Translational Research in Urology

Home Page: www.transresurology.com

Review

Liquid Biopsy in Prostate Cancer Diagnosis and Prognosis: A Narrative Review

Sayed Saeed Tamehri Zadeh[1], Diana Taheri[2], Sepideh Shivarani[1], Fatemeh Khatami[1], Reza Kazemi[3]*

[1]*Urology Research Center, Tehran University of Medical Sciences, Tehran, Iran*

[2]*Department of Pathology, Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran*

[3]*Department of Urology, Isfahan University of Medical Sciences, Isfahan, Iran*

HIGHLIGHTS

- The efficacy of liquid biopsy, in different aspects of prostate cancer, has been investigated.
- Despite tremendous improvements in liquid biopsy in the prostate cancer field, bringing it into routine clinical practices merits further and more robust evidence.

ARTICLE INFO

Receive Date: 04 November 2020
Accept Date: 12 November 2020
Avaliable online: 21 November 2020
DOI: 10.22034/TRU.2021.270071.1061

***Corresponding Author**:
Reza Kazemi
Email: rezakazemi6788@gmail.com
Address: Department of Urology, Isfahan University of Medical Sciences, Hezar-Jerib Ave., Isfahan, Iran

ABSTRACT

Prostate cancer involves a considerable percentage of men worldwide and as be postulated; prostate cancer epidemiology is not restricted to a specific country. Despite tremendous efforts that have been made regarding prostate cancer diagnosis and treatment, this issue remains challenging for urologists and oncologists by far. The routine method for the diagnosis of prostate cancer is a prostate biopsy, which may accompany by several complications that may be detrimental to patients' health. Consequently, an alternative method with lower rates of complications is necessitating. For almost two decades liquid biopsy, an alternative method for cancer diagnosis with obvious benefits in comparison with previous methods of cancer diagnosis, has been at the center of interest of many studies, in particular, studies with prostate cancer subjects. The applicability of liquid biopsy which primarily includes cell-free DNA, circulating tumor cells, RNAs, and exosomes in prostate cancer is the main area of research of recent research. However, using liquid biopsy in routine clinical practices yet has not occurred and further studies with more firm evidence are warranted. Herein, we provided a brief report of advancements that have occurred in prostate cancer.

Keywords: Prostate Cancer; Liquid Biopsy; cell-free DNA; Cancer; Prostate-Specific Antigen

Introduction

Nowadays, prostate cancer is known as the most prevalent cancer and had the second-highest mortality rate following lung cancer in men (1). While substantial advancements in the field of prostate cancer diagnosis and treatments have been gained, the outcomes of current treatment have not been satisfactory enough. The majority of localized prostate tumors respond to radical prostatectomy well enough, but when the tumor becomes metastatic, the main treatment is androgen-deprivation therapy (ADT). Although the tumor responds to ADT immediately, the tumor fails to respond to that eventually. It has been shown that there is no chance of curing metastatic prostate cancer. The unknown mechanism behind the tumor progression and metastasis is the main cause of fail in prostate cancer treatment (1-5).

Liquid biopsy has been introduced as a desirable method for detecting biomarkers. The current method for

diagnosis of malignancies is an invasive biopsy, which contains a variety of complications and the failure rate of invasive biopsy is not low. There are several reasonable reasons in support of the fact that liquid biopsy is a far better method for cancer diagnosis in comparison to invasive biopsy. The foremost benefit of liquid biopsy versus invasive biopsy is relatively less invasivity and thereby, a considerably lower rate of morbidity. Moreover, liquid biopsy can pertain more times than invasive biopsy, which provides us a good view of the malignancy and during the treatment, the resistance to the treatment can be identified. Liquid biopsy is capable of estimating the levels of some tumoral biomarker including, but not limited to cell-free DNA (cfDNA), different RNAs, circulating tumor cells (CTCs), and extracellular vesicles (6, 7) (Figure 1).

Various aspects of liquid biopsy in urological malignancies exclusively prostate cancer have been investigated so far. Herein, we made a narrative review of knowledge that has been achieved with regards to liquid biopsy in prostate cancer.

Cell-free DNA

Although cfDNA has been introduced in 1948, utilizing it as a biomarker for cancer detection has drawn great amounts of attention in two recent decades. It can be released by the primary tumor or metastatic sites and more importantly, relatively low levels of cfDNA can be detected in individuals without any diseases (8). Circulating tumor DNA is a potential biomarker with a high capability to be detected easily, nonetheless, it has a severe limitation that restricted the wide usage that. It has been shown that it remains in the blood for the duration between 16 minutes until 13 hours after surgery or systematic treatment. One of the main obstacles that have been addressed is the method of detecting cfDNA (9). With evolving the new techniques such as whole-genome sequencing and digital PCR, nowadays chasing cfDNA in body fluids is more accessible than before (8).

We found out that lots of studies have been conducted concerning cfDNA in prostate cancer. It is of importance to note that the main focus of previous studies was on detecting cfDNA in blood plasma, but, recent publications show that the other body fluids, for instance, semen and urine have been investigated in the recent literature (10) (Figure 2). Variation in the cDNA's source and also, in the method of cDNA's detection are the two most important reasons behind differences in the cfDNA values in different studies (11).

