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MetastamiRs: The Role of MicroRNAs in the Metastatic Phenotype of Prostate Cancer

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Abstract: MicroRNAs (miRNAs) are short non-coding RNAs that post-transcriptionally regulate protein expression. The human genome encodes more than 2,500 miRNAs, with each being able to modulate several targets, act along a variety of cellular pathways, and affect various tissues. They are frequently dysregulated in cancers and, via their protein targets, act as oncogenes or tumor-suppressors. As such, their effects are pervasive—miRNAs have been implicated in various biological processes including apoptosis, epithelial-to-mesenchymal transition, and angiogenesis. In this context, miRNA involved in metastasis have been termed "metastamiRs". This chapter focuses on the role of miRNAs in the metastatic processes of prostate cancer. Our primary aims are to

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detail specific biological processes and molecular targets through which miRNAs act and that may serve as therapeutic targets. Secondly, we discuss the potential of miRNAs to serve as biomarkers of tumor aggression and thus potentially guide personalized therapy.

Keywords: metastasis-promoting miRNAs in prostate cancer; metastamiRs; metastasis-suppressing miRNAs in prostate cancer; metastatic prostate cancer; microRNAs in prostate cancer

INTRODUCTION

MicroRNAs (miRNAs) are small non-coding RNAs averaging 22 nucleotides in length that generally function by negatively regulating mRNA expression by binding to the 3'UTR of their targets (1). These molecules are found in all major cellular compartments, and are often exported from the cell, where they may function as signaling molecules (2). An individual miRNA can modulate expression of numerous targets based on sequence complementarity between the miRNA and the 3'UTR of an mRNA (3). Similarly, an individual mRNA transcript may be regulated by hundreds of miRNAs, resulting in a network of interactions between miRNAs, their target genes, and their downstream effectors (3). This interactive network contributes significantly towards the regulation of a plethora of biological processes and cellular pathways. While miRNAs typically act to support the normal function of the human body, aberrant expression of these molecules has been implicated in the pathogenesis of numerous human diseases (4).

An area of interest with respect to the impact of miRNA expression on human disease is cancer progression (5). MiRNAs frequently become dysregulated in human cancers through mechanisms such as amplification or deletion of miRNA genes, aberrant transcriptional control of miRNAs, changes in epigenetic regulation and defects in the miRNA biogenesis machinery (6). It has been shown that miRNA dysregulation has a strong influence on the following aspects of cancer phenotype: proliferative capacity, resistance to apoptosis, evasion of growth suppressors, activation of invasion and metastasis via the epithelial-mesenchymal transition (EMT) pathway, and induction of angiogenesis (6). The miRNAs involved in the overall cancer phenotype have been termed "oncomiRs" (7), and their role in the regulation of these processes depends on their interactions with specific targets. MiRNAs that affect the metastatic phenotype when dysregulated can be characterized as having pro- and anti- metastatic effects depending on their net influence on tumor aggressiveness (8). The collection of miRNAs that are specifically associated with the promotion or suppression of metastatic potential and EMT of cancer cells are known as "metastamiRs" (8).

Research on the role of these metastamiRs in the development and progression of cancer has mainly focused on their association with downstream effectors and patient outcomes. Numerous metastasis-associated signaling pathways have been linked to abnormal expression of metastamiRs (9). For example, metastamiR expression has been identified as a driver of the phosphatase and tensin homolog (PTEN)/phosphatidylinositol-3-kinase (PI3K), EGF receptor (EGFR), transforming growth factor-beta (TGFβ), and p53 pathways (9). More generally, miRNAs have been a popular target for translational research approaches such as studying

the predictive ability of specific miRNA expression signatures and their utility as non-invasive biomarkers. For example, a study in bladder cancer has elucidated the ability of miRNA panels to distinguish the aggressiveness of the cancer (10). Additionally, miRNA expression levels in the urine (11), serum (12), and exosomes (13) have shown viability as non-invasive biomarkers in cancer diagnostics. This chapter focuses on the role of metastamiRs in prostate cancer, explore their role in prostate cancer metastasis, and their potential in cancer diagnosis and therapy.

