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Review article

Management and treatment options for patients with de novo and recurrent hormone-sensitive oligometastatic prostate cancer

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ABSTRACT

Probably, patients with de novo (synchronous) and recurrent (metachronous) oligometastatic hormone-sensitive prostate cancer have different oncologic outcomes. Thus, we are challenged with different scenarios in clinical practice, where different treatment options may apply. In the last years, several prospective studies have focused on the treatment of patients with de novo oligometastatic hormone-sensitive prostate cancer. Not only the addition of systemic therapeutic treatments, such as chemotherapy with docetaxel, abiraterone, enzalutamide, and apalutamide, next to androgen deprivation therapy, demonstrated to improve outcomes in these patients but also local therapy of the primary has been demonstrated to improve outcomes of low-volume metastatic disease. Next to radiotherapy, also radical prostatectomy has been reported as a feasible and safe treatment option. Additional metastasis-directed therapy in de novo metastatic disease is currently examined by four trials. In the recurrent metastatic setting, less data are available, and it remains uncertain if patients can be treated in the same way as synchronous oligometastatic disease. Metastasis-directed therapy has demonstrated to prolong outcomes, while data on survival are still missing.
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1. Introduction

Oligometastatic hormone-sensitive prostate cancer (omHSPC) is a subtype of metastatic hormone-sensitive prostate cancer (PCa) with more favorable prognosis than widespread metastatic disease.[1] In 1995, Hellman and Weichselbaum[2] hypothesized that patients with oligometastatic cancers might be suitable for a treatment with curative intent. To date, there is still no consensus in the exact definition of omHSPC. Most studies use a definition for oligometastatic PCa when patients harbor ≤5 metastases.[3] Other studies, such as the CHAARTED study, use a stratification into high-volume (≥4 bone metastases including ≥1 outside vertebral column or spine or visceral metastasis) and low-volume (not high) metastatic disease or according to the LATITUDE trial into high-risk (≥2 high-risk features of the following: ≥3 bone metastasis; visceral metastasis; ≥International Society of Urological Pathology (ISUP) grade 4) and low-risk (not high) disease.[4–6] Next to the ambiguity of the definition of omHSPC, the terminology can further create confusion among the readership because oligometastatic disease can occur in a hormone-sensitive setting or in a castration-resistant scenario. However, not only the hormone status can be used to distinguish this heterogeneous cohort of patients. The time point when metastases occur is also important because treatment options may have different effects in synchronous (de novo) or metachronous (metastases occur later as sign of disease progression) disease, and prognosis differs between the respective subgroups.[1]

The aim of this review was to summarize the current best available evidence regarding management and treatment options of patients with de novo or recurrent omHSPC regarding systemic, local, and metastasis-directed therapy (MDT).

2. Staging

Besides the discrepancy in the terminology for omHSPC, also staging modalities may affect treatment decisions. Owing to the development and wider use of prostate-specific membrane antigen

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Table 1
Overview of therapeutic options for patients with omHSPC.

Treatment option	Abiraterone	Apalutamide	Enzalutamide	Docetaxel	Local treatment	MDT
Suitable for omHSPC	+	+	+	+	+	+
Suitable for synchronous disease	+	+	+	+	+	?
Suitable for metachronous disease	?	+	+	?	–	+
Studies	LATITUDE;[6] STAMPEDE[13]	TITAN[14]	ENZAMET;[15] ARCHES[16]	STAMPEDE;[17] CHAARTED;[5,18] GETUG-AFU 15[19]	STAMPEDE (RT);[20] NCT02742675 (RP, no survival data)[21]	ORIOLE (no survival data)[22]
Definition of patients with omHSPC	Low-risk LATITUDE[a] Low-risk LATITUDE[a] and Low-volume CHAARTED[b]	Low-volume CHAARTED[b]	Low-volume CHAARTED[b]	Low-volume CHAARTED[b] Low-volume CHAARTED[b] Low-volume CHAARTED[b]	Low-volume CHAARTED[b] ≤5 bone or extrapelvic lymph node metastases and no visceral metastases	Recurrent disease, with up to 3 metastases

MDT = metastasis-directed therapy; omHSPC = oligometastatic hormone-sensitive prostate cancer.
[a] Not high risk (≥2 high-risk features of ≥ 3 bone metastasis; visceral metastasis; ≥ISUP grade 4).
[b] Not high volume (≥4 bone metastasis including ≥1 outside vertebral column or spine or visceral metastasis).

