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## SYSTEMATIC REVIEW

# Stereotactic body radiotherapy (SBRT) in metachronous oligometastatic prostate cancer: a systematic review and meta-analysis on the current prospective evidence

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**Objective:** In contrast to traditional views of incurability, patients with oligometastatic disease present with an opportunity for disease eradication with aggressive treatment. There is mounting evidence in support of the role of stereotactic body radiotherapy (SBRT) in oligometastatic prostate cancer (OMPC).
**Methods:** MEDLINE and EMBASE were queried for prospective cohort studies reporting the outcomes of metachronous OMPC treated with SBRT. The primary outcome was overall local control. Secondary outcomes included androgen deprivation therapy-free survival (ADTFS), biochemical recurrence free survival (BCFS), and progression-free survival (PFS). When appropriate, these endpoints were combined in a meta-analysis.
**Results:** We screened 356 abstracts and identified 10 studies to include in our analysis, with a total of 653 patients and 1,111 lesions. The maximum number of lesions included in any single study ranged from 3 to 5. PET-CT staging occurred in 92.4% of all patients. SBRT dose varied, with $BED_{1.5}$ ranging from 152 to 408. Only one Grade 3 bone toxicity was observed. Meta-analysis reported an overall local control rate of 97% (95% CI, 94–100). Median ADTFS was 24.7 months (95% CI, 20.1–29.2 months). Two-year BCFS, PFS, and ADTFS were 33% (95% CI, 11–55), 39% (95% CI, 24–54), and 52% (95%CI, 41–62), respectively. Patients treated with SBRT were half as likely to experience PSA progression than those on observation when looking at randomized control trial data alone.
**Conclusion:** SBRT appears to be effective in controlling overall disease burden in metachronous OMPC patients and is associated with minimal significant toxicity. The current prospective literature is scarce, and further prospective data are needed to guide treatment recommendations.
**Advances in knowledge:** This study provides a comprehensive summary of the prospective evidence reporting the outcomes of SBRT in the management of OMPC patients. We quantify the rates of local control, biochemical-free recurrence, progression-free survival, and ADT-free survival through meta-analysis.

## INTRODUCTION

The oligometastatic state is a clinical state between localized disease and widespread metastases. In contrast to traditional views of incurability, patients with oligometastatic disease present with an opportunity for disease eradication with aggressive treatment. Oligometastases can manifest clinically as synchronous or metachronous disease. Patients with synchronous oligometastases present *de novo* with limited metastatic disease and an untreated primary. Conversely, patients who have had definitive therapy for their primary tumors may have limited recurrence after a disease-free period with metachronous oligometastases.[1]

Several trials have shown a benefit of additional local treatment of the primary tumor when compared to systemic therapy alone in synchronous oligometastatic prostate cancer (OMPC) patients with low disease burden.[2] Similarly, there is mounting interest in investigating the role of radical management of the metastatic lesions themselves in metachronous disease. Recent phase 2 studies have reported promising outcomes utilizing stereotactic body radiotherapy (SBRT) in the treatment of the metastatic lesions in this patient population.[3,4]

We performed a systematic review and meta-analysis with the aim to synthesize the existing prospective evidence in

order to provide oncologists guidance in the management of OMPC patients.

## METHODS

*Search Strategy and Criteria:* This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[5] MEDLINE and EMBASE databases were queried for studies that prospectively collected and reported the outcomes of SBRT in the management of metachronous OMPC from inception to April 1, 2020. Metachronous OMPC was defined as clinical or radiological recurrent disease, with five or less lesions, in patients who have previously had primary management of prostate cancer using local treatment modalities such as surgery or radiotherapy. SBRT was defined as conformal, external beam radiotherapy that accurately delivers high-dose irradiation within 1–10 fractions.[6] The full search strategy is available in Supplementary Material 1. Search results were imported into Covidence (Veritas Health Innovation, Melbourne, Australia) for eligibility determination through abstract and subsequent full-text screening by two independent reviewers (MY and NM). Studies with less than 20 patients, synchronous OMPC, abstracts, and non-English language were excluded. The most recent publication was selected in the event of multiple publications of the same patient cohort. Conflicts were resolved by a third reviewer (FYM). Risk of bias assessment was performed by MY and NM independently according to the MINORS criteria for included single arm observational studies and the Cochrane RoB tool for randomized trials.[7,8] This analysis was not registered with a prospective registry for systematic reviews.

