Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Recurrence

A Meta-analysis

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Purpose: The purpose of this study was to evaluate the treatment efficacy of stereotactic body radiotherapy (SBRT) in oligometastatic prostate cancer recurrence and to assess whether there is any relationship between biologically effective dose (BED) and local control (LC).

Materials and Methods: Eligible studies were identified on Medline, Embase, and the Cochrane Library, and the proceedings of annual meetings through May 2019 were also identified. A meta-regression analysis was performed to assess whether there is a relationship between BED and LC. In the univariate analysis, studies were separated by the study design, the number of metastatic sites, the site of metastases, radiotherapy machine, and prostate-specific antigen level at the time of SBRT. A *P*-value <0.05 was considered significant.

Results: Twenty-three observational studies with a total of 1441 lesions treated were included in the meta-analysis. The proportional rate of LC, progression-free survival, and androgen deprivation–free survival was 0.976 (95% confidence interval [CI]: 0.96-0.98), 0.413 (95% CI: 0.378-0.477), and 20.1 months (95% CI: 14.5-25.6), respectively. In the meta-regression, a linear relationship between BED and LC was detected ($P = 0.017$). Stratifying the BED into 3 levels (BED < 100 Gy3, BED 100 to 130 Gy3, and BED > 130 Gy3), a significant difference was observed between BED < 100 Gy3 (LC = 88%) versus BED > 100 Gy3 (LC = 96%). The rate of any acute and late grade ≥2 toxicity was 1.3% and 1.2%, respectively.

Conclusions: The LC rate with SBRT was excellent with minimal severe acute/late toxicity. Our data suggest a dose relationship between BED and LC, with BED > 100 Gy3 resulting in better rates of LC.

Key Words: prostate cancer, oligometastases, recurrence, stereotactic body radiotherapy

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Oligometastasis is a term proposed by Weichselbaum and Hellman[1] that is also called oligometastatic state and represents an intermediate state between widely disseminated and initial metastatic disease. Hellman and Weichselbaum[2] were the first to formulate the hypothesis that local therapies may cure oligometastatic disease. In their conception, the intermediate state of distant spread disease reflects a transition state wherein the disease still is with a low burden, and with a slow metastatic spreading capacity.[1,2]

In the last years, the metastatic process has been well known for the identification of cellular clones in metastatic tissue biopsies.[3] The identification of cellular clones has shown that the dissemination to developing new metastases is a common phenomenon and that metastatic spread does not always originate from the primary tumor.[3,4] This finding has supported the concept that the early treatment and control of oligometastatic sites can avoid subsequent dissemination and, consequently, can better survival.[5]

According to the hypothesis of Hellman and Weichselbaum,[1,2] the use of ablation treatments to all oligometastatic sites could cure them. This hypothesis has been initially confirmed in cohort studies of the surgical resection or ablation of the oligometastatic disease from colorectal cancer and renal cell carcinoma.[6]

Prostate cancer (PCa) is the most frequent solid tumor in men, and, currently, its natural history is well known.[7] PCa commonly metastasizes to bones and lymph nodes with uncommon visceral involvement during its natural course.[7] In recent years, due to a prominent technological advance in the diagnostic images, the oligometastatic state of PCa can be diagnosticated with high precision.[8]

During the last decade, radiotherapy has also passed by a tremendous technological advance resulting in the development of stereotactic body radiotherapy (SBRT).[9] SBRT is an external radiotherapy technique that delivers high ablative doses in a few fractions.[9] The use of SBRT as an ablative technique for treating oligometastatic PCa has recently increased significantly. The initial results of small cohorts using SBRT to eradicate the oligometastatic PCa sites show excellent local control (LC) with minimal severe toxicity.[10,11] However, the studies are heterogeneous with several different criteria of treatment selection, radiation dose and fractionation, different number of metastatic sites, mixed metastatic sites (bone, lymph nodes, and visceral), distinctive treatment machine (Cyberknife or LINAC), variated initial prostate-specific antigen (PSA) level at the time of SBRT, and different study design. All these factors make it difficult for the interpretation of the SBRT results to be widely applied in clinical practice.

In this context, we designed a meta-analysis of clinical studies to evaluate the treatment outcomes with SBRT in oligometastatic PCa patients exploring whether clinical and technical factors have some impact on the SBRT outcome.

MATERIALS AND METHODS

We conducted this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews

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and Meta-analysis (PRISMA) statement and the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guideline.[12] The approval of the Ethics Committee was not required. Two reviewers performed the research, selected the articles initially by title and abstract, and then read the full article.

A systematic search was conducted by 2 of the investigators in PubMed, the Cochrane Central Register of Controlled Trials, and Embase for studies assessing the treatment outcomes of SBRT for oligometastatic PCa. We have used the following terms ("Prostatic Neoplasms"[Mesh]" OR "Prostate Cancer") AND ("Local"[Mesh] OR "Local Recurrences" OR " Metastasis"[Mesh] "OR "Lymphatic Metastasis"[Mesh] OR "Oligometastatic disease" OR "Recurrent prostate cancer" OR "Oligometastatic state" OR "Recurrence" OR "Lymph node recurrence") AND ("Salvage Therapy"[Mesh] OR "Salvage Treatment" OR "Radiosurgery"[Mesh] OR "Stereotactic Radiosurgery" OR "LINAC Radiosurgery" OR "Linear Accelerator Radiosurgery" OR "CyberKnife Radiosurgery" OR "Stereotaxic Techniques"[Mesh] OR "Stereotactic Techniques" OR "Techniques, Stereotactic" OR "SBRT").