(PSMA) positron emission tomography (PET)/computer tomography (CT), the management and treatment of oligometastatic PCa has gained more and more interest in recent years.[7]. A more frequent use of PSMA-PET/CT also as a primary staging method results in more patients diagnosed with metastases at an earlier time point. A recent randomized trial (ANZCTR12617000005358) demonstrated that PSMA-PET/CT provides superior accuracy compared with conventional imaging.[8] Within 302 randomly assigned patients with high-risk PCa to PSMA-PET/CT or conventional imaging, PSMA-PET/CT had a 27% greater accuracy than conventional imaging (92% vs. 65%; $p < 0{,}0001$). In addition, the authors found a lower sensitivity (38% vs. 85%) and specificity (91% vs. 98%) for conventional imaging compared with PSMA-PET/CT.[8] Yet, the clinical benefit of detecting metastases at an earlier time point remains unclear.[8] In addition, the prognosis and management of patients diagnosed as metastatic by more sensitive staging procedures is unknown. In particular, it is unclear whether patients with metastases, detectable only with PSMA-PET/CT, should be managed using systemic therapies or whether they should be subjected to local and metastases-directed therapies.[9] Evaluation of the aforementioned results by guideline panels is still pending, before recommendations can be given, how to treat patients based on PSMA-PET/CT as primary staging modality.[8,10] To date, the European Association of Urology endorses PSMA-PET/CT only for recurrence but not as primary staging modality.[4]

This said, for omHSPC, not only the number of metastases needs to be taken into account but also the used diagnostic tool has to be considered.

3. Systemic treatment options for de novo and recurrent omHSPC

For decades, androgen deprivation therapy (ADT) was the only evidenced treatment option prolonging outcomes for patients with newly diagnosed metastatic PCa.[11,12] Within the last years, various studies tested new treatment options in this patient cohort. An overview of therapeutic options for patients with omHSPC is given in Table 1.

3.1. Chemotherapy with docetaxel

First results for a benefit from an additional therapy next to ADT therapy in high-volume metastatic PCa patients derived in 2015. CHAARTED revealed that the addition of six cycles of docetaxel in patients with metastatic PCa results in significantly longer overall survival than treatment with ADT alone.[5] The median overall survival was 13.6 months longer with ADT plus docetaxel than ADT alone (Hazard ratio [HR]: 0.61; confidence interval [CI]: 0.47–0.80; $p < 0.001$). This survival benefit only reached significance in patients with high-volume (presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis, HR: 0.60; CI: 0.45–0.81; $p < 0.001$) but not in low-volume disease (HR: 0.60; CI: 0.32–1.13).[5] In a long-term survival analysis of the CHAARTED study, after a median follow-up of 53.7 months, survival benefit was confirmed for high-volume disease (HR: 0.63; CI: 0.50–0.79; $p < 0.001$) but still demonstrated no overall survival benefit in low-volume disease (HR: 1.04; CI: 0.70–1.55; $p = 0.86$).[18]

Later, in the same year, results from the multiarm STAMPEDE trial showed a survival benefit in the M1 subgroup of arm C, where docetaxel was added to the standard of care (HR: 0.76; CI: 0.62–0.92), as well as in the M1 subgroup of arm E, where zoledronic acid and docetaxel have been added to the standard of care (HR: 0.79; CI: 0.66–0.96).[23] Zoledronic acid alone, as well as its addition to docetaxel in arm E, did not improve outcomes.[23]

It is of note that most of the M1 disease of arm C (347/362) and arm E (350/365) had newly diagnosed M1 disease. The amount of metastases was not specified in the inclusion criteria.[23] A recent report with long-term follow-up stratified the STAMPEDE cohort by metastatic burden according to CHAARTED into low- and high-volume metastatic disease.[17] After a median follow-up of 78.2 months, patients had better survival by the addition of docetaxel (HR: 0.81; CI: 0.69–0.95; p: 0.009) with no evidence of heterogeneity of a docetaxel effect between metastatic burden subgroups (interaction p: 0.8). The authors concluded that upfront docetaxel chemotherapy should be considered regardless of the metastatic burden at diagnosis.[17]