Detecting cfDNA in blood plasma has been the mainstay of cfDNA detection and the majority of studies used blood plasma as a source of cfDNA. Blood sampling despite a very simple method, which provides an opportunity to scan the course of patients' treatment, is not sensitive enough, which may lead to confusion. It has been demonstrated that low values of cfDNA in blood plasma can be detected in patients with benign prostate hyperplasia (BPH) (12-14) and even healthy subjects (15, 16). Detection sensitivity of cfDNA can be identified by two main factors: the reference gene and the method of measurement (12, 17). Since the levels of cfDNA in blood samples is not sufficient enough, it seems that quantitative PCR is the best option for measuring cfDNA in a blood sample (18-21). The study that was performed by Gordian et al demonstrated that for patients who have a prostate-specific antigen (PSA) between 4 and 10, patients with cfDNA values higher than 180 ng/ml have a high risk of prostate cancer and finally, they suggested that measuring blood plasma cfDNA value will be beneficial to prevent

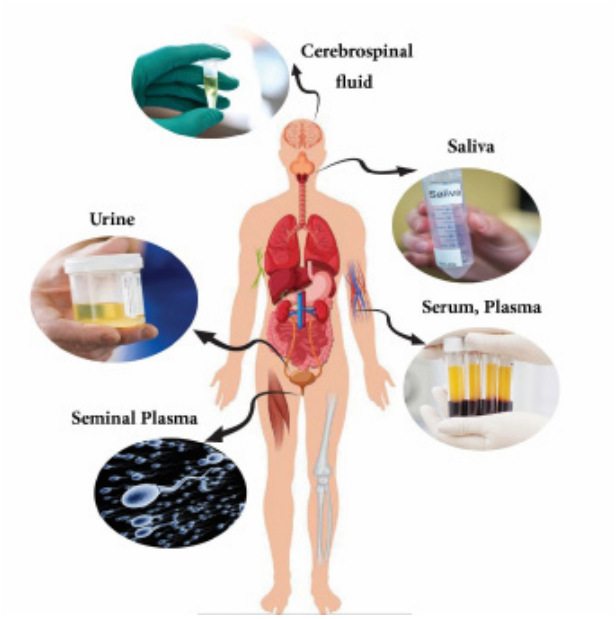

Figure 1. Schematic presentation of body fluids as the liquid biopsy sources

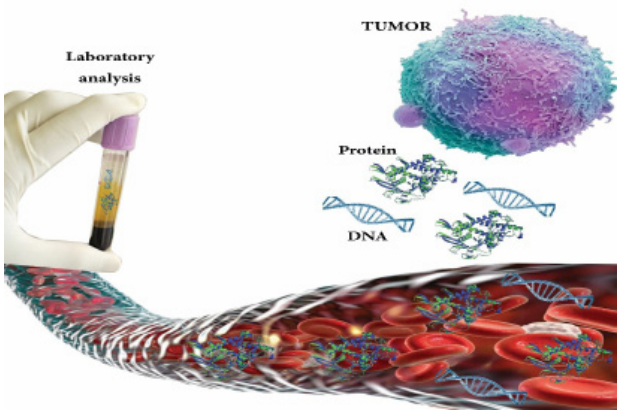

Figure 2. Tumor released its cells (CTCs), DNA fragments (cfDNA), and proteins to the blood

unnecessary biopsy (19).

Several studies have been performed to compare the values of cfDNA in patients with prostate cancer in comparison to patients with BPH and healthy subjects (20, 22). Khani et al illustrated the significant associations between cfDNA level and integrity and prostate cancer. Moreover, they claimed that the values of blood cfDNA and its integrity were higher in patients with BPH than healthy subjects, however, these were not statically significant (20).

Recently, cfDNA is mainly measured by three methods: 1. *spectrophotometric* 2. *fluorometry* 3. *quantitative PCR*. First Muller et al in 2006 sought to estimate the levels of blood plasma cfDNA level by microsatellite analysis. They elucidated that prostate cancer patients have higher values of cfDNA than BPH patients and additionally, loos of heterogenicity were significantly higher in prostate cancer patients than BPH patients (34% vs 22%).

Schwarzenbach et al tried to measured cfDNA levels in the bone marrow of prostate cancer patients. They used a new method to detect cfDNA of blood and bone marrow, called methylation-specific multiplex ligation-dependent probe amplification, which has the potential to detect genetic and epigenetic aberrations of about 37 tumor suppressor genes. At last, they matched 13 samples of blood and bone marrow and found out that the incidence of genetic changes in blood samples (25) was higher than in bone marrow aspirates (11).

Measuring urine cfDNA using this method has been investigated by Casadio et al. They measured urine cfDNA and its integrity in 29 prostate cancer patients and 25 healthy individuals. Sensitivity and specificity cfDNA integrity was estimated to be about 79% and 84%, respectively with considering the cut-off value of 0.04ng/μL, and therefore, they concluded that urine cfDNA integrity can be used for early diagnosis of prostate cancer in clinical practices (23). For the first time, Jung et al used fluorometry on 59 healthy individuals, 34 patients with BPH, and 91 prostate cancer patients to measure cfDNA. They found out that patients with localized prostate cancer had the same levels of cfDNA as healthy individuals had. On the other hand, the values of cfDNA in patients with metastasis, lymph node involvement, and even BPH were much higher than the normal range. The authors proposed that the value of plasma cfDNA is a potent biomarker for predicting prostate cancer patients (13).

Fluorometry as a method for measuring cfDNA levels in urine samples has been evaluated by Xia et al. They assessed before and after treatment copy number variations of urine cfDNA in patients who had undergone docetaxel and androgen deprivation treatment. A significant decrease in copy number variations in 34 genomes occurred after the treatment in comparison with before the treatment (24).

