Title: The use of stereotactic body radiation therapy on oligometastatic recurrent prostate cancer: a systematic review

Running title: SBRT on oligometastatic prostate cancer

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Conflicts of interest: The authors declare they have no conflicts of interest.

Funding: None.

Acknowledgements: None.

ABSTRACT

Purpose: To evaluate the effectiveness and safety of stereotactic body radiation therapy (SBRT) in the management of oligometastatic recurrent prostate cancer patients (ORPCP) by means of a systematic review. The focus was on clinical implications.

Methods and Materials: Six databases were searched (Cochrane CENTRAL, Embase, LILACS, PubMed, Scopus, Web of Science). Hand-searching and gray literature search were also performed to find additional references. The main outcomes were progression-free survival (PFS) and toxicity rates. ADT-free survival (ADT-FS), local control, pattern of clinical recurrence following SBRT, cancer-specific survival and overall survival were also assessed. Risk of bias of individual studies were judged with aid of the Joanna Briggs Institute Critical Appraisal Checklist for Case Series. Quality of evidence was assessed with Grades of Recommendation, Assessment, Development, and Evaluation (GRADE).

Results: Fourteen studies were included, involving 661 patients and 899 metastatic lesions. No randomized controlled trials were found. The articles are from 2011 to 2017. Nine of them were published in 2016 or later. Were treated 561 nodal, 336 bone and 2 liver lesions with SBRT. Adjuvant ADT at time of SBRT was used on 38.7% of the patients. The medians PFS and ADT-FS were around 1 and 3 years after intervention. Local control rates varied from 82 to 100% among researches with low risk of bias. Acute and late grade 2 toxicity were observed in 2.4% and 1.1% of the patients, respectively. One case of acute and two cases of late grade 3 toxicity were registered.

Conclusion: SBRT is a safe approach to prostate cancer metastases. It has the potential to provide long-term disease control and to defer ADT. The local control is excellent, especially when higher radiation doses are employed. Despite promising results, further investigation with randomized controlled trials are required.

INTRODUCTION

Oligometastases is a term proposed to describe an intermediate state between disseminated and early disease. The number and site of metastatic tumors would be limited, with restricted spread capacity. Considering this concept, aggressive local treatment of the metastasis lesions could be applied with curative intent (1,2).

The localized prostate cancer (PCa) is mostly treated with radical prostatectomy, external beam radiotherapy and/or brachytherapy (3). Following the primary treatment, if an oligometastatic recurrence occurs, there is no definitive consensus about how these patients should be managed. In the past decades, they have been mainly handled with palliative androgen deprivation therapy (ADT), despite the indolent nature of the disease (4,5). However, this strategy may lead to several adverse effects, such as loss of libido, weight gain, cardiovascular disorders, and gynecomastia. These conditions negatively impact the quality of life of the patients (6–9).

Due to limitations in diagnostic and treatment methods, local therapy of the metastases has been rarely used. Nevertheless, the advent of ultrasensitive prostate-specific antigen (PSA) assay and positron emission tomography/computed tomography (PET/CT), have contributed to the early detection of recurrence from PCa (10). The PET/CT plays an important role in precision medicine. It allows the identification of exact site and dimensions of metastases. In recent years, tests with high accuracy for PCa have been developed, among which choline- and PSMA-based PET/CT (11–13). Therefore, the oligometastatic recurrent prostate cancer patients (ORPCP) can now be identified and distinguished from those individuals with disseminated disease.

Treatment technics were also improved, noteworthy minimally invasive surgeries and stereotactic body radiation therapy (SBRT). The SBRT uses precise targeting to deliver ablative radiation doses on tumors, while keeping a low toxicity profile (14). Then,

interest in using local approaches to direct treatment of metastases has significantly increased. The clinical implication would be the long-term disease control, with potential to postpone palliative systemic treatment until widespread progression. Furthermore, some patients might be cured of disease (15). Hence, the main goal of the present systematic review is to evaluate the effectiveness and safety regarding the use of SBRT in the management of ORPCP.

