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Systematic Review

A Systematic Review of Circulating Tumor Cells Clinical Application in Prostate Cancer Diagnosis

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Simple Summary: Cell-dependent and cell-independent information drawn from the blood stream were merged into the attractive term "liquid biopsy" and tentatively applied to most segments of cancer management: detection, risk-stratification, personalization of care and follow-up. However, the robust science behind liquid biopsies has not been widely used, thereby remaining a latent and possibly undervalued instrument. Here, we conducted a systematic review of CTCs in prostate cancer management to summarize their use in clinical practice.

Abstract: The purpose of the review is to summarize the recent data on circulating tumor cells (CTC) use in clinical practice. We performed a systematic literature search using two databases (Medline and Scopus) over the past five years and the following terms: (CTC OR "circulating tumor cells" OR "liquid biopsy") AND prostate. The primary outcome was CTC predictive value for prostate cancer (PC) progression and survival. The secondary outcomes were the CTC predictive value for therapy response and the results of CTC detection depending on the assessment method. In metastatic PC, the CTC count showed itself to be a prognostic marker in terms of clinically important features, namely survival rates and response to treatment. CTC concentration was significantly associated with the overall survival and progression-free survival rates. A strong association between the overall survival or progression-free survival rate and CTC concentration could be observed. Variant-7 androgen receptors-positive (AR-V7-positive) patients showed a poor response to androgen receptor signaling (ARS) inhibitors, but this did not compromise their response to taxanes. In localized PC, only positive Cluster of Differentiantion 82 protein (CD82+) correlated with a higher survival rate. CTC count and AR-V7 expression showed itself to be a valuable biomarker for survival in metastatic PC and response to ARS-inhibitors. CTC diagnostic performance for localized PC or for screening and early detection is not high enough to show additional value over the other biomarkers.

Keywords: systematic review; prostate cancer; biomarker; diagnostic; circulating tumor cells (CTC)

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1. Introduction

The natural history of solid tumors is driven by cancer heterogeneity, both spatial within the various sites of the metastatic disease and temporal at the different phases of tumor evolution [1].

After world war 2 (WW2), the pivotal work of Zeidman on the mechanisms of tumor emboli and metastasis unveiled the role of circulating tumor cells (CTCs) in the dynamics of cancer dissemination [2,3]. It is only recently that this paradigm has been fully validated by advances in the technology of capture and characterization of cancer cells and aggregates from blood samples in most solid cancer types, including prostate cancer (PC). At the same time, molecular techniques revealed that the blood compartment was also rich in cell-independent actors such as circulating tumor deoxyribonucleic acid (DNA) [4], cell-free micro-ribonucleic acid (micro-RNA) and extracellular vesicles [5].

Cell-dependent and cell-independent information drawn from the blood stream were merged into the attractive term "liquid biopsy" and tentatively applied to most segments of cancer management: detection, risk-stratification, personalization of care and follow-up.

However, as exemplified in a recent review for prostate cancer [6], the robust science behind liquid biopsies has failed to be used on a routine basis, thereby remaining a latent and possibly undervalued instrument. Here, we conducted a systematic review of CTCs in prostate cancer management according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2. Materials and Methods

2.1. Search Strategy, Inclusion Criteria

The detailed search strategy and review protocol have been published in Prospero (CRD42021239981). The present review followed the PICOS process (Patient, Intervention, Comparison, Outcomes, Studies):

P—patients with prostate cancer

I—detection of CTC in blood

C—histology

O—diagnostic accuracy, predictive value of CTC for cancer progression, survival, treatment response

S—all kinds of original studies

A systematic literature search was performed by scanning the Medline (Pub-Med) and Scopus databases over the past five years using the following search terms: (CTC OR "circulating tumor cells" OR "liquid biopsy") AND prostate. Two authors (AM and AB) independently reviewed headings and abstracts to exclude irrelevant publications such as reviews, comments, papers in languages other than English and articles that dealt with other PC biomarkers or with conditions other than prostate adenocarcinoma (BPH, rare prostatic malignancies, etc.). In the event of disagreement between the reviewers, articles were retained for the following stage in the selection process.

After in extenso review of the publication, two readers (AM and AB) excluded those exclusively focused on laboratory techniques with no clinical relevance. In the event of disagreement, AM and AB sought to justify their decision and tried to resolve the disagreement. If they failed to reach an agreement, a senior researcher (DE) made the final decision. The present systematic review ultimately covered all original articles that addressed the clinical relevance of CTC in PC diagnostics and prognosis for the past five years.

2.2. Data Extraction Outcomes

Raw data, such as number of treated patients, cancer stage and treatment, methodology of CTC and markers expressed on CTC measuring, diagnostic performance was extracted manually from the articles.

The primary outcome was the CTC predictive value for PC progression and survival.

Secondary outcomes were the CTC predictive value for treatment response and results of CTC detection depending on the assessment method.

Due to the high heterogeneity in the studies with regard to methodology and the absence of a control group in most investigations, it was not possible to perform a meta-analysis, although a qualitative narrative synthesis was produced from the published literature.

2.3. Studies Quality Assessment

The level of evidence (LE) for each study was estimated according to the Oxford Centre for Evidence-based Medicine scale [7].

3. Results

3.1. General Characteristics of the Sample

After applying all the selection criteria, the final sample comprised 46 articles on metastatic PC [8–54] (Supplementary Table S1) and 15 articles on localized PC [55–69] (Supplementary Table S2). Three articles focused on CTC application in PC screening and early diagnosis [70–72] (Supplementary Table S3) (PRISMA statement, Figure 1).