Ponti et al have focused on the detection of cfDNA in semen. They demonstrated in 2018 that cfDNA levels of semen in patients with prostate cancer are significantly higher than patients with BPH and healthy subjects (25). They designed another study and reached the same findings. They also claimed that the prevalence of cfDNA fragments, which are longer than 1000 base-pairs, in prostate cancer patients are significantly higher than BPH patients (26).

In 2004, Allen and her colleges designed a study to investigate cfDNA in prostate cancer using quantitative PCR. They measured blood plasma β-globin of 37 prostate cancer, intraepithelial neoplasia, and BPH patients in three different intervals including once before prostate biopsy and 60 minutes, and two weeks later the prostate biopsy. Prostate cancer and intraepithelial neoplasia patients had significantly higher values of cfDNA in comparison to the other group (27).

The association between blood plasma cfDNA and the stage of prostate cancer has been investigated. In patients without prostate cancer metastasis or lymph node involvements, blood plasma cfDNA has a significant association with stage three of prostate cancer, thereby, it can be considered as a marker for prostate cancer monitoring (28).

Several studies have been conducted to distinguish between benign and malignant lesions with DNA integrity, which is measured by quantitative PCR (18, 29). Feng et al measured blood plasma cfDNA and its integrity of 96 prostate cancer patients and 112 BPH patients, whose PSA was higher than 4 ng/ml. The cfDNA distinguishes between BPH and prostate cancer with the sensitivity and specificity of 73.2% and 72.7%, respectively, and DNA integrity with higher sensitivity (81.7%) and specificity (78.8%) can distinguish (18).

Circulating tumor cells

Stem cells are capable of self-renewing, hence they can survive throughout the host life-time. This feature constitutes the rationale for stem cells to be the source of cancers. In the early 1960s, some studies showed that cancers are comprised of cells, which are vary in self-renewal capacity. So, they concluded that the origination of cancers may be several cells, named CTCs (30-33). Prostate cancer is composed of different cells and the histo-structure of prostate cancer in various stages is different as well. In early prostate cancers, both differentiated and undifferentiated cells can be observed, but the majority of cells are differentiated. In contrast to undifferentiated areas, cells, which are located in differentiated areas are positive for PSA and androgen receptor (AR). For late stages of prostate cancers, undifferentiated areas are more prominent than differentiated areas (34-36).

Metastatic lesions of prostate cancer have been assessed and interestingly, they have consisted of different cells similarly. Apart from heterogenicity in prostate cancer structure, heterogenicity in mutations and chromosol rearrangement has been detected (37, 38).

CTCs can be detected through several methods, however, the main focus of most of the studies was toward reverse transcription-polymerase chain reaction (RT-PCR) and immunohistochemistry (IHC) (39, 40). Several extracellular markers, including, but not limited to, *CD117/c-kit*, *CD133*, *CD44*, *α2β1 integrin/ α6 integrin* have been evaluated.

In 2014, the predictive ability of some markers especially CD117/c-kit was assessed by Ker et al. blood serum concentrations of markers before radical prostatectomy and 1-3 months after the surgery were calculated. Among investigated markers, the serum values of only CD117/c-kit decreased significantly following the surgery. The authors reached positive correlations between CD117 and tumor progression and PSA values. At last, they clarified that if prostate tumors are enriched with CD117, they become more aggressive (41).

It has been proposed that CD117 may cooperate with BRCA2 in bone metastasis of prostate cancer patients. It is of proven value that BRCA2 loss led to tumor progression and metastasis in prostate cancer patients. Mainetti et al illustrated expression of CD117 with loss of *BRCA2* triggers prostate cancer cells to migrated into the other side of the body especially bone (42-44).

CD133 expression was measured in 17 healthy subjects,17 patients with high-grade intraepithelial neoplasia, and 65 patients with prostate cancer. It was expressed in 67 prostate cancer patients, 5 of a healthy subject, and none of the high-grade intraepithelial neoplasia patients (45). In another study, the expression of four markers in particular CD1333 was estimated in 38 prostate cancer patients. CD133 was expressed with the normal range or slightly higher than the normal range. Also, it has a positive association with Gleason score (46). Fan et al determined to evaluate the resistance of cells with expression of CD1333 to cisplatin and demonstrated that these cells are more resistant to cisplatin (47).

The role of CD44, which is a multipotential protein, in the proliferation of prostate cancer has been illustrated. Patrawala et al demonstrated that prostate tumors that are positive for CD44 when compared to those which are negative for CD44 are more tended to progress and be metastatic. Additionally, they claimed that prostate tumors positive and negative for CD44 and AR, respectively, are potent to differentiate into tumors positive for both CD44 and AR (48). For prostate cancer to be metastatic, Matrigel through epithelial-mesenchymal transition should be invaded, which has been attributed to prostate cancers positive for CD44, thereby the existence of CD44 for tumor metastasis is required (49). Moreover, prostate cancer positive for CD44 through the Wnt pathway can lead to failure to respond to chemotherapy in patients with castration resistance prostate cancer (50).