MATERIAL AND METHODS

The systematic review was accomplished according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist (16).

Protocol and registration

The systematic review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO, Centre for Reviews and Dissemination, University of York, Heslington, York, United Kingdom; and the National Institute for Health Research, London, United Kingdom) under number CRD42017062556 (17).

Terminology definition

ORPCP was defined based on the number of detectable lesions at time of recurrence. Were considered patients with five or fewer metastatic lesions, regardless of site or dimension. The primary disease must be controlled (18,19).

Eligibility criteria

Studies investigating ORPCP who received SBRT as metastasis directed therapy were included. The articles provided an oncologic outcome (biochemical response or

progression-free survival) and/or toxicity rates. There were no restrictions to the year of publication or language of the study.

The following exclusion criteria were applied: (1) Previous report of the same research group that presents the same population and outcomes. In this case, if multiple publications of the same institution were found, reporting the same population, the most recent one was selected, (2) Insufficient data on ORPCP, (3) Studies with none or less than 5 ORPCP included, (4) Studies without any data on outcome and toxicity, (5) Wrong type of publication/study design as conference abstracts, letters, literature reviews, and personal opinions.

Information sources and search strategy

Studies were identified using a search strategy adapted for each electronic database: Cochrane CENTRAL, Embase, Latin American and Caribbean Health Sciences (LILACS), PubMed, SCOPUS, and Web of Science. A gray literature investigation was performed using Google Scholar. The searches were rerun just before the final analysis and the results were screened for eligible studies. Furthermore, additional studies were identified by a hand-search of the references lists of candidate articles.

Appropriate truncation and word combinations were selected and adapted for each electronic database. All references were managed by the software EndNote (EndNote X7 Basic Thomson Reuters, New York, USA), and duplicates were removed. Electronic database searches were performed on March 23th, 2017. More information on the search strategies is provided in Supplementary data 1.

Study selection

Study selection was conducted in two phases. In phase 1, two reviewers (R.A.V. and E.T.F.) independently screened the titles and abstracts of potentially relevant studies and

selected articles that appeared to meet the inclusion criteria based on their abstracts. In phase 2, the same reviewers independently read the full text of all selected articles and excluded studies that did not meet the inclusion criteria. Any disagreements, either in the first or second phases, were resolved by discussion and agreement between the two reviewers. In case a consensus could not be reached, a third author (P.E.D.R.) was involved to make a final decision. Studies excluded after full-text assessment and the reasons for their exclusion are listed in Supplementary data 2. For phase of screening, data extraction, and analysis was used the ©Covidence (Web-based systematic review tool designed to facilitate the process) (20).

Data collection process and items

Two reviewers (N.F.N. and R.Z.R.) independently collected the data from the selected articles: study characteristics (author, year of publication, country of the study coordinator, temporality of data collection), population characteristics (sample size, age), disease characteristics (number and sites of lesions treated with SBRT, primary disease risk category, PSA value before SBRT,), primary treatment information (SBRT modality used, median time from primary treatment to SBRT), intervention characteristics (restaging method, SBRT treatment machine, use of ADT), median follow-up, oncologic outcomes: progression-free survival (PFS), local control, biochemical control, androgen deprivation therapy-free survival (ADT-FS), cancer-specific survival, overall survival, patterns of clinical recurrence, predictive factors of recurrence, and toxicity (acute and late toxicity). Another reviewer cross-checked all the retrieved information (R.A.V.). The expert became involved, when required, to make a final decision. When the needed data were not complete, the authors were contacted. Pertinent missing information were retrieved.

Risk of bias in individual studies

Methodological quality was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series, a 10-item validated quality appraisal tool. Judgments for each item were assessed as yes (Y), no (N), unclear (U) or not applicable (NA) (21). In order to support the overall appraisal, the number of Y given for each study was counted, which generates a score ranging from 0 to 10. A score of at least 7 was considered to determine a low risk of bias in individual studies.