*Data Extraction:* Data were abstracted by two reviewers (MY and NM) on a standard data abstraction form. Baseline data elements extracted included: number of patients/lesions, positron emission tomography (PET) utilization rate, dose fractionation, concomitant androgen deprivation therapy (ADT) utilization rate, toxicity, among others. Dose fractionation schedules were converted to biologically effective dose (BED) using the formula: $\mathrm{BED} = nd\left[1 + \frac{d}{\frac{\alpha}{\beta}}\right]$, where $n$ is the number of fractions, $d$ is the dose per fraction, and the α/β ratio is assumed to be 1.5 for prostate cancer.[9]

*Outcomes Extraction and Statistical Analysis:* Our primary outcome of interest is local control (LC). Secondary endpoints are local recurrence-free survival (LRFS), androgen deprivation-free survival (ADTFS), biochemical recurrence-free survival (BCFS), and progression-free survival (PFS), and toxicity. PFS and BCFS are differentiated in that the former describes clinically or radiographically detectable disease, while the latter is defined by PSA recurrence.

Studies reporting these endpoints, where appropriate, were weighted by inverse variance and combined in a meta-analysis using a random effects model. Where outcome measures and their variances were not stated, survival curves were reconstructed using Web Plot Digitizer and the 'ifdpc' function in Stata (StataCorp, College Station, TX) as previously described.[10,11] Where variance data was unavailable, studies were weighted by sample size and combined. The individual treatment arms of randomized trials were analyzed separately unless otherwise stated. Heterogeneity among studies was quantified by the $I^2$ statistic, with $I^2$ values exceeding 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively.[12] Quantitative analyses for survival endpoints and proportional endpoints were performed using the 'metan' and 'metaprop' functions, respectively, in Stata v.15.

## RESULTS

*Literature Search:* We screened 355 abstracts and identified 10 studies to include in our analysis, with a total of 653 patients and 1,111 lesions. Six studies were observational cohort series:[13–18] one phase 1 single arm prospective trial (POPSTAR),[19] one phase 2 single arm prospective trial (TRANSFORM),[20] and two phase 2 randomized control trials (RCT) (STOMP and ORIOLE)[3,4] (Supplementary Material 1). Both RCTs enrolled patients with up to three asymptomatic metastatic lesions and did not have ADT for a pre-specified period before enrollment. The treatment arm in ORIOLE consisted entirely of SBRT, whereas STOMP allowed SBRT or surgical resection in their metastasis directed therapy (MDT) arm. Since subgroup analysis was not performed in STOMP, all participants in the MDT arm are analyzed in the current study as having received SBRT, since only a minority underwent resection (19%). Note that only the MDT arms of these RCTs are included in quantitative analyses with the other studies.

All single arm studies were of good or moderate quality as assessed by the MINORS criteria, with a median score of 11/16 (range 9–14) (Supplementary Material 1). The STOMP and ORIOLE trials were determined to have some concerns in the domain of outcome measurement in that the assessors were not blinded to treatment allocation; however the overall risk of bias was low (Supplementary Material 1).

*Patients Characteristics:* Study characteristics are described in Table 1. The maximum number of lesions included in any single study ranged from 2 to 5, with the majority (64%) limited to a maximum of three lesions. PET utilization ranged from 36% to 100% of included patients within a single study, with most studies (73%) having a 100% utilization rate. Overall, 601/653 (92%) patients were staged by PET. Choline PET was the most common modality. SBRT dose varied, but the most frequently utilized dose fractionation schedules included 50 Gy/10 ($n$ = 3), 30 Gy/3 ($n$ = 4), and 20 Gy/1 ($n$ = 3); the $\mathrm{BED}_{1.5}$ ranged from 152 to 408. Five studies treated a proportion of patients who were concurrently on ADT, ranging from 14% to 78% of the total cohort of patients.

