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Hot Topic

Oligometastatic prostate cancer: The game is afoot

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ABSTRACT

Oligometastatic prostate cancer represents an intermediate state between a localized tumor and widespread metastatic disease. Its specific clinical features suggest the existence of a distinct biology which still needs to be elucidated. New imaging techniques like prostate specific membrane antigen (PSMA) PET scans have shown to perform well in the staging and restaging of this category of patients, at different phases of disease evolution. Despite limited prospective evidence, metastasis-directed therapies (MDT) are emerging as valid treatment options able to postpone systemic therapies and probably improve survival outcome. The aim of this review is to shed light on the clinical scenario of prostate cancer patients with limited metastatic disease burden and highlight the role of MDT strategies in this setting.

Introduction

Prostate cancer, the second most frequent tumor and the fifth leading cause of cancer mortality in men [1], is characterized by a wide spectrum of biological behavior, which translates into different clinical presentations ranging from indolent microscopic disease to highly aggressive tumor with a strong tendency to metastasize.

Organ-confined neoplasms are usually amenable to a local approach, with surgery and radiotherapy being at the forefront of the therapeutic strategies and showing comparable levels of disease control and survival rates [2]. In contrast, the metastatic disease state represents an heterogeneous landscape of different stages and manifestations of disease, in which androgen deprivation therapy (ADT), with or without concomitant chemotherapy or 2nd generation anti-androgens, undoubtedly continues to maintain its prominent role [3,4].

It's now more than 20 years since Weichselbaum and Hellman [5] coined the term "oligometastatic" to describe a subgroup of metastatic patients with a limited number of secondary lesions (threshold ranging from 3 to 5) in one or few organs. Such concept carries relevant clinical implications, because it defines an intermediate status between a localized disease and a widespread tumor, which might be amenable to targeted metastasis-directed therapies (MDT) to prevent the development of further disease localizations and possibly to improve overall survival.

Despite a growing number of reports proving the empirical relevance of this approach [6–11], a detailed picture of the underlying biological scenario in oligometastatic prostate cancer is still lacking in the current state of knowledge.

In the absence of predictive molecular markers intended to determine prostate cancer metastatic capacity, the role of imaging becomes crucial in identifying a « true » oligometastatic state. In this regard functional imaging, and more specifically prostate specific membrane antigen (PSMA) positron emission tomography (PET), has shown promise in the assessment of metastatic burden in prostate cancer patients [12].

The aim of the present critical review would be to provide an overview on oligometastatic prostate cancer, including recent evidence on the role of MDT strategies in the *de novo*, oligorecurrent and

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oligoprogressive disease status.

Biology of oligometastatic disease

The progression to metastatic prostate cancer from early tumor stages represents the result of different alterations at the molecular and genome levels which make it a multi-step process, depending not only on the intrinsic properties of the tumor but also being influenced by host response. According to the « Seed and Soil » theory [13], a prerequisite for the metastatic focus implant is the compatibility between the characteristics of the tumor cell and the microenvironment of the target site. It is well known that different subpopulations of cells have invasive skills and are potentially capable to metastasize, i.e. multiple metastases can originate from different progenitors, leading to a biologically heterogeneous setting characterized by subclonal complexity and genome instability, which can hamper the finding of an appropriate therapeutic strategy [14].

Understanding the biology behind the (oligo)metastases could lead to a detailed acknowledgement of those molecular events responsible for the shift from an organ-confined to a disseminated metastatic disease, with tremendous clinical implications and the possibility to identify specific biomarkers able to predict cancer evolution in patients with a localized disease. Despite specific data supporting this assumption are still lacking, different strategies can be adopted in order to approach the molecular genetics of the oligometastatic status [15–17].

An indirect strategy could be a thorough molecular assessment of the early recurrent tumors after a previous radical treatment; indeed, these tumors can be considered to harbor micrometastases at presentation by holding within themselves features enabling successful metastatic dissemination, such as hypoxia, genome instability, and/or clonal diversity. However this approach, as it is for the study of *de novo* oligometastatic patients, requires a considerable amount of data and a follow-up long enough to discriminate between real oligometastatic and rapidly progressing patients.