Two reviewers (N.F.N. and R.Z.R.) performed this process independently. Disagreements between the two reviewers were solved by a third investigator (R.A.V.).

Summary measures

The primary outcomes were PFS and toxicity rates. We also assessed, androgen deprivation therapy-free survival (ADT-FS), local control, cancer-specific survival, overall survival, patterns of clinical recurrence after SBRT and prognostic factors. Measures of frequency, means and medians were considered, as well the median differences or standardized mean differences for continuous outcomes.

Synthesis of results

The overall data combination of the included studies was performed by a qualitative descriptive synthesis. Statistical pooling of data was planned whenever studies were considered combinable and relatively homogeneous in relation to design, interventions and outcomes. Heterogeneity within studies was evaluated by considering clinical differences (participants, interventions and results), methodological (design and risk of bias), and statistical characteristics (effect of studies).

Risk of bias across studies

The quality of evidence was assessed using Grades of Recommendation, Assessment, Development, and Evaluation (GRADE). The criteria for this assessment were study design, risk of bias, imprecision, inconsistency, indirectness, presence of dose-response gradient, magnitude of effect, and all plausible effect that would weakened the effect estimate. The quality of evidence should be characterized as high, moderate, low, or very low. Table of findings was produced with aid of the GRADE online software (GRADEpro GDT, Copenhagen, Denmark), provided by the GRADE Working Group, in association with the Cochrane Collaboration and Members of McMaster University (22,23).

RESULTS

Study selection

The systematic literature search yielded 3,621 citations from five electronic databases. After removing duplicates, 1,895 articles remained. Results from Google Scholar added 30 more references. Three studies were identified by rerunning the searches prior to publication. No additional articles were found by cross-referencing. Following the screening of title and abstracts, the full text of 41 studies were reviewed and 27 were excluded by using eligibility criteria. The exclusion reasons with references are listed in Supplementary data 2. Finally, 14 articles (24–37) were selected for data extraction to perform qualitative synthesis.

Figure 1 details the process of identification, inclusion, and exclusion of studies.

Figure 1 - Flow diagram of literature search and selection process.

Study characteristics

The descriptive characteristics of studies and patients are summarized in Table 1.

Table 1 - Summary of descriptive characteristics of articles included.

All articles were published in English language. Seven of which were carried out in Italy, two in Poland, and two in Germany. Belgium, Netherlands, and United States had one study each. They were all published from 2011 to 2017. No randomized controlled trials were found. Thirteen articles were single-arm case series/cohort studies, and one case control series, with 5 prospective (25–27,32,34) and 9 retrospective researches (24,28–31,33,35–37). The median follow-up period varied from 10.2 to 36.6 months (Table 2).

Table 2 - Summary of descriptive characteristics of interventions and outcomes.

Choline PET/CT was the most commonly used method to identify the clinical recurrence, and was present in all the studies (24–37). However, six of them (27–30,33,35) allowed its substitution for less accurate tests (18F-FDG PET/CT, MRI, CT and/or Bone Scan) in a minority of patients. One study reported the use of PSMA PET/CT (37).

Ten articles (25–29,31,32,34,36,37) standardized some criteria for SBRT treatment failure, being biochemical or clinical progression. The administration of ADT was not standardized neither at time of SBRT (delivered in 38.7% of patients) nor at disease progression. The use of other systemic therapies was also not patterned. A prophylactic pelvic irradiation at time of SBRT was related in 2% of the patients (24,35).

The toxicity was assessed according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria in six studies (24,25,30,31,33,34) and to the Common Terminology Criteria for Adverse Events

(CTCAE) in five others (27–29,32,35). Three articles did not describe the criteria adopted (26,36,37).