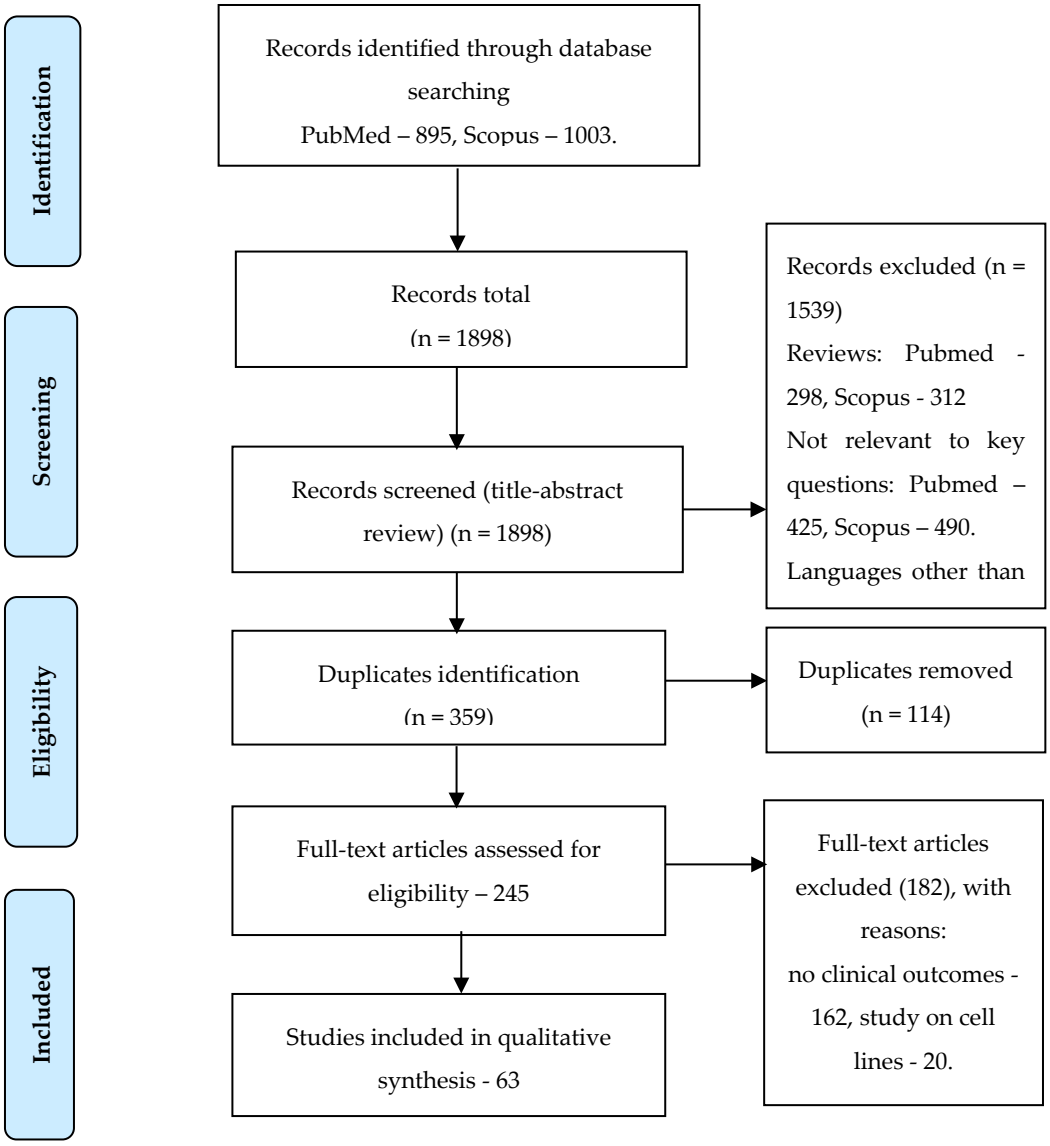

Figure 1. PRISMA statement.

3.2. Methods of CTC Capture and Characterization

Analyzing this field of diagnostic biology is hampered by the high heterogeneity observed in the technology designed to capture CTCs, the methods to characterize cells of epithelial lineage, the expression of results and the correlations researched with various clinical outcomes.

CellSearch® was compared to CellCollectorTM and EPISPOT assay in 86 high-risk localized PC (LE 2b) [56]. Tests were repeated three months after prostatectomy in 52 patients, and the concordance was evaluated on the combined collection. A positive result was defined as the detection of at least one CTC. Although all three methods were positive in approximately 55% of the samples, they were rarely in agreement. CellSearch®

concurred with CellCollectorTM and EPISPOT in 56% and 59.9%, respectively, while the three techniques were concordant only in a minority (37.4%).

The same three techniques were tested in a cohort of 104 newly diagnosed high-risk prostate cancer patients, 19 of whom later proved metastatic (LE 2c) [65]. No tests correlated with age or prostate-specific antigen (PSA) and only CellSearch® detected CTCs significantly more often in metastatic than in localized disease patients (61.1% vs. 14.3%, $p < 0.001$). As a single predictor, it was predictive (AUC ROC: 0.76) of the metastatic stage to an extent comparable to the classical D'Amico's risk factors (PSA, Gleason sum, T stage, AUC ROC: 0.72). Most importantly, the addition of CellSearch® count (threshold: 4CTCs.7.5 mL) to D'Amico's risk factors significantly improved the prediction of metastatic extension (AUC ROC: 0.90), suggesting that the CTCs count carried an important and independent value.

Last, in 47 progressive metastatic castration-resistant PC (mCRPC) patients, CellSearch® was compared to the AdnaTest and to the polymerase chain detection (PCR) detection of five genes involved in the development and function of the prostatic epithelium (KLK2, PSA, HOXB13, GRHL2, FOXA1) (LE 2c) [16]. The AdnaTest ($p = 0.027$) and PCR ($p = 0.001$) results significantly differed from the CellSearch® count. On Kaplan-Meier curves, detections of CTC by AdnaTest or PCR were superior in terms of survival prediction than those of CellSearch® ($\geq$5 cells/7.5 mL).

CTC in metastatic PC (46 studies, 4322 patients, Supplementary Table S1).

In 2009, deBono [73] reported in 276 mCRPC patients that the CTC count assessed by CellSearch® before a new line of chemotherapy was a better predictor of overall survival than any PSA-derived descriptor (LE 3b). Since this seminal report and the Food and Drug Administration (FDA) approval of the assay, CTC count was extensively used in the metastatic setting to predict survival rate and to research actionable characteristics.

In all studies on CRPC but two exploratory reports (LE 4) on biomarkers [21,37], a higher count of CTCs informed decreased the overall survival (OS) rate. This was observed in all types of treatment; from research protocols [11,44,46] to androgen receptor signaling inhibitors, such as abiraterone [32] (LE 4) or chemotherapy with docetaxel [34] (LE 4). Even in the dire situation of CRPC, patients who failed docetaxel, enzalutamide or abiraterone and switched to cabazitaxel, the information gained on survival was substantial (median OS 6.9 and 22.3 months in $\geq$5CTCs and <5CTCs//7.5 mL, respectively) [13] (LE 2b). A similar correlation was observed for progression free survival (PFS) in CRPC patients switching to abiraterone (LE 2b), enzalutamide (LE 4) [18,36] or cabazitaxel [17] (LE 4). Others addressed the dynamics of CTC counts under treatment, confirming that increasing numbers were predictive of decreased survival [27,36,46] (LE 4), while declining numbers predicted good survival [28,46] (LE 4).

Taken together, all reports on mCRPC consistently highlighted the clinical value of CTC counts at baseline and of CTC dynamics under chemotherapy or androgen receptor signaling inhibitors.

Besides informing survival through their numeration, capturing CTCs also afforded crucial insights on their differentiation.

Antonarakis researched CTCs in 202 mCRPC patients starting abiraterone and enzalutamide and analyzed the respective proportion of full length and splice variant-7 (AR-V7) androgen receptor transcripts. CTC and AR-V7 status impacted PSA progression-free survival, PFS and OS with incrementally poorer figures in CTC negative, CTC positive AR-V7 negative and CTC positive AR-V7 positive patients [8] (LE 4). The PROPHECY study (LE 1b) confirmed in patients under AR pathway inhibitors that pretreatment CTC AR-V7 status was correlated to PFS and OS with poorer response for CTC AR-V7 positive patients who still showed at progression a similar response to taxane chemotherapy [9]. It confirmed the pivotal report by Scher where, after adjusting for clinical measures, mCRPC patients harboring pretherapy AR-V7 positive CTCs experienced better OS with taxanes than with AR signaling inhibitors [40] (LE 2b). Whether the AR-V7 status of CTCs is today strong enough to inform clinical decision is still debated [13] (LE 2b), although there is

a tendency in that direction [41] (LE 4). One major limitation to its introduction into the clinical routine is the lack of standardized methods to evaluate and report the AR-V7 status of CTCs, as they varied in the literature from immunofluorescence [10,13,39,40] to mRNA transcript measurements [8,45] (LE 1b). Others reported that patients with CTCs of neuroendocrine differentiation were less likely to respond to AR pathway inhibitors [36] (LE 4).

CTC in localized PC (15 studies, 1450 patients, Supplementary Table S2).

3.3. Pretreatment CTCs Detection

Not all patients with localized prostate cancer were detected with CTCs [55,57,58,63]. The detection rate varied with the characteristics of the population and the technique used, with figures ranging from 73% with an enrichment-free digital pathology of nucleated cells method [64] (LE 2b) to 50% using a microfluidic ratchet system [58] (LE 4) and 7.5% to 11.2% with the FDA-approved Cell Search system [57,66] (LE 4).