THE ROLE OF MICRORNAS IN THE METASTATIC PHENOTYPE OF PROSTATE CANCER

Apart from cutaneous malignancies, prostate cancer is the most common cancer among men in the United States (US), with roughly 250,000 new annual cases (14–16). Behind lung cancer, it is the second leading cause of cancer death in American men (14). Due to a multitude of treatment options that often offer curative potential, localized disease generally portends favorable outcomes, with 5-year survival for localized and regional disease being nearly 100% (17). However, despite noteworthy recent progress in therapeutic measures, metastatic prostate cancer still inflicts significant morbidity and mortality, with the preponderance of fatal cases of prostate cancer attributed to metastatic burden (18–20).

With most prostate cancer-related morbidity and mortality stemming from its metastatic spread, it is important to understand the molecular processes involved in this disease. As more than 50% of miRNA genes are in cancer-associated genomic regions, they control the expression level of pro-metastatic genes by targeting mRNAs at the post-transcriptional level, and thus act as central nodal points for metastatic progression (21, 22). Because of the highly aberrant expression levels and, in some cases, aberrant sequences of miRNAs found in prostate cancer, miRNAs have a particularly crucial regulatory role, acting as promoter or inhibitors of metastasis primarily through regulating invasion, migration, and EMT (Figure1) (18, 21, 23–26). Tables 1 and 2 summarize the product of a vast—and continuously expanding—collection of research that has culminated in our current understanding of the role of miRNAs in prostate cancer metastasis. Importantly, there are miRNAs with documented roles in prostate cancer that have not been included in this chapter, largely due to either limited or conflicting evidence surrounding their metastatic role. Although current experimental methods are often powerful enough to detect the abnormal changes of miRNA expression in prostate cancer, it remains difficult to identify downstream effects of these miRNAs. This is due to multifactorial reasons including complexity of the metastatic cascade, the heterogeneity of the primary prostatic tumors, as well as the convoluted relationship between genetic and environmental factors contributing to the progression of prostate cancer (27–29).

Metastasis-promoting miRNAs in prostate cancer

While metastasis-promoting miRNAs have diverse molecular targets and pathways, they generally encompass interaction with transcription factors, cytokines, receptors, and enzymes involved in cellular proliferation or the metastatic cascade.

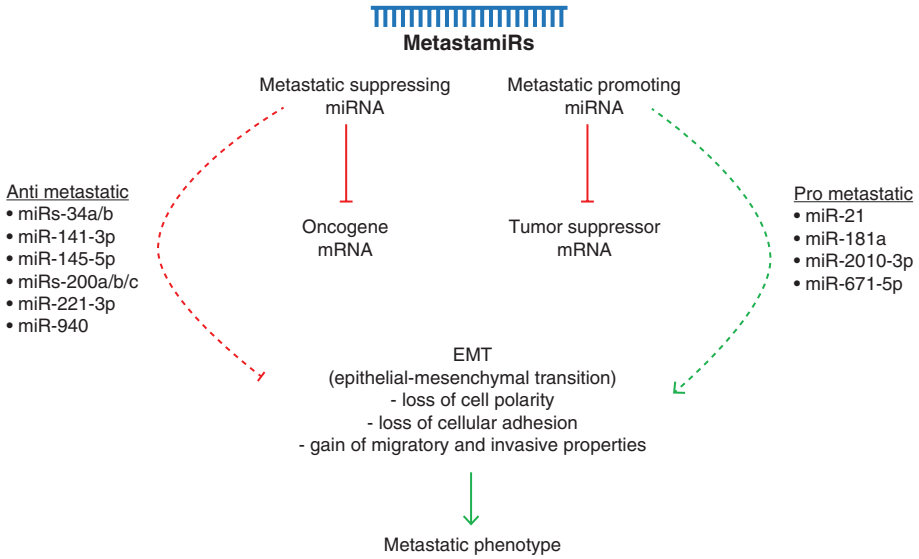

Figure 1. Simplified overview of the role of the effects of metastamiRs on the metastatic phenotype. Metastatic suppressing miRNAs inhibit the metastatic phenotype by attenuating expression of oncogenes that drive epithelial-mesenchymal transition. Conversely, the net effect of metastatic promoting miRNA is to drive epithelial-mesenchymal transition by downregulating the expression of tumor suppressor genes that could otherwise inhibit this process. A few examples of each, prevalent in prostate cancer, are detailed.

