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Liquid Biopsies in Castrate-Resistant Prostate Cancer: Future Prospects in Radiation Oncology

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Abstract

The use of liquid biopsies, based on circulating tumor cells and tumoral DNA, provides information on the molecular patterns and genomics of Castrate-Resistant Prostate Cancer. There is evidence on the role of the androgen receptor variant 7 as a prognostic and as a follow-up tool, especially as a follow-up to treatment response and resistance with Enzalutamide and Abiraterone. Little is known about the genomics of Castrate Resistant Prostate Cancer and its relationship to radiation therapy's sensibility. This is particularly relevant for patients with oligometastatic disease, who could obtain a long control of the disease with radiation. In this narrative review, we summarize the available information on liquid biopsies and Castrate Resistant Prostate Cancer. As radiation oncology evolves towards Genomically Adapted Radiation Dose, the role of liquid biopsies as a possible pre-treatment assessment is a future target. Nonetheless, models have been modeled after other malignancies. This highlights the need for further studies to assess the use of personalized medicine in these patients.

Keywords: Radiotherapy; Prostate Cancer; Receptors Androgen; Liquid Biopsy; Precision Medicine;

Abbreviations

CRPC: Castrate Resistant Prostate Cancer

CTC: Circulating Tumor Cells

EBRT: External Beam Radiation Therapy

GARD: Genomically Adaptated Radiation Dose

Introduction

Malignant cells can be captured as circulating tumor cells (CTC). These arise from detachment from the tumor due to the loss of adhesion molecules from the extracellular matrix [1]. The presence of circulating tumor cells confers a higher risk in the development of metastasis. It can form clusters, and these, in turn, traverse the microvasculature and nest in sites that are conspicuous for their proliferation [2]. Identification of tumor circulating cells, constitute the conception of liquid biopsies [3].

The advent and development of new research techniques in genetics and molecular medicine have enabled extensive research in oncology and has led to a further understanding of specific behavior of different cancer types. Castrate Resistant Prostate Cancer is seen in up to 20.5% and 19.5% of patients with prostate cancer-related death [4]. Although its genomic profile has not been entirely elucidated yet, alterations of the androgen receptor gene are described as an important factor.

Liquid biopsies have shown promising results as a prognostic factor in CRPC and even as an indicator of treatment resistance. The androgen receptor gene and specifically the variant AR-v7, have been identified as possible determinants of resistance to treatment with Enzalutamide and Abiraterone, which can be assessed through

liquid biopsies [5]. This is promising for chemotherapy decisions, but little is known about the role of this variant in the response of radiation therapy.

As radiation oncology keeps evolving towards the use of precision medicine, understanding the mechanisms that can help to determine sensibility or resistance to radiation therapy can lead to changes in fractionation schedules. In this narrative review, we aimed at presenting the available evidence on liquid biopsies and its use in CRPC, and its possible use as a radiosensitivity marker.

Genomic profiling of Castrate-Resistant Prostate Cancer

In the study by Abida et al., from a sample of 451 patients diagnosed with prostate cancer in which 77% had metastatic disease, 12% biochemical recurrence after definitive treatment, and 11 % localized disease, an evaluation of samples was performed using the MSK-IMPACT test (5). This test constitutes a Next Generation Sequencing (NGS) assay based on hybridization capture, which allows the sequencing of 341 genes in paraffin-embedded tissue, detecting mutations, variation in copy number, and rearrangements. Of the samples from patients with metastatic disease, 164 were defined as CRPC, with the majority of the material coming from extra-prostatic lesions. The results found genomic differences between regional- localized disease and metastatic disease, especially in CRPC patients. The average number of nonsynonymous mutations per megabase was higher in CPRC: 4.02 versus 2.08 for hormone-sensitive disease ($p < 0.001$) [6].

Additionally, the selective gene enrichment analysis identified that mutation-associated amplification in the AR (androgen receptor) gene was the most common alteration. Other mutations, mainly found in CPRC, were APC, ATM, CDK12, FANCA, PTEN, RB1, and TP53 [6]. The results of this study place the AR gene as one of the primary markers that cause the castration resistance phenomenon [5, 7-10]. Additionally, the roles of other genes such as APC and ATM were also involved as possible mutation steps for the development of insensitivity to androgen blockade. TP53, as a known gene responsible for the evolution of various types of tumors, appears to be an essential regulatory point, since several early-stage tumors carrying this mutation progressed to metastatic disease [5, 11-13].