Triggiani et al. (35) divided their cohort into two subgroups of patients: non-castration resistant (i.e. oligorecurrent) and castration resistant prostate cancer (i.e. oligoprogressive). They described independent population characteristics and outcomes from each group. On the other hand, Jereczek-Fossa et al. (25) in their 2012's series included not only oligometastatic, but also locally recurrent PCa patients. Independent outcomes were reported, but not population characteristics from each subgroup. Also in respect to samples characteristics, Bouman-Wammes et al. (36) included, as a control group, retrospective data of 20 patients with oligometastatic disease not treated with SBRT. The current review considered only the data from the intervention group.

Risk of bias within studies

Risk of bias assessment is reported in Table 3. Seven studies scored 7 or more "yes" answers and were considered as low risk of bias (25,27,29,31,32,34,36).

Particularly given the retrospective nature of the researches, the items 1, 4 and 5 (addressing inclusions criteria, consecutive inclusion and complete inclusion of participants) were the most common reasons to lower the scores. In question 2, was judged "no" for studies that allowed restaging with methods other than PET/TC. In question 3, was mainly analyzed if articles related a treatment failure definition, a defined follow-up schedule and the use of a validated criteria to grade toxicity.

Table 3 - Risk of bias assessment for individual studies using the JBI Critical Appraisal Checklist for Case Series.

Results of individual studies

The summary of outcomes of individual studies is presented in Table 2. The 2-years PFS rate was reported by seven articles (24,25,27,29,31,34,35), which are shown in Figure 2. The local control rates varied from 82 to 100% among researches with low risk of bias. The medians ADT-FS were presented in five studies and are from 12.3 to 39.7 months (27,32,35–37).

Figure 2 - Progression-free survival (PFS) rates at 2 years.

Among predictive factors of failure investigated, by means of univariate analysis, a short PSA doubling time prior to SBRT was correlated with lower PFS and ADT-FS in two studies (27,35). Muldermans et al. (29) showed correlation of a higher PSA value at time of SBRT and lower PFS rate ($p<0.05$). One other study (34) showed, also with statistical significance, correlation between higher PSA value and worst biochemical response.
The acute and late toxicity profile of individual studies, as well as a global evaluation, are described in Table 4.

Table 4 - Toxicity data associated with stereotactic body radiation therapy. A) Acute toxicity. B) Late toxicity.

Synthesis of results

Overall, 661 patients (range 15-141) with 899 metastatic PCa lesions (range 19-209) were identified in the 14 articles. When described, two thirds of patients were classified as high risk PCa (D'Amico risk group) (38) at primary diagnosis. The median Gleason score was 7.

The sites of the 899 lesions treated with SBRT are shown in Figure 3. The pattern of clinical recurrence after SBRT was not clearly reported by most of articles. Therefore, were summarized only the data from 4 studies in which it was clearly related

(27,31,32,34). The sites of recurrence, as well as the proportion of clinical relapses among all the participants from these 4 studies are also described in Figure 3.

Figure 3 - Sites of lesions treated with SBRT and pattern of first recurrence. A) Sites of the 899 lesions treated with SBRT in all studies; B) Data from 213 patients provided by 4 studies in which the pattern of recurrence was clearly reported. Sum of post-SBRT first recurrences in each site is presented in bold. Proportion of relapses over the patients at risk is presented in parentheses.

Various radiotherapy fractionation schedules were used. The most frequent ones were the administration of 30 Gy divided in 3 fractions (126 treatments), 24 Gy in 3 fractions (82 treatments), 24 Gy in single dose (42 treatments), and 16 Gy in single dose (38 treatments). All the fractionation schedules are listed in Supplementary data 3. The Biologically Effective Dose (BED) with $\alpha/\beta = 3$ Gy was calculated for all the reported schemes and are presented in Figure 4.

Figure 4 - Summary of the Biologically Effective Dose (BED $\alpha/\beta = 3$ Gy) used in all the reported schemes.

Although studies showed adequate homogeneity in patients' characteristics, they presented considerable heterogeneity in outcomes reported. Distinct definitions of treatment failure and different endpoints were employed, such as biochemical PFS, distant PFS or ADT-FS. The administration of ADT was not controlled at adjuvant (used in 37.8% of patients) or progression settings. No measures of association for dichotomous variables were related, given the studies design. Therefore, a quantitative analysis with meta-analysis was not performed.

