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Oligometastatic Prostate Cancer: Definition and Treatment Considerations: A Review of the Literature

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Abstract **Original Research Article**

Background: Oligometastatic disease state is a recent concept of metastatic cancer defined as an intermediate of spread between localized and widely spread metastases. Oligometastatic prostate cancer (PCa) is being diagnosed with a greater frequency during the last decade. Multiple modalities of management of oligometastatic PCa are proposed from targeting all sites of metastases to the treatment of the primary. ***Objective:*** To review the literature regarding management of oligometastatic PCa. ***Method:*** PubMed and ScienceDirect electronic databases were queried for English and French language from 2014 to 2021. Keywords use included "cancer de prostate, oligométastases, oligometastasis and prostate cancer". Preclinical, prospective and retrospective studies were included. ***Result & discussion:*** There were rare published randomized controlled trials evaluating the treatment of oligometastatic PCa. Prospective and retrospective data suggest benefit of primary tumor treatment and Metastasis-directed therapy (MDT), especially using stereotactic body radiotherapy (SBRT). Oligometastatic PCa was defined by number of metastatic lesions clinically evident or radiographically detected (3 to 5). Treatment of the primary (radical prostatectomy or radiotherapy) was associated to a better local control, cancer specific survival, and longer median time to castration resistant PCa. MDT using SBRT has improved distant progression-free survival (DPFS), local progression-free survival (LPFS) in many studies. ***Conclusions:*** Available data suggest that local therapies such as prostatectomy and radiotherapy can be performed safely and might prevent the need for future palliative treatments. Similarly, MDT such as SBRT carry a low risk of toxic effects and provides excellent local control**.** Further trials are necessary and should aim to report outcomes in a consistent and systematic manner.

Keywords: Oligometastasis, prostate cancer.

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men and the fifth leading cause of cancer deaths worldwide [1]. Although, localized PCa is highly curable with a five-year survival rate reaching 100%, the presence of metastases typically indicates an incurable disease state. In fact, the contemporary median survival of patients with metastatic PCa presenting with distant metastases is approximately 4 to 5 years [2, 3]. The concept of oligometastatic cancer, defined by Hellman and Weichselbaum in 1995 as an intermediate malignant state between local-regional (potentially curable) and wide- spread metastatic (typically incurable) disease. In oligometastatic cancer, the number and location of metastatic disease sites are limited, with patients typically having ≤ 5 distant metastases by the conventional definition [4, 5]. Oligometastases are observed either at the time of initial presentation (de novo), or as a pattern of limited recurrence (oligorecurrence) following a curative treatment attempt of localized cancer. Moreover, an oligometastatic state may potentially be induced from a widely metastatic state if there is effective systemic therapy which eradicates micrometastatic disease and leaves only gross disease behind [6].

Oligometastatic PCa continues to be defined as a disease state which is limited in total disease burden and not rapidly spreading to other sites, usually by number of metastatic lesions clinically evident or radiographically detected. Although many literatures propose various definitions of oligometastatic PCa, most of which are generally defined as less than or equal to three or five extrapelvic metastatic sites [7, 8]. Knowledge about oligometastatic cancer has continued

to mature over the past two decades [9]. In the meanwhile, emerging genomic data have shown different biological pathways between widespread and limited metastatic diseases for multiple primary cancers, as well as PCa [10, 11]. Technological evolutions of the last 10-20 years, in particular in radiotherapy with the contribution of SBRT (by linear accelerator microlames or Cyberknife) and methods of targets like tracking, have largely contributed to the revolution of concepts in the management of oligometastatic disease and PCa in particular. Treatment strategies have shifted during the past 10 years from palliative treatments towards objectives of prolonged survival with preserved quality of life in patients with limited metastatic disease and a general preserved state.

METHODS

PubMed and ScienceDirect electronic databases were queried for English and French language from 2014 to 2021. Keywords use included "cancer de prostate, oligométastases, oligometastasis and prostate cancer". Preclinical, prospective and retrospective studies were included.

