduced to 121 by excluding review articles, case studies and those lacking relevance to the topic (Figure 1). Duplicated articles were then removed. Full-text articles were assessed for eligibility using inclusion and exclusion criteria. Finally, 18 studies (11-28) were selected for data extraction and subsequent analysis. All articles were published in the English language between 2009 and 2018. One randomised-controlled trial and one case–control study (25) were identified. Among the other 16 studies, four were prospective (12, 13, 18, 21) and 12 were retrospective (11, 14-17, 20, 22-24, 26-28).

Fourteen studies (11-24) reported on the use of SBRT, one study reported on the use of radical prostatectomy (RP) with neoadjuvant ADT (25), one study each reported on the use of lymph node dissection (LND) (26), combined use of RP and LND (27) and ADT with external beam radiation therapy (EBRT) (28). The characteristics of the 18 studies and included patients are presented in Table II.

Triggiani *et al*. divided their cohort into two subgroups of patients, non-castration-resistant (*i.e*. oligorecurrent) and castration-resistant (*i.e*. oligoprogressive). They described independent population characteristics and clinical outcomes in each subgroup (23). Although the randomised phase II trial published by Ost *et al*. in 2018 evaluated the utility of SBRT in patients with oligometastatic prostate cancer, the trial permitted both surgery (including extended pelvic LND) and SBRT interventions in the treatment group (19). The data from this trial were therefore not considered in the results but are included in the discussion for completeness.

Efficacy of interventions. Table III summarises the treatment outcomes across the included studies. The time frame for all survival outcomes was dependent on the follow-up time of the patients, with the median follow-up ranging from 6 to 63 months.

PFS. PFS was reported in 15 studies, of which 11 reported PFS following SBRT for oligometastatic prostate cancer (11-17, 20, 22-24). This ranged from 74% at 6 months, 43.2-72% at 1 year, 35.7% at 19.8 months, 21.6-45% at 2 years, 42.6% at 30 months, 31% at 3 years, 42.6% at 30 months and 15% at 5 years. Eight out of the 11 studies also reported median PFS from 7.36-24 months.

Four studies reported PFS following current standard of care therapy (25-28). One study investigated the use of concurrent ADT and EBRT, with 3-year PFS reported as 58.6% (28). Three-year PFS was 46.9% in another study which investigated the use of salvage LND (26). One also reported median PFS to be 38.6 months when RP was used after neoadjuvant ADT (25). The only study reporting 7-year PFS was that of Gandaglia *et al*., where PFS was 45% when both RP and LND were the intervention (27).

LCR and ADT-FS. LCR was reported in 12 studies, all on the use of SBRT for patients with oligometastatic prostate cancer (11-18, 20, 22-24). The LCR was reported as ranging from 100% at 6-12 months, 100% at 18.6 months, 82-100% at 2 years, 98% at 30.18 months to 93% at 3 years. The only study reporting 5-year LCR was that of Ost. *et al*., where LCR was reported to be 92% at 5 years (20). They also reported that higher radiation dose gave better local control with a 3-year LCR of 99% for patients treated with a biologically effective dose >100 Gy *versus* 79% for those