Risk of bias across studies

Bearing in mind the studies design, the quality of the evidence about the outcomes evaluated by the GRADE system was assessed as low (Supplementary data 4). Overall, indirectness reduced quality is due to the lack of a balanced control group. The quality of evidence for acute toxicity was considered moderate, while the assessment of PFS, another critical outcome, lowered the grade to low. Even though there is a significant imprecision (PFS rates was mainly used, while most of studies did not reached the median PFS), the large effect presented and the lack of PSMA PET/PT (possibly reducing the demonstrated effect) kept it as low. ADT-FS, not a critical outcome, was judged as very low due to risk of bias, inconsistency, and imprecision. Controversially, evidence for local control rate was considered high for the large effect (rates around 100%), dose response, and plausible factor (use of low radiation doses) reducing effect items.

DISCUSSION

Summary of evidence

The present systematic review investigated the available evidence to state the effectiveness and safety of SBRT on ORPCP management. The included studies showed high homogeneity in their patients' characteristics, but moderate heterogeneity in outcomes reported.

Above all, aggressive treatment of metastases demands an accurate diagnostic method. In other words, a highly sensitive and specific test. Most patients evaluated in this review were restaged with Choline-based PET/CT at time of recurrence. This modality prevailed in the studies, but only one reported the use of PSMA PET/CT, which have an even greater accuracy in detecting PCa metastases (11,12,39). This may have led to

understaged diseases. That is, a higher false negative rate, and then some patients may have been undertreated. Novel researches within PSMA PET/CT can help to select candidates to SBRT, improve the chance of eradication of all oligometastatic sites, and then provide better outcomes in this setting, especially the distant PFS.

In 2015, Ost et al. (40) published a pooled analysis of all the available data up to that moment (18,24–27,41,42). With a total of 119 patients, the median distant PFS was 21 months (95% confidence interval [CI], 15–27). The 3- and 5-year distant PFS was 31% and 15%, respectively. A BED > 100 Gy was associated with a higher local control rate when compared to lower doses ($p = 0.01$). In another similar analysis, the same author investigated the pattern of failure after SBRT, and suggested that most patients relapse in a oligometastatic manner (43). Also, analyzing data from 4 studies (27,31,32,34) in which the pattern of recurrence was clearly described, only 5.4% of the participants had disseminated disease at first relapse. These data favor the idea that patients could benefit from repeated SBRT sessions until widespread progression, improving the disease control.

Among data collected from studies included in this review, the median PFS varies around 1 and 3 years in studies with low risk of bias. This outcome was still not reached in some series due to short follow-up. The 2-years PFS rates ranged from 30% to 63.5%. Many individuals did not present disease progression, but the follow-up period is short to state the rate of patients who might be cured of the metastatic disease.

The benefit of disease control could be put in place as the possibility of postponing the use of systemic therapies until widespread progression, keeping patients free from its adverse effects. In this context, data about ADT-FS were assessed. Despite only 5 studies have shown clear results, the data suggests that SBRT on metastases could defer ADT for a median time of about 1 to 3 years, consistently with PFS (27,28,32,35–37).

The overall survival is not a reliable outcome to measure the effectiveness of SBRT on ORPCP. It can be explained by the natural history of this disease, with usually indolent growing. These patients are long-term survivors and are frequently submitted to various systemic therapies along time.

The studies showed excellent local control rates of the metastases. It is noteworthy that all studies in which ever fractionation schedules had a BED $\geq$ 108 Gy (α/β = 3 Gy), no in-field recurrence was seen. That is to say a local control rate of 100% at last follow-up (25,27,32,36). Although satisfactory, worst results were reported by studies presenting a significant number of patients treated with lower radiation doses (24,29,30,33–35). Fractionation schedules with higher doses, such as 30 Gy in 3 fractions or single fraction $\geq$ 18 Gy, have proven effective and are good options for the management of these patients.