The lists containing the articles and reviews were checked, and possible related articles were tracked to complement the electronic query. Searches were performed from January 2000 to March 2019 and were limited to publications in English.

Study Selection

We included only studies evaluating the treatment outcomes of SBRT in patients with oligometastatic PCa independently of the number of sites and sites of metastatic lesion. Retrospective, prospective, nonrandomized, and randomized studies were included. Case reports were excluded.

Patients

We included studies of patients with the diagnosis of PCa previously treated with surgery, radiotherapy or a combination of both who developed recurrence or progression from PCa. Studies using any kind of positron emission tomography/computed tomography (choline, fluorodeoxyglucose, or prostate-specific membrane antigen) and a combination or not with other imaging modalities (computed tomography and/or nonrelapse mortality) to restage the oligometastatic state were allowed. Patients could be hormone naive or not, in using of androgen deprivation or not.

Intervention

We evaluate the efficacy of SBRT for oligometastatic PCa recurrence. Thus, studies using any fractionation of SBRT to treat systemic recurrence or progression of PCa were included. Studies using Cyberknife or LINAC to perform the SBRT were allowed.

Outcomes

Primary outcomes were LC, progression-free survival (PFS), androgen deprivation therapy–free survival (ADT-FS), and toxicity rate classified by Radiation Therapy Oncology Group or common toxicity criteria scale. Toxicity was classified as acute and late, and we reclassified both acute and late toxicity as any acute/late toxicity combining the development of gastrointestinal toxicity, genitourinary toxicity, pain, and fracture. We include in our analysis only toxicity with grade ≥ 2. The following subgroups were created and evaluated with meta-regression analysis: biologically effective dose (BED), treatment machine (Cyberknife or LINAC), number of metastatic sites (≤ 3 or 4 to 5), initial PSA at the time of SBRT, type of metastatic site (bone, lymph node, or mixed), and study design (retrospective or prospective study). The meta-regression investigated whether there was any relationship between these variables and LC.

Clinical Data

The data from the patient, treatment characteristics, and outcomes for all studies included were retrieved. The following characteristics were retrieved: number and sites of lesions treated with SBRT, PSA value before SBRT, SBRT treatment machine, use of androgen deprivation therapy (ADT), median follow-up, PFS, LC, ADT-FS, and acute and late toxicity. Two reviewers were in charge to gather all data for all studies included using a standardized data extraction form. A third reviewer (A.C.F.) was used to solve different issues by consensus.

Methodological Quality Assessment

Two authors (G.A.V./C.A.V.) independently judged the potential for risk of bias of the studies using the MINORS, a methodological index for nonrandomized studies. The items were scored 0 if not reported; 1 when reported but inadequate; and 2 when reported and adequate. The maximum MINORS score is 16 points for noncomparative studies. We considered low risk of bias when studies fulfilled all MINORS criteria; or when they scored $>70\%$ in the global scale. We considered high risk of bias in all other scores. If only abstracts were available, they were automatically assessed to be at high risk of bias. The consensus was reached by the 2 reviewers, and, when there was disagreement, a third reviewer was decisive.

Data Synthesis and Analysis

The rates of events of each outcome were calculated using the proportion rate (PR) of patients who developed outcomes of interest with the 95% confidence interval (CI).[13] The I^2 statistic assessed statistical heterogeneity. An I^2 value of $<25\%$ was interpreted as a low level of heterogeneity.[13,14] We used the random-effect model due to a relevant variation in studies' characteristics. To enhance the comparability of the different therapeutic regimens and to estimate the relationship between radiation dose and LC, the BED of the various radiation schedules was estimated. When several schedules were used in the same study, we considered the median dose for the calculations. Two distinct methods were utilized to examine and explain the diversity among results of different studies: subgroup analyses and meta-regression.

A meta-regression analysis estimated the relationship between BED and LC. The BED was calculated by $BED = nD(1+[D/\{\alpha/\beta\}])$, where n = number of fractions, D = dose/fraction, nD = total dose, and α/β is the alpha/beta ratio and is considered to be 3 for PCa. A P-value <0.05 was considered significant in all analyses. The meta-analysis was performed using the Open Meta-Analyst free open software.

RESULTS

We identified 23 studies[10,11,15–34] including 1441 lesions that received SBRT to control the oligometastatic PCa. Figure 1 describes the search strategy and the reasons for the exclusion of some studies.

Fifteen studies were retrospective, and there were 8 prospective studies, with 2 of them being phase II randomized trials, and all of them were published from 2008 to 2019. The Cyberknife was used in 7 studies, whereas 13 used LINAC, and 3 studies did not give any information about the radiotherapy machine to perform SBRT. Table 1 summarizes the characteristics of the 23 studies included in the present meta-analysis. Using the MINORS score for rating the risk of bias of studies, we stipulated high risk of bias as a MINORS score $<70\%$. In general, pooling all the studies, the mean value of the score was 75% (68.75% to 100%). Two studies achieved an ideal MINORS score of 100%, and these studies were also the prospective studies included in our meta-analysis, and only 1 study published in abstract form reached