*Outcomes and Quantitative Synthesis:* Outcome measures are summarized in Table 2. One study uniquely reported treatment escalation-free survival (TEFS). This is a composite endpoint defined by ADT initiation for patients who were not on ADT, second-line ADT or chemotherapy for patients on concurrent ADT at enrollment, or palliative radiotherapy. Treatment escalation occurred at the discretion of the clinical team based on PSA

Table 1. Characteristics of included prospective studies

| First Author | | Muacevic (14) | Decaestecker (13) | Kneebone (16) | Jereczek-Fossa (15) | Ost[a] (3) | Siva[b] (19) | Gomez-Iturriaga (17) | Bowden[b] (20) | Pasqualetti (18) | Philips[a] (4) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | | 2013 | 2014 | 2016 | 2017 | 2018 | 2018 | 2019 | 2020 | 2020 | 2020 |
| Country | | Germany | Belgium | Australia | Italy | Belgium | Australia | Spain | Australia | Italy | United States |
| Number of Patients | | 40 | 50 | 57 | 94 | 31 | 33 | 49 | 199 | 46 | 54 |
| Number of Lesions | | 64 | 70 | 73 | 124 | 51 | 50 | 93 | 429 | 67 | 90 |
| Age (mean) | | 66 | 59 | 64 | 70.7 | 62 | 70 | 71 | 67.4 | 70 | 68 |
| Maximum Lesions per Patient | | 2 | 3 | 3 | 5 | 3 | 3 | 5 | 5 | 3 | 3 |
| PET Utilization (proportion, type) | | 1 (choline) | 1 (FDG, choline) | 1 (PSMA) | 0.96 (choline) | 1 (choline) | 1 (NaF) | 1 (choline) | 0.76 (choline) | 1 (choline) | 1 (PSMA) |
| Median Time to SBRT from Diagnosis (years) | | - | 4.8 | 5.6 | 5.2 | 5.3 | - | 3.2 | 3.8 | 5.8 | - |
| Median Follow up (months) | | 14 | 24 | 16 | 19 | 36 | 24 | 24 | 35 | 29 | 19 |
| Primary Tumor Treatment Modality | EBRT (%) | | 18 (16) | 7 (13) | 19 (20) | 7 (23) | 15 (45) | 7 (14) | 185 (93) | 2 (4) | 6 (17) |
| | RP (%) | | 6 (12) | 20 (35) | 39 (42) | 2 (7) | 18 (54) | 14 (29) | 9 (4.5) | 17 (37) | 30 (83) |
| | RP+EBRT (%) | | 36 (72) | 30 (52) | 34 (36) | 22 (70) | | 25 (51) | | 27 (59) | |
| | Other (%)[c] | | | | 2 (2) | | | 1 (2) | 3 (1.5) | | |
| Median BED1.5 (Gy) | | 287 | 217 (70% patients) 230 (30% patients) | Bone: 216 (5% patients) and 287 (26% patients) Node: 383 (26% patients) and 230 (42% patients) | 152 | 230 | 287 | Bone: 152 Node: 147 | 217 | 189 | 211 |
| Concomitant ADT utilization (proportion) | | 0.48 | 0 | 0 | 0.36 | 0 | 0 | 0.78 | 0.14 | 0.53 | 0 |

SBRT – stereotactic body radiotherapy, PET – positron emission tomography, FDG – fluorodeoxyglucose, PSMA - prostate specific membrane antigen, NaF – sodium fluoride, BED – biologically effective dose, ADT – androgen deprivation therapy, EBRT – external beam radiotherapy, RP – radical prostatectomy

[a]Phase 2 randomized control trial.

[b]Single arm prospective trial.

[c]Other primary treatment modalities include brachytherapy and cryotherapy.