Expression of *α2* integrin and *α6-integrin*, stem cell markers, in 461 prostate cancer patients have been assessed. *α2 integrin* and *α6-integrin* were expressed in 94.7% and 28.4% of the patients. Significant relationships between *α2-integrin* and *α6-integrin* expression and PSA greater and lower than 10ng/ml, respectively, have been detected. Furthermore, *α6-integrin* associated significantly with Gleason score<7 and stage 2 of the tumor. The *α6-integrin* maintains a predictive value to diagnosis a local recurrence of the tumor (51). Assessing the expression of these two markers and c-Met in the bone marrow of patients with prostate cancer revealed significant associations between expression greater than 0.1% of the three markers and tumor metastasis, stages, and death related to the tumor (52).

RNA

Lines of research stated that a variety of RNAs maintain a mandatory role in protein production, which is a complex process. Ample evidence is existing in support of the fact that non-coding RNAs (ncRNAs), which are produced as a result of continuous genome transcription, are implicated in several diseases in particular cancers (53-55). Non-coding RNAs are consist of two major subgroups short non-coding RNAs and long non-coding RNAs (LncRNAs). Different categorizations of LncRNAs currently exist. For instance, one of the well-known categorizations of LncRNAs is based on the location of LncRNAs on the genome (56).

Prostate cancer antigen 3 (PCA3) is a LncRNA that only express in prostate glands and has been known as a marker that controls the survival of prostate cancer cells through moderating AR signaling. The most important PCA3 advantageous over PSA is the situations, for example, BPH that impacts the values of PSA are not able to change the values of PCA3 (57-59). Groskopf and his colleges measured urine values of PCA3 and PSA of 52 healthy subjects (age<45 years old), 21 men who had undergone radical prostatectomy, and 70 patients scheduled to be biopsied. For the patients scheduled to be biopsied, urine PCA3 sensitivity and specificity were calculated near 70% and 80%, respectively. Lower specificity and higher sensitivity were obtained for PSA. PCA3 was detected in none except one (had recurrent prostate cancer) of the patients with radical prostatectomy (60).

The predictive ability of LncRNAs in prostate cancer was evaluated since the Gleason score contains several limitations (61). The values of SChLAP1 in patients

who experienced radical prostatectomy, which is a LncRNAs, increases as prostate cancer progresses, and more importantly, for patients with high concentrations of SChLAP1 before the surgery, worsen outcomes following the surgery can be expected (62). The expression of PCAT14, another LncRNA, in 585 prostate cancer patients was investigated. Negative associations between LncRNA expression and Gleason score, metastasis, cancer-related death, and biochemical recurrence were achieved in two different studies (63, 64). Prostate cancer tissues contain higher values of urothelial carcinoma-associated 1 (UCA1) than normal prostate tissues. The inverse association between level of UCA1 and prognosis of patients with prostate cancer was observed. Likely, KLF4, which had a significant relationship with UCA1, expressed in higher concentrations in patients with prostate cancer than healthy subjects (65). The prostate tumor which is positive for UCA1 in comparison with negative ones is more resistant to radiotherapy (66).

Exosomes

Exosomes are a well-validated component of normal and tumoral cells component. The main roles of exosomes are communication between cells and transmission of materials, for instance, DNAs, RNAs, and proteins necessitates for cells 'survival (67). According to several years of experience, they are responsible for prostate cancer metastasis, resistance to chemotherapy, and development. As mentioned above, they can be secreted from tumoral cells, and these exosomes through impacting recipient cells, provide situations, which are desirable for prostate cancer development and metastasis (68, 69). The mechanism responsible for inducing prostate cancer progression and metastasis was explained by Beheshti and his co-workers. They pointed out that prostate cancer exosomes cause apoptosis reduction, enhancement in the progression of prostate cancer cells, and transmission of proteins with the ability to prevent apoptosis (70). In another study, it was proposed prostate cancer exosomes through an interruption in immune system function may lead to tumor progression and metastasis (71). Prostate cancer exosomes are capable of transferring αvβ6 integrin, a marker that only exists on prostate tumoral cells, to cells negative for this integrin, which leads to enhancement in cell adhesion and migration (72). Exosomes are potent in influencing epithelial-mesenchymal transition, which is an inseparable part of tumor metastasis.

Exosomes can enhance prostate cancer resistance to drugs and chemotherapy. In the comprehensive review that was performed by Min et al, drug efflux, comprising genes with drug resistance capacity, and cross-talk between pathways of cellular signaling are proposed as the mechanisms that cause drug resistance in patients with different cancers exclusively prostate cancer (73). Exosomes involve in bone metastasis of prostate cancer. Exosomes, which are derived from prostate cancer, can prohibit osteoclast function and differentiation and in contrast, stimulate the function of osteoblast. Hence, they have a major role in osteoblastic bone metastasis (74).

Former research expressed that microRNAs (miRNAs), a well-known ncRNA (75), may participate in tumor growth, progression, differentiation, and apoptosis (76). The main functions of miRNAs are attributed to two subgroups of miRNAs including micro-miRNAs and tumor-suppressor miRNAs. miR-21 has been proven to act as an ono-miRNAs in prostate and bladder malignancies. (77) miR-125 is the other example of onco-miRNAs in prostate cancer (78), however, for breast cancer patients, it acts as a tumor suppressor (79).

Some studies have addressed the predictive value of exosomal miRNAs (80-82). Li et al designed a study to investigate different aspects of miR-141. First, they showed that prostate cancer patients had higher values of miR-141 than healthy individuals and even BPH patients. Values of miR-141 in metastatic patients were also higher versus patients with localized prostate cancer. They found out that this marker can distinguish between localized and metastatic prostate cancers with a sensitivity of 80% and specificity of 87.1% (82).