RESULTS & DISCUSSION

Concept of oligometastatic prostate cancer

Since 2015, more than 600 papers have been published about oligometastatic cancer, and one out of five specifically focused on PCa patients [12]. In 2015, the St Gallen Advanced PCa Consensus Conference (APCCC) stated that the presence of ≤3 synchronous metastases (bone and/or lymph nodes) is the most meaningful definition of oligometastatic PCa[13]. However, in 2017 the APCCC thoroughly explored the oligometastatic concept highlighting several topics of debate, including number and site of lesions, castration-sensitive or castration- resistant setting, synchronous versus metachronous metastases and imaging modality used to identify metastases [14].

In fact, oligometastatic PCa comprises a spectrum of numerous conditions, ranging from de novo oligometastatic cancer at diagnosis to oligometastatic castration-resistant disease, which differ widely. These distinct settings entail wide variations in terms of biology, benefit from treatments and prognosis [2, 15]. In 2016, Saluja *et al*. showed that the concept of oligometastases in general has been exponentially rising in the last decade, as shown by a Pubmed trend analysis and similarly, there has also been a marked increase in interest over the past 2 years for oligometastatic PCa (Fig. 1)[16].

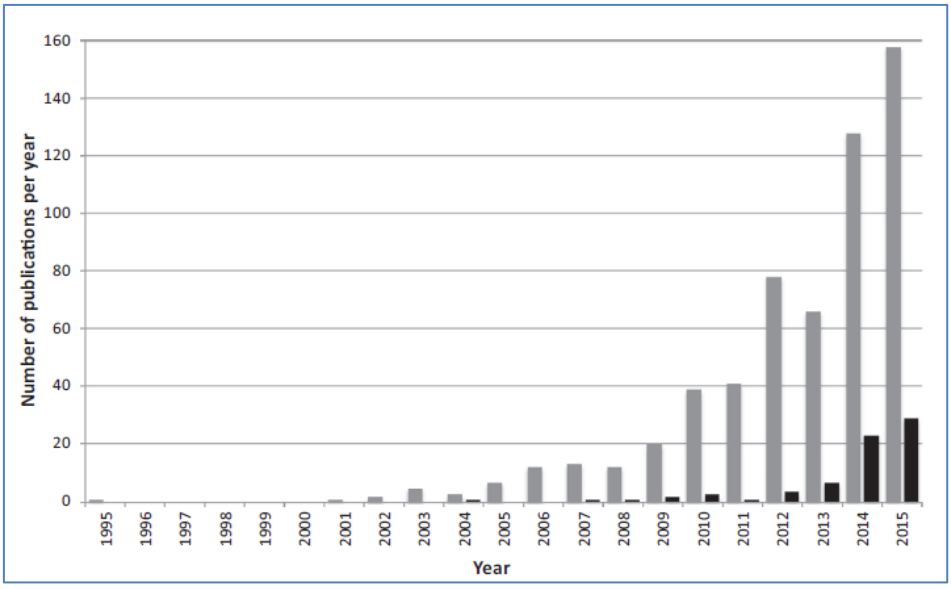

Fig-1: "PubMed-listed publications on oligometastases in general by year" Saluja *et al*. [16]

- Gray bars: search strategy used: [oligometastatic OR oligometastasis OR oligometastases]
- Black bars: search strategy used: [oligometastatic OR oligometastasis OR oligometastases] AND [prostate cancer]

Impact of treatment of the primary tumor in oligometastatic prostate cancer

Increasing local control of the disease can be used to reduce the complications of local development (urinary, compression, pain...) and may decrease metastatic spread from the primitive site, which could be a cell sanctuary (resistant to general treatment). If conclusive results have been seen in metastatic kidney or colon cancer, little data is available in metastatic PCa.

- **Cytoreductive prostatectomy**

It is often thought that radical prostatectomy (RP) does not improve prognosis in patients whose

cancer has spread systemically beyond the prostate, and removal of prostate gland in these patients may offer only palliative care by alleviating local symptoms[17,18]. Traditionally, definite local therapy such as RP is usually performed for locally or pelvic confined PCa [19-21]. There is no recommendation yet for surgery or radiation on the primary tumor in current practice guidelines because of the lack of high level evidence supporting the treatment of primary tumor in metastatic PCa patients [19, 22, 23]. However, many studies have reported encouraging results in this context of oligometastatic disease, all reports to date are observational data or retrospective reviews.