Table 2. Study Outcomes

| First Author | Local Control | Local Recurrence-Free Survival | | Androgen Deprivation-Free Survival | | Biochemical Recurrence-Free Survival | | Progression-Free Survival | | Treatment Escalation-Free Survival | | Grade ≥ 3 Toxicity (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall (%) | 2 year (%) | Median (mo) | 2 year (%) | Median (mo) | 2 year (%) | Median (mo) | 2 year (%) | Median (mo) | 2 year (%) | Median (mo) | |
| Muacevic (14) | 97 | 96 | NR | | | | | | | | | 0 |
| Decaestecker (13) | 100 | | | 60 | 25 | | | 35 | 19 | | | 0 |
| Kneebone (16) | | | | | | 16 | 11 | | | | | 0 |
| Jereczek-Fossa (15) | 90 | 84 | NR | | | | | 30 | 17 | | | 0 |
| Ost* (3) | 100 | | | 44 | 21 | 28 | 10 | | | | | 0 |
| Siva†(19) | | 93 | NR | 48 | | | | | | | | 3 -VCF |
| Gomez-Iturriaga (17) | 89 | | | | | | | | | | | 0 |
| Bowden†(20) | | | | | | | | | | 52 | 27 | 0 |
| Pasqualetti (18) | 96 | | | | 29 | | | | | | | 0 |
| Philips* (4) | 99 | | | | | 57 | NR | 58 | NR | | | 0 |
| **Quantitative Synthesis (95% CI)** | **97 (94–100)** | **88.7 (5.4) ‡** | | **52 (41–62)** | **24.7 (20.1–29.2)** | **33 (11–55)** | | **39 (24–54)** | | | | |

mo – months, VCF – vertebral compression fracture, NR – not reached, CI – confidence interval
[a]Phase 2 randomized control trial
[b]Phase 1 single arm trial
[c]Standard deviation

progression, infield recurrence, development of >5 new metastases, or clinical concern at rate of disease progression.[20] Notably, only one Grade 3 toxicity was reported among all studies; a vertebral compression fracture that required instrumentation.[19]

The overall local control rate was 97% (95% CI, 94–100) as reported by seven studies (Figure 1).[3,4,13–15,17,18] The overall local control rates ranged from 89% to 100% of all treated lesions. The

Figure 1. Overall local control.