Concerning adverse effects, very low rates of acute and late toxicity were registered. Among all studies, only 1 patient had acute grade 3 toxicity. Two participants had late grade 3 events. Thus, SBRT is a safe approach to nodes and bone lesions in prostate cancer patients.

The number of publications concerning this topic is rapidly increasing. Nine of the articles included were published from 2016 onwards (29–37). At least 4 ongoing randomized trials are investigating the use of SBRT on ORPCP. The NCT01558427 (STOMP trial) is a phase 2 study being run from Belgium that compares the direct treatment of metastases (surgery or SBRT) with active surveillance. It will be completed soon. The NCT02680587 (ORIOLE trial) is comparing SBRT with observational approach. The NCT02685397 is studying the management of castration-resistant PCa with oligometastases. Finally, the NCT02759783 (CORE study) is evaluating SBRT versus conventional care, it also includes breast and lung cancer patients, though.

Limitations

The most considerable limitation about this evidence is the lack of a randomized controlled trial. Furthermore, restaging with PSMA PET/CT could give more accurate results. Follow-up period of the patients is still short. No study had more than 4 years of median follow-up. That is insufficient time to evaluate the possibility of curing the metastatic disease.

Among the systemic therapies offered, the type, duration and timing of administration was not predefined. This contributes to the heterogeneity of the interventions. The outcomes reported were moderately heterogeneous. Studies varied on endpoints and on definitions of treatment failure. No studies reported quality of life assessment, which would be more important in studies with a control group, though.

CONCLUSIONS

SBRT is a safe modality to treat nodes and bone metastases on PCa. Its use in the oligometastatic recurrent setting is promising, as it has the potential to provide long-term control of disease, deferring palliative androgen deprivation therapy, and probably not varying the overall survival. The local control rates are excellent, especially when higher radiation doses are employed (BED $\geq$ 108 Gy). Fractionation schedules such as 30 Gy in 3 fractions and single fraction $\geq$ 18 Gy showed to be effective. Further investigation with randomized controlled trials are required. This systematic review suggests that future studies use PSMA PET/CT on restaging. The trials must control the use of ADT in adjuvant and progression settings. Quality of life assessment can help to clarify the SBRT benefits.

Conflict of interest

The authors declare they have no conflicts of interest.

REFERENCES

1. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995 Jan;13(1):8–10.
2. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol. 2011 Mar 22;8(6):378–82.
3. Wolff RF, Ryder S, Bossi A, Briganti A, Crook J, Henry A, et al. A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer. Eur J Cancer. 2015 Nov;51(16):2345–67.
4. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU Guidelines on Prostate Cancer. Part II: Treatment of Advanced, Relapsing, and Castration-Resistant Prostate Cancer. Eur Urol. 2014 Feb;65(2):467–79.
5. Fakhrejahani F, Madan RA, Dahut WL. Management Options for Biochemically Recurrent Prostate Cancer. Curr Treat Options Oncol. 2017 May 22;18(5):26.
6. Botrel TEA, Clark O, dos Reis RB, Pompeo ACL, Ferreira U, Sadi MV, et al. Intermittent versus continuous androgen deprivation for locally advanced, recurrent or metastatic prostate cancer: a systematic review and meta-analysis. BMC Urol. 2014 Dec 25;14(1):9.
7. Katzenwadel A, Wolf P. Androgen deprivation of prostate cancer: Leading to a therapeutic dead end. Vol. 367, Cancer Letters. 2015. p. 12–7.
8. Nguyen PL, Alibhai SMH, Basaria S, D'Amico A V., Kantoff PW, Keating NL, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Vol. 67, European Urology. 2015. p. 825–36.
9. Rhee H, Gunter JH, Heathcote P, Ho K, Stricker P, Corcoran NM, et al. Adverse effects of androgen-deprivation therapy in prostate cancer and their management. BJU Int. 2015 Apr;115(S5):3–13.
10. Tilki D, Kim S Il, Hu B, Dall'Era MA, Evans CP. Ultrasensitive prostate specific antigen and its role after radical prostatectomy: A systematic review. J Urol. 2015;193(5):1525–31.
11. Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, et al. Comparison of PET imaging with a 68Ga-labelled PSMA ligand and 18F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2014;41(1):11–20.
12. Witkowska-Patena E, Mazurek A, Dziuk M. 68Ga-PSMA PET/CT imaging in