Intriguingly, comparing the detection of cells of epithelial lineage (EpCAM+) in healthy controls and localized prostate cancer patients revealed the presence of CTCs in a minority of controls, accounting for the poor accuracy and sensitivity figures of the technique (53.2% and 40.0%, respectively) [63] (LE 2b). Similar caution in cancer detection was previously voiced in the pioneering paper by Davis [55] (LE 2b), who showed that a comparable minority of cancer patients (21%) and men with elevated PSA, but no tumor detected on extended prostate biopsy (20%) were detected with CTCs by Cell-Search. Of note, as shown in a short series of brachytherapy patients, small traumatisms to the parenchyma may induce in a minority the mobilization of epithelial cells into the blood stream [60] (LE 4), a fact of unknown clinical significance that was also reported at the time of transrectal ultrasound biopsies [74].

Regarding the pathological stage, no correlation between baseline CTC counts [55–58] was observed in radical prostatectomy cohorts, although highlighting features associated with epithelial–mesenchymal transition in the CTCs was observed in one series associated with extracapsular extension [67] (LE 4).

The hypothesis that in localized PC, biological characteristics were as important as the simple numeration of CTCs was later supported by the observation that the lack of Cluster of Differentiantion 82 protein (CD82) expression on CTCs was associated with poor survival, compared to CTC negative or CTC positive CD82 positive patients who shared the same long-term survival profiles [61] (LE 4). This intriguing result emphasized the value of going beyond simple detection or numeration to get insight into the molecular landscape of the CTC compartment. Here, the presence of CD82, a tumor suppressor gene involved in cell adhesion to protein matrix, showed similar good prognosis as the absence of CTCs. In the same line, the presence of CTCs with high androgen receptor expression was associated with B-cell receptor (BCR) and metastatic progression in a small series of high-risk localized prostate cancer patients undergoing radical prostatectomy [64] (LE 2b).

3.4. Post Treatment CTCs Evaluation

To our knowledge, only one study tested CTCs after surgery with the objective of identifying those at high risk of recurrence [62] (LE 2b). Blood samples and bone marrow biopsies were harvested one month after surgery and processed with standard immunochemistry techniques to research "minimal residual disease" in 321 localized prostate cancer patients. Intriguingly, cancer cells in the blood stream or in the bone marrow carried independent information and were potent enough to drive a predictive model that accurately predicted long-term PSA-free survival, independent of the classical predictors of tumor differentiation, PSA, pT stage or resection margins.

Another report, which detailed the dynamics of CTCs numeration by Cell Search during the course of radiotherapy and adjuvant hormone deprivation, failed to highlight any relationships with known clinical predictors or recurrence in 65 patients followed for a median period of 55 months [66] (LE 4).

In conclusion, radical prostatectomy and radiotherapy series confirmed that the presence of CTCs in the blood stream was an early event in the natural history of prostate cancer in some patients. While the simple CTC count was of little bearing, further characterization in terms of differentiation might highlight those with impaired survival expectations.

CTC in PC screening and early diagnostics PC (3 studies, 1455 patients, Supplementary Table S3).

Three studies focused on CTC detection. The largest (1223 patients) and most recent used an inhouse assay based on the immunochemistry detection of PSA and P504S-positive epithelial cells [70]. Detecting at least 1 CTC per 8 mL of blood ex-hibited higher sensitivity (0.97, 95%CI: 0.94–0.98), than the classical predictors of PSA density (0.60 95%CI: 0.54–0.65) and % of free PSA (0.42, 95%CI: 0.34–0.44). More importantly, the reported positive likelihood ratio (4.52, 95%CI 3.9–5.1) and negative likelihood ratio (0.02, 95%CI 0.01–0.03) values of the test suggested that a positive test increased 4-fold the odds of detecting cancer, while a negative test decreased 50-fold the odds of a positive biopsy. Again, 18.3% of patients with no cancers detected on biopsies showed CTCs, accounting for a specificity of 0.79. In terms of biopsy strategy, the authors suggested that introducing CTC detection could reduce by 40% the number of biopsies at the cost of missing 3% of clinically significant ISUP 2–3 cancers.

Another study researched those cells of the epithelial lineage before random biopsies using pancytokeratin antibodies and characterized their androgen receptor expression [72]. The expression of the androgen receptor and of the epithelial growth factor receptor was also detailed in the corresponding prostatic tissue. Testing for CTCs was disappointing, with more patients detected with CTCs in those with negative biopsies than positive biopsies (21.6% and 14.3%, respectively). However, it was noteworthy that most CTCs were androgen receptor negative, in line with the relationship existing between low AR expression and epithelial-mesenchymal phenotype, the first step required for the mobilization of epithelial cells into the bloodstream [75].

In conclusion, the use of CTCs in screening and the selection of patients to recommend for biopsies is still in its infancy. The main study was surprisingly positive given the controversial value of CTCs in known cancer patients. The main limitations to the clinical development of the technique in screening are the lack of standardization of the technique, the volume of the blood sample tested, and the limitations of standard biopsies in the era of the MRI-pathway and image-guided biopsies.

4. Discussion

The first and foremost information was that competition between commercial techniques of detection, variations in the definition and characterization of CTCs as well as the profusion of clinical outcomes unfortunately obscured this promising field of research.

Most systems are based on the capture in a blood sample of cells showing some degree of epithelial differentiation, such as the expression of cytokeratin (e.g., Cell-Search® [76,77]) or of epithelial membrane markers (e.g., Cell Collector® EpCAM [78]). Such an approach may be biased by the rarity of CTCs that may be missed in a blood sample of limited volume (median sample volume was 10 mL, range from 1 to 40 mL) as well as by the physical presentation of CTCs that may undergo mesenchymal transition [67] and under expression or abrogation of their epithelial markers or present with platelets, stromal cells or monocytes as cellular aggregates that may cloak them from detection [79].

Many original solutions were tested to respond to these limitations; direct capture into the blood stream (Gilupi®, [78]), unrestricted automated analysis of all blood nucleated cells (EpicSciences, [80]) or reverse transcription of mRNA of lysed blood cells (ADnatest [16]) before multiplex PCR, capture based on the physical properties of cancer cells (EPIC Sciences [80], HD-CTC assay [81], ScreenCell [82], ISET [83]) including their flow in microfluidic chips [84]. All methods showed some clinical correlation, attesting to the wide potential for innovation in this field of diagnostic and predictive medicine. We feel it necessary to mention that FDA recently granted breakthrough device designation to

TriNetra™, a lab-on-chip device, for the detection of CTCs and CTCs clusters in prostate cancer developed by DATAR Cancer genetics [85]. The technology was previously approved in Europe by the National Institute for Health Care Excellence. In the conducted studies the test has confirmed its capability to detect early-stage cancer with accuracy up to 99% without any false-positives. The test does not differentiate prostate cancer subtypes. However, it can identify an underlying squamous cell carcinoma or a neuroendocrine tumor potentially linked with prostate or another primary organ. Appropriate rule-out investigations would be needed to confirm that.

Irrespective of such ingenuity, only the CellSearch® method was FDA-approved and is considered the current gold standard (26/56 studies, Supplementary Tables S1 and S2). The Hamburg group must be congratulated for conducting a robust comparison of this technique with other methods of detection at all three stages of the natural history of PC [16,56,65].

The logistics of the technique are precise, from blood collection in a dedicated tube (7.5 mL, Cell Save Preservation Tube), transfer at room temperature (15–30 °C) to the laboratory where a proprietary automated preparation system (CELLTRACKS® AUTOPREP®) is required for the immunomagnetic selection of circulating cells expressing the epithelial cell adhesion molecule (EpCAM) and their subsequent immunostaining. Lastly, a semi-automated fluorescence microscope (CELLTRACKS ANALYZERII®) is ultimately used to obtain a semiquantitative characterization of cancer cells. Even though the technology is FDA-approved and was used extensively in breast cancer, melanoma, colon cancer and prostate cancer [86], it is still restricted to research use only.