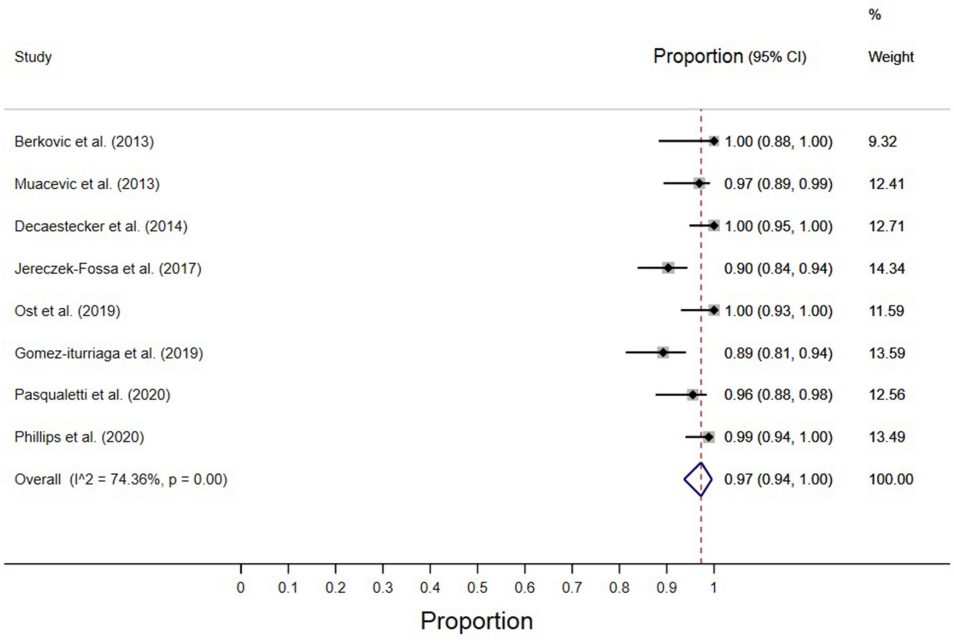
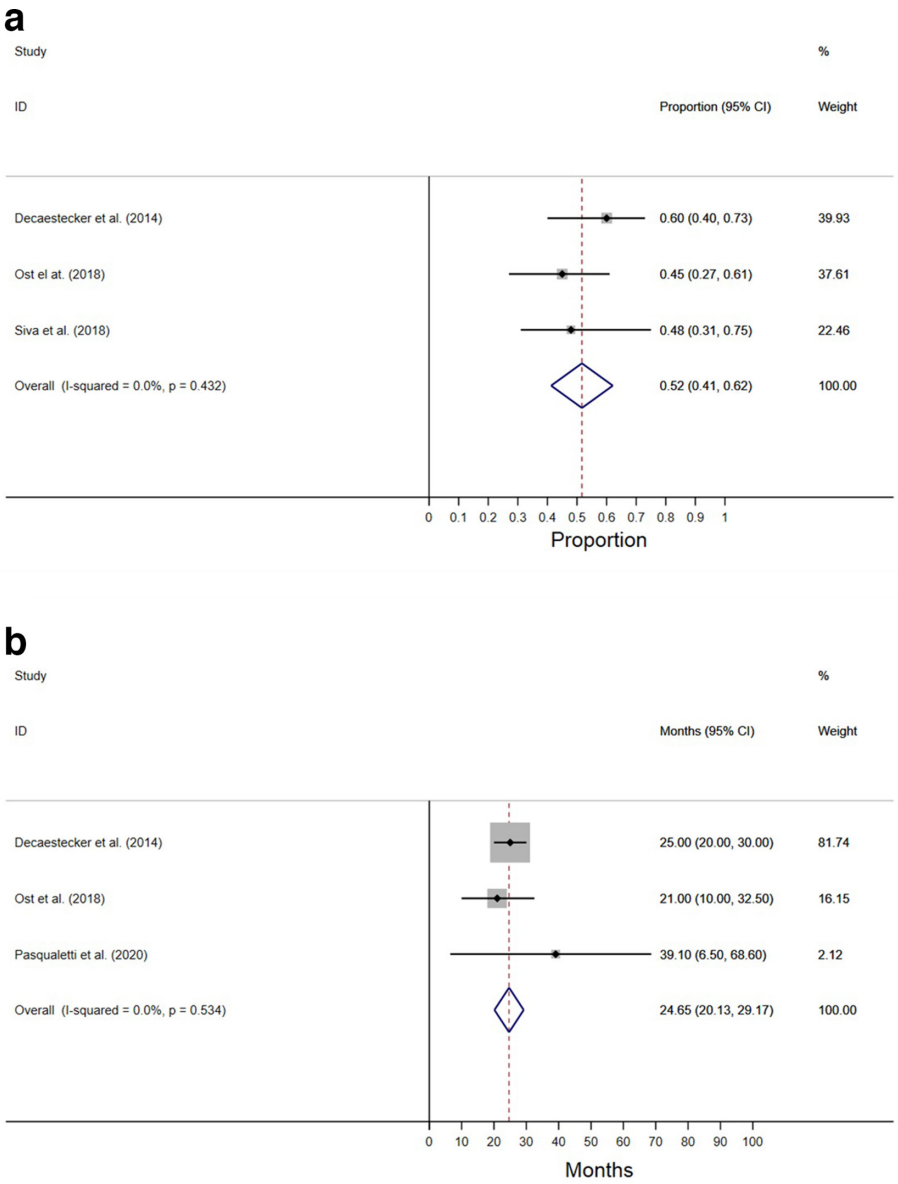


Figure 2. Androgen deprivation-free survival. (A) 2 year (B) median




2-year LRFS rate was reported by three studies; their weighted mean was 88.7% (SD = 5.4).[14,15,19]

ADTFS is graphically summarized in Figure 2. Median and 2-year survivals were reported as an outcome by four studies.[3,13,18,19] Meta-analysis of these outcomes reported an overall median ADTFS of 24.7 months (95% CI, 20.1–29.2), and a 2-year ADTFS of 52% (95% CI, 41–62).