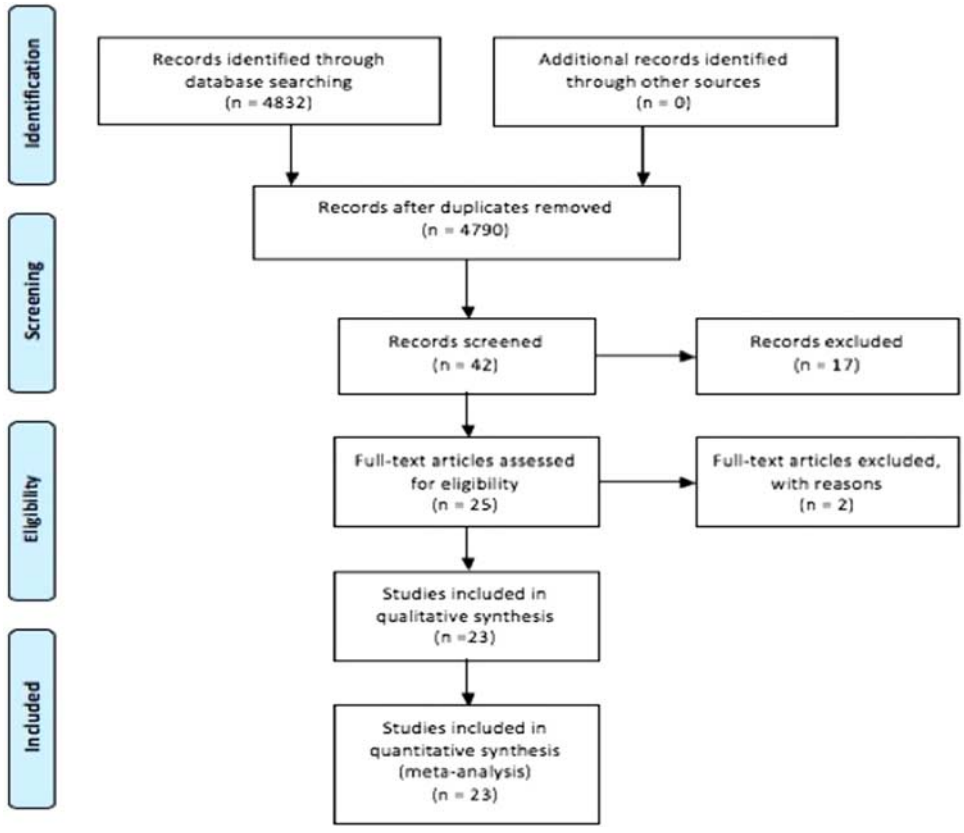

FIGURE 1. Flowchart according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). full color online

68.75%, as demonstrated in Figure 2. Considering the primary treatment performed before SBRT described in the studies, external beam radiation therapy (EBRT)+ADT, radical retropubic prostatectomy (RRP), and RRP+EBRT were the most common ones being described in 19, 17, and 12 studies, respectively (Supplemental Material, Fig. 1a, Supplemental Digital Content 1, http://links.lww.com/AJCO/A312). At the patient level, RRP +EBRT—35.7%, RRP—27.6%, and EBRT+ADT—26.9% were the most frequent treatments included in the studies (Supplemental Material, Fig. 1b, Supplemental Digital Content 1, http://links.lww.com/AJCO/A312).

LC

All studies reported the LC as an outcome. In total, the 23 studies gathered 1441 lesions treated by SBRT; the PR for LC including all studies was 0.976 (95% CI: 0.96-0.98) (Fig. 3). In the univariate analysis with meta-regression, no significant difference was observed between the subgroups comparing ≤ 3 and 4 to 5 metastatic sites; site of metastases stratified by mixed, bone, and lymph node; treatment machine (LINAC vs. CK); and initial PSA (≤ 4.5 vs. >4.5), as described in Table 2. A significant relationship was identified between BED and LC in the meta-regression ($P=0.017$) (Fig. 4). Stratifying the BED into 3 levels, BED <100 Gy3, 100 to 130 Gy3, and BED >130 Gy3, a significant difference for LC was observed among the studies of BED <100 Gy3 and other levels, as shown in Figure 5 and Table 2.

PFS

Ten studies (762 patients) had PFS as an outcome. Pooling all studies, the SBRT resulted in a PR of 0.413 (95% CI: 0.378-0.477) (Fig. 6A).

ADT-FS

Five studies reported ADT-FS as an outcome. The pooled ratio of all studies resulted in a mean ADT-FS of 20.1 months (95% CI: 14.5-25.6) (Fig. 6B).

Acute and Late Toxicity

Eighteen studies (1152 lesions) reported acute toxicity. Combining all studies, the proportional rate of any acute toxicity grade ≥ 2 was 0.013 (95% CI: 0.007-0.02) (Fig. 7). Evaluating the late toxicity, 18 studies reported their results. Pooling the outcomes of these studies, the proportional rate of any late toxicity grade ≥ 2 was 0.012 (95% CI: 0.005-0.018) (Fig. 8).