Whereas some of these metastasis-promoting miRNAs directly activate oncogenic pathways via known proto-oncogenes, others silence or suppress tumor-suppressive pathways to promote prostate cancer metastasis. For example, Ren et al. demonstrated that miR-210-3p sustains the activation of nuclear factor kappa-B (NF-κB) signaling by targeting tumor necrosis factor-α (TNFα), which increases the capacity for cellular invasion, migration, EMT, and formation of bone metastases (19, 30). On the other hand, Yu et al. showed that miR-671-5p targets known tumor suppressor SOX6 and inhibits its expression, preventing the transcription of downstream tumor suppressive proteins and thus resulting in cell proliferation, migration, and invasion (26, 31). Table 1 details specific metastasis-promoting miRNAs implicated in prostate cancer, their molecular targets, and function in promoting metastasis (32–46).

Metastasis-suppressing miRNAs in prostate cancer

While there are a diverse number of targets detailed within the literature, several of these pathways are represented across multiple miRNAs, highlighting their global influence in the metastatic process. For example, miRs -141-3p, -212, -200, -204-5p, and -532-3p all influence and downregulate the activity of NF-κB at some operational level, while miRs -33a, -132, -34a, b, -212, and -200 all act on transforming growth factor-β (TGF-β) to inhibit metastasis (47–62). Ultimately, these molecular processes suppress the transformation of localized prostate

TABLE 1 **Summary of metastasis-promoting miRNAs involved in prostate cancer, with impacted pathways, targets, and resulting oncologic outcomes**

miRNA	Targets/Regulators	Function	Reference
miR-9	E-cadherin, SOCS5, StarD13	Promotes migration, invasion, EMT, and spontaneous metastasis	(32, 33)
miR-18a	STK4	Promotes cell motility, migration, and invasion	(34, 35)
miR-21	MARKS, PDCD4, TPM1, AR	Promotes apoptosis resistance, motility, and invasion potential via several molecular mechanisms	(36–38)
miR-32	RAC2, BTG2	Promotes proliferation of prostatic epithelium and inhibits apoptosis.	(39, 40)
miR-181a	TGIF2, LEF1	Promotes cell migration, invasion, and EMT via SMAD2/3 activation and Wnt signaling.	(41, 42)
miR-210-3p	TNIP, SOCS1	Promotes invasion, migration, EMT, and formation of bone metastasis via NF-κB activation.	(19, 30)
miR-429	P27Kip1	Promotes cell proliferation. Restricts arrest in G1 phase of cell cycle.	(19, 43)
miR-454	NDRG2	Promotes cell proliferation and invasion via Wnt/β-catenin signaling.	(44)
miR-671-5p	SOX6, NFIA-CRYAB axis	Promotes cell proliferation, migration, and invasion.	(31, 45)
miR-629-5p	AKAP13	Drives cell proliferation, migration, and invasion.	(46)

cancer to metastatic disease. Table 2 delineates many of the known metastasis-suppressing miRNAs in prostate cancer (63–92).

miRNAs as biomarkers and therapeutics in prostate cancer

The diagnostic standard for prostate cancer is either a transrectal or transperineal biopsy guided by a transrectal ultrasound (TRUS). Indication for biopsy is generally a prostate-specific antigen (PSA) level or change outside of clinically accepted parameters. The classification of prostate cancer is based on Gleason score (gleaned from biopsy results), PSA level, and other clinical considerations, which together inform therapeutic options and prognosis. Recently, prostate genomics has garnered clinical attention, with multiple assays becoming clinically available to help guide clinical decision making. While these assays further elucidate patient-specific risk, currently available resources are still not sufficient to predict true metastatic potential, particularly at the time of metastatic initiation or transition (19, 93–99). In addition, inconsistencies of Gleason score between prostate