Conversely, results from the GETUG-AFU 15 trial that have been reported in 2013 showed no survival benefit for the addition of 9 cycles of docetaxel to ADT.[24] It is noteworthy that 32% (62/192 that received docetaxel) developed metastasis after treatment for localized disease and harbored recurrent metastatic disease. In a post-hoc analysis, after a median follow-up of 83.9 months, a nonsignificant 20% reduction in the risk of death in the high-volume subgroup was reported by the addition of docetaxel, with no survival improvement in the low-volume subgroup.[19] Definition of high- and low-volume disease in this analysis was in line with the stratification of the CHAARTED trial.

It remains debatable why patients in the STAMPEDE trial with low-volume omHSPC had a benefit by the addition of docetaxel but not in CHAARTED and GETUG-AFU 15. Patients with low-volume metachronous omHSPC seem to have a more favorable outcome compared with low-volume synchronous omHSPC, as recently reported by Francini et al.[1] One possibility could be that most patients in the STAMPEDE trial harbored synchronous metastatic disease and approximately 50% of the CHAARTED and 30% of the GETUF-AFU 15 had metachronous omHSPC. Because metachronous low-volume omHSPC have a more favorable outcome, less events will occur and no statistical difference in the outcome might be seen. This potentially can explain the discrepancy in the results for low-volume patients between the three studies.

Taken together, in patients with synchronous omHSPC, the use of docetaxel to ADT should be considered as a possible treatment option. However, it remains uncertain if also patients with metachronous omHSPC benefit from docetaxel.

3.2. Novel antihormonal therapies

Shortly after the results for docetaxel as additive systemic therapy in patients with omHSPC, novel antihormonal therapies with upfront combination therapies replacing ADT alone have been introduced.[12]

3.2.1. Abiraterone

In 2017, first results from LATITUDE demonstrated a significant increase in overall (HR: 0.62; CI: 0.51–0.76; p < 0.001) and radiographic progression-free survival for the addition of abiraterone vs. placebo to ADT. The median follow-up was 30.4 months. Included patients had newly diagnosed high-risk, metastatic, hormone-sensitive PCa, documented by a positive bone scan, CT, or magnetic resonance imaging. In addition, patients were required to have at least two of three risk factors: a Gleason score of 8 or more, at least three bone lesions, or the presence of measurable visceral metastasis.[6] Similar results for overall survival (HR: 0.61; CI: 0.49–0.75) for the addition of abiraterone to ADT were reported for metastatic patients of arm G of the STAMPEDE trial, after a median follow-up of 40 months.[25] A post-hoc analysis of the STAMPEDE cohort, stratified according to the LATITUDE trial into low- and high-risk metastatic disease, as well as according to the CHAARTED study into low- and high-volume disease, revealed a survival advantage and longer failure-free survival for the addition of abiraterone to ADT not only in high-risk/high-volume disease but also in low-risk/low-volume disease.[13]

The STAMPEDE trial included only 98 patients with recurrent disease.[25] Therefore, reliable statements are not possible for metachronous disease. In addition, in the LATITUDE trial, only patients with synchronous omHSPC have been included.

In conclusion, abiraterone represents a treatment option for synchronous omHSPC, while it remains unclear, if patients with metachronous omHSPC benefit by the addition of abiraterone.

3.2.2. Apalutamide

Recently, results from TITAN demonstrated a benefit in overall survival for the addition of apalutamide to ADT vs. placebo (HR: 0.67; CI: 0.51–0.89; p = 0.005) after a median of 22.7 months.[14] Of the 1,052 randomized patients, 16.4% had previous prostatectomy or radiotherapy and 10.7% had received previous docetaxel therapy; 62.7% had high- and 37.3% low-volume disease. The authors performed several subgroup analyses for what the trial was not powered upfront that still yielded some interesting findings. An improvement in overall survival for high-volume disease (HR: 0.68; CI: 0.50–0.92) was recorded. In low-volume disease, only a tendency to an improved survival (HR: 0.67; CI: 0.34–1.32) was seen, probably caused by the small number of events (n = 34) in this subgroup. Patients with visceral plus bone metastasis showed no improvement in overall survival (HR: 0.99; CI: 0.55–1.77).[14]

In patients with metachronous disease, an improvement in radiographic progression-free survival can be seen (HR: 0.41; CI: 0.22–0.78) for apalutamide. However, Hove improvement in overall survival closely failed to reach significance (HR: 0.40; CI: 0.15–1.03), which again might be caused by the few events (n = 18) that occurred in this small subgroup (n = 144).[14]

In brief, the addition of apalutamide to ADT offers a therapeutic option for synchronous and metachronous omHSPC patients.