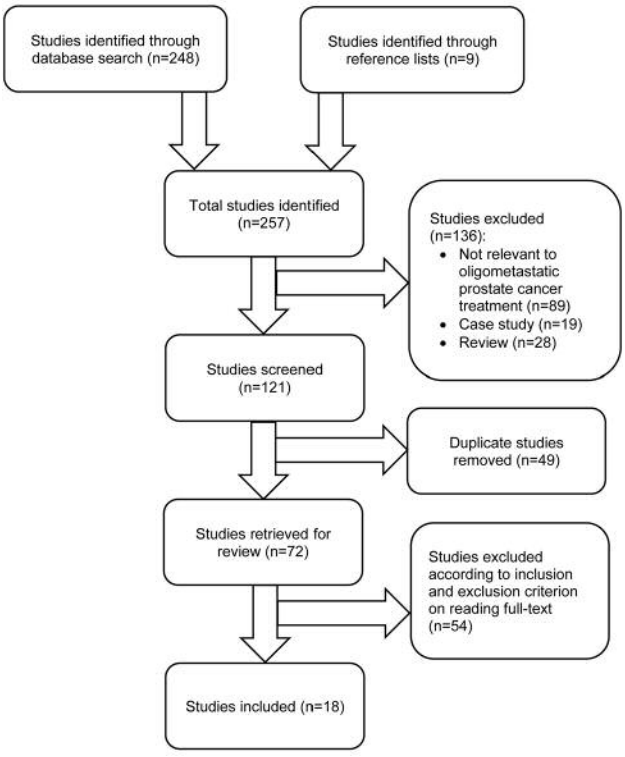

Figure 1. *Flowchart of included and excluded studies*.

treated with <100 Gy. Out of these 12 studies, two evaluated LC following CyberKnife-based stereotactic radiation therapy for oligometastatic prostate cancer, reported as 100% at 12 months and 88% at 16.9 months, respectively (14, 16). One study evaluating LCR following CyberKnife-based stereotactic radiosurgery reported as 95.5% at 24 months (18).

ADT-FS was reported in seven studies on the use of SBRT for oligometastatic prostate cancer (11, 13, 15, 20-23). The median ADT-FS was reported as ranging from 12.3 to 39.7 months. One-year ADT-FS was reported by three studies to be 82% (11), 82% (13) and 67.4% (23), respectively. They also reported 2-year ADT-FS of 54% (11), 60% (13) and 47.3% (23), respectively.

Toxicity. Treatment toxicity was reported in 16 studies, 12 (11-17, 20-24) on SBRT and four (25-28) on standard of care therapy. Generally, no significant grade 3 toxicity was reported in SBRT studies, with only five patients reporting grade 3 toxicity in two studies (13, 16). For the standard of care studies, three used the Clavien–Dindo grading system, with toxicity ranging from grade 1 to 3b (25-27). One study reported no more than grade 2 toxicity using the CTCAE grading system (28).

Table II. *Demographics and treatment found in studies on oligometastatic prostate cancer.*

Demographics			Treatment		
Author, year (Ref) type of study	No. of patients	Location of metastases (no. of lesions)	Primary therapy (no. of patients)	SBRT (dose and fractionation) and other therapies	Concurrent/adjuvant therapy (no. of patients)
Ahmed *et al*., 2013 (12) Prospective	17	Bone (n=19) LN (n=1) Liver (n=1)	Prostatectomy (n=15) EBRT (n=2)	Bone lesion: Median dose of 20 (range=8-24) Gy 1 fr (range=1-3 fr) Retroperitoneal lymph node: 50 Gy/5 fr Liver lesion: 60 Gy/3 fr	Adjuvant androgen suppression (n=15)
Berkovic *et al*., 2013 (11) Retrospective	24	Bone (n=16) LN (n=13)	RP (n=3) RT (n=4) RP + RT (n=17)	Median dose of 50 (range=40-50) Gy 10 fr (range=8-10 fr)	-
Decaestecker *et al*., 2014 (13) Prospective	50	LN (n=38) Bone (n=31) Viscera (n=1)	RP (n=6) RP + RT (n=22) RP + RT + ADT (n=14) RT + ADT (n=6) RT (n=2)	SBRT 50 Gy/10 fr + 1-month ADT (35 patients) Mean dose of 30 Gy/3 fr (15 patients)	1-Month ADT (n=35)
Detti *et al*., 2015 (14) Retrospective	30	LN (n=39)	RP ± RT + HT (n=25) RT ± HT (n=5)	CBK-SRT ranging from 24 Gy/1 fr to 36 Gy/3 fr	Concomitant ADT (n=14)
Ingrosso *et al*., 2017 (15) Retrospective	40	LN (n=47)	EBRT (n=11) Prostatectomy ± PLND (n=10) RP + RT (n=17) Brachytherapy (n=2)	Median dose of 35 (range=12-50) Gy 5 fr (range=1-5 fr)	Concomitant ADT (n=21)
Jereczek *et al*., 2012 (16) Retrospective	34	Recurrent primary (n=15) Peri-anastomotic recurrence (n=4) LN (n=16) Metastatic lesion (n=3)	RT ± ADT (n=20) RP ± LND ± ADT ± RT (n=14)	Median CBK-SRT dose of 30G (range=30-36) Gy 4.5 fr (3-5 fr)	Concomitant ADT with CBK-SRT (n=18) Chemotherapy (n=1)
Jereczek *et al*., 2009 (17) Retrospective	14	LN (n=16)	RT (n=1) RT + ADT (n=2) RP + ADT (n=1) RP + RT ± ADT (=10)	LINAC-SRT mean dose of 27 Gy in 5 fr (7 patients) CBK-SRT mean dose of 33 Gy in 4 fr (7 patients)	Concomitant ADT (n=8)
Muacevic *et al*., 2013 (18) Prospective	40	Bone (n=64)	Surgery (n=3) Chemotherapy (n=8) HT (n=19) RT (n=8)	CBK-SRS median dose of 20 Gy in 1 fr	Concomitant ADT (n=9)
Ost *et al*., 2018 (19) Randomised-controlled trial	25	LN (17 patients) Non-LN (14 patients)	RP and/or RT	30 Gy in 3 fr	-
Ost *et al*., 2016 (20) Retrospective	119	LN (n=72) Bone (n=43) Other (n=4)	RP (n=21) RP + RT (n=37) RP + RT + ADT (n=31) RT + ADT (n=22) RT (n=8)	At least 30 Gy in 5 fr	ADT (n=60)
Pasqualetti *et al*., 2016 (21) Prospective	29	LN (n=25) Bone (n=20)	-	24 Gy in 1 fr (Dexamethasone administered 1 h) 27 Gy in 3 fr	-
Habl *et al*., 2017 (22) Retrospective	15	Bone (n=20)	Surgery (n=14) Hormone-chemotherapy + surgery (n=1)	25-40 Gy in 5 fr	Concomitant ADT (n=3)
Triggiani *et al*., 2017 (23) Retrospective	NCR 100	LN (n=49) Bone (n=21)	RP (n=7) RT (n=10) BRT (n=1)	Median BED dose= 116 Gy	Concomitant ADT (n=24)