Molecular mechanisms involved in resistance to castration

The understanding of the importance of the AR gene and thereof the androgen receptor has allowed us to characterize in-depth the phenomenon of resistance to castration. Three of the possible mechanisms that can lead to overexpression of the receptor are self-modulation, alteration in cofactors, and intra-tumoral synthesis of ligands [14-15]. Besides, point mutations in the AR gene can lead to conformational changes, resulting in the binding of non-specific ligands, such as other steroid hormones like progesterone, cortisol, or weak androgens, possibly converting antagonists in agonists [16-18]. Changes in cofactors, both co-activators, and co-repressors, can also lead to overexpression of the androgen receptor [19-20]. Finally, extragonadal production of androgens allows disease growth in the absence of classical stimulation of male sex hormones. This aspect can manifest as a mechanism of resistance to androgen therapies [21-22].

This understanding drove the development of new drugs that directly block the androgen receptor or suppress all production like enzalutamide and abiraterone. The former is a signaling inhibitor of the androgen receptor, which binds directly to the binding domain of androgens, therefore, displacing natural ligands, and the latest is a cytochrome P450 17A1 inhibitor, that depletes adrenal and intra-tumoral production of androgens [23-26]. Both drugs have demonstrated clinical effectiveness in clinical studies that prolonged survival results in patients with CPRC [27-29].

Liquid biopsies in CRPC

An assessment of CTC has been made to determine the use of liquid biopsies in CRPC. The identification of CTCs has been associated with reduced survival in both sensitive and resistant to castration metastasic disease [30-32]. CTCs can be used as a prognostic factor and as a predictor of primary resistance to treatment with abiraterone or enzalutamide. Thus, leading to an increase in research on the role of liquid biopsies in CRPC patients.

Antonarakis ES et al. evaluated the presence of CTC in CPRC in patients treated with either of the two drugs. Moreover, they evaluated possible variants that provided resistance in CRPC. Mainly the androgen receptor variant 7, since it's the only variant that results in the production of mRNA and a functional protein, therefore it presents activation even in the absence of the right ligand [33-35]. Their results revealed that the detection of androgen receptor splice variant 7 (AR-V7) in circulating tumor cells (CTCs) was associated with primary resistance to enzalutamide and abiraterone therapy. Patients with this marker tended to have higher serum prostate-specific antigen levels, worse general functional status, and having received a higher number of previous hormone therapy lines. The proportion of patients that achieved a biochemical response was 53% for enzalutamide and 55% for abiraterone. When stratifying these patients by the presence of ARv7, the response rate in positive patients was 0% in both groups, confirming by linear regression, the presence of this marker as a predictor of biochemical response ($p < 0.0001$) [35].

In a time-to-event analysis (adjusted for the presence of complete androgen receptor mRNA), progression-free- survival of biochemical progression and clinical or radiological progression was better in patients with the absence of ARv7 ($p < 0.001$ for all comparisons). Furthermore, the Cox regression model, adjusted for the presence of complete androgen receptor and previous use of enzalutamide or abiraterone, showed the impact of ARv7 on

biochemical progression-free survival for abiraterone (HR 17.51 [95% CI 3.53-87.03], p <0.001) and enzalutamide (HR 3.4 [95% CI 1.43-8.08], p = 0.006) [35].

For overall survival, preliminary results indicate shorter periods in the presence of ARv7, reaching a median survival of 5.5 months (HR 6.9, [95% CI 1.7 - 28.1], p = 0.002) for ARv7 + treated with enzalutamide and 10.6 months (HR 12.7, [95% CI 1.3 - 125.3], p = 0.006) under the same conditions treated with abiraterone, compared to a median not reached when this marker was negative. Additionally, 16 patients who were negative for ARv7 at the start of the study underwent a conversion during the administration of these drugs. As for the response rates, once this phenomenon occurred, they were reduced to 0%, and the biochemical progression-free survival was reduced to a median of 1.4 months (95% CI 0.9-2.6 months). In summary, this study rigorously and prospectively validated the use of CTC-based liquid biopsies as a predictive tool for response to abiraterone or enzalutamide in patients with metastatic CRPC and further establishes a hypothesis of a possible mechanism of resistance gain once the therapy has been instituted [35].