TABLE 2 **Summary of metastasis-suppressing miRNAs involved in prostate cancer, with impacted pathways, targets, and resulting oncologic outcome**

miRNA	Targets/Regulators	Function	Reference
miR-19a-3p	SMAD2/4, PMEPA1	Inhibits cell invasion and migration.	(63)
miR-33a	TGFBRI, EN-2	Inhibits cell proliferation, invasion, and colony formation.	(49, 50)
miR-34a,b	CD44, TGF-β/SMAD3	Suppresses tumor migration, clonogenic expansion, invasion, and progression via WNT/B-catenin, JAK/STAT3, PI3K/AKT pathways.	(19, 50, 61, 64–66)
miR-132	SOX4	Inhibits cell migration, invasion, and EMT via suppression of TGFβ-mediated signaling.	(51, 60)
miR-141-3p	TRAF5-6, RUNX1, MMP2/9	Suppresses cell invasion and migration via inhibition of NF-κB, EMT, and promotes apoptosis.	(47, 48)
miR-145-5p	E-cadherin, fibronectin, HEF1, OCT3, c-Myc, KLF4, WIP1, TWIST1	Suppresses bone metastasis by downregulating EMT via increasing E-cadherin expression and decreasing fibronectin expression. Decreases colony formation, decreases tumor spheroid formation and cellular cloning.	(67–71)
miR-148a-3p	DNMT1	Induces apoptosis and reduces cellular proliferation.	(72)
miR-152-3p	TMEM97, NOL4	Suppresses cell viability, invasion, and promotes cell-cycle arrest at S and G2/M.	(73, 74)
miR-195-5p	Fra-1, MMP1/9	Inhibits cell motility, migration, and invasion.	(73, 75)
miR-200a, b,c	NF-kβ, SNAI2, ZEB, TGF-β, BRD4	Inhibits cell migration, adhesion, and angiogenesis.	(19, 54–56)
miR-204-5p	NF-kβ, TRAF1, TAB3, MAP3k3, BCL2	Suppresses invasion, migration, and dissemination of cancer cells into bone.	(57, 58)
miR-212	SOX4, BMI-1, EN2	Suppresses proliferation, promotes arrest of cell cycle, and inhibits EMT.	(51–53)
miR-221-3p	VEGFR2, SIRT1	Suppresses cell proliferation, migration, and colony formation.	(76–79)
miR-224-5p	UAP1, HK2, CHIT1, TOP2A, RRM2	Inhibits cell proliferation and migration.	(80, 81)
miR-335	EGR3, eNOS	Reduces cell viability and angiogenesis of the cell line, reducing migration, and invasive capacity.	(82–84)
miR-505-3p	SMAD2/4, PMEPA1	Inhibits cell invasion and migration.	(85)
miR-532-3p	TRAF1,2,4	Inhibits tissue invasion, cell migration, and bone metastasis.	(59)
miR-543	eNOS	Impairs migration and invasive capacity.	(84, 86)
miR-802	FLOT2	Suppresses cell migration, invasion and EMT.	(87, 88)
miR-940	MIEN1	Suppresses migration and invasion. Attenuates anchorage-independent growth ability via the Wnt/β-catenin, MAPK, PI3K-Akt pathways.	(89–91)
miR-3622a	SNAI2, ZEB1	Inhibits EMT.	(92)

biopsy and radical prostatectomy are frequent. Moreira Leite et al. (100) found Gleason score was underestimated in 29% of cases, and it was overestimated in 14% of cases. As such, there remains an urgent clinical need for alternative biomarkers to improve the diagnosis and prognosis of prostate cancer. miRNAs have considerable potential to fill this diagnostic, prognostic, and potentially therapeutic void (19, 101, 102).