3.2.3. Enzalutamide

Shortly after TITAN, results of the ENZAMET trial became available. Here, enzalutamide plus ADT was compared with a standard nonsteroidal antiandrogen plus ADT. After a median follow-up of 34 months, enzalutamide demonstrated an improvement in prostate specific antigen (PSA) progression-free (HR: 0.39; p < 0.001), clinical progression-free (HR: 0.40; p < 0.001), and overall survival (HR: 0.67; CI: 0.52–0.86; p = 0.002).[15] Similarly to TITAN, also ENZAMET was not powered for subgroup analyses. It is noteworthy that, compared with TITAN, ENZAMET includes more patients with low-volume disease, resulting in more events (n = 68) for this cohort. Subgroup analyses of ENZAMET revealed a significant survival benefit in low-volume disease (HR: 0.43; CI: 0.26–0.72) and a tendency to an improved survival for high-volume disease (HR: 0.80; CI: 0.59–1.07). In line with TITAN, in the subgroup of patients with visceral metastases, enzalutamide demonstrated no survival benefit (HR: 1.05; CI: 0.54–2.02).[15] Results of ENZAMET are corroborated by the findings from ARCHES.[16] In this phase III trial, 1,150 men with hormone-sensitive metastatic PCa were randomly assigned 1:1 to enzalutamide or placebo, plus ADT, stratified by disease volume and prior docetaxel chemotherapy. ARCHES could demonstrate a significant improvement in radiographic progression-free survival, which represented the primary study outcome, regardless of disease volume and chemotherapy use.[16]

Data from ENZAMET in patients with previous local treatment showed a trend toward better overall survival (HR: 0.72; CI: 0.47–1.09) and significantly longer clinical progression-free survival (HR: 0.42; CI: 0.31–0.57) for the addition of

enzalutamide to ADT.[15] In conclusion, enzalutamide represents an option for synchronous and metachronous omHSPC.

Shortly after the introduction of docetaxel as additive systemic therapy in patients with omHSPC, with abiraterone, apalutamide, and enzalutamide novel antihormonal therapies with upfront combination therapies replacing ADT alone have been introduced. Direct comparisons between these therapies are scant.[12] Until such reports directly comparing the available systemic therapies become available, it remains treating physicians' decision-making together with the patient to choose the optimal treatment for each individual patient with omHSPC.

To date, there is no evidence if a combination of local therapy and additional systemic therapy, next to ADT, might further prolong disease progression. Until results of ongoing trials that evaluate combination therapies in patients with omHSPC, such as the phase III study for patients with metastatic hormone-naïve PCa (PEACE1, NCT01957436), this question remains unanswered.

4. Local treatment options for de novo omHSPC

In 2014, Culp et al.[26] suggested that local treatment of the primary in patients with metastatic PCa is associated with a survival benefit compared with no local treatment. However, their report was based on a retrospective analysis of the Surveillance, Epidemiology, and End Results database, with all its inherent limitations. Since then, the number of studies on local therapy has continuously increased.

4.1. Radiotherapy

The prospective randomized HORRAD trial comparing ADT with ADT with external beam radiotherapy to the prostate in a cohort of 432 patients with primary bone metastatic disease did not show a significant difference in overall survival, although the authors could not exclude a potential benefit in low-volume disease (<5 metastases), due to the confidence interval in the subgroup analysis.[27] Soon after, results from the H arm of the STAMPEDE trial demonstrated a significant improved overall survival (HR: 0.68, 95% CI: 0.52–0.90; $p = 0.007$) and failure-free survival (HR: 0.59, 95% CI: 0.49–0.72; $p < 0.0001$) for the addition of radiotherapy to the standard of care in low burden metastatic disease (defined according the CHAARTED criteria).[20]