Radiosensitivity and Genomically Adaptated Radiation Dose (GARD)

In general, tumor cells have a spectrum of sensibility to radiation therapy; this comes from a large number of in vitro studies and is related to the tumor cells' origin and histology. Currently, equivalent doses administrated during a radiation treatment course are defined by the tumor histology. This is known as the "one fits all" model and has been the basis for dose prescription in recent decades [36]. This methodology is based on administering a biologically effective dose on a fractionation scheme. This principle seeks to affect primarily tumor cells and allow healthy cells and surrounding tumor lesions to regenerate and reduce significant damage while achieving tumor ablation [37]. The ratio of total administered dose and its adjustment by fractionation establish the concept of biologically equivalent dose.

Considering the discovery of molecular patterns in the field of precision medicine, it is worth mentioning that in a disease as genetically heterogeneous as cancer, the prescription of a standard dose for a pathology does not seem to be the most indicated. Based on this hypothesis, Scott JG's group re-evaluated the iso-effect models, taking into account, precisely, certain genomic markers109. Using a microarray test that sought to determine the expression of the AR, cJun, STAT1, PKC, RelA, cABL, SUMO1, PAK2, HDAC1, and IRF1 genes, the researchers created a panel that allows determining the possible degree of resistance of a tumor based on these previously known markers 110. To identify these genes, the researchers subjected 48 tumor cell lines to 2 Gy of radiation, measuring the survival percentage of each line. By analyzing the expression of 7000 genes, using a regression model, they were able to identify these with good reliability [38]. By incorporating the radiosensitivity index into the equation of the quadratic linear iso-effect model, where:

$$\alpha = (ln\ RSI + \beta n * d^2) / -n * d$$

RSI, Radiosensibility Index

$$\text{GARD} = n * d((\ln RSI + \beta n d^2) / -n * d + \beta d)$$

The authors searched genomic data in a database of the Moffitt Cancer Center, and 17 other institutions since 2016 within the framework of the Total Cancer Care protocol, calculating the GARD index, which translates, genomic adjusted radiant dose in a wide range of tumors including prostate. When estimating these indices in 186 samples of prostate tumors, they found that there is a large heterogeneity in the radiosensitivity behavior is wide in prostate tumors, and no clear tendency to indicate that a standard dose can benefit all prostate cohorts.

Clinical validation was performed on a group of patients with breast carcinoma. When comparing the results obtained by GARD, in outcomes such as distant metastasis-free survival, the researchers found that patients whose tumors received a GARD classification above the 75th percentile, obtained a longer time in this survival, compared to more radioresistant tumors. Validations in other cohorts included patients with lung cancer (n = 60), glioblastoma (n = 98), and pancreatic cancer (n = 40). These results, although they have only been validated in these types of tumors, open the door to the use of molecular profiling by gene expression by microarrays to the utility of assigning personalized doses in radiotherapy. Additionally, it constitutes the base for the design of phase III clinical experiments, where GARD characterization can be used to allocate patients in different treatment arms. Although these results have not been validated in prostate cancer, they could be very striking in the future.

The benefit of radiotherapy on primary lesions in metastatic prostate cancer

Control of the tumoral lesions, including in metastatic disease, is a critical aspect of increasing patient survival. In oligometastatic states, where the treatment of multiple injuries is possible, the SABR-Comet study demonstrated in a group of patients with various diagnoses (colorectal sinus tumors, lung, and prostate) a significant benefit in progression-free survival (HR 0.47, [95% CI 0.3 - 0.76], p = 0.0012). Although the study comes from a small sample size, only 16 for prostate cancer, results are better than the benefit of radiotherapy in the control of a limited number of metastases [39].

In prostate cancer, where most studies come from tumors sensitive to castration, the treatment of the primary tumor is beneficial even in metastatic disease. In a joint analysis of the HORRAD AND STAMPEDE clinical studies, a total of 2126 patients were evaluated and treated with hormone deprivation therapy. Radiotherapy was added as control of the primary lesion (STOPCAP M1 group). When the patients from the STAMPEDE study who only received hormonal blockers are compared to the 216 from HORRAD

who received hormonal deprivation therapy and radiotherapy, the latter has benefits in terms of time to biochemical progression (HR 0.74 [95% CI 0.67-0.82], p <0.001) and time of progression-free of disease failure (HR 0.76 [0.69-0.84], p <0.001). Subgroup analysis showed an increase in 3-year survival in patients, especially with four or fewer metastases [40].