Culp *et al*., using the SEER database, they evaluated the role of local therapy in men documented stage M1a–c (American Joint Committee on Cancer stage) PCa. A total of 8,185 patients with metastatic PCa were identified. RP was performed in 245 patients with 67.4% 5-yr OS, and 75.8% 5-yr disease specific survival. Brachytherapy was performed in 129 patients with 52.6% 5-yr OS, and 61.3% 5-yr disease specific survival. The remaining 7,811 patients underwent no local therapy with only 22.5% 5-yr OS, and 48.7% 5-yr disease specific survival. The results suggested that local therapies with either RP or brachytherapy were associated with improve overall and disease specific survival. However, this study had some limitations that RP was performed in only about 3% of the population, and there might be selection bias [24]. Antwi and Everson also analyzed patients from the same SEER database with propensity score methods for risk adjustment, and found similar results. They also observed that patients underwent RP after diagnosis with metastatic PCa was associated with 73% (Hazard ratio [HR] 0.27, 95% CI: 0.20-0.38) lower risk of all-cause mortality, and 72% (HR 0.28, 95% CI: 0.20-0.39) reduced risk of death from PCa [25].

Aggressive transurethral resection of the prostate (TURP) is another form of cytoreductive surgery. Qin *et al*. retrospectively reviewed metastatic hormone sensitive PCa patients underwent palliative TURP and found that this resulted in a better and more prolonged response to androgen depriving therapy (ADT) with a trend towards improvement in disease specific and OS. (54) TURP may provide an alternative approach for cytoreductive surgery besides RP [26].

A retrospective case series from 2007 to 2014 comprising 106 patients with newly diagnosed metastatic PCa from the USA, Germany, Italy, and Sweden (published in 2014) on 1,206 metastatic patients, concluded that local treatment (surgery or radiotherapy) was not discriminating in terms of specific and overall survival (OS) [27]. Fossati *et al*. confirmed that the specific mortality was 30% higher if there was no local treatment offered in metastatic PCa for selected patients [28]. The role of the local control, even initial, was underlined in slowing the evolution towards PCa resistant to castration. Using data from 263 patients from five Australian institutions, the 45 patients who had RP had fewer local complications (20%) compared to 173 patients without local treatment (54.3%; p = 0.001) or 45 patients treated with radiotherapy (46.7%; p = 0.007). Vesical obstruction was rare after RP (4.4%), more frequent after radiotherapy (35.5%) or in the absence of local treatment (42.8%)[29].

Heidenreich *et al*. reported a case-control study to compare patients with minimal metastatic disease who underwent RP with ADT with metastatic PCa patients who received only ADT in control group. 23 patients who underwent RP in addition to ADT were the patients who had clinically localized PCa with ≤ 3 bone metastatic sites, and no visceral disease. Whereas, other 38 patients in the control group received only ADT .Patients in RP group had significantly better clinical progression free survival (38.6 vs. 26.5months, p=0.032), cancer specific survival rates (95.6% vs 84.2%, p=0.043), and longer median time to castration resistant PCa (40 vs. 29 months, p=0.04), but OS was not different. There was no statistically significant different in terms of clinical stage, Gleason score, prostate-specific antigen (PSA), and extent of metastases between two groups [30].

Patrikidou *et al*. found that up to 78% of patients who have de novo Metastatic PCa will suffer significant local symptoms such as pelvic pain, dysuria, hematuria, and urinary retention throughout their disease course. These patients required palliative RP, cystectomy, or pelvic exenteration to alleviate the symptoms. Therefore, initial definite locoregional treatment at earlier time point in these patients may have a role to prevent the development of late local symptoms. They concluded that a possible advantage of RP in metastatic PCa is the prevention of late symptomatic local progression [31].

In 2017, Gandaglia *et al*. reported outcomes of 11 patients with oligometastatic PCa who underwent RP in a single-institutional series. These patients had a 7-year progression free survival and cancer-specific survival rates of 45% and 82%, respectively. This study had several limitations: small retrospective review with only 11 patients, patients who underwent RP had good performance status, low disease volume, and favorable PSA level and there was no control group in this study, so the outcomes of this study could not be determined [32].

- **Radiotherapy to the primary tumor**

While the place of combining radiotherapy with ADT in patients with locally advanced PCa has already been shown, the place of locoregional treatment in cases of the metastatic stage remains unclear.

In a retrospective study of 369 patients who received local treatment with radiotherapy, Singh *et al*. observed that patients with <5 metastases have a survival rate of 45% (10 years after diagnosis) compared to 18% in patients with more than 5 metastases. In addition, patients with initially few metastases have more local progression of their disease, unlike patients with polymetastatic disease [33].