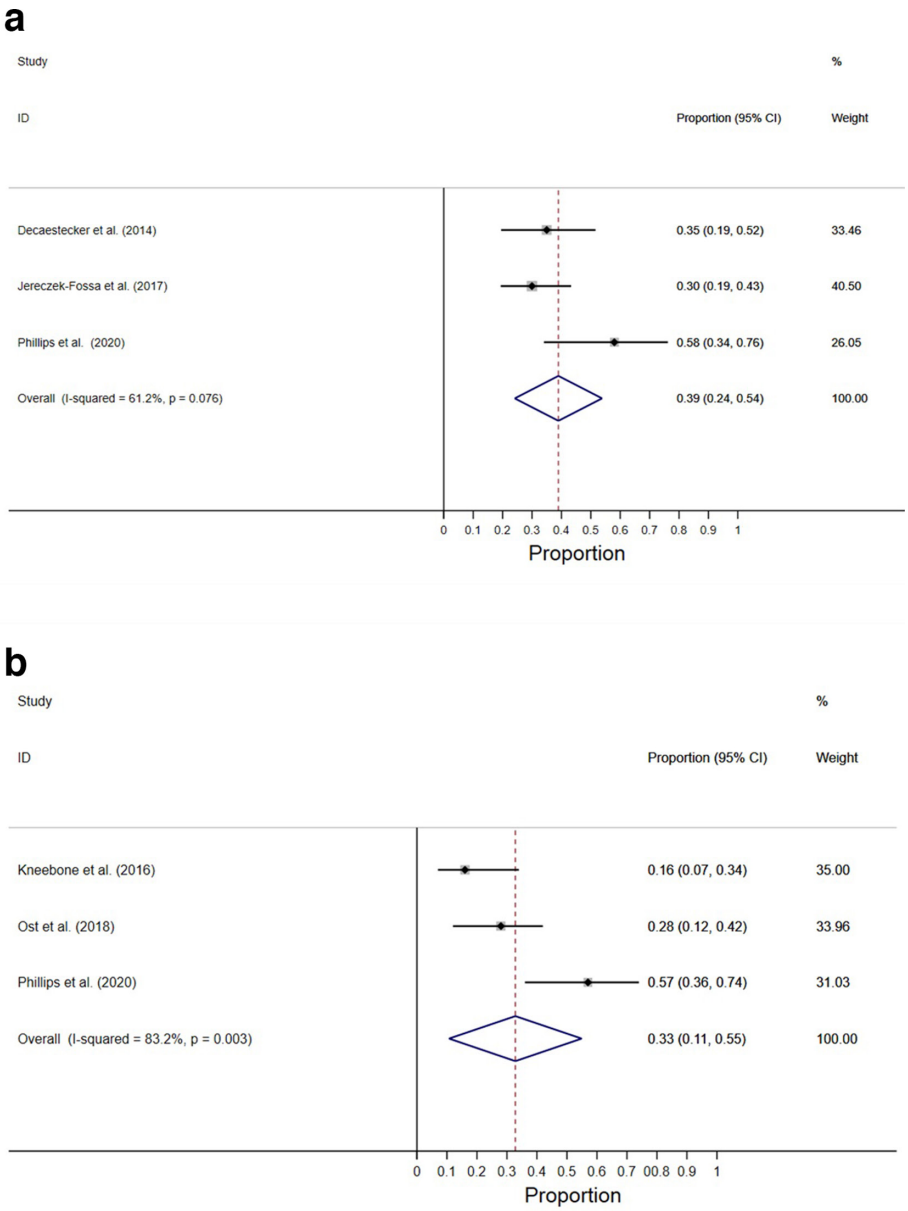
The 2-year PFS was 39% (95% CI, 24–54), as reported by three studies (Figure 3A).[4,13,15] The 2-year BCFS was 33% (95% CI, 11–55) as synthesized from three studies (Figure 3B).[3,4,16] The hazard ratios of the difference in risk of PSA progression between MDT and observation arms were also reported by the two included RCTs.[3,4] Meta-analysis of these trials showed that MDT was associated with significantly lower PSA progression risk than compared to observation, with nearly half of the risk of progression (HR 0.45; 95% CI, 0.28–0.73) (Figure 4).

## DISCUSSION

OMPC represents a unique subset of metastatic prostate cancer patients in which the control of the limited metastatic disease burden is thought to decrease the seeding of other clinical sites of progression. As such, the paradigm of OMPC management is evolving, and there is a trend towards aggressive escalation in the management of these patients to sustain prolonged disease control.

The evidence supporting MDT in OMPC patients is developing. Both surgical resection and SBRT are recognized modalities in MDT; the former limited mainly to nodal metastases, while the latter can be implemented to treat boney or visceral disease.[21] Through our systematic search, we found that a significant proportion of the