The current literature in metastatic PC correlated CTC detection and characterization (neuroendocrine differentiation, AR-V7 expression) to the response to androgen deprivation, progression free survival and overall survival [8,10,40,41]. However, the results were less supportive for localized and locally advanced disease, where most authors failed to confirm robust clinical value, except for CD82 CTC status and survival. So, at the current state, CTC detection showed prognostic value in metastatic PCa and even allowed prediction of response to a particular treatment. It may justify the introduction of CTC testing into common practice for such patients. In contrast, obtained data showed no significance for CTC assessment outside of clinical trials in patients with localized disease or suspicious of PCa.

Besides CTC, other subsets of tumor-related cells may be detected in the blood stream, in particular, circulating tumor stem cells (CSC). While CTCs are thought to be predominantly biomarkers, CSCs have distinctive features such as high chemo-resistance and may be directly related to metastasis formation [87]. CSC inhibition may even be applied for targeted therapy in the future [88]. However, the issue of CSC identification and clinical application was beyond the scope of the present review. We intend to conduct a separate review of this topic.

One limitation of our work is the fact that the included articles are rather heterogeneous in terms of methods and outcomes. However, we intended to provide a comprehensive review of all the possible applications of CTC in PC over the last five years and tried to determine the future direction of this issue.

5. Conclusions

CTC count and AR-V7 expression showed themselves to be a valuable biomarkers for survival in metastatic PC and response to ARS-inhibitors. CTC diagnostic performance for localized PC or for screening and early detection is not high enough to show additional value over the other biomarkers.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/cancers14153802/s1, Table S1: CTC in metastatic PC; Table S2: CTC in non-metastatic PC; Table S3: CTC in PC screening and diagnostics, Table S4: CTC detection: manufacturers and technology.

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review and editing: D.E. and B.M.; Supervision: D.E. All authors have read and agreed to the published version of the manuscript.

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References

1. Keller, L.; Pantel, K. Unravelling Tumour Heterogeneity by Single-Cell Profiling of Circulating Tumour Cells. *Nat. Rev. Cancer* **2019**, *19*, 553–567. [CrossRef] [PubMed]
2. Zeidman, I. The Fate of Circulating Tumors Cells. I. Passage of Cells through Capillaries. *Cancer Res.* **1961**, *21*, 38–39. [PubMed]
3. Zeidman, I. Metastasis: A Review of Recent Advances. *Cancer Res.* **1957**, *17*, 157–162. [PubMed]
4. Wan, J.C.M.; Massie, C.; Garcia-Corbacho, J.; Mouliere, F.; Brenton, J.D.; Caldas, C.; Pacey, S.; Baird, R.; Rosenfeld, N. Liquid Biopsies Come of Age: Towards Implementation of Circulating Tumour DNA. *Nat. Rev. Cancer* **2017**, *17*, 223–238. [CrossRef] [PubMed]
5. Tkach, M.; Théry, C. Communication by Extracellular Vesicles: Where We Are and Where We Need to Go. *Cell* **2016**, *164*, 1226–1232. [CrossRef]
6. Casanova-Salas, I.; Athie, A.; Boutros, P.C.; DelRe, M.; Miyamoto, D.T.; Pienta, K.J.; Posadas, E.M.; Sowalsky, A.G.; Stenzl, A.; Wyatt, A.W.; et al. Quantitative and Qualitative Analysis of Blood-Based Liquid Biopsies to Inform Clinical Decision-Making in Prostate Cancer. *Eur. Urol.* **2021**, *79*, 762–771. [CrossRef]
7. Phillips, B.; Ball, C.; Sackett, D.; Badenoch, D.; Straus, S.; Haynes, B.; Dawes, M.; Howic, J. Oxford Centre for Evidence-Based Medicine: Levels of Evidence. March 2009. Available online: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009 (accessed on 14 March 2021).
8. Antonarakis, E.S.; Lu, C.; Luber, B.; Wang, H.; Chen, Y.; Zhu, Y.; Silberstein, J.L.; Taylor, M.N.; Maughan, B.L.; Denmeade, S.R.; et al. Clinical Significance of Androgen Recept or Splice Variant-7MRNA Detection in Circulating Tumor Cells of Men with Metastatic Castration-Resistant Prostate Cancer Treated with First & Second-Line Abiraterone & Enzalutamide. *J. Clin. Oncol.* **2017**, *35*, 2149–2156. [CrossRef]
9. Armstrong, A.J.; Halabi, S.; Luo, J.; Nanus, D.M.; Giannakakou, P.; Szmulewitz, R.Z.; Danila, D.C.; Healy, P.; Anand, M.; Rothwell, C.J.; et al. Prospective Multicenter Validation of Androgen Receptor Splice Variant 7 and Hormone Therapy Resistance in High-Risk Castration-Resistant Prostate Cancer: The PROPHECY Study. *J. Clin. Oncol.* **2019**, *37*, 1120–1129. [CrossRef]
10. Armstrong, A.J.; Luo, J.; Nanus, D.M.; Giannakakou, P.; Szmulewitz, R.Z.; Danila, D.C.; Healy, P.; Anand, M.; Berry, W.R.; Zhang, T.; et al. Prospective Multicenter Study of Circulating Tum or Cell AR-V7 and Taxane Versus Hormonal Treatment Outcomes in Metastatic Castration-Resistant Prostate Cancer. *JCO Precis. Oncol.* **2020**, *4*, 1285–1301. [CrossRef]
11. Autio, K.A.; Dreicer, R.; Anderson, J.; Garcia, J.A.; Alva, A.; Hart, L.L.; Milowsky, M.I.; Posadas, E.M.; Ryan, C.J.; Graf, R.P.; et al. Safety and Efficacy of BIND-014, A Docetaxel Nanoparticle Targeting Prostate-Specific Membrane Antigen for Patients with Metastatic Castration-Resistant Prostate Cancer: A Phase2 Clinical Trial. *JAMA Oncol.* **2018**, *4*, 1344–1351. [CrossRef]
12. Barata, P.C.; Cooney, M.; Mendiratta, P.; Gupta, R.; Dreicer, R.; Garcia, J.A. Phase I/II Study Evaluating the Safety and Clinical Efficacy of Temsirolimus and Bevacizumab in Patients with Chemotherapy Refractory Metastatic Castration-Resistant Prostate Cancer. *Investig. New Drugs* **2019**, *37*, 331–337. [CrossRef] [PubMed]
13. Belderbos, B.P.S.; Sieuwerts, A.M.; de Hoop, E.O.; Mostert, B.; Kraan, J.; Hamberg, P.; Van, M.N.; Beaufort, C.M.; Onstenk, W.; van Soest, R.J.; et al. Associations between AR-V7 Status in Circulating Tumour Cells, Circulating Tumour Cell Count and Survival in Men with Metastatic Castration-Resistant Prostate Cancer. *Eur. J. Cancer* **2019**, *121*, 48–54. [CrossRef] [PubMed]
14. Beltran, H.; Jendrisak, A.; Landers, M.; Mosquera, J.M.; Kossai, M.; Louw, J.; Krupa, R.; Graf, R.P.; Schreiber, N.A.; Nanus, D.M.; et al. The Initial Detection and Partial Characterization of Circulat in Tumor Cells in Neuroendocrine Prostate Cancer. *Clin. Cancer Res.* **2016**, *22*, 1510–1519. [CrossRef]
15. Chung, J.S.; Wang, Y.; Henderson, J.; Singhal, U.; Qiao, Y.; Zaslavsky, A.B.; Hovelson, D.H.; Spratt, D.E.; Reichert, Z.; Palapattu, G.S.; et al. Circulating Tumor Cell–Based Molecular Classifier for Predicting Resistance to Abiraterone and Enzalutamide in Metastatic Castration-Resistant Prostate Cancer. *Neoplasia* **2019**, *21*, 802–809. [CrossRef] [PubMed]
16. Danila, D.C.; Samoila, A.; Patel, C.; Schreiber, N.; Herkal, A.; Anand, A.; Bastos, D.; Heller, G.; Fleisher, M.; Scher, H.I. Clinical Validity of Detecting Circulating Tumor Cells by Adna Tet Assay Compared With Direct Detection of Tumor MRNA in Stabilized Whole Blood, as a Biomarker Predicting Overall Survival for Metastatic Castration-Resistant Prostate Cancer Patients. *Cancer J.* **2016**, *22*, 315–320. [CrossRef]
17. DeKruijff, I.E.; Sieuwerts, A.M.; Onstenk, W.; Kraan, J.; Smid, M.; Van, M.N.; VanDerVlugt-Daane, M.; Oomen-DeHoop, E.; Mathijssen, R.H.J.; Lolkema, M.P.; et al. Circulating Tumor Cell Enumeration and Characterization in Metastatic Castration-Resistant Prostate Cancer Patients Treated with Cabazitaxel. *Cancers* **2019**, *11*, 1212. [CrossRef]
18. DeLaere, B.; Oeyen, S.; VanOyen, P.; Ghysel, C.; Ampe, J.; Ost, P.; Demey, W.; Hoekx, L.; Schrijvers, D.; Brouwers, B.; et al. Circulating Tumor Cells and Survival in Abirater one-and Enzalutamide-Treated Patients with Castration-Resistant Prostate Cancer. *Prostate* **2018**, *78*, 435–445. [CrossRef]