Table II. *Continued*

Table II. *Continued*

Demographics			Treatment		
Author, year (Ref) type of study	No. of patients	Location of metastases (no. of lesions)	Primary therapy (no. of patients)	SBRT (dose and fractionation) and other therapies	Concurrent/adjuvant therapy (no. of patients)
	CR 41	LN (n=117) Bone (n=22)	RP + adjuvant (n=7) RP + salvage RT (n=11) ADT only (n=5) RP (n=24) RT (n=16) BRT (n=2) RP + adjuvant (n=35) RP + salvage RT (n=23)	Median BED dose= 116 Gy	.
Muldermans *et al*., 2016 (24) Retrospective	66	LN (n=6) Bone (n=74) Other (n=1)	RP (n=20) RT (n=3) RP + adjuvant RT (n=9) RP + salvage RT (n=26) RT + salvage RP (n=1) RT + cryotherapy (n=1) Chemotherapy (n=6)	Median dose of 16 Gy/1 fr (71 lesions) 30 Gy/3 fr (6 lesions) 50 Gy/5 fr (4 lesions)	Adjuvant ADT (n=42)
Heidenreich *et al*., 2015 (25) Case-control	23	Bone (n=≤3 lesions)	-	ADT + retropubic RP	Neoadjuvant ADT for all
Karnes *et al*., 2015 (26) Retrospective	52	LN (n=range 1-5 lesions)	RP ± LND (n=52) Post-RP therapy (n=41): 78.8%	Salvage LND	Adjuvant HT (n=43, 82.7%)
Gandaglia *et al*., 2017 (27) Retrospective	11	Bone: 1 in two patients 2 in four patients ≥3 but ≤5 in five patients	-	RP + extended LN dissection	Neoadjuvant ADT (n=2, 18%) Adjuvant ADT (n=10, 91%) RT (n=7, 64%)
Schick *et al*., 2013 (28) Retrospective	50	LN (n=50) → 63.5% Bone (n=25) → 31.5% Other (n=4) → 5%	None, n=7, 14% RT ± ADT, n=10, 20% Surgery ± salvage RT ± ADT, n=33, 66%	ADT + EBRT (median delivered effective dose=64 Gy)	-

RT: Radiation therapy; BED: biologically effective dose; SBRT: stereotactic body RT; EBRT: external body RT; BRT: brachytherapy; RP: radical prostatectomy; ADT: androgen-deprivation therapy; LN: lymph node; LND: lymph node dissection; CBK: CyberKnife; HT: hormonal therapy; NCR: non-castration-resistant; CR: castration-resistant; SRT: stereotactic RT; SRS: stereotactic radiosurgery.