In a recent paper, Pitroda et al. [16] proposed a different strategy providing an integrative molecular analysis of liver metastases from oligometastatic colorectal cancer patients who underwent metastasectomy. As a result of their multilevel investigation, authors managed to identify three different subtypes of liver metastases; the information they obtained from the transcriptional analysis of mRNA and microRNA networks integrates clinical risk stratification for prediction of long-term survival after the surgical procedure. More specifically, patients with the most favorable molecular subtype have a 10-year survival of 95% following metastasectomy and therefore they could be reasonably excluded from additional systemic therapies. In contrast, those with unfavorable subtypes do not benefit from MDT and require systemic therapy. According to the authors, the molecular heterogeneity of colorectal liver metastases contributes to differences in terms of outcome for the patients.

Another study from Lussier et al. [15] supports the hypothesis that the development of specific molecular markers can predict which oligometastatic patients eventually fail to become polymetastatic. The researchers extracted RNA from 42 paraffin embedded samples of both primary and metastatic tumors treated with stereotactic body radiotherapy (SBRT) and profiled the resultant microRNAs; they find out that unique prioritized features of a potential microRNA classifier were associated with persistence in an oligometastatic state, i.e. the expression of different microRNA patterns derived from patients points out the molecular differences between a “true” oligometastatic phenotype and the one undergoing further progression towards a polymetastatic state.

These findings could pave the way for further studies aiming to provide a molecular classification of patients with limited metastases located in different sites and originating from different primary sites, including prostate. The genomics and the transcriptomics of both localized hormone-sensitive and metastatic castration-resistant tumors have been extensively studied [18]. Similarly, recent initiatives have started collecting molecular data from oligometastatic prostate cancer in order to provide us a more precise definition of this entity and decipher the molecular events involved in disease progression [19]. Furthermore, it is essential to discriminate between synchronous (*de novo* metastases) and metachronous disease (oligorecurrence), because these two conditions are likely to represent distinct biological states, with implications for the correct adoption of MDT strategies in this setting.

Imaging

Despite the relatively frequent occurrence of oligometastates in prostate cancer, a universally accepted definition is lacking. More specifically, the exact location and maximum number of lesions that characterize the oligometastatic state are still debated. In 2017, the Advanced Prostate Cancer Consensus Conference (APCCC) proposed to limit the term oligometastatic to those patients presenting with three or fewer bone or lymph node metastases [20], whereas other authors consider five lesions as the limit of the oligometastatic state [21].

Such quantitative definitions underline the importance of various imaging techniques in correctly classifying this subgroup of patients, who are usually mildly or non-symptomatic and may potentially be treated with curative intent. However, standard imaging modalities for prostate cancer staging, i.e. bone scintigraphy, thoraco-abdomino-pelvic CT and/or morphological magnetic resonance imaging (MRI), have a poor diagnostic accuracy for detecting low burden disease [22], underestimating the number of secondary lesions; in this setting, modern imaging techniques including PET/CT with specific tracers and whole-body MRI have shown to outperform classical imaging, although their influence on clinical management of prostate cancer remains debated [23].

Importantly, the so-called oligometastatic state can be observed at different stages in the disease, ranging from the *de novo* metastatic setting to oligorecurrent hormone-sensitive disease after a primary treatment or to the progressive castration-resistant phase. At each disease state, imaging techniques should be selected based on the clinical question and the therapeutic implications.

In the context of modern imaging methods, radiolabeled choline PET/CT represents a promising technique for determining nodal and bone involvement in the primary staging of intermediate- and high-risk prostate cancer. 18F-choline PET/CT outperforms conventional imaging in the detection of bone metastases with a sensitivity of 79%, a specificity of 97% and a diagnostic accuracy of 84% [24]. For lymph node staging, its sensitivity ranges between 33 and 100% and its specificity between 95% and 100% [25]. 68Ga-PSMA PET/CT has demonstrated even higher sensitivity and specificity in the detection of nodal disease [26], and a better accuracy in the detection of bone and visceral metastases if compared with standard techniques [27,28]. Whole body-MRI (WB-MRI) shows good performance in the detection of bone lesions, with a diagnostic accuracy of 81.4%, but is of less value to detect lymph node metastases [29].