4.2. Radical prostatectomy

In 2015, a small retrospective case–control study from Germany including 23 patients with ≤3 bone metastases demonstrated that cytoreductive prostatectomy is feasible in well-selected men.[28] Recently, another small retrospective report showed similar outcomes compared with arm H of the STAMPEDE trial for cytoreductive radical in with low-volume metastatic disease, according to CHAARTED trial.[29]

During the American Urology Association congress meeting 2019, first results from Testing radical prostatectomy in men with oligometastatic PCa that has spread to the bone (ISRCTN15704862) have been reported. Testing radical prostatectomy in men with oligometastatic PCa that has spread to the bone demonstrated that it is feasible to randomize men with oligometastatic PCa to standard of care versus that plus cytoreductive prostatectomy. Early results indicate acceptable perioperative and short-term oncological outcomes.

At the virtual European society for medical oncology (ESMO) congress 2020, first results of the prospective randomized Chinese NCT02742675 phase II trial were reported. Here, 200 patients with omHSPC (≤5 metastases and no visceral metastases) were randomized to ADT vs. ADT + local therapy (radical prostatectomy was recommended, while radiotherapy was administrated to those refused prostatectomy or with unresectable tumor). Of all, 88.5% in the local therapy cohort received radical prostatectomy, with a surgical complication rate of 3.5% (Clavien-Dindo ≥3b). After a median follow-up of 28 months, the authors report an improved radiographic progression-free survival for the group with local therapy (HR: 0.50; CI: 0.28–0.87; $p = 0.015$).[21] However, longer follow-up is required to answer if the addition of local therapy will consolidate in an improved overall survival, which represented the secondary outcome of the study.[21]

Currently, there are several randomized trials with pending results investigating cytoreductive radical prostatectomy in patients with omHSPC (NCT01751438, NCT03678025, NCT03456843, NCT03655886, NCT03988686). Moreover, the announced M arm of the STAMPEDE trial will further help to clarify if surgery as local treatment is similarly effective to radiotherapy in patients with omHSPC. Owing to the results of the H arm of the STAMPEDE trial, the Impact of Radical Prostatectomy as Primary Treatment in Patients with PCa with Limited Bone Metastases trial (NCT02454543) was closed early.

In general, local treatment in patients with omHSPC is advisable due to the benefit in overall survival. Until results on survival of the aforementioned trials become available, the effectiveness of cytoreductive prostatectomy can only be assumed to be equal to radiotherapy as local treatment option in low-volume omHSPC, when considered.

5. MDT for de novo and recurrent omHSPC

Previous studies indicate that patients with synchronous and metachronous omHSPC have different oncologic outcomes.[1] This suggests that therapy options are not fully transferable between both scenarios. So far, there is no evidence that additional treatment of metastatic sites improves the outcome in patients with de novo omHSPC. Currently, there are four recruiting or ongoing trials evaluating the role of MDT in patients with de novo omHSPC. The small phase II single-arm study NCT03298087 will assess the impact of stereotactic body radiotherapy directed to the metastasis in patients with 1–5 metastasis at imaging (PSMA-PET-CT included) on PSA levels at 6 months after treatment. The PLATON trial (NCT03784755), a randomized phase III trial, will test if stereotactic body radiotherapy directed to the metastasis, next to systemic and/or local therapy, in patients with ≤5 metastases improves failure-free survival. In addition, also the multiarm phase II METACURE trial (NCT03436654) will include patients from very high-risk localized to low-volume metastatic PCa, defined by ≤3 bone lesions based on conventional imaging that can be treated with 3 radiation isocenters. The arms include combinations of ADT + apalutamide ± abiraterone acetate and prednisone, and the primary endpoint is pathologic complete response and minimal residual disease at radical prostatectomy. However, the secondary endpoint is undetectable PSA with noncastrate levels of testosterone, and patients with low-volume disease will further be treated with stereotactic radiotherapy.

Last but not least, arm M of STAMPEDE will further clarify the role of MDT in omHSPC. Arm M will not only test if surgery as local treatment is similar to radiotherapy as a local treatment option in omHSPC but also test if the addition of stereotactic ablative body radiotherapy (SABR) to metastatic sites further improves overall survival. Arm M will exclusively consist of oligometastatic (≤5 extrapelvic metastases) patients, relying on bone and CT scan.