Discussion

Optimal treatment of oligometastatic prostate cancer is controversial. Previously, the majority of such patients were treated with ADT even those with minimal disease, such as a single lesion (2). In recent years, evidence has shown the potential of ADT to have a negative impact on quality of life (29, 30). As a result, clinical surveillance has been suggested as an alternative to immediate ADT in patients who strongly wish to avoid ADT-related side-effects (19, 31, 32).

Limited retrospective studies have suggested that interventions, including local or metastasis-directed therapy using surgery and RT, can improve survival outcomes with minimal risk of adverse effects. In recent years, SBRT was used in several studies to delay the initiation of ADT without compromising the survival rate, and a significant lower toxicity profile was achieved (11, 13).

Efficacy of SBRT. The first study reporting SBRT for oligometastatic prostate cancer was published in 2009 by Jereczek-Fossa *et al*., who described outcomes of men with isolated lymph node metastasis detected by choline positron-emission tomography/computed tomography and treated with CyberKnife image-guided SBRT. At a mean follow-up of 18.6 months, the PFS rate was 35.7% at 19.8 months, and local control rate was reported as 100% (17). A similar result was demonstrated in 2012 with a larger cohort of patients with local recurrence, peri-anastomotic recurrence, single lymph node metastasis and single distant metastasis (16). The 30-month PFS was 42.6% at a median follow-up of 16.9

Table III. *Follow-up and treatment outcome of studies on oligometastatic prostate cancer.*