DISCUSSION

The evidence on the treatment of oligometastatic PCa recurrence with SBRT predominantly consists of small heterogeneous studies.[14–33] The present meta-analysis aimed to reduce the heterogeneity by pooling data from different institutions treating oligometastatic PCa recurrence with SBRT. We evaluate the SBRT outcomes in patients with oligometastatic PCa recurrence using broad inclusion criteria such as patients receiving ADT or not, patients with any number of metastatic sites, or any site of metastases, treated by any radiotherapy machine, and any SBRT schedule and PSA level at the time of SBRT. Using this strategy, we identify 23 studies with 1441 lesions treated with SBRT. Our outcomes confirm that SBRT produces an excellent LC rate for oligometastatic PCa recurrence, and BED has a direct relationship with the LC. The BED ranged from 88 to 162 Gy3, and, by stratifying it into 3 levels, it was evident that a BED >100 Gy3 should be recommended,

TABLE 1. Characteristics of Studies Included in the Meta-analysis

References	No. Lesions	BED (Median) (Gy3)	Age (Median) (y)	PSA (Median)	No. Sites	RT Machine	Study Design	Sites of Metastases
Casamassima et al[10]	25	109	68	NR	NR	LINAC	R	LND
Jereczek-Fossa et al[11]	38	90	68	3.2	≤3	Cyberknife	R	Bone, LND
Ahmed et al[17]	21	153	65	NR	≤5	LINAC	P	Bone, LND, viscera
Berkovic et al[16]	29	133	67	6.6	≤3	LINAC	R	Bone, LND
Muacevic et al[15]	64	153	66	5.4	≤2	Cyberknife	P	Bone
DecaesteCyberknifeer et al[18]	70	133	59	5.1	≤3	LINAC	P	Bone, LND, viscera
Ponti et al[19]	18	116	72	6.6	≤2	LINAC	R	LND
Pasqualetti et al[24]	45	162	69	3.43	≤3	LINAC	P	Bone, LND
Muldermans et al[25]	81	102	70	1.9	≤5	LINAC	R	Bone, LND, viscera
Detti et al[20]	39	144	65	4.1	NR	Cyberknife	R	LND
Ost et al[21]	119	80 to >140	69		≤3		R	Bone, LND, viscera
Napieralska et al[22]	31	134	69	4.7	≤5	Cyberknife	R	LND
Napieralska et al[23]	71	91	66	2.16	≤5	Cyberknife	R	Bone
Ingrosso et al[29]	47	115	74	4.2	NR	LINAC	R	LND
Bouman-Wammes et al[26]	54	130	68	4.5	≤4	LINAC	R	Bone, LND
Triggiani et al[27]	209	116	69	2.4	≤3	LINAC	P	Bone, LND
Habl et al[28]	20	106	72	1.99	≤5	LINAC	R	Bone
Jereczek-Fossa et al[35]	124	88	70	3.5	≤5	LINAC	R	LND
Ost et al[32]	31	130	62		≤3	LINAC	R	Bone, LND, viscera
Pasqualetti et al[34]	78	108	69	3.4	≤5	LINAC	R	Bone, LND
Siva et al[30]	50	153	70	6.4	≤3		P	Bone, LND
Fanetti et al[31]	77	88	72	3.35	≤5	Cyberknife	R	Bone
Conde Moreno et al[33]	67	—		NR	≤5	—	P	Bone, LND

BED indicates biologically effective dose; LND, lymph node dissection; NR, not reported; P, prospective PSA, prostate-specific antigen, R, retrospective; RT, radiotherapy.

once no significant difference between BED 100 to 130 Gy3 versus BED > 130 Gy3 was observed. This finding is relevant for clinical practice to guide the radiation oncologist to choose a different SBRT schedule depending on the clinical situation. The association observed here is similar to the relationship between BED with SBRT and LC in other tumors. In lung cancer, for instance, Zhang et al,[36] in a meta-analysis including 34 observational studies with a total of 2587 patients, obtained a higher 2- or 3-year overall survival rate in the BED of 100 to 140 Gy10 than in the BED of <100 Gy10.

Moreover, the relationship between radiotherapy dose and LC is well known for PCa. A meta-analysis of randomized

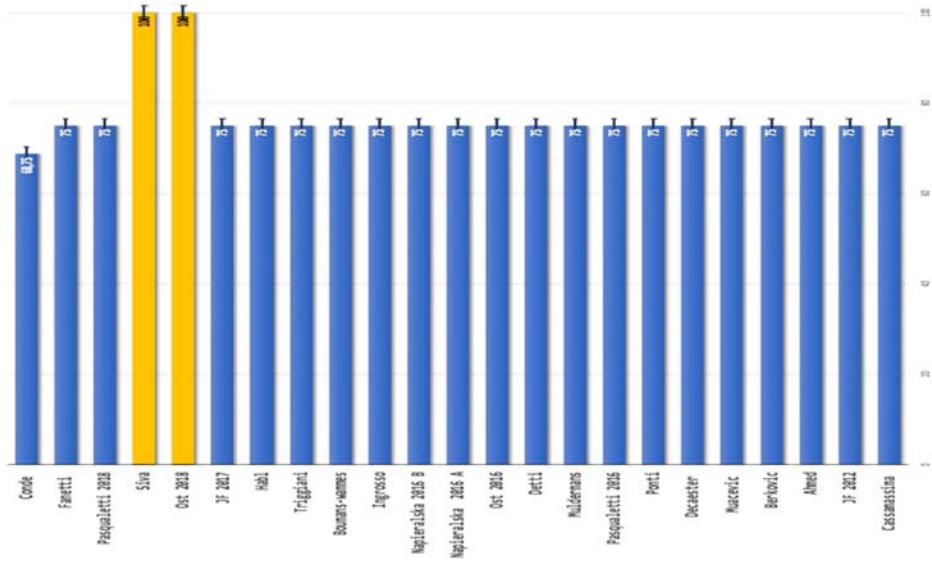

FIGURE 2. MINORS (methodological index for nonrandomized studies) score rating of each study. full color online