Figure 3. 2 year (A) progression-free survival (B) biochemical-free survival



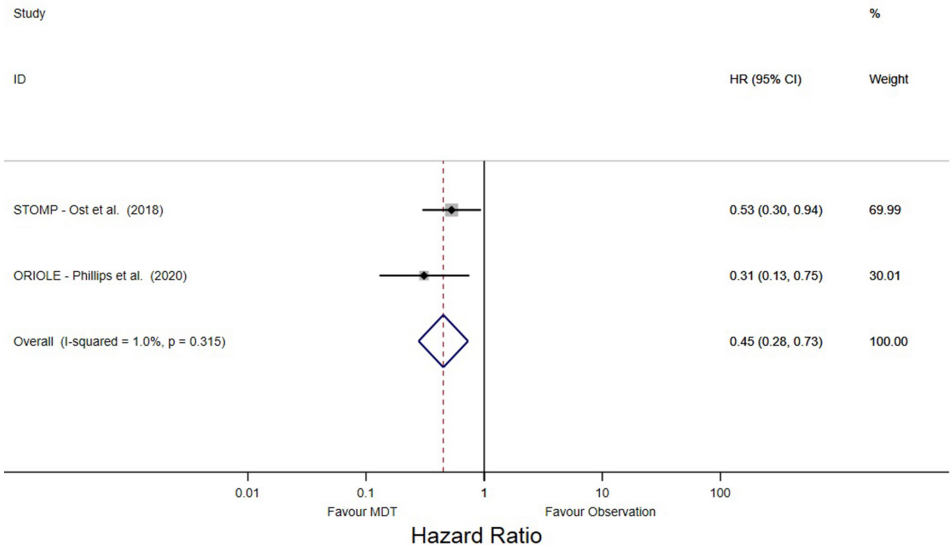

OMPC SBRT literature consists of retrospective studies. By nature of their design, these studies are subject to selection and informational biases, and as such excluded from our systematic review.

To our knowledge, the current study is the first to synthesize only the existing high-quality, prospective literature. We identified several prospective cohort studies meeting our stringent eligibility criteria, including two single arm trials, as well as two phase 2 RCTs. Despite the smaller size of these studies, together they represent the best current evidence supporting SBRT in the MDT of metachronous OMPC patients.

Our results suggest that OMPC patients treated with SBRT may experience excellent local control rates greater than 95%. This is in keeping with the reported outcomes from several prospective trials investigating the role of SBRT in oligometastatic disease. The seminal SABR-COMET trial reported an overall local control rate of 70%. However, enrolled patients had mixed metastatic histologies, with only 21% of patients having OMPC and 17% of patients having lung primaries, which tend to be less indolent.[22] Similarly, Gomez et al reported an 88% local control rate in the MDT arm of a phase 2 trial investigating local consolidative treatment in oligometastatic lung cancer patients.[23]

Because of the effective local control, most disease progression occurs distantly. As such, we observed sustained biochemical control rates, with roughly one-third of patients in our pooled analysis remaining free of biochemical failure at 2 years. Analysis of just the STOMP and ORIOLE trials showed that patients in the observation arm were twice as likely to experience PSA progression than if they received MDT. A recent update of the STOMP trial was presented at the 2020 American Society of Clinical Oncology

Figure 4. Hazard ratio from randomized control trials. Abbreviations: HR – hazard ratio, MDT – metastasis directed therapy




(ASCO) meeting. At 5 years, ADTFS remained significantly superior in the MDT arm (34%) compared to the control (8%), with a HR of 0.57 (80%CI, 0.38–0.84).[24]

Furthermore, we found that clinical progression and the need for ADT initiation are prolonged for up to 18 months and over 2 years, respectively, for approximately half of these patients receiving SBRT. This is significant as ADT use, in addition to short-term vasomotor and erectile dysfunction adverse effects, is associated with significant long-term toxicities such as osteoporosis and coronary heart disease; it can decrease overall quality of life.[25,26] Financial toxicity is also another consideration. The average 3-month injection costs a little over $1000 Canadian in a single payer system like Ontario, Canada.[27] Additionally, there is evidence that complications from ADT utilization, such as insufficiency fractures, can nearly double healthcare costs for patients.[28]

Importantly, excess toxicity appears to be limited from SBRT. There was only one Grade 3 bone toxicity observed among over 600 patients and 1000 treated lesions. This is supported by a previous review of the retrospective literature surrounding SBRT utilization in this patient population, where Grade 2–3 toxicities were observed in only 13% of treated patients. Only one Grade 3 urinary toxicity occurred.[29] The promising safety profile of SBRT certainly presents it as a promising treatment option in the management of OMPC patients.