19. Gorges, T.M.; Riethdorf, S.; von Ahsen, O.; Nastaly, P.; Röck, K.; Boede, M.; Peine, S.; Kuske, A.; Schmid, E.; Kneip, C.; et al. Heterogeneous PSMA Expression on Circulating Tumor Cells-a Potential Basis for Stratification and Monitoring of PSMA-Directed Therapies in Prostate Cancer. *Oncotarget* **2016**, *7*, 34930–34941. [CrossRef]
20. Graf, R.P.; Hullings, M.; Barnett, E.S.; Carbone, E.; Dittamore, R.; Scher, H.I. Clinical Utility of the Nuclear-Localized AR-V7 Biomarker in Circulating Tumor Cells in Improving Physician Treatment Choice in Castration-Resistant Prostate Cancer. *Eur. Urol.* **2020**, *77*, 170–177. [CrossRef]
21. Hofmann, L.; Sallinger, K.; Haudum, C.; Smolle, M.; Heitzer, E.; Moser, T.; Novy, M.; Gesson, K.; Kroneis, T.; Bauernhofer, T.; et al. A Multi-analyte Approach for Improved Sensitivity of Liquid Biopsies in Prostate Cancer. *Cancers* **2020**, *12*, 2247. [CrossRef]
22. Josefsson, A.; Damber, J.E.; Welén, K. AR-V7 Expression in Circulating Tumor Cells as a Potential Prognostic Marker in Metastatic Hormone-Sensitive Prostate Cancer. *Acta Oncol.* **2019**, *58*, 1660–1664. [CrossRef] [PubMed]
23. Josefsson, A.; Linder, A.; Flondell Site, D.; Canesin, G.; Stiehm, A.; Anand, A.; Bjartell, A.; Damber, J.E.; Welén, K. Circulating Tumor Cells as a Marker for Progression-Free Survival in Metastatic Castration-Naïve Prostate Cancer. *Prostate* **2017**, *77*, 849–858. [CrossRef] [PubMed]
24. Kozminsky, M.; Fouladdel, S.; Chung, J.S.; Wang, Y.; Smith, D.C.; Alva, A.; Azizi, E.; Morgan, T.; Nagrath, S. Detection of CTC Clusters and a Dedifferentiated RNA-Expression Survival Signature in Prostate Cancer. *Adv. Sci.* **2019**, *6*, 1801254. [CrossRef] [PubMed]
25. León-Mateos, L.; Abalo, A.; Casas, H.; Anido, U.; Rapado-González, Ó.; Vieito, M.; Suárez-Cunqueiro, M.; Gómez-Tato, A.; Abal, M.; López-López, R.; et al. Global Gene Expression Characterization of Circulating Tumor Cells in Metastasic Castration-Resistant Prostate Cancer Patients. *J. Clin. Med.* **2020**, *9*, 2066. [CrossRef]
26. León-Mateos, L.; Casas, H.; Abalo, A.; Vieito, M.; Abreu, M.; Anido, U.; Gómez-Tato, A.; López, R.; Abal, M.; Muinelo-Romay, L. Improving Circulating Tumor Cells Enumeration and Characterization to Predict Outcome in First Line Chemotherapy MCRPC Patients. *Oncotarget* **2017**, *8*, 54708–54721. [CrossRef]
27. Lorente, D.; Olmos, D.; Mateo, J.; Dolling, D.; Bianchini, D.; Seed, G.; Flohr, P.; Crespo, M.; Figueiredo, I.; Miranda, S.; et al. Circulating Tumour Cell Increase as a Biomarker of Disease Progression in Metastatic Castration-Resistant Prostate Cancer Patients with Low Baseline CTC Counts. *Ann. Oncol.* **2018**, *29*, 1554–1560. [CrossRef]
28. Lorente, D.; Olmos, D.; Mateo, J.; Bianchini, D.; Seed, G.; Fleisher, M.; Danila, D.C.; Flohr, P.; Crespo, M.; Figueiredo, I.; et al. Decline in Circulating Tumor Cell Count and Treatment Outcome in Advanced Prostate Cancer. *Eur. Urol.* **2016**, *70*, 985–992. [CrossRef]
29. Mandel, P.C.; Huland, H.; Tiebel, A.; Haese, A.; Salomon, G.; Budäus, L.; Tilki, D.; Chun, F.; Heinzer, H.; Graefen, M.; et al. Enumeration and Changes in Circulating Tumor Cells and Their Prognostic Value in Patients Undergoing Cytoreductive Radical Prostatectomy for Oligometastatic Prostate Cancer—Translational Research Results from the Prospective ProMPT Trial. *Eur. Urol. Focus* **2021**, *7*, 55–62. [CrossRef]
30. Marín-Aguilera, M.; Jiménez, N.; Reig, Ò.; Montalbo, R.; Verma, A.K.; Castellano, G.; Mengual, L.; Victoria, I.; Pereira, M.V.; Milà-Guasch, M.; et al. Androgen Receptor and Its Splicing Variant 7 Expression in Peripheral Blood Mononuclear Cells and in Circulating Tumor Cells in Metastatic Castration-Resistant Prostate Cancer. *Cells* **2020**, *9*, 203. [CrossRef]
31. Massard, C.; Oulhen, M.; LeMoulec, S.; Auger, N.; Foulon, S.; Abou-Lovergne, A.; Billiot, F.; Valent, A.; Marty, V.; Loriot, Y.; et al. Phenotypic and Genetic Heterogeneity of Tumor Tissue and Circulating Tumor Cells in Patients with Metastatic Castration resistant Prostate Cancer: A Report from the PETRUS Prospective Study. *Oncotarget* **2016**, *7*, 55069–55082. [CrossRef]
32. Miyamoto, D.T.; Lee, R.J.; Kalinich, M.; LiCausi, J.A.; Zheng, Y.; Chen, T.; Milner, J.D.; Emmons, E.; Ho, U.; Broderick, K.; et al. An RNA-Based Digital Circulating Tumor Cell Signature Is Predictive of Drug Response and Early Dissemination in Prostate Cancer. *Cancer Discov.* **2018**, *8*, 288–303. [CrossRef]
33. Nagaya, N.; Nagata, M.; Lu, Y.; Kanayama, M.; Hou, Q.; Hotta, Z.-u.; China, T.; Kitamura, K.; Matsushita, K.; Isotani, S.; et al. Prostate-Specific Membrane Antigen in Circulating Tumor Cells Is a New Poor Prognostic Marker for Castration-Resistant Prostate Cancer. *PLoS ONE* **2020**, *15*, e0226219. [CrossRef] [PubMed]
34. Okegawa, T.; Itaya, N.; Hara, H.; Tambo, M.; Nutahara, K. Epidermal Growth Factor Receptor Status in Circulating Tumor Cells as a Predictive Biomarker of Sensitivity in Castration-Resistant Prostate Cancer Patients Treated with Docetaxel Chemotherapy. *Int. J. Mol. Sci.* **2016**, *17*, 2008. [CrossRef] [PubMed]
35. Okegawa, T.; Ninomiya, N.; Masuda, K.; Nakamura, Y.; Tambo, M.; Nutahara, K. AR-V7 in Circulating Tumor Cells Clusterasa Predictive Biomarker of Abirater one Acetate and Enzalutamide Treatment in Castration-Resistant Prostate Cancer Patients. *Prostate* **2018**, *78*, 576–582. [CrossRef] [PubMed]
36. Pal, S.K.; He, M.; Chen, L.; Yang, L.; Pillai, R.; Twardowski, P.; Hsu, J.A.; Kortylewski, M.; Jones, J.O. Synaptophys in Expression on Circulating Tumor Cells in Patients with Castration Resistant Prostate Cancer Undergoing Treatment with Abirater one Acetate or Enzalutamide. *Urol. Oncol. Semin. Orig. Investig.* **2018**, *36*, 162.e1–162.e6. [CrossRef]
37. Pereira-Veiga, T.; González-Conde, M.; León-Mateos, L.; Piñeiro-Cid, R.; Abuín, C.; Muinelo-Romay, L.; Martínez-Fernández, M.; Brea Iglesias, J.; García González, J.; Anido, U.; et al. Longitudinal CTCs Gene Expression Analysis on Metastatic Castration-Resistant Prostate Cancer Patients Treated with Docetaxel Reveals New Potential Prognos is Markers. *Clin. Exp. Metastasis* **2021**, *38*, 239–251. [CrossRef]