In patients with biochemical recurrence (BCR), the role of imaging is of crucial importance to discriminate between truly oligometastatic patients, amenable to MDT and those with disseminated disease, requiring systemic therapies. In this setting, 68Ga-PSMA PET/CT outperforms 18F/11C-Choline PET for both nodal and bone recurrences at PSA levels < 5 ng/ml [10]. Furthermore, PSMA-PET outperforms all other imaging modalities for PSA values between 0.2 and 1, 1–2 and > 2 ng/ml, with a recurrence detection rates of 58%, 76% and 95%, respectively, although histopathological confirmation of tumor recurrence was not obtained. [10]. Current EAU guidelines have implemented the use of PSMA-PET at biochemical relapse and strongly recommend to perform this exam to exclude positive lymph nodes or distant metastases in patients fit for curative salvage treatments [30]. WB-MRI can be matched with pelvic multiparametric MRI for a combined detection of local recurrence and regional/distant metastases, with valid performances even at low PSA values [31].

Ultimately, imaging may play a pivotal role in determining disease progression in metastatic castration-resistant prostate cancer (mCRPC) receiving systemic therapies. More specifically, modern imaging techniques could be particularly helpful in early detection of metastatic progression which might benefit from early second-line ADT, with or without the addition of MDT strategies. However, standard imaging using contrast-enhanced CT, MRI and bone scintigraphy remains the gold standard at this stage of disease, despite their low sensitivity to treatment response [32]. Choline-PET has a positive predictive value of 99% and a negative predictive value of 81% to detect lesions which do not respond to treatment in mCRPC [33] and, when executed early, it may be useful to predict clinical outcome of patients undergoing therapy with abiraterone acetate, enzalutamide or radium-223 [34]. While PSMA-PET does not seem to have a role in this setting, response criteria have been established for WB-MRI evaluation, even if data comes from small single-center studies [35].

Further complementary validation of new imaging modalities with common conventional imaging would be, especially in the context of clinical studies, key to better identify for the future actionable oligometastatic disease.

De novo oligometastatic patients: treating the primary?

It has been estimated that 4% of prostate cancer patients present with metastases at the time of diagnosis [36]. This patient population suffers from a more aggressive disease than those who progress with metachronous metastases, as demonstrated by a shorter time to castration resistance and worse survival outcomes [37]. Although standard ADT still represents the cornerstone of systemic therapy, the above-described clinical scenario has shown to benefit from the concurrent adoption of other systemic treatments, including docetaxel and abiraterone acetate [3,38]. More specifically, abiraterone acetate has recently shown to improve all survival endpoints in low-burden metastatic hormone sensitive prostate cancer (mHSPC) and up-front therapy combined with ADT should be administered to these patients [39].

The role of local therapy in this patient population has recently been re-evaluated, with accumulating evidences in favor of adding local treatment to the primary tumor in *de novo* metastatic prostate cancer patients. Rusthoven et al. [40] retrospectively analyzed the impact of adding EBRT or radical prostatectomy (RP) to standard ADT. They compared survival outcomes of 5844 patients with *de novo* metastatic castration sensitive patients receiving ADT only with 538 patients undergoing upfront EBRT and 69 patients undergoing radical prostatectomy; after a median follow-up of 5.1 years, the combined approach EBRT + ADT showed a significant overall survival (OS) benefit with a 18-month improvement compared with ADT alone. During the same time interval, a secondary analysis comparing survival outcomes of patients treated with RT + ADT vs RP + ADT demonstrated no significant differences between the 2 regimens, whereas both therapies showed superiority when compared to ADT alone. Several other non-randomized studies and patient cohort studies found similar results [41–43], although the relevance of these results is limited by the retrospective design, the limited number of patients and different treatment regimens.

The recently published HORRAD trial [44] is a multicenter prospective randomized trial including primary bone widespread metastatic prostate cancer patients and evaluating the impact of radiotherapy to the primary tumor along with ADT, compared with ADT alone; after a median follow-up time of 47 months, no survival benefit was shown for the combined treatment group. It is important to note that patients in this study had high PSA values (median value of 125 ng/mL and 149 ng/mL in patients treated with EBRT + ADT and ADT alone, respectively), high volume of bone metastases and the only required staging method was bone scintigraphy. According to their findings, authors suggest not to perform radiotherapy to the prostate in patients with primary bone metastatic prostate cancer, although they do not exclude a possible benefit, especially in the setting of lower disease burden.

