Oligometastatic Prostate Cancer

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The oligometastatic prostate cancer state is defined as the presence of a number of lesions ≤ 5 and has been significantly correlated with better survival if compared to a number of metastases > 5. In particular, patients in an oligometastatic setting could benefit from a metastates directed therapy, which could control the disease delaying the start of systemic therapies. For this reason, the selection of true-oligometastatic patients who could benefit from such approach is particularly important in this setting.

Keywords: oligometastatic prostate cancer ; biomarker ; miRNA ; CTC ; epi-miRNA

1. Introduction

Prostate cancer (PCa) is the most commonly diagnosed solid-organ malignancy and the second leading cause of cancer death in men worldwide [1]. Despite the high long-term survival in localized PCa, metastatic PCa remains largely associated with an overall low survival rate [2].

Recently, a growing interest is directed towards oligometastatic prostate cancer (OMPC), as the presence of a number of lesions ≤ 5 has been significantly correlated with better survival if compared to a number of metastases > 5 [3]. The *oligometastatic* concept was introduced for the first time by Hellman and Weichselbaum in 1995 to describe an intermediate phase between localized disease and extensive metastatic state [4]. To date, there is still no univocal definition of the oligometastatic state, even if in the scientific community, it is commonly considered as the presence of up to 3–5 lesions [5][6]. It is necessary to distinguish between two conditions of OMPC: synchronous OMPC (metastases that are already detectable at the initial diagnosis of primary tumor) and metachronous OMPC (metastases that are detected or become clinically evident at later stages of the disease course after initiation of treatment of the primary tumor treatment). Our review examines the latter scenario.

The efficacy of local ablative treatments directed towards metastatic lesions (metastases directed treatments—MDTs) in patients with OMPC was extensively investigated, with the aim of preventing the systemic spread of the disease and delaying the start of systemic androgen deprivation therapies (ADT) [1][7][8][9][10][11][12][13][14]. Nevertheless, the use of MDTs is still controversial due to the paucity of prospective randomized efforts. Notably, the publication of results from the SABR-COMET, STOMP and ORIOLE trials has fostered further research in the field, and upcoming evidence is likely to further modify the treatment scenario for this subset of patients [15][16][17]. In this perspective, ongoing studies such as the RADIOSA trial, a randomized phase II clinical trial [18] aiming to compare stereotactic body radiotherapy (SBRT) alone and in combination with 6 months ADT for the treatment of oligorecurrent-castration-sensitive-PCa (OCS-PCa), could foster the use of MDT in a selected subset of PCa patients.

With the emerging use of whole-body magnetic resonance imaging (WB-MRI) and Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT), it has become easier to detect the presence of metastases in patients with early biochemical recurrence [19][20][21][22][23][24]. Despite the accuracy of these investigations, it is likely that a number of patients who are already polimetastatic will escape detection, especially at low prostate-specific antigen (PSA) levels, with negative consequences on correct clinical choices [25][26].

Since the oligometastatic state has a peculiar behavior as compared with heavy burden disease, the existence of distinct underlying biological and molecular mechanisms was hypothesized [27]. The use of PSA alone, due to its poor specificity, seems to be increasingly limited in discerning the different categories of PCa patients; therefore, the identification of other markers could provide additional information to individuate the correct prognosis and consequently propose the best treatment course, especially in OMPC [28]. Ideally, these analytes should be easily obtainable in a non-invasive manner, easy to implement across facilities, reproducible and as inexpensive as those that can be collected from serum.

For these reasons, the identification of novel biomarkers could potentially improve the treatment of advanced PCa by identifying selected oligometastatic patients who could benefit from MDT.

2. Emerging Biomarkers for the Identification of True Oligometastatic Patients Eligible for MDT

2.1. Liquid Biopsy and Next Generations Sequencing (NGS)

Definitive diagnosis of PCa is traditionally based on histopathological analysis. Nevertheless, due to the multifocal nature of most PCas [29], as the tumor progresses, the static result from a biopsy sample will become even more inadequate to reflect dynamics of tumor evolution and its underlying biological modifications under the selective pressure of cancer therapies. These difficulties can be ascribed to the intrinsic difficulties in obtaining biopsy samples from metastases and to the inability to perform selective genetic tests on biopsy-derived tissue. Furthermore, complications may also arise from the invasive nature of biopsy procedures, which make not all cancer patients eligible for surgery due to their intrinsic fragility.

Nowadays, even with new imaging technologies allowing an increasingly early detection, the diagnosis of oligometastasis is currently based exclusively on traditional radiological investigations. Nevertheless, objective categorization of true oligometastatic patients from the ones with a trend to progress to poly-metastatic patients relies on the profile of the biological behavior of the tumor; for this purpose, a minimally invasive real-time monitoring method could be beneficial for both patients and clinicians. This could avoid expensive treatments with limited clinical benefit and potential associated toxicity or, alternatively, provide a group of oligometastatic patients with curative treatment.

Liquid biopsy has recently emerged as a promising minimally invasive approach allowing to overcome the static bioptic approach and to reflect the dynamic tumor modifications over time, specifically those involving its genomic evolution [29][30]. Through liquid biopsy, different biomarkers, commonly extracted from blood, urine or saliva, can be characterized, including circulating tumor cells (CTCs), circulating cell-free DNA (cfDNA) such as circulating tumor DNA (ctDNA), miRNA and exosomes [31][32].

2.2. Circulating Tumor Cells (CTCs)

CTCs are cancer cells originating from macroscopic tumor sites (either primary or metastases) and released into the bloodstream. Here, CTCs could be found as single CTCs or CTC clusters, with the latter being more often associated with a higher metastatic potential [33][34].