Due to the relative abundance of miRNAs in various biological fluids and their stability and resistance to degradation in diverse storage media, miRNAs are considered strong candidates as molecular biomarkers for prostate cancer (19, 89, 91, 95, 96, 101). There are two distinct theoretical approaches concerning their utility: diagnostics, in which miRNAs can indicate presence or absence of disease; and prognostics, in which miRNAs aid in risk stratification and therapeutic guidance. Concerning the first application, numerous pre-clinical studies have investigated miRNA expression trends in those with prostate cancer compared to non-malignant controls in various isolated body fluids (such as serum, plasma, urine, and semen) in order to identify miRNAs that predict the presence of disease. While individual miRNAs are often studied, the utilization of miRNA panels has bolstered diagnostic value as well (76, 103–106). However, this field requires further development, as much of the current data is complicated by a lack of consistency between miRNA signatures and reproducibility. Proposed sources of these limitations include diversity of sample types (primary tumor, metastatic tissue, blood, urine, serum, plasma, etc.), study design, patient selection, study size, and most importantly, the intrinsic molecular heterogeneity of the disease (19, 101). Nevertheless, the idea of a miRNA panel as a non-invasive disease marker continues to make great headway, in hopes of a clinical application in the near future.

Concerning the utility of miRNA as a disease prognosticator, proposed clinical applications include the prediction of biochemical recurrence after primary treatment, the likelihood of transition to castration-resistant prostate cancer, and a generalized assessment of response to future therapy (101). Biochemical recurrence risk is an important clinical factor, as de-novo rise in serum PSA after treatment can be predictive of metastatic spread. Multiple studies have investigated the role of miRNAs in this prediction, with various miRNA panels showing promising results (37, 107–115). Of particular interest is a miR index quote (miQ) proposed by Larne et al., which utilized four miRNAs (miRs -96-5p, -183-5p, -145-5p, and - 221-5p) to predict tumor aggressiveness in early organ-confined stages and was able to predict recurrence after radical prostatectomy with greater accuracy than PSA, with an AUC of 0.78 (115).

Progression of disease after androgen deprivation therapy is known as castration-resistant prostate cancer and is a significant contributor to prostate cancer morbidity and mortality. Multiple miRNAs have been documented as predictive of castration resistance and many are associated with the androgen receptor pathway as either direct or indirect regulators (40, 116, 117). While several studies have demonstrated differential expression patterns of miRNA between castrate-sensitive and castration-resistant prostate cancer, miRNA-based modeling that predicts a transition from castrate-sensitive to castrate-resistant disease will require further development and refining (36, 40, 77, 116, 118, 119).

MicroRNAs have also been promoted as biomarkers to guide personalized therapy by tailoring therapeutic options and monitoring for response. To this end, several studies have investigated miRNAs as predictors of both chemo- and

radio-sensitivity and have proposed models that are able to predict response rates to both systemic chemotherapy as well as radiation (101, 120–129). While these studies show promise, investigations into radio- and chemo- sensitivity have largely taken place in a non-clinical, *in vitro* setting, and further research is needed to determine if these trends are clinically transferable.

CONCLUSION

There remains a need for prostate cancer markers beyond what is currently available, and miRNAs have the potential to serve as both diagnostic and prognostic biomarkers. For example, as the diagnosis of prostate cancer requires invasive and often repetitive biopsies, utilization of miRNAs as binary markers of the presence or absence of disease would both reduce morbidity associated with prostate cancer workup and healthcare-associated procedural costs (130–133). Further, as current prognostic algorithms lack the ability to truly predict metastatic risk in prostate cancer, miRNAs may refine clinical decision making (19, 93, 94, 96, 98). While further research is needed to bring the utilization of miRNAs as disease biomarkers to their full clinical potential, they remain a promising tool to improve diagnostics and prognostics in urologic malignancies.