In STAMPEDE, local prostate radiotherapy combined with standard systemic treatment was compared to standard of care only (ADT, with or without docetaxel according to the time of recruitment) [45]. In the overall treatment population, local approach to the prostate improved progression failure-free survival (HR 0.68, 95% CI 0.68, 0.84), but not OS (HR 0.92, 95% CI 0.80 1.06). Interestingly, a pre-specified subgroup analysis showed that local radiotherapy did improve OS in patients with a low burden of disease (HR 0.68, 95% CI 0.52, 0.90), but not in men with high disease burden (defined as four or more bone metastases with at least one occurring outside the axial skeleton and/or visceral metastases).

Taken together, these data support the use of local therapy to the primary tumor in the *de novo* oligometastatic setting. It is noteworthy that in the 2017 APCCC consensus meeting [20], more than two thirds of the panelists voted in the context of an oligometastatic disease for a therapeutic strategy which would include local ablative treatment of the primary site and of all metastases. The amended version of the ongoing EORTC 1414 PEGASUS trial (ClinicalTrials.gov Identifier: NCT02799706) and the new arm in STAMPEDE [43] will hopefully help for the future to elucidate in oligometastatic prostate cancer patients the role of ablative radiotherapy of all disease sites, while the currently recruiting SWOG NCT03678025 trial will provide further data on the role of surgery in this setting.

Metastasis-directed therapy and oligorecurrent patients: the current evidence

The majority of patients who relapse after previously treated primary prostate cancer generally present with no more than three lesions, defined oligorecurrences, which usually arise in regional lymph nodes and to a lesser extent in bones in a hormone-sensitive phase of the disease [46].

One of the most significant implications of the seed and soil theory is that the process of metastasis usually occurs in form of spread between distant sites rather than exploiting separate pathways which necessarily involve the primary tumor [47]; this assumption suggests that metastases may be able to act as primary tumors themselves, with the possibility of seeding and originating new metastases. In accordance with Hellman & Weichselbaum, targeting oligorecurrence with a MDT approach (surgery or ablative radiotherapy) might prevent the occurrence of further metastatic diffusion of disease and eventually improve survival [5]. Furthermore, as reported by several retrospective studies, MDT can delay the start of ADT, and its related side effects occurrence, by counteracting disease clinical progression [8–11,48].

Data from the first three prospective trials exploring the role of MDT in the setting of oligorecurrent prostate cancer patients have been recently published. The STOMP trial is a multicenter, randomized, phase II trial comparing MDT to all lesions (either metastasectomy or SBRT) versus surveillance alone in 62 oligorecurrent prostate cancer patients after primary treatment with curative aim [49]. Patients in the arm receiving MDT experienced a longer ADT-free survival than those who underwent surveillance alone (median value of 21 versus 13 months, respectively). Furthermore, a PSA response in three out of four patients was also demonstrated in the interventional arm, with comparable benefit of MDT on nodal and non-nodal metastases and excellent safety profile (no grade 2 or higher toxicity). The Australian POPSTAR trial [50] is a prospective, single-center, phase I study evaluating the safety and the feasibility of single-fraction SBRT in a group of 33 oligorecurrent prostate cancer patients presenting with nodal and/or bone metastatic lesions. Both the primary endpoints were met, with 97% of patients receiving the planned treatment and only one grade 3 adverse event reported. Similarly to the STOMP, this trial showed a PSA decline following SBRT in almost the same percentage of patients confirming the ability of MDT to the delay the need for palliative ADT by almost

2 years in the subgroup of patients who were ADT-free at treatment time. Ultimately, Kneebone et al. [51] provided the first observational experience of PSMA-based MDT, showing high levels of distant failure in a setting of 57 ADT-free oligometastatic prostate cancer patients.