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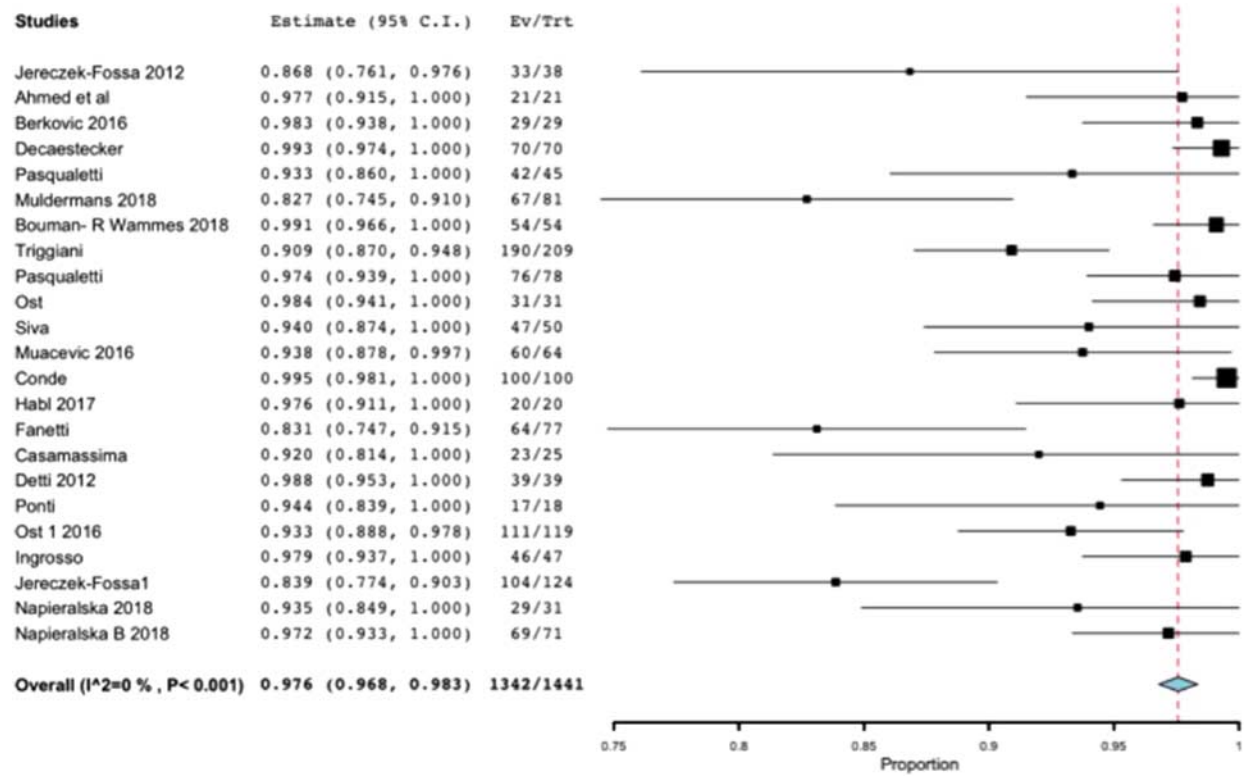

FIGURE 3. Meta-analysis of local control including all studies. CI indicates confidence interval; Ev/Trt, event/treated. full color online

clinical trials published in 2009 compared low radiotherapy dose (< 74 Gy) versus high dose (≥ 74 Gy).[37] This study showed a clear and significant benefit on biochemical control for high-dose radiotherapy and a linear relationship between total dose and biochemical control.

As regards the other potential factors that could affect the SBRT outcome, in the subgroup analysis, none of the factors assessed showed any association with the LC. Thus, it is reasonable to consider SBRT for patients with up to 5 sites of oligometastatic PCa recurrence, independently of the site of metastases and the PSA value at the moment of SBRT.

The LC was also not influenced by the study design. In the univariate analysis, no significant difference in the LC on comparing the rates in retrospectives studies (LC = 95.6%) and prospective studies (LC = 98%) was detected, which attests to the reproducibility of SBRT results in the real world.

Five studies included patients with oligometastatic PCa recurrence who were hormone naive and reported ADT-FS as an outcome. The practical benefit of LC is to translate it into the chance of postponing the use of systemic therapies until widespread PCa progression, keeping patients free from its adverse effects. SBRT produced around 20 months of ADT-FS, being a plausible treatment option for selected oligometastatic PCa recurrence patients. The high LC rate achieved with SBRT provides a satisfactory rate of PFS. The proportional rate of PFS, including 10 studies with 720 lesions treated, was 0.41 (95% CI: 0.37-0.44). However, it is imperative to highlight that the majority of studies had a short follow-up (median: 2 y) to evaluate the PFS for PCa as an outcome. The short follow-up time of the studies is also the main reason why we do not evaluate overall survival as an endpoint.