miRNAs also have the potential to reach therapeutics, which would be clinically impactful. Since a single miRNA can regulate several separate targets involved in oncologic molecular pathways, targeting the miRNA may be beneficial on multiple molecular levels, thus providing redundancy in a therapeutic mechanism. Pre-clinical studies hope to take advantage of this redundancy with the development of novel therapeutic approaches. These methodologies generally fall under two categories: miRNA mimics or miRNA inhibitors (19). Mimics replace lost or downregulated tumor-suppressive endogenous miRNAs and promote their downstream anti-oncogenic effects via targeting the 3'-UTR of the targeted oncogenes. miRNA inhibitors are antisense oligonucleotides, or anti-miRNAs, that inhibit endogenous tumor-promoting miRNAs via direct binding to the small RNA species within the RNA-induced silencing complex, thus reversing their downstream effects (19). While the therapeutic benefit of this approach is intuitive, it is functionally complicated by the necessity of effective delivery strategies. Two primary approaches include intra-tumoral therapy and systemic therapy, with particular attention focused on the latter as this would have the greatest effect on metastatic tumor burden. Proposed delivery methods include cationic-lipid transfection, polyethyleneimine or magnetic nanoparticles, atelocollagen, or viral vectors. (66, 134–140). While the majority of current research remains at the pre-clinical level, some miRNAs have reached early clinical development. For example, Hong et al. conducted a Phase 1 clinical trial into a miR-34a mimic MRX34, but the trial was discontinued due to its side effect profile (141). Certainly, further research is needed to further develop these therapeutic options, but *in vitro* and *in vivo* studies thus far show great promise for the future clinical application of miRNA as a therapeutic avenue in cancer.

While the subject of this chapter is miRNAs, an understanding of an increasingly popular area of research—long non-coding RNAs (lncRNAs)—is necessary to understand the context of miRNA within this realm. These RNAs are an

emerging class of transcripts that are coded by the genome but not translated into protein. While not translated, ongoing research has uncovered their crucial roles in cellular and physiologic functions including chromatin dynamics, gene expression, growth, differentiation, and development (142–144). Unsurprisingly, emerging studies have shown that lncRNAs play an important regulatory role alongside metastamiRs in prostate cancer. For example, Huang et al. reported that lncRNA SNHG1 was upregulated in prostate cancer cells and had roles in regulating proliferation, migration, invasion, and inhibition of apoptosis via repression of miR-383–5p (145). Certainly, this growing body of research suggests that the true processes occurring *in vivo* surrounding oncomiRs and metastamiRs are far more complex than their individual targeting pathways alone, and that further research is required to fully comprehend these relationships.

While discrepancies and inconsistencies remain, studies continue to better elucidate the vast and often redundant mechanisms through which they exert their oncologic effects to regulate characteristics of metastasis such as angiogenesis, cellular proliferation, migration, invasion, and EMT. Though this research is still in its infancy from a clinical perspective, efforts toward a more refined understanding are underway, with hopes of soon reaching the full clinical potential of oncomiRs and metastamiRs in combating prostate cancer and metastasis.

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REFERENCES

1. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. Front Endocrinol (Lausanne). 2018;9:402. https://doi.org/10.3389/fendo.2018.00402
2. Makarova JA, Shkurnikov MU, Wicklein D, Lange T, Samatov TR, Turchinovich AA, et al. Intracellular and extracellular microRNA: An update on localization and biological role. Progress in Histochemistry and Cytochemistry. 2016;51(3):33–49. https://doi.org/10.1016/j.proghi.2016.06.001
3. Lewis BP, Shih I -hung, Jones-Rhoades MW, Bartel DP, Burge CB. Prediction of mammalian microRNA targets. Cell. 2003;115(7):787–98. https://doi.org/10.1016/S0092-8674(03)01018-3
4. Tüfekci KU, Öner MG, Meuwissen RLJ, Genç Ş. The Role of MicroRNAs in Human Diseases. In: Yousef M, Allmer J, editors. miRNomics: MicroRNA Biology and Computational Analysis [Internet]. Totowa, NJ: Humana Press; 2014 [cited 2022 Jan 24]. p. 33–50. (Methods in Molecular Biology). https://doi.org/10.1007/978-1-62703-748-8_3
5. Bracken CP, Scott HS, Goodall GJ. A network-biology perspective of microRNA function and dysfunction in cancer. Nat Rev Genet. 2016;17(12):719–32. https://doi.org/10.1038/nrg.2016.134
6. Peng Y, Croce CM. The role of MicroRNAs in human cancer. Signal Transduct Target Ther. 2016;1:15004. https://doi.org/10.1038/sigtrans.2015.4
7. Esquela-Kerscher A, Slack FJ. Oncomirs - microRNAs with a role in cancer. Nat Rev Cancer. 2006;6(4):259–69. https://doi.org/10.1038/nrc1840