Since CTCs may reflect the current tumor status, there is a growing interest in identifying genomic alterations in CTCs that could aid the decision workflow in targeted therapies.

A recent study by Gkontela et al. [34] provided insights about how CTC clusters intrinsic differences have a direct impact on the DNA methylation status and thus influence important regulatory regions related to cancer proliferation, suggesting that agents disrupting these clusters could suppress spontaneous metastatic formations.

A 2020 study by Faugeroux et al. [35] emphasized the potential of CTCs in representing metastases mutational content and tumor diversity that would be otherwise inaccessible. Therefore, by offering real-time monitoring of a constantly evolving disease and detecting potentially critical SNPs via liquid biopsy, CTC sequencing can serve an unmet need for optimal therapy selection and precision medicine.

2.3. Circulating Cell-Free DNA (cfDNA)

cfDNA, or ctDNA, shed from apoptotic and necrotic cells, comprises both genomic and mitochondrial DNA and can be used as a biomarker to characterize the mutational and epigenomic status in advanced solid tumors [36]. The ctDNA concentration in plasma was correlated with both tumor size and clinical stage of the malignancy [37][38]. Additionally, the half-life of these molecules is relatively short (1–2 h), which provides real-time insight into the tumor status. Clinical studies showed that healthy individuals present lower cfDNA levels, indicating a relatively simple analysis involving the mere cfDNA quantification as a valuable biomarker [39][40]. The exact measure of cfDNA can be challenging due to the high fragmentation degree and the overall low concentration. The main source of cfDNA is also controversial. In fact, while the serum presents a higher concentration of cfDNA molecules, serum-derived samples are often contaminated by a clotting process, and therefore plasma is actually considered a more valuable cfDNA source despite the lower overall concentration [41][42].

As the total cfDNA increases with the tumor growth, it was hypothesized that cfDNA derives directly from living tumor cells and that CTCs could be an alternative cfDNA source [43].

2.4. Exosomes

It was speculated that a better understanding of the determinants of oligometastases could come from molecular studies on the signaling between the primary tumor and its metastatic sites. Exosomes are nanoscale extracellular vesicles that have a role in the exchange of genetic material, implicated in tumor cell growth and invasion, favoring disease dissemination by creating a pro-tumor micro-environment and the creation of premetastatic niches [44][45][46][47].

By analyzing the exosome proteins derived from PCa cells, the researchers found a high level of molecules stimulating tumor cell migration and metastases, such as the b4 and avb6 integrins, vinculin and the Trop-2 transmembrane glycoprotein [48][49]. In addition, cancer-derived exosomes can promote EMT through miRNAs, which play an important role in the conversion from benign to malignant cancers and in the regulation of the response to docetaxel, such as miR-34 in prostate cancer cells and cell-derived exosomes targeting Bcl-2 [50].

On the basis of these findings, the role of exosomes in the early phases of tumor metastatization seems to make them interesting and worth to be explored biomarkers for future diagnostic approaches in the oligometastatic setting.

3. Conclusions

Further research is needed to evaluate novel biomarkers as promising tools to be implemented in the therapeutic workflow in the oligometastatic setting. Overall scientific evidence analyzed here will be applied to the prospective phase II RADIOSA trial [18]. In particular, a deeper understanding of the molecular workings underlying the oligometastatic clinical entity could unravel novel suitable biomarkers that could aid the clinical management of the oligometastatic PCa patient. The most attractive ones are CTCs, cf DNA and miRNA, with technologies such as liquid biopsies and NGS expected to play an important role in the clinical setting.

Additional molecular biology research is also needed in order to establish and define consistent isolation and quantification methods for specific biomarkers assessment. In this scenario, different ongoing trials for biomarker identification in PCa [51] (**Table 1**) or ongoing trials as the phase 2 Oriole trial and the RADIOSA trial [17][18] might provide additional insights on the biology of the oligometastatic state, laying the bases for the identification of new biomarkers for the accurate outlining of true oligometastatic patients. Overall, this could pave the way to a better personalized medicine approach in the OMPC setting.

Table 1. Summary of ongoing trials (all in the recruiting phase) for the identification of predictive biomarkers for prostate cancer.

Trial ID	Trial Description	Study Type	Conditions	Interventions	Outcomes Measures	Estimated Primary Completion Date
NCT04324983	BioPoP, Identification of Predictive Biomarkers	Interventional	Prostate Cancer Recurrent	Blood sample	-Rate of complete biochemical response -Prostate cancer-specific treatment-free survival after salvage surgery - Questionnaire Quality of life	December 2021

Trial ID	Trial Description	Study Type	Conditions	Interventions	Outcomes Measures	Estimated Primary Completion Date
NCT03902951	Antiandrogen Therapy and SBRT in Treating Patients With Recurrent, Metastatic Prostate Cancer	Interventional, Phase II	-Metastatic Prostate Adenocarcinoma -Recurrent Prostate Carcinoma	-Drugs: Abiraterone Acetate/Apalutamide/Leuprolide Acetate -Stereotactic Body Radiation Therapy	-Percent of patients achieving a PSA < 0.05 ng/mL -Time to biochemical/ radiographic progression -Time to initiation of alternative antineoplastic therapy -Prostate cancer-specific Survival -Health-related quality of life -Biomarker analysis	July 2021
NCT03421015	Genetic Analysis of Prostate Cancer to Identify PredictiveMarkers of Disease Relapse or Metastatic Evolution	Observational Retrospective	Prostate Cancer	-	-The genetic alteration frequencies of TMPRSS2-ERG gene fusion •Frequency of amplification of proto-oncogenes (MYC, AR, PIK3CA) •Frequency of mutations or deletions of tumor suppressor genes (PTEN, TP53, NKX3-1), •Frequency of point mutations modifying protein function	July 2020

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