Survival of castration-resistant prostate cancer patients can be predicted by using the combination of miR-1290 and miR-375. 20 months of follow-up showed that patients who have higher values of miR-1290 and miR-375 in comparison to patients whose values of those are within the normal range have significantly higher mortality rates (83).

Conclusions

Liquid biopsy which primarily includes cell-free DNA, circulating tumor cells, RNAs, and exosomes in can change the prostate cancer diagnosis for the better.

Authors' contributions

All authors contributed equally. All authors reviewed and approved the final version of the manuscript.

Acknowledgments

Special thanks to Department of Urology, Isfahan University of Medical Sciences, Isfahan, Iran.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for this research.

Ethical statement
Not applicable.

Data availability
Not applicable.

Abbreviations

ADT	Androgen deprivation therapy
cfDNA	Cell-free DNA
CTC	Circulating tumor cell
PSA	Prostate-specific antigen
UCA1	Urothelial carcinoma-associated 1

References

1. Shen MM, Abate-Shen C. Molecular genetics of prostate cancer: new prospects for old challenges. Genes & development. 2010;24(18):1967-2000.
2. Cooperberg MR, Moul JW, Carroll PR. The changing face of prostate cancer. Journal of Clinical Oncology. 2005;23(32):8146-51.
3. Debes JD, Tindall DJ. Mechanisms of androgen-refractory prostate cancer. New England Journal of Medicine. 2004;351(15):1488-90.
4. Feldman BJ, Feldman D. The development of androgen-independent prostate cancer. Nature Reviews Cancer. 2001;1(1):34-45.
5. Li H, Tang DG. Prostate cancer stem cells and their potential roles in metastasis. Journal of surgical oncology. 2011;103(6):558-62.
6. Bettegowda C, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, et al. Detection of circulating tumor DNA in early-and late-stage human malignancies. Science translational medicine. 2014;6(224):224ra24-ra24.
7. Di Meo A, Bartlett J, Cheng Y, Pasic MD, Yousef GM. Liquid biopsy: a step forward towards precision medicine in urologic malignancies. Molecular cancer. 2017;16(1):80.
8. Elshimali YI, Khaddour H, Sarkissyan M, Wu Y, Vadgama JV. The clinical utilization of circulating cell free DNA (CCFDNA) in blood of cancer patients. International journal of molecular sciences. 2013;14(9):18925-58.
9. Qin Z, Ljubimov VA, Zhou C, Tong Y, Liang J. Cell-free circulating tumor DNA in cancer. Chinese journal of cancer. 2016;35(1):1-9.
10. Ponti G, Maccaferri M, Percesepe A, Tomasi A, Ozben T. Liquid biopsy with cell free DNA: new horizons for prostate cancer. Critical Reviews in Clinical Laboratory Sciences. 2020:1-17.
11. Bronkhorst AJ, Ungerer V, Holdenrieder S. Early detection of cancer using circulating tumor DNA: biological, physiological and analytical considerations. Critical reviews in clinical laboratory sciences. 2020;57(4):253-69.
12. Ellinger J, Bastian PJ, Haan KI, Heukamp LC, Buettner R, Fimmers R, et al. Noncancerous PTGS2 DNA fragments of apoptotic origin in sera of prostate cancer patients qualify as diagnostic and prognostic indicators. International journal of cancer. 2008;122(1):138-43.
13. Jung K, Stephan C, Lewandowski M, Klotzek S, Jung M, Kristiansen G, et al. Increased cell-free DNA in plasma of patients with metastatic spread in prostate cancer. Cancer letters. 2004;205(2):173-80.
14. Mueller I, Urban K, Pantel K, Schwarzenbach H. Comparison of genetic alterations detected in circulating microsatellite DNA in blood plasma samples of patients with prostate cancer and benign prostatic hyperplasia. Annals of the New York Academy of Sciences. 2006;1075(1):222-9.
15. Bastian PJ, Palapattu GS, Yegnasubramanian S, Lin X, Rogers CG, Mangold LA, et al. Prognostic value of preoperative serum cell-free circulating DNA in men with prostate cancer undergoing radical prostatectomy. Clinical Cancer Research. 2007;13(18):5361-7.
16. Ponti G, Maccaferri M, Manfredini M, Kaleci S, Mandrioli M, Pellacani G, et al. The value of fluorimetry (Qubit) and spectrophotometry (NanoDrop) in the quantification of cell-free DNA (cfDNA) in malignant melanoma and prostate cancer patients. Clinica Chimica Acta. 2018;479:14-9.
17. Ramachandran K, Speer CG, Fiddy S, Reis IM, Singal R. Free circulating DNA as a biomarker of prostate cancer: comparison of quantitation methods. Anticancer research. 2013;33(10):4521-9.
18. Feng J, Gang F, Li X, Jin T, Houbao H, Yu C, et al. Plasma cell-free DNA and its DNA integrity as biomarker to distinguish prostate cancer from benign prostatic hyperplasia in patients with increased serum prostate-specific antigen. International urology and nephrology. 2013;45(4):1023-8.
19. Gordian E, Ramachandran K, Reis IM, Manoharan M, Soloway MS, Singal R. Serum free circulating DNA is a useful biomarker to distinguish benign versus malignant prostate disease. Cancer Epidemiology and Prevention Biomarkers. 2010;19(8):1984-91.