For the use of MDT in patients with recurrent omHSPC, some evidence does exist. In 2017, results from the phase II STOMP trial became available. In this small sample size study, including 62

patients with recurrent omHSPC (≤3 metastases), diagnosed on choline PET-CT, the benefit of MDT was assessed.[30] After a median follow-up of 3 years, a longer, median ADT-free survival was reported for the MDT group vs. the surveillance group (HR: 0.60; 80%-CI: 0.40−0.90, p = 0.11).[30] At the ASCO 2020 congress meeting, 5-year results of the STOMP trial were reported, confirming the previous results. Five-year ADT-free survival was 8% for the surveillance group and 34% for the MDT group (HR: 0.57; 80%-C: 0.38−0.84; p = 0.06).[31]

Recently, results of the randomized phase II ORIOLE trial were reported. In this study, 54 patients with recurrent omHSPC (≤3 metastases based on conventional imaging) received SABR vs. observation.[22] Progression at 6 months occurred in 7 of 36 patients (19%) receiving SABR and 11 of 18 patients (61%) undergoing observation (p = 0.005). Treatment with SABR improved median progression-free survival (not reached vs 5.8 months; HR: 0.30; CI: 0.11−0.81; p = 0.002). These results further corroborate the potential benefit of MDT in recurrent omHSPC. Despite the benefit of MDT on progression-free and ADT-free survival within the ORIOLE and STOMP trial, it still remains uncertain whether MDT also improves survival in patients with recurrent omHSPC. A first hint can be drawn from the SABR-COMET trial.[32] Here, SABR in patients with various recurrent oligometastatic cancers was associated with improved median overall survival (41 vs. 28 months, HR: 0.57; CI: 0.30−1.10; p = 0.090).[32] However, it is noteworthy that only 16 of 99 patients with recurrent oligometastatic cancers (≤5 metastases) harbored PCa. Therefore, MDT needs still to be considered as an experimental treatment option.

Currently, there are two phase II studies and one phase III study recruiting patients with recurrent omHSPC to assess combinations of MDT and systemic therapy options. The single-arm, phase II study of systemic and tumor-directed therapy for recurrent oligometastatic M1 PCa (NCT03902951) will assess the efficacy of combined systemic (ADT + abiraterone + apalutamide) therapy and MDT for recurrent omHSPC (M1a/b with ≤5 metastases) staged by PSMA-PET/CT. A randomized phase II trial (POSTCARD, NCT03795207) will assess the effect of durvalumab, an immunotherapeutic agent, in addition to MDT (stereotactic body radiation therapy) in patients with recurrent omHSPC (≤5 metastases on fluorocholine, fluciclovine, or Ga-PSMA PET/CT). Last but not least, two arms of the multiarm Phase III Study of PET-Directed Local or Systemic Therapy Intensification in Prostate Cancer Patients With Post-Prostatectomy Biochemical Recurrence (NCT04423211) will further help to clarify the role of apalutamide alone or in combination with MDT in patients with recurrent omHSPC. All patients will receive a fluciclovine PET/CT scan at baseline, with no restrictions to positive extrapelvic metastases.

Taken together, MDT has demonstrated to prolong ADT-free and progression-free survival in patients with recurrent omHSPC with ≤3 metastases, while data on survival are still missing.

6. Summary

Patients with de novo and recurrent omHSPC have different oncologic outcomes. Thus, we are challenged with different scenarios in clinical practice, where different treatment options may apply.

In the last years, several prospective studies have focused on the treatment of patients with de novo omHSPC. Not only the addition of systemic therapeutic treatments, such as chemotherapy with docetaxel, abiraterone, enzalutamide, and apalutamide, next to ADT, demonstrated to improve outcomes in these patients but also local therapy of the primary has been demonstrated to improve outcomes of low-volume metastatic disease. Next to radiotherapy, also radical prostatectomy has been reported as a feasible and safe treatment option. Additional MDT in de novo metastatic disease is currently examined by four trials.

In the recurrent metastatic setting, less data are available, and it remains uncertain if patients can be treated in the same way as synchronous oligometastatic disease. MDT has demonstrated to prolong outcomes, while data on survival are still missing.

Conflicts of interest

There is no conflict of interest to report.

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