38. Scher, H.I.; Graf, R.P.; Schreiber, N.A.; Jayaram, A.; Winquist, E.; McLaughlin, B.; Lu, D.; Fleisher, M.; Orr, S.; Lowes, L.; et al. Assessment of the Validity of Nuclear-Localized And Rogen Receptor Splice Variant 7 in Circulating Tumor Cells as a Predictive Biomarker for Castration-Resistant Prostate Cancer. *JAMA Oncol.* **2018**, *4*, 1179–1186. [CrossRef]
39. Scher, H.I.; Graf, R.P.; Schreiber, N.A.; McLaughlin, B.; Jendrisak, A.; Wang, Y.; Lee, J.; Greene, S.; Krupa, R.; Lu, D.; et al. Phenotypic Heterogeneity of Circulating Tumor Cells Informs Clinical Decisions between AR Signaling Inhibitors and Taxanes in Metastatic Prostate Cancer. *Cancer Res.* **2017**, *77*, 5687–5698. [CrossRef]
40. Scher, H.I.; Lu, D.; Schreiber, N.A.; Louw, J.; Graf, R.P.; Vargas, H.A.; Johnson, A.; Jendrisak, A.; Bambury, R.; Danila, D.; et al. Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker with Outcomes and Survival in Castration-Resistant Prostate Cancer. *JAMA Oncol.* **2016**, *2*, 1441–1449. [CrossRef]
41. Sepe, P.; Verzoni, E.; Miodini, P.; Claps, M.; Ratta, R.; Martinetti, A.; Mennitto, R.; Sottotetti, E.; Procopio, G.; Cappelletti, V.; et al. Could Circulating Tumor Cells and ARV7 Detection Improve Clinical Decisions in Metastatic Castration-Resistant Prostate Cancer? The Istituto Nazionale Dei Tumori (INT) Experience. *Cancers* **2019**, *11*, 980. [CrossRef]
42. Sharp, A.; Welti, J.C.; Lambros, M.B.K.; Dolling, D.; Rodrigues, D.N.; Pope, L.; Aversa, C.; Figueiredo, I.; Fraser, J.; Ahmad, Z.; et al. Clinical Utility of Circulating Tumour Cell Androgen Recept or Splice Variant-7 Status in Metastatic Castration-Resistant Prostate Cancer. *Eur. Urol.* **2019**, *76*, 676–685. [CrossRef] [PubMed]
43. Tagawa, S.T.; Antonarakis, E.S.; Gjyrezi, A.; Galletti, G.; Kim, S.; Worroll, D.; Stewart, J.; Zaher, A.; Szatrowski, T.P.; Ballman, K.V.; et al. Expression of AR-V7 and ARV567 Esin Circulating Tumor Cells Correlates with Outcomes to Taxane Therapy in Men with Metastatic Prostate Cancer Treated in Taxynergy. *Clin. Cancer Res.* **2019**, *25*, 1880–1888. [CrossRef] [PubMed]
44. Thakur, M.K.; Heilbrun, L.; Dobson, K.; Boerner, J.; Stark, K.; Li, J.; Smith, D.; Heath, E.; Fontana, J.; Vaishampayan, U. Phase I Trial of the Combination of Docetaxel, Prednisone, and Pasireotide in Metastatic Castrate-Resistant Prostate Cancer. *Clin. Genitourin. Cancer* **2018**, *16*, e695–e703. [CrossRef]
45. Tommasi, S.; Pilato, B.; Carella, C.; Lasorella, A.; Danza, K.; Vallini, I.; De Summa, S.; Naglieri, E. Standardization of CTCAR-V7PCR Assay and Evaluation of Its Role in Castration Resistant Prostate Cancer Progression. *Prostate* **2019**, *79*, 54–61. [CrossRef] [PubMed]
46. Vogelzang, N.J.; Fizazi, K.; Burke, J.M.; DeWit, R.; Bellmunt, J.; Hutson, T.E.; Crane, E.; Berry, W.R.; Doner, K.; Hainsworth, J.D.; et al. Circulating Tumor Cells in a Phase 3 Study of Docetaxel and Prednisone with or without Lenalidomide in Metastatic Castration-Resistant Prostate Cancer. *Eur. Urol.* **2017**, *71*, 168–171. [CrossRef] [PubMed]
47. Wang, C.; Zhang, Z.; Chong, W.; Luo, R.; Myers, R.E.; Gu, J.; Lin, J.; Wei, Q.; Li, B.; Rebbeck, T.R.; et al. Improved Prognostic Stratification Using Circulating Tum or Cell Clusters in Patients with Metastatic Castration-Resistant Prostate Cancer. *Cancers* **2021**, *13*, 268. [CrossRef]
48. Xu, L.; Mao, X.; Guo, T.; Chan, P.Y.; Shaw, G.; Hines, J.; Stankiewicz, E.; Wang, Y.; Oliver, R.T.D.; Ahmad, A.S.; et al. The Novel Association of Circulating Tumor Cells and Circulating Megakaryocytes with Prostate Cancer Prognosis. *Clin. Cancer Res.* **2017**, *23*, 5112–5122. [CrossRef]
49. Chong, W.; Zhang, Z.; Luo, R.; Gu, J.; Lin, J.; Wei, Q.; Li, B.; Myers, R.; Lu-Yao, G.; Kelly, W.K.; et al. Integration of Circulating Tumor Cell and Neutrophil-Lymphocyte Ratio to Identify High-Risk Metastatic Castration-Resistant Prostate Cancer Patients. *BMC Cancer* **2021**, *21*, 655. [CrossRef]
50. Hayes, B.; Brady, L.; Sheill, G.; Baird, A.M.; Guinan, E.; Stanfill, B.; Dunne, J.; Holden, D.; Vlajnic, T.; Casey, O.; et al. Circulating Tumour Cell Numbers Correlate with Platelet Count and Circulating Lymphocyte Subsets in Men with Advanced Prostate Cancer: Data from the ExPeCT Clinical Trial (CTRIAL-IE15-21). *Cancers* **2021**, *13*, 4690. [CrossRef]
51. Francolini, G.; Loi, M.; Salvestrini, V.; Mangoni, M.; Detti, B.; DiCataldo, V.; Aquilano, M.; Pinzani, P.; Salvianti, F.; Desideri, I.; et al. Prospective Assessment of AR Splice Variant and PSMA Detection on Circulating Tumor Cells of MCRPC Patients: Preliminary Analysis of Patients Enrolled in PRIMERA Trial (NCT04188275). *Clin. Exp. Metastasis* **2021**, *38*, 451–458. [CrossRef]
52. Ladurner, M.; Wieser, M.; Eigentler, A.; Seewald, M.; Dobler, G.; Neuwirt, H.; Kafka, M.; Heidegger, I.; Horninger, W.; Bektic, J.; et al. Validation of Cell-Free RNA and Circulating Tumor Cells for Molecular Marker Analysis in Metastatic Prostate Cancer. *Biomedicines* **2021**, *9*, 1004. [CrossRef]
53. DiLorenzo, G.; Zappavigna, S.; Crocetto, F.; Giuliano, M.; Ribera, D.; Morra, R.; Scafuri, L.; Verde, A.; Bruzzese, D.; Iaccarino, S.; et al. Assessment of Total, PTEN–, and AR-V7+ Circulating Tumor Cell Count by Flow Cytometry in Patients with Metastatic Castration-Resistant Prostate Cancer Receiving Enzalutamide. *Clin. Genitourin. Cancer* **2021**, *19*, e286–e298. [CrossRef] [PubMed]
54. Maillet, D.; Allioli, N.; Péron, J.; Plesa, A.; Decaussin-petrucci, M.; Tartas, S.; Sajous, C.; Ruffion, A.; Crouzet, S.; Freyer, G.; et al. Her 2 Expression in Circulating Tumor Cells Is Associated with Poor Outcomes in Patients with Metastatic Castration-resistant Prostate Cancer. *Cancers* **2021**, *13*, 6014. [CrossRef] [PubMed]
55. Davis, J.W.; Nakanishi, H.; Kumar, V.S.; Bhadkamkar, V.A.; McCormack, R.; Fritsche, H.A.; Handy, B.; Gornet, T.; Babaian, R.J. Circulating Tumor Cells in Peripheral Blood Samples from Patients with Increased Serum Prostate Specific Antigen: Initial Results in Early Prostate Cancer. *J. Urol.* **2008**, *179*, 2187–2191. [CrossRef] [PubMed]
56. Kuske, A.; Gorges, T.M.; Tennstedt, P.; Tiebel, A.K.; Pompe, R.; Preißer, F.; Prues, S.; Mazel, M.; Markou, A.; Lianidou, E.; et al. Improved Detection of Circulating Tumor Cells in Non-Metastatic High-Risk Prostate Cancer Patients. *Sci. Rep.* **2016**, *6*, 39736. [CrossRef]