20. Khani M, Hosseini J, Mirfakhraie R, Habibi M, Azargashb E, Pouresmaeili F. The value of the plasma circulating cell-free DNA concentration and integrity index as a clinical tool for prostate cancer diagnosis: a prospective case–control cohort study in an Iranian population. Cancer management and research. 2019;11:4549.
21. Reis I, Ramachandran K, Speer C, Gordian E, Singal R. Serum GADD45a methylation is a useful biomarker to distinguish benign vs malignant prostate disease. British journal of cancer. 2015;113(3):460-8.
22. Seyedolmohadessin SM, Akbari MT, Nourmohammadi Z, Basiri A, Pourmand G. Assessing the Diagnostic Value of Plasma-Free DNA in Prostate Cancer Screening. Iranian biomedical journal. 2018;22(5):331.
23. Casadio V, Calistri D, Tebaldi M, Bravaccini S, Gunelli R, Martorana G, et al., editors. Urine cell-free DNA integrity as a marker for early bladder cancer diagnosis: preliminary data. Urologic Oncology: Seminars and Original Investigations; 2013: Elsevier.
24. Xia Y, Huang C-C, Dittmar R, Du M, Wang Y, Liu H, et al. Copy number variations in urine cell free DNA as biomarkers in advanced prostate cancer. Oncotarget. 2016;7(24):35818.
25. Ponti G, Maccaferri M, Micali S, Manfredini M, Milandri R, Bianchi G, et al. Seminal cell free DNA concentration levels discriminate between prostate cancer and benign prostatic hyperplasia. Anticancer Research. 2018;38(9):5121-5.
26. Ponti G, Maccaferri M, Manfredini M, Micali S, Torricelli F, Milandri R, et al. Quick assessment of cell-free DNA in seminal fluid and fragment size for early non-invasive prostate cancer diagnosis. Clinica Chimica Acta. 2019;497:76-80.
27. ALLEN D, BUTT A, CAHILL D, WHEELER M, POPERT R, Swaminathan R. Role of cell-free plasma DNA as a diagnostic marker for prostate cancer. Annals of the New York Academy of Sciences. 2004;1022(1):76-80.
28. Altimari A, Grigioni ADE, Benedettini E, Gabusi E, Schiavina R, Martinell A, et al. Diagnostic role of circulating free plasma DNA detection in patients with localized prostate cancer. American journal of clinical pathology. 2008;129(5):756-62.
29. Fawzy A, Sweify KM, El-Fayoumy HM, Nofal N. Quantitative analysis of plasma cell-free DNA and its DNA integrity in patients with metastatic prostate cancer using ALU sequence. Journal of the Egyptian national cancer institute. 2016;28(4):235-42.
30. Bruce WR, Van Der Gaag H. A quantitative assay for the number of murine lymphoma cells capable of proliferation in vivo. Nature. 1963;199(4888):79-80.
31. Hamburger AW, Salmon SE. Primary bioassay of human tumor stem cells. Science. 1977;197(4302):461-3.
32. Sabbath KD, Ball ED, Larcom P, Davis RB, Griffin JD. Heterogeneity of clonogenic cells in acute myeloblastic leukemia. The Journal of clinical investigation. 1985;75(2):746-53.
33. Southam CM, Brunschwig A. Quantitative studies of autotransplantation of human cancer. Preliminary report. Cancer. 1961;14(5):971-8.
34. Azmi AS, Sarkar FH. Prostate cancer stem cells: molecular characterization for targeted therapy. Asian journal of andrology. 2012;14(5):659.
35. Mulholland DJ. PSA-negative/low prostate cancer cells: the true villains of CRPC? Asian journal of andrology. 2012;14(5):663.
36. Qin J, Liu X, Laffin B, Chen X, Choy G, Jeter CR, et al. The PSA−/lo prostate cancer cell population harbors self-renewing long-term tumor-propagating cells that resist castration. Cell stem cell. 2012;10(5):556-69.
37. Gundem G, Van Loo P, Kremeyer B, Alexandrov LB, Tubio JM, Papaemmanuil E, et al. The evolutionary history of lethal metastatic prostate cancer. Nature. 2015;520(7547):353-7.
38. Hong MK, Macintyre G, Wedge DC, Van Loo P, Patel K, Lunke S, et al. Tracking the origins and drivers of subclonal metastatic expansion in prostate cancer. Nature communications. 2015;6(1):1-12.
39. Doyen J, Alix-Panabières C, Hofman P, Parks SK, Chamorey E, Naman H, et al. Circulating tumor cells in prostate cancer: a potential surrogate marker of survival. Critical reviews in oncology/hematology. 2012;81(3):241-56.