Satkunasivam *et al*. in a retrospective study of 4069 patients with PCa, collected between 2004 and 2009, compared the impact on survival after local treatment with radical prostatectomy, intensity modulated radiation therapy (IMRT) or conformal radiation therapy (CRT). 47 patients underwent radical prostatectomy, 88 from IMRT and 107 from CRT. 3827 patients did not receive local treatment. The risk of specific mortality from PCa was reduced by 52% in patients who underwent radical prostatectomy, by 62% in the patient who received an IMRT. However, no benefit was observed in patients who underwent CRT compared to those who did not receive local treatment [34].

Recently, there were two prospective randomized control trials evaluating the effect of local radiotherapy in patients with newly diagnosed metastatic PCa which are HORRAD and STAMPEDE trials.

In the HORRAD trial, 432 men with newly-diagnosed hormone-sensitive PCa, PSA>20 ng/ml and bone metastases, were randomized to receive ADT with or without prostate radiotherapy. Median time to PSA progression was longer in the radiotherapy group compared to ADT alone (15 vs. 12 months, HR: 0.78 (95% CI, 0.63–0.97); p = 0.02). Data on OS resulted inconclusive (HR: 0.90 (95% CI, 0.70–1.14)), this trial raised the possibility that survival might be improved in a subgroup of patients with fewer than five bone metastases (HR: 0.68 (95% CI, 0.42–1.10))[35].

STAMPEDE study is a multicenter randomized controlled phase 3 trial, compared the outcomes of ADT with radiotherapy to the primary tumor to ADT alone, in 2061 patients with de novo metastatic PCa. Radiotherapy to the primary delivered 55 Gray (Gy) in 20 fractions over four weeks or 36 Gy in 6 fractions over six weeks. Radiotherapy improved failure-free survival (HR: 0.76 (95% CI, 0.68–0.84); p < 0.0001), but not OS (HR: 0.92 (95% CI, 0.80–1.06); p = 0.266). However, in the sub-groups analysis, the low metastatic burden subgroup, as per CHAARTED criteria, had significant benefit in both failure-free (HR 0.59, 95% CI 0.49–0.72) and OS (HR 0.68, 95% CI 0.52–0.90)[36]. High metastatic burden is defined as ≥ 4 bony metastases with one or more outside the pelvis or vertebral bodies, or visceral metastases, or both. All other patients were classified to have low metastatic burden [3].

Metastasis-directed therapy for oligometastatic prostate cancer

Systemic treatment with ADT and/or chemotherapy remains at the core of treating metastatic PCa [[37]. However, MDT has emerged as an alternative approach for a subset of patients with oligometastatic disease [4]. In this setting, the rationale for MDT is to eradicate the cancerous lesion(s), delay exposure to next-line systemic therapy and delay progression to a castration resistant state [38].

- **Stereotactic body radiotherapy (SBRT)**

There are sparse data describing outcomes of SBRT for patients with oligometastatic PCa. SBRT is used to deliver a high dose of radiation very precisely to an extra cranial target. Treatment is typically given as a single dose or a small number of fractions [39].

A prospective study of 17 men with 21 metastatic PCa lesions were treated with SBRT between February 2009 and November 2011. All patients had a detectable (PSA) at the time of SBRT, and 11 patients (65%) had hormone-refractory (HR) disease. Treatment sites included bone (n=19), lymph nodes (n=1), and liver (n=1). For patients with bone lesions, the median dose was 20 Gy in a single fraction. Local control (LC) was 100%, and the PSA nadir was undetectable in 9 patients (53%), lower than pre-treatment levels in 15 patients (88%), and continued to decline or remain undetectable in 12 patients (71%) at a median follow-up of 6 months. Reported toxicities included one case each of grade 2 dyspnea and back pain, there were no cases of grade ≥3 toxicity following treatment [8].