recurrent prostate cancer: Where are we now? Cent Eur J Urol. 2017;70(1):37–43.

13. Meredith G, Wong D, Yaxley J, Coughlin G, Thompson L, Kua B, et al. The use of ^{68} Ga-PSMA PET CT in men with biochemical recurrence after definitive treatment of acinar prostate cancer. BJU Int. 2016 Oct;118:49–55.
14. Folkert MR, Timmerman RD. Stereotactic ablative body radiosurgery (SABR) or Stereotactic body radiation therapy (SBRT). Adv Drug Deliv Rev. 2016 Jan 15;109:3–14.
15. Ost P, Bossi A, Decaestecker K, De Meerleer G, Giannarini G, Karnes RJ, et al. Metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer: A systematic review of the literature. Vol. 67, European Urology. European Association of Urology; 2015. p. 852–63.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int J Surg. 2010;8(5):336–41.
17. Vilela RA, Faria ET, Ferreira EB, Gadia R, Reis PED. The use of stereotactic body radiotherapy for oligometastatic recurrent prostate cancer treatment: a systematic review. PROSPERO: International prospective register of systematic reviews. CRD42017062556 2017.
18. Ahmed KA, Barney BM, Davis BJ, Park SS, Kwon ED, Olivier KR. Stereotactic body radiation therapy in the treatment of oligometastatic prostate cancer. Front Oncol. 2012;2(November 2011):215.
19. Tosoian JJ, Gorin MA, Ross AE, Pienta KJ, Tran PT, Schaeffer EM. Oligometastatic prostate cancer: definitions, clinical outcomes, and treatment considerations. Nat Rev Urol. 2016 Oct 11;14(1):15–25.
20. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org.
21. Joanna Briggs Institute. JBI Critical Appraisal Checklist for Case Series. Joanna Briggs Inst Crit Apprais tools. 2016;1–7.
22. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011 Apr;64(4):401–6.
23. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations [Internet]. The GRADE Working Group. 2013 [cited 2017 Mar 31]. Available from:

http://gdt.guidelinedevelopment.org/app/handbook/handbook.html

24. Casamassima F, Masi L, Menichelli C, Bonucci I, Casamassima E, Lazzeri M, et al. Efficacy of eradicative radiotherapy for limited nodal metastases detected with choline PET scan in prostate cancer patients. 2011;49–55.
25. Jereczek-Fossa BA, Beltramo G, Fariselli L, Fodor C, Santoro L, Vavassori A, et al. Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. Int J Radiat Oncol Biol Phys. 2012;82(2):889–97.
26. Muacevic A, D M, Kufeld M, D M, Rist C, D M, et al. Safety and feasibility of image-guided robotic radiosurgery for patients with limited bone metastases of prostate cancer. URO. 2013;31(4):455–60.
27. Decaestecker K, Meerleer G De, Lambert B, Delrue L, Fonteyne V, Claeys T, et al. Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence. 2014;1–10.
28. Detti B, Bonomo P, Masi L, Doro R, Cipressi S, Iermano C, et al. Stereotactic radiotherapy for isolated nodal recurrence of prostate cancer. World J Urol. 2015 Aug 24;33(8):1197–203.
29. Muldermans JL, Romak LB, Kwon ED, Park SS, Olivier KR. Stereotactic body radiation therapy for oligometastatic prostate cancer. Int J Radiat Oncol Biol Phys. 2016 Jun 1;95(2):696–702.
30. Napieralska A, Miszczyk L, Stapor-Fudzinska M. CyberKnife Stereotactic Ablative Radiotherapy as an Option of Treatment for Patients With Prostate Cancer Having Oligometastatic Lymph Nodes: Single-Center Study Outcome Evaluation. Technol Cancer Res Treat. 2016;15(5):661–73.
31. Ingrosso G, Trippa F, Maranzano E, Carosi A, Ponti E, Arcidiacono F, et al. Stereotactic body radiotherapy in oligometastatic prostate cancer patients with isolated lymph nodes involvement: a two-institution experience. World J Urol. 2017;35(1):45–9.
32. Pasqualetti F, Panichi M, Sainato A, Matteucci F, Galli L, Cocuzza P, et al. [(18)F]Choline PET/CT and stereotactic body radiotherapy on treatment decision making of oligometastatic prostate cancer patients: preliminary results. Radiat Oncol. 2016 Dec 22;11(1):9.
33. Napieralska A, Miszczyk L, Stapor-Fudzinska M. CyberKnife stereotactic radiosurgery and stereotactic ablative radiation therapy of patients with prostate