57. Meyer, C.P.; Pantel, K.; Tennstedt, P.; Stroelin, P.; Schlomm, T.; Heinzer, H.; Riethdorf, S.; Steuber, T. Limited Prognostic Value of Preoperative Circulating Tumor Cells for Early Biochemical Recurrence in Patients with Localized Prostate Cancer. *Urol. Oncol. Semin. Orig. Investig.* **2016**, *34*, 235.e11–235.e16. [CrossRef]
58. Todenhöfer, T.; Park, E.S.; Duffy, S.; Deng, X.; Jin, C.; Abdi, H.; Ma, H.; Black, P.C. Microfluidic Enrichment of Circulating Tumor Cells in Patients with Clinically Localized Prostate Cancer. *Urol. Oncol. Semin. Orig. Investig.* **2016**, *34*, 483.e9–483.e16. [CrossRef]
59. Roviello, G.; Corona, S.P.; Bonetta, A.; Cappelletti, M.R.; Generali, D. Circulating Tumor Cells Correlate with Patterns of Recurrence in Patients with Hormone-Sensitive Prostate Cancer. *Onco. Targets Ther.* **2017**, *10*, 3811–3815. [CrossRef]
60. Tsumura, H.; Satoh, T.; Ishiyama, H.; Tabata, K.I.; Takenaka, K.; Sekiguchi, A.; Nakamura, M.; Kitano, M.; Hayakawa, K.; Iwamura, M. Perioperative Search for Circulating Tumor Cells in Patients Undergoing Prostate Brachy therapy for Clinically Nonmetastatic Prostate Cancer. *Int. J. Mol. Sci.* **2017**, *18*, 128. [CrossRef]
61. Murray, N.P.; Aedo, S.; Fuentealba, C.; Reyes, E. 10 Year Biochemical Failure Free Survival of Men with CD82 Positive Primary Circulating Prostate Cells Treated by Radical Prostatectomy. *Asian Pac. J. Cancer Prev.* **2018**, *19*, 1577–1583. [CrossRef]
62. Murray, N.P.; Aedo, S.; Fuentealba, C.; Reyes, E.; Salazar, A. Minimum Residual Disease in Patients Post Radical Prostatectomy for Prostate Cancer: Theoretical Considerations, Clinical Implications and Treatment Outcome. *Asian Pac. J. Cancer Prev.* **2018**, *19*, 229–236. [CrossRef] [PubMed]
63. Choi, S.Y.; Lim, B.; Kyung, Y.S.; Kim, Y.; Kim, B.M.; Jeon, B.H.; Park, J.C.; Sohn, Y.W.; Lee, J.H.; Uh, J.H.; et al. Circulating Tumor Cell Counts in Patients with Localized Prostate Cancer Including Thoseunder Active Surveillance. *In Vivo* **2019**, *33*, 1615–1620. [CrossRef] [PubMed]
64. Salami, S.S.; Singhal, U.; Spratt, D.E.; Palapattu, G.S.; Hollenbeck, B.K.; Schonhoft, J.D.; Graf, R.; Louw, J.; Jendrisak, A.; Dugan, L.; et al. Circulating Tumor Cells as a Predictor of Treatment Response in Clinically Localized Prostate Cancer. *JCO Precis. Oncol.* **2019**, *3*, 1–9. [CrossRef] [PubMed]
65. Cieślikowski, W.A.; Budna-Tukan, J.; Świerczewska, M.; Ida, A.; Hrab, M.; Jankowiak, A.; Mazel, M.; Nowicki, M.; Milecki, P.; Pantel, K.; et al. Circulating Tumor Cells as a Marker of Disseminated Disease in Patients with Newly Diagnosed High-Risk Prostate Cancer. *Cancers* **2020**, *12*, 160. [CrossRef]
66. Zapatero, A.; Gómez-Caamaño, A.; Cabeza Rodriguez, M.Á.; Muinelo-Romay, L.; Martin De Vidales, C.; Abalo, A.; Calvo Crespo, P.; Leon Mateos, L.; Olivier, C.; Vega Piris, L.V. Detection and Dynamics of Circulating Tumor Cells in Patients with High-Risk Prostate Cancer Treated with Radio therapy and Hormones: A Prospective Phase II Study. *Radiat. Oncol.* **2020**, *15*, 137. [CrossRef] [PubMed]
67. Liu, H.; Ding, J.; Wu, Y.; Wu, D.; Qi, J. Prospective Study of the Clinical Impact of Epithelial and Mesenchymal Circulating Tumor Cells in Localized Prostate Cancer. *Cancer Manag. Res.* **2020**, *12*, 4549–4560. [CrossRef] [PubMed]
68. Knipper, S.; Riethdorf, S.; Werner, S.; Tilki, D.; Graefen, M.; Pantel, K.; Maurer, T. Possible Role of Circulating Tumour Cells for Prediction of Salvage Lymph Node Dissection Outcome in Patients with Early Prostate Cancer Recurrence. *Eur. Urol. Open Sci.* **2021**, *34*, 55–58. [CrossRef]
69. Lian, S.; Yang, L.; Feng, Q.; Wang, P.; Wang, Y.; Li, Z. Folate-Recept or Positive Circulating Tumor Cell Is a Potential Diagnostic Marker of Prostate Cancer. *Front. Oncol.* **2021**, *11*, 4051. [CrossRef]
70. Murray, N.P.; Fuentealba, C.; Salazar, A.; Reyes, E. Platelet-to-Lymphocyte Ratio and Systemic Immune-Inflammation Index versus Circulating Prostate Cells to Predict Significant Prostate Cancer at First Biopsy. *Turk. J. Urol.* **2020**, *46*, 115–122. [CrossRef]
71. Bhakdi, S.C.; Suriyaphol, P.; Thaicharoen, P.; Grote, S.T.K.; Komoltri, C.; Chaiyaprasithi, B.; Charnkaew, K. Accuracy of Tumour-Associated Circulating Endothelial Cells as a Screening Biomarker for Clinically Significant Prostate Cancer. *Cancers* **2019**, *11*, 1064. [CrossRef]
72. Puche-Sanz, I.; Alvarez-Cubero, M.J.; Pascual-Geler, M.; Rodríguez-Martínez, A.; Delgado-Rodríguez, M.; García-Puche, J.L.; Expósito, J.; Robles-Fernández, I.; Entrala-Bernal, C.; Lorente, J.A.; et al. A Comprehensive Study of Circulating Tumour Cells at the Moment of Prostate Cancer Diagnos is: Biological and Clinical Implications of EGFR, A Rand SNPs. *Oncotarget* **2017**, *8*, 70472–70482. [CrossRef] [PubMed]
73. de Bono, J.S.; Scher, H.I.; Montgomery, R.B.; Parker, C.; Miller, M.C.; Tissing, H.; Doyle, G.V.; Terstappen, L.W.W.M.; Pienta, K.J.; Raghavan, D. Circulating Tumor Cells Predict Survival Benefit from Treatment in Metastatic Castration-Resistant Prostate Cancer. *Clin. Cancer Res.* **2008**, *14*, 6302–6309. [CrossRef] [PubMed]
74. Hara, N.; Kasahara, T.; Kawasaki, T.; Bilim, V.; Tomita, Y.; Obara, K.; Takahashi, K. Frequency of PSA-MRNA-Bearing Cells in the Peripheral Blood of Patients after Prostate Biopsy. *Br. J. Cancer* **2001**, *85*, 557–562. [CrossRef] [PubMed]
75. Zhu, M.-L.; Kyprianou, N. Role of Androgens and the Androgen Receptor in Epithelial-mesenchymal Transition and Invasion of Prostate Cancer Cells. *FASEB J.* **2010**, *24*, 769–777. [CrossRef]
76. Gradilone, A.; Iacovelli, R.; Cortesi, E.; Raimondi, C.; Gianni, W.; Nicolazzo, C.; Petracca, A.; Palazzo, A.; Longo, F.; Frati, L.; et al. Circulating Tumor Cells and "Suspicious Objects" Evaluated through Cell Search® in Metastatic Renal Cell Carcinoma. *Anticancer Res.* **2011**, *31*, 4219–4221.
77. Theil, G.; Fischer, K.; Weber, E.; Medek, R.; Hoda, R.; Lücke, K.; Fornara, P. The Use of a New Cell Collector to Isolate Circulating Tumor Cells from the Blood of Patients with Different Stages of Prostate Cancer and Clinical Outcomes-A Proof-of-Concept Study. *PLoS ONE* **2016**, *11*, e0158354. [CrossRef]
78. Ferreira, M.M.; Ramani, V.C.; Jeffrey, S.S. Circulating Tumor Cell Technologies. *Mol. Oncol.* **2016**, *10*, 374–394. [CrossRef]