Ost *et al*. reported a retrospective multicenter analysis of metastatic PCa patients diagnosed with ≤ 3 metachronous metastases treated with SBRT. 119 patients were treated for 163 metastatic lesions. DPFS, defined as the absence of new metastatic lesions, at 3 and 5-year was 31% and 15% respectively. Although not significant (p = 0.09), the median DPFS of SBRT versus SBRT and adjuvant ADT was 18 compared with 25 months. The 3 and 5-year LPFS was 93% and 92%, respectively. A lower radiotherapy dose predicted for a higher local recurrence rate with a 3-years LPFS of 79% for patients treated with a biologically effective dose (BED) <100 Gy versus 99% for patients treated with >100 Gy (p = 0.01)[7].

Siva *et al*. explored outcomes of single fraction stereotactic ablative radiotherapy (SABR) for patients with oligometastatic prostate. 33 patients received SABR to a total of 50 oligometastases between 2013 and 2014 and were followed for 2 years. Patients received a single fraction of 20 Gy SABR to all visible (1–3) sites of disease. The 1 and 2-year LPFS was 97% and 93%, and DPFS was 58% and 39%, respectively. In those not on ADT the 2-year freedom from ADT was 48%. There was no significant difference from baseline quality of life observed. Limitations of this trial were

small sample size, limited duration of follow-up, and lack of a control arm [40].

In 2019, Patel *et al*. reported a retrospective cohort analysis of 51 patients with 64 metastatic bone-only PCa with ≤3 sites of disease. Presenting with metachronous or synchronous disease to the Royal Marsden Hospital between July 2011 and March 2018. All patients were treated with SBRT using Cyberknife radiotherapy, 2 patients were treated using a C-arm Linac machine as well for a separate metastasis. Median follow-up was 23 months. During the follow-up period, 4 patients (7.8%) died. 1, 2, 3, and 4-year OS rates were 97%, 97%, 92.6%, and 73%, respectively. Median progression-free survival (PFS) was 11 months (95% CI 8–25). At 1 year, 21 patients (45.1%) had progressed, at 2 years, 2 more patients (7.1%) had progressed. Median PFS was significantly different between hormone-sensitive patients (24 months) and castrate-resistant patients (3 months). No patients experienced grade 3 or 4 toxicities [41].

Recently, interim analysis of a prospective single institution study of men relapsing with up to five synchronous lesions following definitive local treatment for primary PCa. The aim was to determine the proportion of patients not requiring treatment escalation following SBRT. 199 patients were enrolled to receive fractionated SBRT (50 Gray in 10 fractions) to each visible lesion. 14 patients were castration resistant at enrolment. The proportion of patients not requiring treatment escalation 2 years following SBRT was 51.7% (95% CI: 44.1–59.3%). The median length of treatment escalation-free survival over the entire follow-up period was 27.1 months (95% CI; 21.8–29.4 months). Prior ADT predicted a significantly lower rate of freedom from treatment escalation at 2 years compared to no prior ADT (odds ratio = 0.21, 95% CI: 0.08–0.54, p = 0.001). There was no difference in the efficacy of SBRT when treating 4–5 vs. 1–3 initial lesions. PSA decline was induced in 75% of patients, with PSA readings falling to an undetectable level in six patients. No late grade three toxicities were observed. These interim results suggest that SBRT can be used to treat up to five synchronous PCa oligometastases to delay treatment escalation [42].

Although the data available to date suggest that SBRT may play a role in the management of oligometastatic PCa, further studies are needed to better quantify the benefits of this approach, the subgroups that will benefit most and the optimal combination and timing with other systemic treatments.

- **Other techniques of metastasis-directed therapy**

Metastases can be treated locally by several techniques, such as surgery, radiofrequency, cryotherapy and chemo-embolization. But few studies are available to evaluate them in the management of oligometastatic PCa.

- **Ongoing randomized clinical trials including patients with oligometastatic prostate cancer**

Three prospective registered trials are currently recruiting patients with oligometastatic PCa. The first trial (NCT01558427) is a randomized phase 2 trial comparing MDT (surgery or SBRT) with active surveillance followed by ADT at progression for oligometastatic recurrence (three or fewer metastases). This trial includes only patients who are not castrated at the time of oligometastasis with a controlled primary tumor. The primary end point is the time to the start of palliative ADT. The underlying hypothesis is that patients under active surveillance will progress faster compared with those treated with MDT. No adjuvant ADT will be administered. The second trial (NCT01777802) is an observational study for patients with oligometastatic PCa (three or fewer metastases) both with untreated and treated primary tumors undergoing SBRT. The primary outcome measure is the induction of anti-PCa immunity. The hypothesis is that SBRT is able to induce a robust anti-tumoral immune response, as recently suggested [43].