Concerning adverse effects, SBRT had dismal rates of acute and late grade ≥ 2 toxicity. Even when grouping all kinds of toxicities (genitourinary, gastrointestinal, pain, and fracture),

TABLE 2. Meta-regression Analysis of Potential Factors Associated With the Local Control

Covariates	Studies	Coefficients	Lower Bound	Upper Bound	*P*
Study design					
Retrospective	15	Ref			
Prospective	8	0.03	0.003	0.07	0.08
No. sites					
≤ 3 sites	12	Ref			
4-5 sites	10	0.1	0.05	0.2	0.601
Sites of metastases					
Mixed	13	Ref			
Bone	4	0.19	0.071	0.33	0.472
LND	6	0.16	0.062	0.30	0.497
Radiotherapy machine					
Cyberknife	7	Ref			
LINAC	13	0.19	0.066	0.33	0.423
BED level (Gy3)					
< 100	4	Ref			
100-130	6	0.068	0.01	0.02	0.021
> 130	9	0.066	0.011	0.021	0.018
PSA at time of SBRT					
≤ 4.5	13	Ref			
> 4.5	7	0.02	0.01	0.07	0.192

BED indicates biologically effective dose; LND, lymph node dissection; PSA, prostate-specific antigen; Ref, reference; SBRT, stereotactic body radiotherapy.

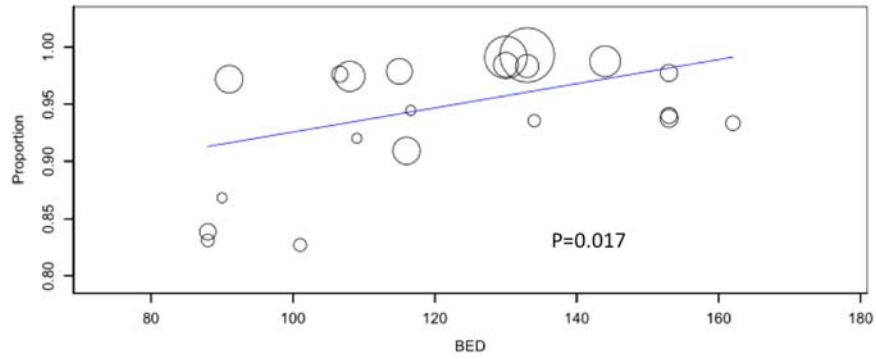

FIGURE 4. Meta-regression analysis between local control rate and biologically effective dose (BED). full color online

the occurrence of grade 2 acute/late toxicity was extremely low, and any grade 3 toxicity was very rare. Regarding the RT machines, seven used cyberknife and fifteen LINAC machines to delivery the treatment, and no significant association as for the LC as the toxicity was observed.

Although our data demonstrate an impressive effect of SBRT on LC for oligometastatic PCa recurrence, they have some limitations. First, the follow-up period of patients was too short for a disease with a long natural history. Second, the BED was calculated using a median value of several fractionations' schedule. Third, among the studies, the type, duration, and timing of androgen deprivation were not well established. However, none of these factors change the interpretation of the outstanding effect of SBRT on LC with low toxicity for oligometastatic PCa recurrence.

CONCLUSIONS

In our analysis, SBRT for oligometastatic PCa recurrence produced excellent LC with minimal acute and late severe toxicity. Our data suggest a dose relationship between BED and LC of lesions treated by SBRT. When studies were classified according to the BED level, it was explicit that patients treated with low BED (BED < 100 Gy3) have lower LC than those treated with high BED (BED 100 to 130 Gy3). The meta-regression analysis did not detect any association between LC and the number of metastatic sites, PSA level at the time of SBRT, and site of metastasis. These findings reinforce the broad application of the SBRT in this clinical scenario.

Our study also demonstrated that SBRT is capable of postponing the administration of ADT with a satisfactory PFS. However, based on bias in the initial studies, the heterogeneity