Author, year (Ref) type of study	Median follow-up (range)	ADT-free survival	Local control	Progression-free survival	Toxicity, n (%)*
Ahmed *et al*., 2013 (12)	6 (2-24) months	-	100% At 6 months	6-Month=74% 12-Month=40%	CTCAE 3.0 Grade 1, n=1 (6%) Grade 2, n=2 (12%)
Berkovic *et al*., 2013 (11)	24 (1-72) months	1-Year=82% 2-Year=54% Median=38 (95% CI =18-58 months)	100% At 2 years	1-Year=72% 2-Year=42% Median=18 months	Grading system not specified Grade 2 GU – 8% Grade 2 GI – 6%
Decaestecker *et al*., 2014 (13)	24 (IQR=8-52) months	1-Year=82% 2-Year=60% Median=25 (CI=20-30 months)	100% At 24 months	1-Year=64% 2-Year=35% Median=19 months	CTCAE 3.0 Grade 1, n=7 (14%) Grade 2, n=3 (6%)
Detti *et al*., 2015 (14)	12 (2-24.9) months	-	100% At 12 months	1-Year=54%	CTCAE 4.0 Grade 1, n=1 (3%) Grade 2, n=1 (3%)
Ingrosso *et al*., 2017 (15)	23.8 (3.73-79.8) months	40% At last follow-up Mean=26.18 (range=3.96-59.46) months	98% At 30.18 months	2-Year=44% Median=24 months	RTOG/EORTC Late grade 3, n=1 (3%)
Jereczek *et al*., 2012 (16)	16.9 (3-35.4) months	-	88% At 16.9 months	30-Month=42.6% Median=17 months	RTOG/EORTC Acute Grade 1, n=4 Grade 2, n=2 Grade 3, n=2 Late Grade 1, n=4 Grade 2, n=3 Grade 3, n=2
Jereczek *et al*., 2009 (17)	Mean 18.6 (10.1-30.7) months	-	100% At 18.6 months	19.8-Month=35.7% Mean=12.7 months	RTOG/EORTC Grade 2, n=1 (3%)
Muacevic *et al*., 2013 (18)	10.2 (3-48)	-	95.5% At 2 years	-	-
Ost *et al*., 2018 (19)	3 (IQR=2.3-3.8) years	Median=21 (80% CI =14-29) months	100% At 3 years	39% At 3 years (polymetastatic progression)	CTCAE 4.0 Grade 1, n=2 (8%)
Ost *et al*., 2016 (20)	3 (IQR=1.75-4) years	Median=28 (95% CI=16.2-69.7) months	93% At 3 years 92% At 5 years	3-Year=31% 5-Year=15% Median=18 months	CTCAE 4.0 Grade 1, n=7 (14%) Grade 2, n=3 (3%)
Pasqualetti *et al*., 2016 (21)	11.5 (3-40) months	Median=39.7 (95% CI=17.2-62.1) months	-	-	CTCAE 4.0 Grade 1
Habl *et al*., 2017 (22)	22.5 (7-53.7) months	Median=12.3 (range=2.6-36.1) months	100% At 2 years	Median=7.3 (range=2-54 months)	No toxicity observed
Triggiani *et al*., 2017 (23)	NCR 20.4 (3-72) months	1-Year=67.4% 2-Year=47.3% Median=20.9 months	92.8% At 2 years	1-Year=64.4% 2-Year=43.0% Median=18 months	CTCAE 4.0 Grade 1 GI, n=4 Grade 1 GU, n=1 Grade 2 GU, n=2
	CR 24 Months	Second-line STFS 1-Year=78.4% 2-Year=41.3% Median=22 months	90.2% At 2 years	1-Year=43.2% 2-Year=21.6% Median=11 months	CTCAE 4.0 Grade 1 GI (n=1)
Muldermans *et al*., 2016 (24)	16 (3-49) months	-	82% At 2 years	2-Year=45%	CTCAE 4.0 Acute pain, n=8 (12%) Grade 1, n=6 (9%) Grade 2, n=2 (3%)
Heidenreich *et al*., 2015 (25)	34.5 (7-75) months	-	-	Median=38.6 (range=42-52) months	Clavien Grade 1, n=4 (17.4%) Grade 2, n=2 (8.7%) Grade 3a, n=2 (8.7%) Grade 3b, n=1 (4.3%)
Karnes *et al*., 2015 (26)	20 (IQR=8-33) months	-	-	3-Year=46.9%	Grade 2, n=2 (3.8%) Grade 3, n=2 (3.8%)

Table III. *Continued*

Table III. *Continued*

Author, year (Ref) type of study	Median follow-up (range)	ADT-free survival	Local control	Progression-free survival	Toxicity, n (%)*
Gandaglia *et al*., 2017 (27)	63 (IQR=48-77) months	-	-	7-Year=45%	Grade 1, n=2 (18%) Grade 2, n=2 (18%) Grade 3a, n=1 (9%) Grade 3b, n=1 (9%)
Schick *et al*., 2013 (28)	31 (9-89) months	-	-	3-Year Biochemical=54.5% Clinical=58.6%	CTCAE 3.0 No >Grade 2 toxicity

CTCAE: Common Terminology Criteria for Adverse Events 3.0/4.0 (38); IQR: interquartile range; RTOG/EORTC: Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (39); RT: radiation therapy; NCR: non-castration-resistant; CR: castration-resistant; STFS: systemic treatment-free survival.

months. Similarly, Muacevic *et al*. prospectively evaluated the feasibility of a single fractional CyberKnife robotic radiosurgery in 40 patients with one or two bone metastases. Local control was achieved in 95.5% of patients at 2-year follow-up. Of note, 68% of the patients were treated with ADT during follow-up, and PFS was not reported (18).