Several comparative phase 2 and phase 3 trials are currently accruing to provide further comparative data on the efficacy of SBRT in OMPC. The GETUG 36, PLATON, ARTO, and PCS-IX trials are all phase 2 or 3 RCTs enrolling only OMPC patients that directly compare the addition of SBRT to standard of care systemic therapy modalities.[30–33] The SABR-COMET-10 and CORE phase 3 trials enroll oligometastatic patients of multiple histologies including prostate, and similarly will compare the addition of SBRT with standard management alone.[34] The mature results of these trials are highly anticipated.

There is evolving evidence that oligometastatic lesions represent a biologically distinct entity from widely disseminated disease. Favorable primary tumor biology, inhospitable target organ microenvironment, and decreased circulatory system viability are a few contributory factors posited to explain this distinction.[35] Preclinical studies have proven the existence of genetic and phenotypic differences between metastatic tumor cells when compared to the primary.[36] Early in vitro studies have shown that the primary tumor itself may possess a heterogeneous population of cells of varying metastatic potential.[37–39] Clinically, specific genetic markers have been identified to be associated with worse outcomes.[40,41]

As a parallel component of the ORIOLE study, circulating tumor DNA (ctDNA) and peripheral T-cell receptor DNA from a subset of participants were analyzed and stratified based on the presence of high-risk genetic markers. The investigators reported a significant improvement in PFS in the non-high-risk subgroup with SBRT compared to observation, whereas no difference was observed in the high-risk subgroup. Furthermore, they found patients treated with SBRT had more pronounced T-cell clonal expansion. Interestingly, greater peripheral baseline clonality was associated with composite endpoint progression at 180 days in patients in the treatment arm, but not the observation arm, suggesting that this biological signal may portend a better prognosis in patients who receive SBRT.[4] Translational correlative studies such as these are certainly encouraged in future prospective studies to better define the patient prototype who may benefit from aggressive MDT.

Clinical patient selection remains an essential component in determining the optimal management of OMPC patients. Four key prognostic factors associated with better prognosis in oligometastic patients include young age, good performance status, indolent disease (protracted disease-free period between primary and recurrence), and low disease burden.[42]

Nevertheless, there remains variation in aspects of the definition and management of OMPC patients among global experts. At the 2017 advanced prostate cancer consensus conference, opinion was divided on the definition of OMPC as well as the management of these patients. There appeared to be an even split of proponents advocating for the use of local ablative treatment with short course ADT, and those who advocated for ADT or other systemic therapy alone.[43] Subsequently, in the 2019 Dutch Multidisciplinary Consensus Meeting, there remained divide on the optimal management of OMPC patients, including the role for SBRT. Panel consensus was limited by lack of evidence, further underscoring the need for ongoing prospective evaluation in this matter.[44]

Limitations of the current analysis include the small number of studies eligible for inclusion in our study, with some heterogeneity in the reported endpoints. For each endpoint, only 3–4 studies were eligible for appropriate quantitative synthesis. Furthermore, only two studies were randomized control trials that allowed for direct within study comparison of intervention and control arms.[3,4] The remainder were single arm studies which precluded the pooling of treatment effects in the manner of a traditional meta-analysis. Some survival endpoints required recapitulation through digital reconstruction of published survival curves; although this methodology boasts a high degree of precision, it may not represent the exact study values.[11] Nevertheless, we adhered to widely accepted methodology to ensure that only high-quality literature evidence was synthesized in an appropriate statistical manner in respect to the endpoints of interest. Other considerations include the heterogeneous utilization rate of ADT among included cohorts, which may ultimately influence the outcomes of interest in this current analysis. These studies, however, represent the minority of patients. The formal trials, STOMP, ORIOLE, or POPSTAR had strict eligibility criteria that did not allow for ADT utilization for a prespecified period preceding trial enrollment. Future prospective trials are expected to have the same degree of stringency in order to improve the detection of the true treatment effect of SBRT.

## CONCLUSION

SBRT appears to be effective in controlling local disease burden in metachronous OMPC patients and delaying clinical progression and the initiation of ADT. It is associated with minimal significant toxicities. Although extremely promising, there is limited, high-quality evidence to support its current use as standard of care. We await the results of ongoing RCTs to provide further guidance of the role of SBRT in the management of OMPC patients.

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