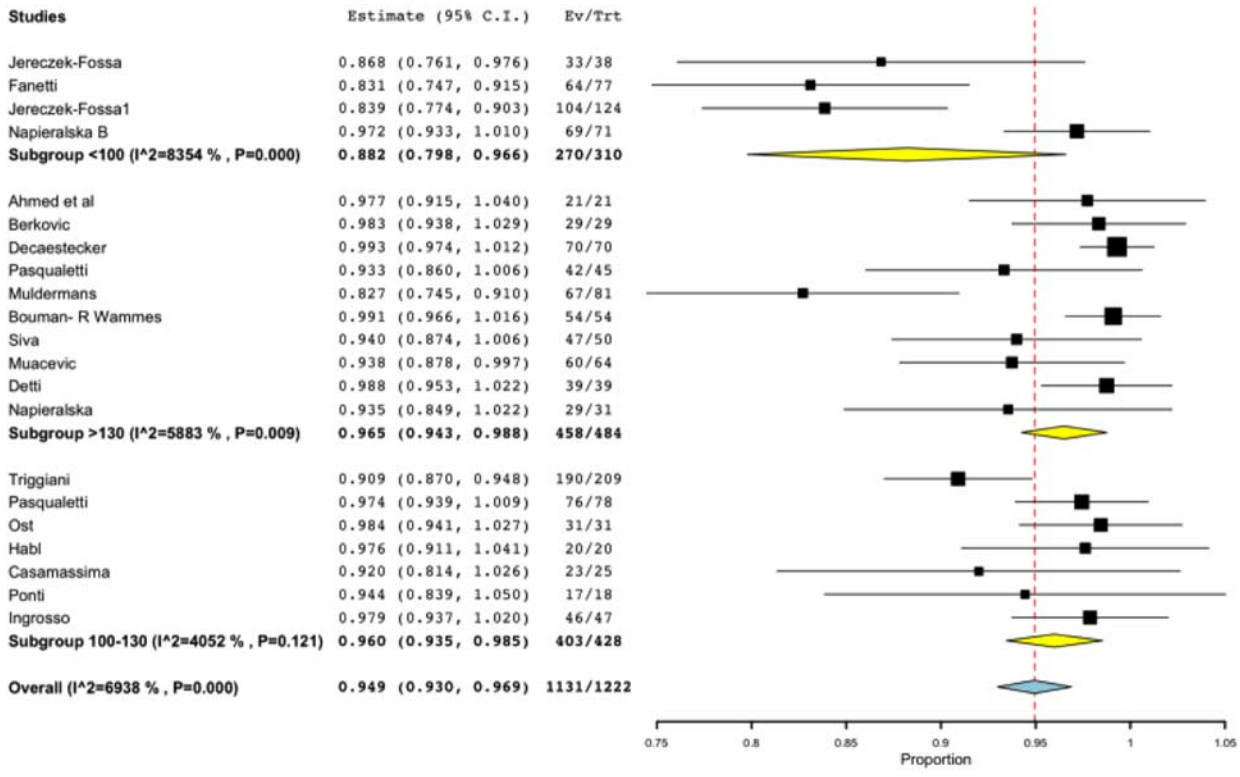

FIGURE 5. Subgroup analysis evaluating local control according to the biologically effective dose level. CI indicates confidence interval; Ev/Trt, event/treated. full color online

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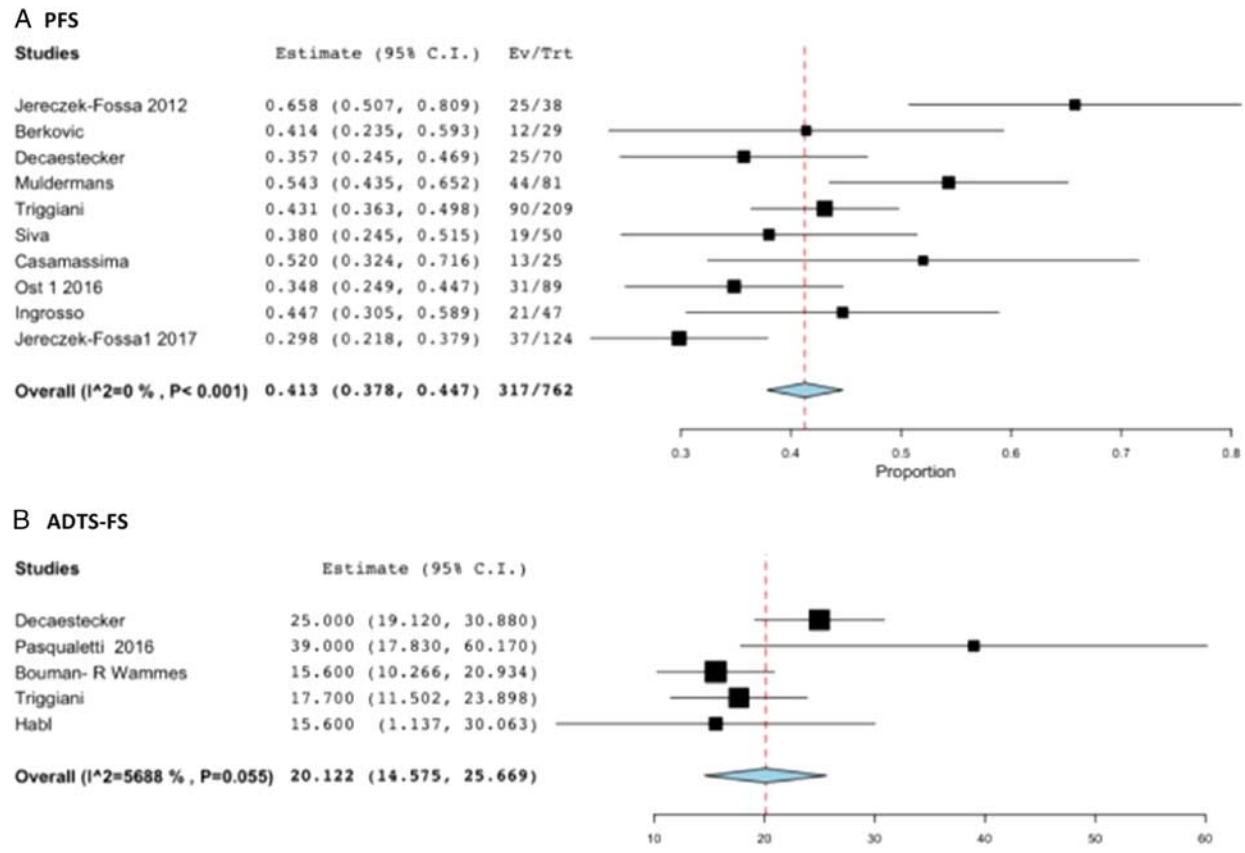

FIGURE 6. A, PFS rate of studies reporting this outcome. B, Mean ADT-FS of studies reporting this outcome. ADT-FS indicates androgen deprivation therapy–free survival; CI, confidence interval; Ev/Trt, event/treated; PFS, progression-free survival. full color online