8. Hurst DR, Edmonds MD, Welch DR. Metastamir - the field of metastasis-regulatory microRNA is spreading. Cancer Res. 2009;69(19):7495–8. https://doi.org/10.1158/0008-5472.CAN-09-2111
9. Wang J, Du Y, Liu X, Cho WC, Yang Y. MicroRNAs as Regulator of Signaling Networks in Metastatic Colon Cancer. Biomed Res Int. 2015;2015:823620. https://doi.org/10.1155/2015/823620
10. Inamoto T, Uehara H, Akao Y, Ibuki N, Komura K, Takahara K, et al. A Panel of MicroRNA Signature as a Tool for Predicting Survival of Patients with Urothelial Carcinoma of the Bladder. Dis Markers. 2018;2018:5468672. https://doi.org/10.1155/2018/5468672
11. Kutwin P, Konecki T, Borkowska EM, Traczyk-Borszyńska M, Jabłonowski Z. Urine miRNA as a potential biomarker for bladder cancer detection - a meta-analysis. Cent European J Urol. 2018; 71(2):177–85.
12. Tusong H, Maolakuerban N, Guan J, Rexiati M, Wang W-G, Azhati B, et al. Functional analysis of serum microRNAs miR-21 and miR-106a in renal cell carcinoma. Cancer Biomarkers. 2017;18(1):79–85. https://doi.org/10.3233/CBM-160676
13. Lorenc T, Klimczyk K, Michalczewska I, Słomka M, Kubiak-Tomaszewska G, Olejarz W. Exosomes in Prostate Cancer Diagnosis, Prognosis and Therapy. Int J Mol Sci. 2020;21(6):2118. https://doi.org/10.3390/ijms21062118
14. Key Statistics for Prostate Cancer | Prostate Cancer Facts [Internet]. [cited 2022 Jan 26]. Available from: https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html
15. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018;68(6):394–424. https://doi.org/10.3322/caac.21492
16. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7–30. https://doi.org/10.3322/caac.21590
17. Survival Rates for Prostate Cancer [Internet]. [cited 2022 Jan 26]. Available from: https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/survival-rates.html
18. Weiner AB, Matulewicz RS, Eggener SE, Schaeffer EM. Increasing incidence of metastatic prostate cancer in the United States (2004–2013). Prostate Cancer Prostatic Dis. 2016;19(4):395–7. https://doi.org/10.1038/pcan.2016.30
19. Oh-Hohenhorst SJ, Lange T. Role of Metastasis-Related microRNAs in Prostate Cancer Progression and Treatment. Cancers (Basel). 2021;13(17):4492. https://doi.org/10.3390/cancers13174492
20. Elmehrath AO, Afifi AM, Al-Husseini MJ, Saad AM, Wilson N, Shohdy KS, et al. Causes of Death Among Patients With Metastatic Prostate Cancer in the US From 2000 to 2016. JAMA Network Open. 2021;4(8):e2119568. https://doi.org/10.1001/jamanetworkopen.2021.19568
21. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, et al. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci U S A. 2004;101(9):2999–3004. https://doi.org/10.1073/pnas.0307323101
22. Lopez-Camarillo C, Marchat LA, Arechaga-Ocampo E, Perez-Plasencia C, del Moral-Hernandez O, Castaneda-Ortiz EJ, et al. MetastamiRs: Non-Coding MicroRNAs Driving Cancer Invasion and Metastasis. Int J Mol Sci. 2012;13(2):1347–79. https://doi.org/10.3390/ijms13021347
23. Bhagirath D, Yang TL, Dahiya R, Saini S. MicroRNAs as Regulators of Prostate Cancer Metastasis. In: Schatten H, editor. Cell & Molecular Biology of Prostate Cancer: Updates, Insights and New Frontiers [Internet]. Cham: Springer International Publishing; 2018 [cited 2022 Feb 4]. p. 83–100. (Advances in Experimental Medicine and Biology). https://doi.org/10.1007/978-3-319-95693-0_5
24. Calin GA, Croce CM. MicroRNA signatures in human cancers. Nat Rev Cancer. 2006;6(11):857–66. https://doi.org/10.1038/nrc1997
25. Bonci D, Coppola V, Patrizii M, Addario A, Cannistraci A, Francescangeli F, et al. A microRNA code for prostate cancer metastasis. Oncogene. 2016;35(9):1180–92. https://doi.org/10.1038/onc.2015.176
26. Aghdam SG, Ebrazeh M, Hemmatzadeh M, Seyfizadeh N, Shabgah AG, Azizi G, et al. The role of microRNAs in prostate cancer migration, invasion, and metastasis. J Cell Physiol. 2019;234(7):9927–42. https://doi.org/10.1002/jcp.27948
27. Tang Y, Yan W, Chen J, Luo C, Kaipia A, Shen B. Identification of novel microRNA regulatory pathways associated with heterogeneous prostate cancer. BMC Syst Biol. 2013;7(Suppl 3):S6. https://doi.org/10.1186/1752-0509-7-S3-S6