79. Werner, S.L.; Graf, R.P.; Landers, M.; Valenta, D.T.; Schroeder, M.; Greene, S.B.; Bales, N.; Dittamore, R.; Marrinucci, D. Analytical Validation and Capabilities of the Epic CTC Platform: Enrichment-Free Circulating Tumour Cell Detection and Characterization. *J. Circ. Biomark.* **2015**, *4*, 3. [CrossRef]
80. Bazhenova, L.; Nieva, J.J.; Kolatkar, A.; Luttgen, M.; Marinucci, D.; Bethel, K.; Kuhn, P. Performance of the High-Definition Circulating Tumor Cells (HD-CTC) Assay in Patients with Non-Small Cell Lung Cancer (NSCLC). *J. Clin. Oncol.* **2012**, *30*, e21074. [CrossRef]
81. Rizzo, M.I.; Ralli, M.; Nicolazzo, C.; Gradilone, A.; Carletti, R.; DiGioia, C.; DeVincentiis, M.; Greco, A. Detection of Circulating Tumor Cells in Patients with Laryngeal Cancer Using Screen Cell: Comparative Pre- and Post-Operative Analysis and Association with Prognosis. *Oncol. Lett.* **2020**, *19*, 4183–4188. [CrossRef]
82. Farace, F.; Massard, C.; Vimond, N.; Drusch, F.; Jacques, N.; Billiot, F.; Laplanche, A.; Chauchereau, A.; Lacroix, L.; Planchard, D.; et al. A Direct Comparison of Cell Search and ISET for Circulating Tumour-Cell Detection in Patients with Metastatic Carcinomas. *Br. J. Cancer* **2011**, *105*, 847–853. [CrossRef] [PubMed]
83. Nagrath, S.; Sequist, L.V.; Maheswaran, S.; Bell, D.W.; Irimia, D.; Ulkus, L.; Smith, M.R.; Kwak, E.L.; Digumarthy, S.; Muzikansky, A.; et al. Isolation of Rare Circulating Tumour Cells in Cancer Patients by Microchip Technology. *Nature* **2007**, *450*, 1235–1239. [CrossRef] [PubMed]
84. Dennis, A. Legacy Biomarker Qualification Project Status Update | Semantic Scholar. Published 2018. Available online: https://www.semanticscholar.org/paper/Legacy-Biomarker-Qualification-Project-Status-Denis/b890af390b45104bf9232b8417a8b9b9f2476b93 (accessed on 28 July 2022).
85. FDA Grants Breakthrough Status to TriNetra-Prostate Blood Test to Detect Early-Stage Prostate Cancer. Available online: https://www.onclive.com/view/fda-grants-breakthrough-status-to-trinetra-prostate-blood-test-to-detect-early-stage-prostate-cancer (accessed on 28 July 2022).
86. Wang, L.; Balasubramanian, P.; Chen, A.P.; Kummar, S.; Evrard, Y.A.; Kinders, R.J. Promise and Limitsof the CellSearch Platform for Evaluating Pharmacodynamics in Circulating Tumor Cells. *Semin. Oncol.* **2016**, *43*, 464–475. [CrossRef] [PubMed]
87. Luo, Y.T.; Cheng, J.; Feng, X.; He, S.J.; Wang, Y.W.; Huang, Q. The viable circulating tumor cells with cancer stem cells feature, where is the way out? *J. Exp. Clin. Cancer Res.* **2018**, *37*, 38. [CrossRef] [PubMed]
88. Thomas, E.; Thankan, R.S.; Purushottamachar, P.; Huang, W.; Kane, M.A.; Zhang, Y.; Ambulos, N.; Weber, D.J.; Njar, V.C.O. Transcriptome Profiling Reveals That VNPP433-3β, the Lead Next-generation Galeterone Analog Inhibits Prostate Cancer Stem Cells by Downregulating Epithelial–Mesenchymal Transition and Stem Cell Markers. *Mol. Carcinog.* **2022**, *61*, 643–654. [CrossRef] [PubMed]