40. Shaffer DR, Leversha MA, Danila DC, Lin O, Gonzalez-Espinoza R, Gu B, et al. Circulating tumor cell analysis in patients with progressive castration-resistant prostate cancer. Clinical Cancer Research. 2007;13(7):2023-9.
41. Wiesner C, Nabha SM, Bonfil RD, Dos Santos EB, Yamamoto H, Meng H, et al. C-kit and its ligand stem cell factor: potential contribution to prostate cancer bone metastasis. Neoplasia. 2008;10(9):996-1003.
42. Castro E, Eeles R. The role of BRCA1 and BRCA2 in prostate cancer. Asian journal of andrology. 2012;14(3):409.
43. Mainetti LE, Zhe X, Diedrich J, Saliganan AD, Cho WJ, Cher ML, et al. Bone-induced c-kit expression in prostate cancer: A driver of intraosseous tumor growth. International journal of cancer. 2015;136(1):11-20.
44. Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell. 2002;108(2):171-82.
45. Ugolkov AV, Eisengart LJ, Luan C, Yang XJ. Expression analysis of putative stem cell markers in human benign and malignant prostate. The Prostate. 2011;71(1):18-25.
46. Fan X, Liu S, Su F, Pan Q, Lin T, editors. Effective enrichment of prostate cancer stem cells from spheres in a suspension culture system. Urologic Oncology: Seminars and Original Investigations; 2012: Elsevier.
47. Miyazawa K, Tanaka T, Nakai D, Morita N, Suzuki K. Immunohistochemical expression of four different stem cell markers in prostate cancer: High expression of NANOG in conjunction with hypoxia-inducible factor-1α expression is involved in prostate epithelial malignancy. Oncology letters. 2014;8(3):985-92.
48. Patrawala L, Calhoun T, Schneider-Broussard R, Li H, Bhatia B, Tang S, et al. Highly purified CD44+ prostate cancer cells from xenograft human tumors are enriched in tumorigenic and metastatic progenitor cells. Oncogene. 2006;25(12):1696-708.
49. Klarmann GJ, Hurt EM, Mathews LA, Zhang X, Duhagon MA, Mistree T, et al. Invasive prostate cancer cells are tumor initiating cells that have a stem cell-like genomic signature. Clinical & experimental metastasis. 2009;26(5):433-46.
50. Yun E-J, Zhou J, Lin C-J, Hernandez E, Fazli L, Gleave M, et al. Targeting cancer stem cells in castration-resistant prostate cancer. Clinical Cancer Research. 2016;22(3):670-9.
51. Hoogland AM, Verhoef EI, Roobol MJ, Schröder FH, Wildhagen MF, van der Kwast TH, et al. Validation of stem cell markers in clinical prostate cancer: α6-Integrin is predictive for non-aggressive disease. The Prostate. 2014;74(5):488-96.
52. Ricci E, Mattei E, Dumontet C, Eaton CL, Hamdy F, van der Pluije G, et al. Increased expression of putative cancer stem cell markers in the bone marrow of prostate cancer patients is associated with bone metastasis progression. The Prostate. 2013;73(16):1738-46.
53. Dunham I, Birney E, Lajoie BR, Sanyal A, Dong X, Greven M, et al. An integrated encyclopedia of DNA elements in the human genome. 2012.
54. Ling H, Vincent K, Pichler M, Fodde R, Berindan-Neagoe I, Slack FJ, et al. Junk DNA and the long non-coding RNA twist in cancer genetics. Oncogene. 2015;34(39):5003-11.
55. Nord AS, Blow MJ, Attanasio C, Akiyama JA, Holt A, Hosseini R, et al. Rapid and pervasive changes in genome-wide enhancer usage during mammalian development. Cell. 2013;155(7):1521-31.
56. Hua JT, Chen S, He HH. Landscape of noncoding RNA in prostate cancer. Trends in Genetics. 2019;35(11):840-51.
57. Bussemakers MJ, Van Bokhoven A, Verhaegh GW, Smit FP, Karthaus HF, Schalken JA, et al. Dd3:: A new prostate-specific gene, highly overexpressed in prostate cancer. Cancer research. 1999;59(23):5975-9.
58. Deras IL, Aubin SM, Blase A, Day JR, Koo S, Partin AW, et al. PCA3: a molecular urine assay for predicting prostate biopsy outcome. The Journal of urology. 2008;179(4):1587-92.
59. Lemos AEG, Ferreira LB, Batoreu NM, de Freitas PP, Bonamino MH, Gimba ERP. PCA3 long noncoding RNA modulates the expression of key cancer-related genes in LNCaP prostate cancer cells. Tumor Biology. 2016;37(8):11339-48.
60. Groskopf J, Aubin SM, Deras IL, Blase A, Bodrug S, Clark C, et al. APTIMA PCA3 molecular urine test: development of a method to aid in the diagnosis of prostate cancer. Clinical chemistry.