The preliminary findings of the Baltimore ORIOLE trial (ClinicalTrials.gov: NCT02680587) [52], a phase II multi-center randomized study comparing observation versus SBRT in the setting of oligometastatic hormone sensitive patients, have recently been presented at the last ESTRO congress in Barcelona. The results of this study seem to be comparable to those observed in the STOMP trial, validating the safety and efficacy of SBRT in this setting. Moreover, by integrating PSMA PET/CT, this study will provide additional answers on the performance of new imaging modalities over conventional imaging for the detection of oligometastases and response evaluation following MDT.

Several open questions remain on the best treatment strategy for oligorecurrent prostate cancer patients. First, although retrospective series and prospective trials showed a clear benefit on progression-free survival rates, a clear OS benefit has not yet been demonstrated for prostate cancer patients. Nonetheless, in the multicenter phase II SABR COMET trial [53] recently presented during the last ASTRO meeting, patients with up to five metastases of different histology including prostate cancer treated with SBRT experienced a significant OS gain compared to patients receiving palliative standard of care (41 versus 28 months). However, in such setting of potentially long survivors, OS can be a difficult endpoint to reach in designed clinical studies; on this regard, metastasis-free survival (MFS) may be integrated in future trials as an independent predictor of survival in men with recurrent prostate cancer, following what has been suggested for the localized disease [54].

Second, in oligorecurrent nodal prostate cancer, treatment options include the use of salvage lymph node dissection (sLND) or radiotherapy strategies, with focal versus extensive treatment approaches considered both as valid treatment alternatives. Promising results with focal SBRT approaches targeting the nodal disease only have been reported [10], while more extensive radiation fields including the whole pelvis have been proposed by other centers [9,11,55]. Results of the OLIGOPELVIS GETUG P07 study (ClinicalTrials.gov Identifier: NCT02274779) [56], the first phase II trial exploring the role of elective nodal irradiation in oligorecurrent prostate cancer with up to 5 nodes, are eagerly awaited. As far as sLND is concerned, Fossati et al. reported about the largest series of nodal oligorecurrent prostate cancer patients, diagnosed with either choline or PSMA PET/CT: at 1-year, 25% of the patients included in the analysis (n = 654) experienced early clinical recurrence [57]. A recent systematic review by Ploussard et al. [58] confirms the safety and the feasibility of such surgical approach, despite long-term oncological and functional outcomes are not available yet. The role of adjuvant RT after sLND in improving PFS is an open issue, with institutional results showing a potential benefit from nodal irradiation [59].

However, questions arise on the optimal treatment strategy to adopt in patients with oligorecurrent prostate cancer with exclusive nodal involvement, a disease entity characterized by a better prognosis compared to recurrence with bone or visceral metastases [60], Although treatment strategies using whole-pelvic RT with elective nodal irradiation and boost to the positive nodes or sLND are probably associated with better progression-free survival rates, an improvement on the long-term outcome as compared to repeated SBRT has not been demonstrated yet. Moreover, better compliance and lower toxicity may be expected with focal SBRT as compared to elective treatments. The ongoing STORM trial (ClinicalTrials.gov Identifier: NCT03569241), a phase II trial randomizing oligorecurrent prostate cancer patients with up to 3 nodes between a MDT strategy (sLND or SBRT) versus the same strategy with inclusion of a pelvic irradiation, will probably provide in the next future answers to these open questions.

MDT for the “oligoprogressors”: more than simply betting our bottom dollar

ADT represents the mainstay of treatment for metastatic prostate cancer patients, since Huggins and Hodges demonstrated the androgen dependence of prostate cancer cells survival [61]. However, long-term androgen ablation leads to the origin of castrate-resistant clones which are no longer repressed by the first line standard approach and generally require the adoption of another systemic therapy.

In patients with oligometastatic spread from primary tumors other than prostate cancer, these is accumulating evidence supporting the role of EBRT to the progressive lesions in patients that progressed under systemic therapy; this condition has been described as oligoprogressive disease and patients were defined “oligoprogressors”. During the last ASTRO meeting, Gomez et al. reported results of a randomized phase II trial of stage IV oligometastatic non-small cell lung non-progressing after a frontline systemic therapy and randomized to receive ablative therapy to all lesions compared to maintenance therapy or surveillance alone. After a median FU of 39 months, local ablative therapies to all lesions resulted not only in a better PFS rate [62] but also in a significant OS benefit (41 versus 17 months) [63]. In another report, Gan et al. [64] observed 6 and 12-month local control rates of 100 and 86% after SBRT in a cohort of patients diagnosed with oligoprogressive ALK-rearranged NSCLC who were under crizotinib; furthermore, these patients could remain on crizotinib for longer time, with a possible associated overall survival benefit.