cancer bone metastases. Neoplasma. 2016 Jan;63(2):304–12.

34. Jereczek-Fossa BA, Fanetti G, Fodor C, Ciardo D, Santoro L, Francia CM, et al. Salvage Stereotactic Body Radiotherapy for Isolated Lymph Node Recurrent Prostate Cancer: Single Institution Series of 94 Consecutive Patients and 124 Lymph Nodes. Clin Genitourin Cancer. 2017;15(4):e623–32.
35. Triggiani L, Alongi F, Buglione M, Detti B, Santoni R, Bruni A, et al. Efficacy of stereotactic body radiotherapy in oligorecurrent and in oligoprogressive prostate cancer: new evidence from a multicentric study. 2017;(April):1–6.
36. Bouman-Wammes EW, van Dodewaard-De Jong JM, Dahele M, Cysouw MCF, Hoekstra OS, van Moorselaar RJA, et al. Benefits of Using Stereotactic Body Radiotherapy in Patients With Metachronous Oligometastases of Hormone-Sensitive Prostate Cancer Detected by [18F]fluoromethylcholine PET/CT. Clin Genitourin Cancer. 2017 Mar 29;
37. Habl G, Straube C, Schiller K, Duma MN, Oechsner M, Kessel KA, et al. Oligometastases from prostate cancer: local treatment with stereotactic body radiotherapy (SBRT). BMC Cancer. 2017 Dec 22;17(1):361.
38. D'Amico A V, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA. 1998 Sep 16;280(11):969–74.
39. Morigi JJ, Stricker PD, van Leeuwen PJ, Tang R, Ho B, Nguyen Q, et al. Prospective Comparison of 18F-Fluoromethylcholine Versus 68Ga-PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy. J Nucl Med. 2015;56(8):1185–90.
40. Ost P, Jereczek-Fossa BA, As N Van, Zilli T, Muacevic A, Olivier K, et al. Progression-free Survival Following Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Treatment-naive Recurrence: A Multi-institutional Analysis. Eur Urol. 2016;69(1):9–12.
41. Schick U, Jorcano S, Nouet P, Rouzaud M, Vees H, Zilli T, et al. Androgen deprivation and high-dose radiotherapy for oligometastatic prostate cancer patients with less than five regional and/or distant metastases. Acta Oncol. 2013;52(8):1622–8.
42. Aitken K, Tree A, Thomas K, Nutting C, Hawkins M, Tait D, et al. Initial UK

Experience of Stereotactic Body Radiotherapy for Extracranial Oligometastases: Can We Change the Therapeutic Paradigm? Clin Oncol. 2015;27(7):411–9.

43. Ost P, Jereczek-Fossa BA, Van As N, Zilli T, Tree A, Henderson D, et al. Pattern of Progression after Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Nodal Recurrences. Clin Oncol. 2016 Sep;28(9):e115–20.