Furthermore, the results of the PEACE-1 study in the other STAMPEDE arms will allow providing information on the impact of radiation therapy in addition to treatment with docetaxel or abiraterone. As for other prospective studies, combinations of systemic treatment versus treatment of the primary tumor (surgery or radiotherapy), as well as the comparison between radiotherapy and surgery for primary control in metastatic disease and sequential treatment of the primary and metastatic sites, are ongoing (SWOG S1802, NCT03678025, TROMBONE, g-RAMPP, SIMCAP, NCT02913859).

The relevance in the characterization of the oligometastatic disease lies in establishing a group of patients in which their survival to treat these injuries is allowed to increase. Based on this hypothesis, the disease's characterization should emphasize the use of precision medicine tools to test this concept. Regarding the CPRC, the reason for this review, should be that the genomic characterization of the different behaviors of this disease, would allow evaluating which patients would benefit from the treatment of oligometastatic disease, beyond the palliative benefit, seeking to increase survival, both global and free- progression.

In a study including 101 cases of CPRC in which where samples were taken from metastatic sites, amplification of the promoter region in the AR gene was detected in 81% of men and other structural variants such as CDK12 mutations with tandem duplications of the same gene, P53 inactivation and inactivation with deletions in BRCA2. Additionally, another subtype of castration-resistant disease was found which had biallelic CDK12 losses, implying a worse outcome in terms of curability after treatment of metastases 114 [41].

Abstracting from the previously exposed information, added to the evidence provided by studies of active disease control treatment (pelvis with evidence of malignant prostatic lesions or extra pelvic and bone visceral disease) who found a possible subgroup of patients who would benefit from This treatment, I propose the following definition of oligometastatic disease in CPRC: "Presence of metastatic disease with evidence of less than 5 extracerebral lesions capable of ablative treatment, which offers a benefit in terms of survival to treated patients."

Inherently, to be able to study favorably after treatment, you must have specific knowledge of the molecular biology of the tumor that meets the other characteristics of this definition. Taking into account that this characterization is not known, it is proposed how to address this problem in the following section.

Liquid biopsies and determining radio sensibility in CRPC

The benefits of liquid biopsies and their information on molecular patterns of the disease could lead to regular assessment in CRPC. The first validated marker is ARv7, which, as previously stated, is useful as an initial and prognostic tool, and as a follow-up to treatment with enzalutamide or abiraterone in patients with CRPC. In addition to this, the test must be able to identify tumors that are going to obtain control with radiotherapy. Therefore, the use of the GARD, as previously explained, can be useful to create a predictive value regarding the response of the illness.

Conclusion

In conclusion, the CPRC is a pathology which does not have yet an in-depth genomic characterization. Especially, little is known in predictive terms of outcomes for patients treated with radiotherapy. This is particularly relevant for patients with oligometastasic disease, who could possibly obtain a long control of the disease with radiation. The present review summarizes the available information, and highlights the need for further studies to assess the use of personalized medicine in this patient.

Key points

- The entry of radiotherapy towards personalized medicine may lead to the abandonment of the "one fits all" model.
- The traditional Linear-Quadratic Isoeffect Model is based on the radiosensitivity in cell cultures, and the dose was estimated by the percentage of cells that survived specific doses. Now radiosensitivity can be based on the expression of genes involved in radiosensitivity and radioresistance **(GARD)**.
- The implementation of genomic studies can lead to personalized radiation doses: high GARD to ablative doses in radioresistant tumors and low GARD to save and avoid radiation in patients who do not benefit from it.
- CPRC is a pathology which does not have an in-depth genomic characterization yet, especially in predictive terms in patients treated with radiotherapy.
- Th benefits of liquid biopsies in their forms of ctDNA and CTC can provide information on molecular patterns (presence of ARv7) and its relationship with radiosensitivity (GARD) can be useful to create a predictive value in terms of the response of oligometastatic disease to radiation therapy.

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