CONCLUSION

In the future, oligometastatic PCa is likely to be defined based on genomic and biological features in addition to pertinent clinical criteria. For now, a definition based on up to five detectable lesions is widely employed and is reasonable for use [44]. Available data suggest that local therapies such as prostatectomy and radiotherapy can be performed safely in the presence of metastatic disease and might prevent the need for future palliative treatments. Similarly, MDT such as SBRT carry a low risk of toxic effects and provide excellent local control. At this time, insufficient data are available to draw conclusions regarding the effect of aggressive therapies on overall or cancer-specific survival. Prospective, well-controlled trials are necessary and should aim to report outcomes in a consistent and systematic manner.

REFERENCES

1. Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet-Tieulent, J., & Jemal, A. (2015). Global cancer statistics, 2012. *CA: a cancer journal for clinicians*, *65*(2), 87-108.
2. Gravis, G., Fizazi, K., Joly, F., Oudard, S., Priou, F., Esterni, B., ... & Soulie, M. (2013). Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *The lancet oncology*, *14*(2), 149-158.
3. Sweeney, C. J., Chen, Y. H., Carducci, M., Liu, G., Jarrard, D. F., Eisenberger, M., ... & DiPaola, R. S. (2015). Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *New England Journal of Medicine*, *373*(8), 737-746.
4. Weichselbaum, R. R., & Hellman, S. (2011). Oligometastases revisited. *Nature reviews Clinical oncology*, *8*(6), 378-382.