2006;52(6):1089-95.
61. Buhmeida A, Pyrhönen S, Laato M, Collan Y. Prognostic factors in prostate cancer. Diagnostic pathology. 2006;1(1):1-15.
62. Mehra R, Shi Y, Udager AM, Prensner JR, Sahu A, Iyer MK, et al. A novel RNA in situ hybridization assay for the long noncoding RNA SChLAP1 predicts poor clinical outcome after radical prostatectomy in clinically localized prostate cancer. Neoplasia. 2014;16(12):1121-7.
63. Shukla S, Zhang X, Niknafs YS, Xiao L, Mehra R, Cieślik M, et al. Identification and Validation of PCAT14 as Prognostic Biomarker in Prostate Cancer. Neoplasia. 2016;18(8):489-99.
64. White NM, Zhao SG, Zhang J, Rozycki EB, Dang HX, McFadden SD, et al. Multi-institutional Analysis Shows that Low PCAT-14 Expression Associates with Poor Outcomes in Prostate Cancer. European urology. 2017;71(2):257-66.
65. Na XY, Liu ZY, Ren PP, Yu R, Shang XS. Long non-coding RNA UCA1 contributes to the progression of prostate cancer and regulates proliferation through KLF4-KRT6/13 signaling pathway. International journal of clinical and experimental medicine. 2015;8(8):12609-16.
66. Fotouhi Ghiam A, Taeb S, Huang X, Huang V, Ray J, Scarcello S, et al. Long non-coding RNA urothelial carcinoma associated 1 (UCA1) mediates radiation response in prostate cancer. Oncotarget. 2017;8(3):4668-89.
67. Javidi MA, Ahmadi AH, Bakhshinejad B, Nouraee N, Babashah S, Sadeghizadeh M. Cell-free microRNAs as cancer biomarkers: the odyssey of miRNAs through body fluids. Medical oncology (Northwood, London, England). 2014;31(12):295.
68. Mashouri L, Yousefi H, Aref AR, Ahadi AM, Molaei F, Alahari SK. Exosomes: composition, biogenesis, and mechanisms in cancer metastasis and drug resistance. Mol Cancer. 2019;18(1):75.
69. Wu K, Xing F, Wu SY, Watabe K. Extracellular vesicles as emerging targets in cancer: Recent development from bench to bedside. Biochimica et biophysica acta Reviews on cancer. 2017;1868(2):538-63.
70. Hosseini-Beheshti E, Choi W, Weiswald LB, Kharmate G, Ghaffari M, Roshan-Moniri M, et al. Exosomes confer pro-survival signals to alter the phenotype of prostate cells in their surrounding environment. Oncotarget. 2016;7(12):14639-58.
71. Lundholm M, Schröder M, Nagaeva O, Baranov V, Widmark A, Mincheva-Nilsson L, et al. Prostate tumor-derived exosomes down-regulate NKG2D expression on natural killer cells and CD8+ T cells: mechanism of immune evasion. PloS one. 2014;9(9):e108925.
72. Fedele C, Singh A, Zerlanko BJ, Iozzo RV, Languino LR. The αvβ6 integrin is transferred intercellularly via exosomes. The Journal of biological chemistry. 2015;290(8):4545-51.
73. Min L, Garbutt C, Hornicek F, Duan Z. The Emerging Roles and Clinical Potential of Exosomes in Cancer: Drug Resistance. Diagnostic and Therapeutic Applications of Exosomes in Cancer: Elsevier; 2018. p. 285-311.
74. Webber JP, Spary LK, Sanders AJ, Chowdhury R, Jiang WG, Steadman R, et al. Differentiation of tumour-promoting stromal myofibroblasts by cancer exosomes. Oncogene. 2015;34(3):290-302.
75. Catalanotto C, Cogoni C, Zardo G. MicroRNA in control of gene expression: an overview of nuclear functions. International journal of molecular sciences. 2016;17(10):1712.
76. Huang X, Liang M, Dittmar R, Wang L. Extracellular microRNAs in urologic malignancies: chances and challenges. International journal of molecular sciences. 2013;14(7):14785-99.
77. Catto JW, Alcaraz A, Bjartell AS, White RDV, Evans CP, Fussel S, et al. MicroRNA in prostate, bladder, and kidney cancer: a systematic review. European urology. 2011;59(5):671-81.
78. Shi XB, Xue L, Ma AH, Tepper CG, Kung HJ, White RWd. miR-125b promotes growth of prostate cancer xenograft tumor through targeting pro-apoptotic genes. The Prostate. 2011;71(5):538-49.
79. Sorrentino A, Liu C-G, Addario A, Peschle C, Scambia G, Ferlini C. Role of microRNAs in drug-resistant ovarian cancer cells. Gynecologic oncology. 2008;111(3):478-86.
80. Bryant R, Pawlowski T, Catto J, Marsden G, Vessella R, Rhees B, et al. Changes in circulating microRNA levels associated with prostate cancer. British journal of cancer. 2012;106(4):768-74.
81. Endzeliņš E, Berger A, Melne V, Bajo-Santos C, Soboļevska K, Ābols A, et al. Detection of circulating miRNAs: comparative analysis of extracellular vesicle-incorporated miRNAs and cell-free miRNAs in whole plasma of prostate cancer patients. BMC cancer. 2017;17(1):730.
82. Li Z, Ma Y-Y, Wang J, Zeng X-F, Li R, Kang W, et al. Exosomal microRNA-141 is upregulated in the serum of prostate cancer patients. OncoTargets and therapy. 2016;9:139.
83. Huang X, Yuan T, Liang M, Du M, Xia S, Dittmar R, et al. Exosomal miR-1290 and miR-375 as prognostic markers in castration-resistant prostate cancer. European urology. 2015;67(1):33-41.

Author (s) biosketches
Tamehri Zadeh SS, PhD, Urology Research Center, Tehran University of Medical Sciences, Tehran, Iran.
Email: keykavosgholami@yahoo.com
Taheri D, Professor, Department of Pathology, Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
Email: keykavosgholami@yahoo.com
Shivarani S, PhD, Urology Research Center, Tehran University of Medical Sciences, Tehran, Iran.
Email: keykavosgholami@yahoo.com
Khatami F, PhD, Urology Research Center, Tehran University of Medical Sciences, Tehran, Iran.
Email: f-khatami@alumnus.tums.ac.ir
Kazemi R, Assistant Professor, Department of Urology, Isfahan University of Medical Sciences, Isfahan, Iran.
Email: rezakazemi6788@gmail.com

How to cite this article
Tamehri Zadeh SS, Taheri D, Shivarani S, Khatami F, Kazemi R. Liquid Biopsy in Prostate Cancer Diagnosis and Prognosis: A Narrative Review. Translational Research in Urology. 2020 Nov; 2(4): 139-146.
DOI: 10.22034/TRU.2021.270071.1061
URL: http://www.transresurology.com/article_124715.html