Despite CyberKnife-based SBRT, conventional LINAC-based SBRT has also been used in patients with oligometastatic prostate disease. Ahmed *et al*. published a study in 2013 which reported on survival for 18 patients with a total of 21 lesions of bone, lymph node or viscera following SBRT. With a median follow-up of 6 months, the 6-month and 12-month PFS was 74% and 40%, with 100% LCR at 6 months (12). In 2016, Ost *et al*. reported on a similar group of patients. In their series of 119 patients, the 3-and 5-year PFS rates were 31% and 15%, respectively, and corresponding LCRs were 93% and 92%. Of note, among their cohort of patients, 60 had adjuvant ADT, and the median PFS of those treated with SBRT *versus* SBRT and adjuvant ADT was reported as 18 months compared with 25 months, this result was reported as not statistically significant (p=0.09) (20). The 3-year PFS of 31% is comparable with studies reporting on oligometastatic recurrences of other primary tumour types. Kang *et al*. reported a PFS of 25% at 3 years for those with colorectal oligometastases following SBRT (33). Another study by Sharma *et al*. also demonstrated a 3-year PFS of 25% for patients treated with SBRT for pulmonary oligometastases (34).

Detti *et al*. reported their clinical experience in SBRT for isolated nodal metastases from prostate cancer. The 1-year PFS was 54% and the LCR was 100% at 1 year. Of note, 14 patients were receiving hormonal therapy at the time of SBRT (14). In 2017, Ingrosso *et al*. published a similar study which involved 40 patients with 47 metastatic lymph node lesions. The 2-year PFS was 44% and the LCR was 98% at 30.2 months (15). These survival rates are comparable with a study reporting on oligometastases from other primary sites to abdominal lymph nodes (35). The 12- and 24-month PFS rates were 29.5% and 19.7%, respectively with an LCR of 77.8% at 1 year. These results indicate that SBRT has the potential to yield similar or better treatment outcomes in oligometastatic prostate cancer compared to other primary sites.

Considering toxicity, very low rates of acute and late toxicity were registered for SBRT. Among all SBRT studies evaluated, only three patients had acute grade 3 toxicity and a further two had late grade 3 events (13, 16). However, it should be noted that as most of the included studies were retrospective, toxicity may have been under-reported. The follow-up times reported were insufficient to thoroughly assess late toxicity.

Potential of SBRT to delay ADT. In 2013, Berkovic *et al*. published the first study reporting on an end point of deferral of systemic treatment. Patients received SBRT with a median dose of 50 Gy in 10 fractions for ≤3 bone or lymph node metastases. A median deferral of palliative ADT of 38 months (95% confidence intervaI=18-58 months) was demonstrated. The study also showed that repeated salvage SBRT for metachronous disease was feasible, without significant toxicity (11). A similar study was reported in 2014 by Decaestecker *et al*. for 50 men with ≤3 lymph node, bone or viscera metastases who were treated with repeated SBRT at 50 Gy in 10 fractions or 30 Gy in three fractions. The median ADT-FS was 25 months (95% confidence intervaI=20–30 months) (13). Later in 2016, Pasqualetti *et al*. evaluated the outcome of the delay of systemic therapy delivery in patients with hormone-naïve and castration-resistance oligometastatic prostate cancer. The study reported the clinical outcomes of 29 patients with a total of 45 active lesions treated with SBRT. The median delay of systemic therapy was 39.7 months (95% confidence intervaI=17.2-62.1 months) (21).

Many studies emphasise the possibility of delaying ADT treatment and, therefore, the onset of endocrine resistance. Moreover, the utility of SBRT to improve patient quality of life by deferring ADT omission is reported. In fact, it is well-recognised that ADT administration can be a source of complications, especially in terms of cardiovascular adverse events and metabolic syndrome (36). Further phase II randomised trials are needed to explore this but there appears to be the potential to create a paradigm in the treatment of low-volume lymph node and bone metastatic disease with SBRT.

Castration resistant versus non-castration resistance disease. SBRT has been shown to be effective in patients who have developed a castration-resistant condition, characterised by rising prostate-specific antigen level, appearance of new metastases or dimensional progression of previous metastases (37). Triggiani *et al*. compared the efficacy of SBRT between patients with non-castration-resistant prostate cancer and those with castration-resistant disease. In 41 patients with castration-resistant disease with 49 lymph node lesions and 21 bone lesions a PSA rise was detected during ADT and they were subsequently treated with SBRT. After a median follow-up of 24 months, 1- and 2-year PFS rates were 43.2% and 21.6%, respectively. The 1- and 2-year second-line systemic treatment-free survival rates defined as the time between the first day of SBRT to the start of systemic therapies (such as abiraterone, enzalutamide or docetaxel) were 74.8% and 41.3%, respectively (23). These outcomes illustrate the potential of SBRT in this aggressive setting.