5. Weichselbaum, R. R., & Hellman, S. (2011). Oligometastases revisited. *Nature reviews Clinical oncology*, *8*(6), 378-382.
6. Cheung, P., Thibault, I., & Bjarnason, G. A. (2014). The emerging roles of stereotactic ablative radiotherapy for metastatic renal cell carcinoma. *Current opinion in supportive and palliative care*, *8*(3), 258-264.
7. Ost, P., Jereczek-Fossa, B. A., Van As, N., Zilli, T., Muacevic, A., Olivier, K., ... & De Meerleer, G. (2016). Progression-free survival following stereotactic body radiotherapy for oligometastatic prostate cancer treatment-naive recurrence: a multi-institutional analysis. *European urology*, *69*(1), 9-12.
8. Ahmed, K. A., Barney, B. M., Davis, B. J., Park, S. S., Kwon, E. D., & Olivier, K. R. (2013). Stereotactic body radiation therapy in the treatment of oligometastatic prostate cancer. *Frontiers in oncology*, *2*, 215.
9. Berkovic, P., De Meerleer, G., Delrue, L., Lambert, B., Fonteyne, V., Lumen, N., ... & Ost, P. (2013). Salvage stereotactic body radiotherapy for patients with limited prostate cancer metastases: deferring androgen deprivation therapy. *Clinical genitourinary cancer*, *11*(1), 27-32.
10. Lussier, Y. A., Xing, H. R., Salama, J. K., Khodarev, N. N., Huang, Y., Zhang, Q., ... & Weichselbaum, R. R. (2011). MicroRNA expression characterizes oligometastasis (es). *PloS one*, *6*(12), e28650.
11. Wuttig, D., Baier, B., Fuessel, S., Meinhardt, M., Herr, A., Hoefling, C., ... & Wirth, M. P. (2009). Gene signatures of pulmonary metastases of renal cell carcinoma reflect the disease-free interval and the number of metastases per patient. *International journal of cancer*, *125*(2), 474-482.
12. D'Angelillo, R. M., Francolini, G., Ingrosso, G., Ravo, V., Triggiani, L., Magli, A., ... & Magrini, S. M. (2019). Consensus statements on ablative radiotherapy for oligometastatic prostate cancer: a position paper of Italian Association of Radiotherapy and Clinical Oncology (AIRO). *Critical Reviews in Oncology/Hematology*, *138*, 24-28.
13. Gillessen, S., Omlin, A., Attard, G., De Bono, J. S., Efstathiou, E., Fizazi, K., ... & Tombal, B. (2015). Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. *Annals of Oncology*, *26*(8), 1589-1604.
14. Gillessen, S., Attard, G., Beer, T. M., Beltran, H., Bossi, A., Bristow, R., ... & Omlin, A. (2018). Management of patients with advanced prostate cancer: the report of the Advanced Prostate Cancer Consensus Conference APCCC 2017. *European urology*, *73*(2), 178-211.
15. Francini, E., Gray, K. P., Xie, W., Shaw, G. K., Valença, L., Bernard, B., ... & Sweeney, C. J. (2018). Time of metastatic disease presentation and volume of disease are prognostic for metastatic hormone sensitive prostate cancer (mHSPC). *The Prostate*, *78*(12), 889-895.
16. Saluja, R., Cheung, P., Zukotynski, K., & Emmenegger, U. (2016, May). Disease volume and distribution as drivers of treatment decisions in metastatic prostate cancer: from chemohormonal therapy to stereotactic ablative radiotherapy of oligometastases. In *Urologic Oncology: Seminars and Original Investigations* (Vol. 34, No. 5, pp. 225-232). Elsevier.
17. Potosky, A. L., Harlan, L. C., Stanford, J. L., Gilliland, F. D., Hamilton, A. S., Albertsen, P. C., ... & Litwin, M. S. (1999). Prostate cancer practice patterns and quality of life: the Prostate Cancer Outcomes Study. *Journal of the National Cancer Institute*, *91*(20), 1719-1724.
18. Canby-Hagino, E. D., Swanson, G. P., Crawford, E. D., Basler, J. W., Hernandez, J., & Thompson, I. M. (2005). Local and systemic therapy for patients with metastatic prostate cancer: should the primary tumor be treated?. *Current prostate reports*, *3*(4), 153-159.
19. Heidenreich, A., Bastian, P. J., Bellmunt, J., Bolla, M., Joniau, S., van der Kwast, T., ... & Mottet, N. (2014). EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent—update 2013. *European urology*, *65*(1), 124-137.
20. Dezube, A. R., & Jaklitsch, M. T. (2020). Minimizing residual occult nodal metastasis in NSCLC: recent advances, current status and controversies. *Expert Review of Anticancer Therapy*, *20*(2), 117-130.
21. Bolla, M., van Poppel, H., Tombal, B., Vekemans, K., Da Pozzo, L., De Reijke, T. M., ... & Collette, L. (2012). Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *The Lancet*, *380*(9858), 2018-2027.
22. Heidenreich, A., Bastian, P. J., Bellmunt, J., Bolla, M., Joniau, S., van der Kwast, T., ... & Mottet, N. (2014). EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. *European urology*, *65*(2), 467-479.
23. Mohler, J. L. (2016). Prostate Cancer, Version 1.2016. J Natl Compr Canc Netw 14, 19–30 (2016).
24. Culp, S. H., Schellhammer, P. F., & Williams, M. B. (2014). Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. *European urology*, *65*(6), 1058-1066.
25. Antwi, S., & Everson, T. M. (2014). Prognostic impact of definitive local therapy of the primary tumor in men with metastatic prostate cancer at diagnosis: a population-based, propensity score analysis. *Cancer epidemiology*, *38*(4), 435-441.
26. Qin, X. J., Ma, C. G., Ye, D. W., Yao, X. D., Zhang, S. L., Dai, B., ... & Swanson, G. P. (2012, March). Tumor cytoreduction results in better response to androgen ablation—a preliminary report of palliative transurethral resection of the prostate in metastatic hormone sensitive prostate cancer. In *Urologic Oncology: Seminars and Original Investigations* (Vol. 30, No. 2, pp. 145-149). Elsevier.
27. Sooriakumaran, P., Karnes, J., Stief, C., Copsey, B., Montorsi, F., Hammerer, P., ... & Graefen, M. (2016). A multi-institutional analysis of perioperative outcomes in 106 men who underwent radical