Based on these assumptions, even in mCRPC MDT could potentially play a role in ablating clonogens which are resistant to the systemic therapies and bring the patient back to a responsive state of disease [65].

While Decaestecker et al. have provided data about the safety and the efficacy of SBRT re-treatment in hormone-sensitive patients who recurred with no more than 3 lesions after a previous course of ablative therapy [66], some retrospective reports have demonstrated the role of MDT in the setting of advanced prostate cancer resistant to ADT, exploring the potential benefit of PFS and the possibility to prolong the time to the start of second line systemic treatments [67]. A subgroup analysis of the SBRT SG-05 multicenter prospective phase II trial (ClinicalTrials.gov Identifier: NCT02192788), testing SBRT with ADT in a cohort of oligometastatic prostate cancer patients, has shown that after a median follow-up of 9.8 months 8 of the 12 mCRPC patients (66%) included in the study were free from disease progression at last follow-up, and therefore could be spared from second generation hormonal therapy [68].

Different ongoing trials are exploring the role of ablative therapies in the mCRCP setting. The Canadian PCS IX study (ClinicalTrials.gov Identifier: NCT02685397) is an adaptive phase II/III randomized trial including oligometastatic CRPC patients and evaluating SBRT as a way to delay disease progression and postpone the onset of second-line systemic therapy. Recruited patients receive either standard of care (SOC), i.e. LHRH + Enzalutamide, or SOC + SBRT; radiological progression-free survival was chosen by the investigators as primary endpoint of the study. Based on the evidence coming from single reports [69,70], several trials (NCT03556904, NCT03503344, NCT03449719) are also investigating the combination of SBRT with a systemic treatment in this setting of patients, with the aim to determine if this approach can retard the onset of second-line therapy resistance and, ultimately, improve treatment response.

Conclusion and future perspectives

More molecular data are needed to fully characterize the biology of the oligometastatic prostate cancer patients and properly classify this intermediate state of spread between single metastasis and disseminated disease.

Newer imaging techniques such as choline PET, WB-MRI and above

Table 1
Selected ongoing trials in oligometastatic PCa.