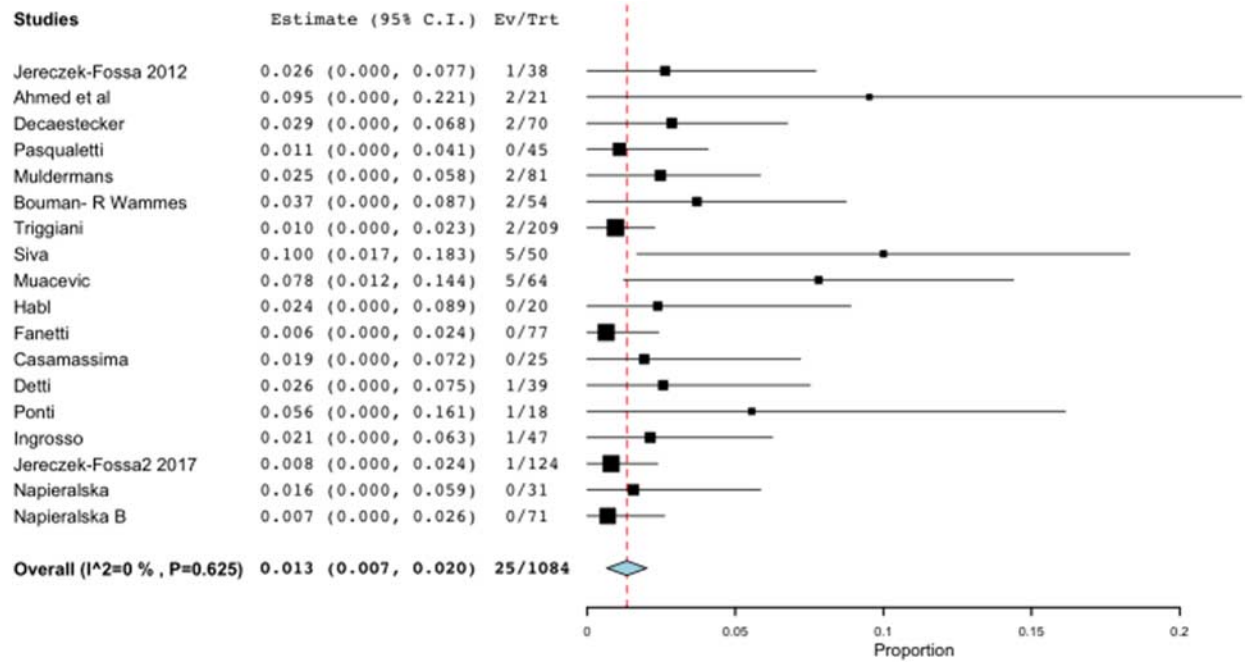

FIGURE 7. Any acute toxicity grade ≥2. CI indicates confidence interval; Ev/Trt, event/treated. full color online

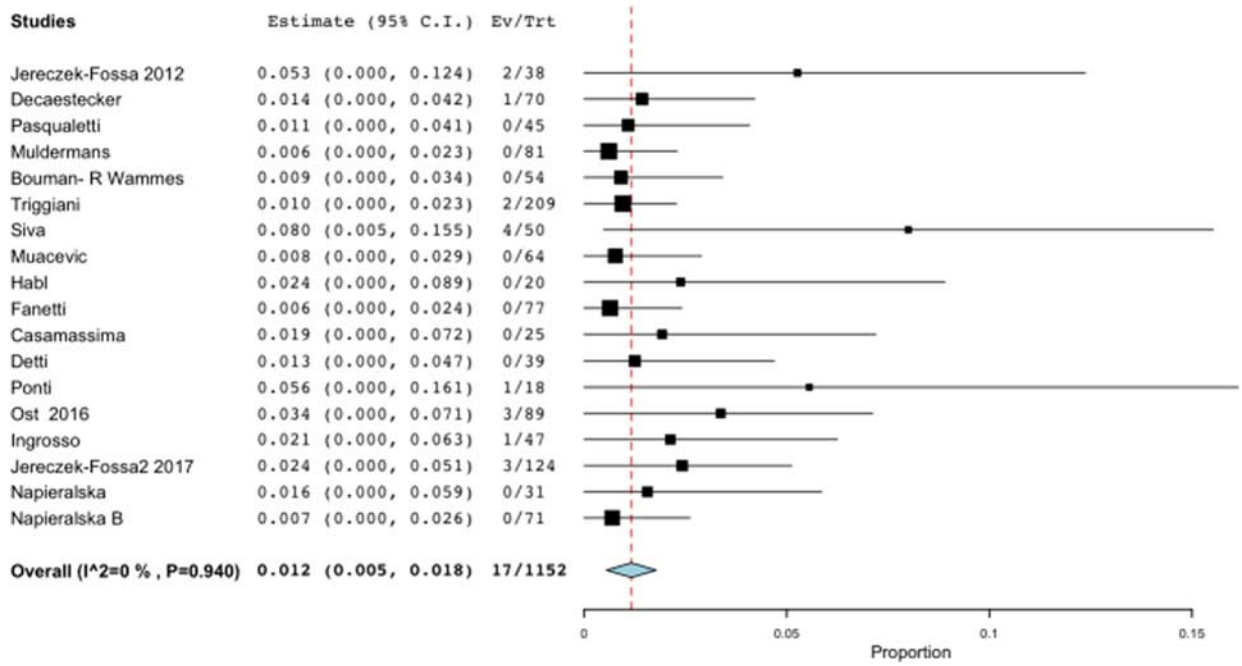

FIGURE 8. Any late toxicity grade ≥2. CI indicates confidence interval; Ev/Trt, event/treated. full color online

among them, and the limitation of the meta-analysis of observational studies, more evidence is required to establish the optimal BED for patients with oligometastatic PCa recurrence. We hope to examine or confirm the relationship between BED and LC/survival in future randomized clinical studies.

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