prostatectomy for distant metastatic prostate cancer at presentation. *European urology*, *69*(5), 788-794.
28. Fossati, N., Trinh, Q. D., Sammon, J., Sood, A., Larcher, A., Sun, M., ... & Abdollah, F. (2015). Identifying optimal candidates for local treatment of the primary tumor among patients diagnosed with metastatic prostate cancer: a SEER-based study. *European urology*, *67*(1), 3-6.
29. Won, A. C., Gurney, H., Marx, G., De Souza, P., & Patel, M. I. (2013). Primary treatment of the prostate improves local palliation in men who ultimately develop castrate-resistant prostate cancer. *BJU international*, *112*(4), E250-E255.
30. Heidenreich, A., Pfister, D., & Porres, D. (2015). Cytoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: results of a feasibility and case-control study. *The Journal of urology*, *193*(3), 832-838.
31. Patrikidou, A., Brureau, L., Casenave, J., Albiges, L., Di Palma, M., Patard, J. J., ... & Loriot, Y. (2015, May). Locoregional symptoms in patients with de novo metastatic prostate cancer: morbidity, management, and disease outcome. In *Urologic Oncology: Seminars and Original Investigations* (Vol. 33, No. 5, pp. 202-e9). Elsevier.
32. Gandaglia, G., Fossati, N., Stabile, A., Bandini, M., Rigatti, P., Montorsi, F., & Briganti, A. (2017). Radical prostatectomy in men with oligometastatic prostate cancer: results of a single-institution series with long-term follow-up. *European urology*, *72*(2), 289-292.
33. Singh, D., Yi, W. S., Brasacchio, R. A., Muhs, A. G., Smudzin, T., Williams, J. P., ... & Okunieff, P. (2004). Is there a favorable subset of patients with prostate cancer who develop oligometastases?. *International Journal of Radiation Oncology* Biology* Physics*, *58*(1), 3-10.
34. Satkunasivam, R., Kim, A. E., Desai, M., Nguyen, M. M., Quinn, D. I., Ballas, L., ... & Gill, I. S. (2015). Radical prostatectomy or external beam radiation therapy vs no local therapy for survival benefit in metastatic prostate cancer: a SEER-medicare analysis. *The Journal of urology*, *194*(2), 378-385.
35. Boevé, L. M., Hulshof, M. C., Vis, A. N., Zwinderman, A. H., Twisk, J. W., Witjes, W. P., ... & van Andel, G. (2019). Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: data from the HORRAD trial. *European urology*, *75*(3), 410-418.
36. Parker, C. C., James, N. D., Brawley, C. D., Clarke, N. W., Hoyle, A. P., Ali, A., ... & Sydes, M. R. (2018). Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *The Lancet*, *392*(10162), 2353-2366.
37. Cornford, P., Bellmunt, J., Bolla, M., Briers, E., De Santis, M., Gross, T., ... & Mottet, N. (2017). EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. *European urology*, *71*(4), 630-642.
38. Giannarini, G., Fossati, N., Gandaglia, G., Cucchiara, V., Ficarra, V., Mirone, V., ... & Briganti, A. (2018). Will image-guided metastasis-directed therapy change the treatment paradigm of oligorecurrent prostate cancer?. *European Urology*, *74*(2), 131-133.
39. Potters, L., Kavanagh, B., Galvin, J. M., Hevezi, J. M., Janjan, N. A., Larson, D. A., ... & Rosenthal, S. A. (2010). American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. *International journal of radiation oncology, biology, physics*, *76*(2), 326-332.
40. Siva, S., Bressel, M., Murphy, D. G., Shaw, M., Chander, S., Violet, J., ... & Foroudi, F. (2018). Stereotactic abative body radiotherapy (SABR) for oligometastatic prostate cancer: a prospective clinical trial. *European urology*, *74*(4), 455-462.
41. Patel, P. H., Chaw, C. L., Tree, A. C., Sharabiani, M., & van As, N. J. (2019). Stereotactic body radiotherapy for bone oligometastatic disease in prostate cancer. *World journal of urology*, *37*(12), 2615-2621.
42. Bowden, P., See, A. W., Frydenberg, M., Haxhimolla, H., Costello, A. J., Moon, D., ... & Everitt, C. (2020). Fractionated stereotactic body radiotherapy for up to five prostate cancer oligometastases: interim outcomes of a prospective clinical trial. *International journal of cancer*, *146*(1), 161-168.
43. Durante, M., Reppingen, N., & Held, K. D. (2013). Immunologically augmented cancer treatment using modern radiotherapy. *Trends in molecular medicine*, *19*(9), 565-582.
44. Tosoian, J. J., Gorin, M. A., Ross, A. E., Pienta, K. J., Tran, P. T., & Schaeffer, E. M. (2017). Oligometastatic prostate cancer: definitions, clinical outcomes, and treatment considerations. *Nature Reviews Urology*, *14*(1), 15-25.