Study	Phase	No. of pts	Control arm	Experimental arm	Recruitment status	Population	No. of oligomets	Primary endpoint
NCT02274779 (OLIGOPELVIS)	II	70		ADT + IMRT (N+, Pelvis, Prostate Bed)	Active, Not recruiting	Oligorecurrent to pelvic N	≤5	bRFS
NCT02680587 (ORIOLE)	II	54	Observation	SBRT	Active, Not recruiting	Oligorecurrent HSPC	≤3	PFS
NCT02685397 (PCS IX)	Adaptive II/III	130	LH-RH agonist + Enza	LH-RH agonist + ENZA + SBRT	Recruiting	Oligo-progressive CRPC	≤5	Radiographic PFS
NCT01859221	N/A	48		SBRT	Active, Not recruiting	Oligorecurrent HSPC vs CRPC	≤3	PFS
NCT02192788	II	68		SBRT	Recruiting	Oligometastatic/Oligorecurrent	≤5	DPFS
NCT02563691 (CROP)	I/II	60		SBRT	Recruiting	Oligorecurrent HSPC/ Oligometastatic "de novo"	≤5	Late Toxicity
NCT03304418 (RROPE)	IIa	20		SBRT + ^{223}Ra	Recruiting	Oligorecurrent HSPC/ Oligometastatic "de novo"	≤5	Time to ADT
NCT02971358	I/II	50		RP	Recruiting	Oligometastatic/Oligorecurrent	≤5	Toxicity
NCT02935023	II	47		CIRT	Recruiting	Oligometastatic "de novo"	< 3	bRFS
NCT02716974	II	33		ADT-CHT + RT/RP + SBRT	Recruiting	Oligometastatic "de novo"	≤5	Safety and Therapeutic Benefit
NCT03358563	I (early)	30		ADT-CHT + RP	Recruiting	Oligometastatic "de novo"	≤3	pCR
NCT03043807	II	33		ADT-CHT + ART + SBRT	Recruiting	Oligorecurrent	≤5	Toxicity
NCT03525288	II/III	130	Conventional RT	PSMA-PET Guided RT	Recruiting	Oligometastatic "de novo"	≤5	FFS
NCT02742675	II	200	ADT	ADT + RP/RT	Recruiting	Oligometastatic "de novo"	≤5	PFS
NCT03007732	II	42		ADT + Pembro + SBRT + SD-101	Recruiting	Oligometastatic " de novo"	≤4	Change rate of PSA < nadir + 2 ng/ml
NCT03556904 (FORCE)	II	72	SOC (CHT or AA/ ENZA)	SOC + SBRT/EBRT	Recruiting	Oligo-progressive CRPC	≤5	PFS
NCT02816983	II	110		SBRT	Recruiting	Oligo-progressive CRPC	≤3	bRFS and OS
NCT03449719 (ARTO)	II	174	AA	AA + SBRT	Not yet recruiting	Oligo-progressive CRPC	≤3	PSA response
NCT03569241 (STORM)	II	178	MDT + ADT	MDT + ADT + WPRT	Recruiting	Oligorecurrent HSPC (nodes)	≤3	MFS
NCT03361735	II	24		ADT + SBRT + ^{223}Ra	Recruiting	Oligorecurrent HSPC/ Oligometastatic "de novo"	≤4	TTF and ORR
NCT03503344 (PILLAR)	II	60	Apalutamide	Apalutamide + SBRT	Not yet recruiting	Oligo-progressive CRPC	≤5	bRFS
NCT00544830	II	29		ADT + IMRT	Active, Not recruiting	Oligometastatic " de novo"	≤5	bRFS
NCT02759783 (CORE)	II	206*	SOC	SOC + SBRT	Recruiting	Oligorecurrent HSPC	≤3	PFS

PCa: prostate cancer; **ADT**: androgen deprivation therapy; **IMRT**: intensity-modulated radiation therapy; **N**: nodes; **bRFS**: biochemical relapse-free survival; **SBRT**: stereotactic body radiation therapy; **HSPC**: hormone-sensitive prostate cancer; **PFS**: progression-free survival; **LH-RH**: luteinizing hormone-releasing hormone; **ENZA**: Enzalutamide; **CRPC**: Castration-resistant prostate cancer; **N/A**: not applicable; **DPFS**: disease progression-free survival; **^{223}Ra**: Radium 223 Dichloride; **RP**: radical prostatectomy; **CIRT**: carbon-ion radiotherapy; **CHT**: chemotherapy; **RT**: radiotherapy; **pCR**: pathologic complete response; **ART**: adjuvant radiotherapy; **PSMA-PET**: prostate-specific membrane antigen positron emission tomography; **FFS**: failure-free survival; **Pembro**: Pembrolizumab; **PSA**: prostate-specific antigern; **SOC**: standard of care; **AA**: Abiraterone Acetate; **OS**: overall survival; **MFS**: metastasis-free survival; **MDT**: metastasis-directed therapy; **WPRT**: whole-pelvis radiotherapy; **TTF**: time to failure; **ORR**: objective response rate.

* Including other primitive tumors different from prostate.

all PSMA PET show good performance for the detection of oligometastasis, but require further validations.

In the setting of *de novo* oligometastatic disease, adding local approach to the primary tumor seems to be safe and beneficial for those patients presenting with low burden of disease.

Despite MDT remains an investigational therapeutic strategy in oligorecurrent cancer, we currently have at our disposal not only retrospective reports but also encouraging data from the first prospective trials, in which targeting the metastasis has proven to be safe, feasible and potentially advantageous in terms of survival outcomes; nevertheless, this approach may also have an important role in the oligoprogressive setting, delaying disease evolution and allowing these patients to remain on their current systemic therapy.

The results of several ongoing trials will certainly add more insight on the topic (see Table 1), in order to identify the most appropriate integrated therapeutic approach towards the cure of patients with limited metastatic disease.

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