Comparison of SBRT to standard-of-care management. In this review, the treatment outcomes of patients who received standard of care therapies, including active surveillance, were also evaluated. A randomised phase II trial by Ost *et al*. in 2018 compared the outcomes of such therapies to SBRT. A total of 62 patients with oligometastatic recurrent prostate cancer were randomly assigned to surveillance or metastasis-directed therapy. The median follow-up time was 3 years. The median ADT-FS for control and intervention groups were 13 months and 21 months, respectively. The median biochemical PFS was better in the treatment arm (6 months vs. 10 months; HR, 0.53; p=0.03), with a 100% local control in these patients at 3 years. No grade 2 or higher toxicity was observed (19). These data are consistent with the findings from the single-arm studies. However, it was not possible to compare the PFS endpoint as most of the studies reported distant not biochemical PFS.

In 2013, Schick *et al*. published a study of 50 patients treated with EBRT and concomitant ADT with 3-year clinical PFS of 58.6% (95% confidence intervaI=43.9–73.5 months) (28). Another three studies reported the use of surgery (either RP, LND or both) in patients with oligometastatic disease (25-27). Three-year PFS was 46.9% in 52 patients treated with LND. (26) PFS at 7 years was 45% in 11 patients treated with RP and LND in another study. Of note, 10 patients (91%) received adjuvant ADT (27). Median PFS was 38.6 months in a study with 23 patients treated with cytoreductive RP, but all patients received neoadjuvant ADT. (25) Comparing 3-year PFS, standard-of-care therapies demonstrated superior outcomes ranging from 46.9-58.6% *versus* 31% for patients treated with SBRT. However, the definition of PFS differed between the studies. As no studies including standard of care reported their LCR, more data are needed for confirmation.

Current studies. There are three ongoing randomised controlled trials on this topic. NCT02680587 (ORIOLE trial) is making a comparison of SBRT to an observational approach, while NCT02685397 is learning the management of castration-resistant prostate cancer. Finally, NCT02759783 (CORE study), which also includes patients with breast and lung cancer, is evaluating SBRT *versus* conventional care.

Limitations. Risk of bias was high in the included studies as 12 were retrospective and only one was a randomised controlled trial. Additionally, the included studies used different toxicity grading systems, making meaningful comparison across the studies difficult. Although the studies showed similarity in patient characteristics, they presented considerable heterogeneity in the clinical treatment outcomes reported. Distinct definitions of treatment failure and different primary endpoints were employed, such as PFS, LCR and ADT-FS. ADT was not controlled in an adjuvant or progression setting. Patients in the majority of the studies were treated with concurrent/neoadjuvant/concomitant/adjuvant therapies which contributed to the heterogeneity of the interventions reported in this review

The follow-up period of patients treated with SBRT is still short. The longest follow-up in studies was 3 years. The outcomes reported were moderately heterogenous. Studies varied on the endpoints reported and the definitions of treatment failure. A quantitative analysis was not possible, and nor were there subgroup analyses (*i.e*. lesions sites, number of lesions). Only one randomised controlled trial reported quality-of-life assessment.

Conclusion

The use of SBRT in the oligometastatic recurrent setting is promising, as it has the potential to control disease with the possibility of deferring palliative androgen-deprivation therapy. LCRs are excellent as compared to conventional therapies, especially when higher radiation doses are delivered (biologically effective dose >100 Gy). However, the PFS rate

may be inferior compared to the other therapies discussed, no significant grade 3 toxicity was observed using SBRT. However, a longer follow-up time is required to assess late toxicity. Quality-of-life assessment should be included as a trial endpoint in future studies to better assess the potential benefit of SBRT.

Conflicts of Interest

The Authors have no conflicts of interest to disclose.

Authors' Contributions

Bonan Zhang reviewed all papers and co-wrote the article. Michelle Leech co-wrote the article.

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