28. Lin Y, Chen J, Shen B. Interactions Between Genetics, Lifestyle, and Environmental Factors for Healthcare. In: Shen B, editor. Translational Informatics in Smart Healthcare [Internet]. Singapore: Springer; 2017 [cited 2022 Jan 27]. p. 167–91. (Advances in Experimental Medicine and Biology). https://doi.org/10.1007/978-981-10-5717-5_8
29. Zhu Z, Wen Y, Xuan C, Chen Q, Xiang Q, Wang J, et al. Identifying the key genes and microRNAs in prostate cancer bone metastasis by bioinformatics analysis. FEBS Open Bio. 2020;10(4):674–88. https://doi.org/10.1002/2211-5463.12805
30. Ren D, Yang Q, Dai Y, Guo W, Du H, Song L, et al. Oncogenic miR-210-3p promotes prostate cancer cell EMT and bone metastasis via NF-κB signaling pathway. Mol Cancer. 2017;16:117. https://doi.org/10.1186/s12943-017-0688-6
31. Yu Y, Wang Z, Sun D, Zhou X, Wei X, Hou W, et al. miR-671 promotes prostate cancer cell proliferation by targeting tumor suppressor SOX6. European Journal of Pharmacology. 2018;823:65–71. https://doi.org/10.1016/j.ejphar.2018.01.016
32. Seashols-Williams SJ, Budd W, Clark GC, Wu Q, Daniel R, Dragoescu E, et al. miR-9 Acts as an OncomiR in Prostate Cancer through Multiple Pathways That Drive Tumour Progression and Metastasis. PLoS One. 2016;11(7):e0159601. https://doi.org/10.1371/journal.pone.0159601
33. Chen L, Hu W, Li G, Guo Y, Wan Z, Yu J. Inhibition of miR-9-5p suppresses prostate cancer progress by targeting StarD13. Cell Mol Biol Lett. 2019;24(1):20. https://doi.org/10.1186/s11658-019-0145-1
34. Shen K, Cao Z, Zhu R, You L, Zhang T. The dual functional role of MicroRNA-18a (miR-18a) in cancer development. Clin Transl Med. 2019;8:32. https://doi.org/10.1186/s40169-019-0250-9
35. Hsu T-I, Hsu C-H, Lee K-H, Lin J-T, Chen C-S, Chang K-C, et al. MicroRNA-18a is elevated in prostate cancer and promotes tumorigenesis through suppressing STK4 in vitro and in vivo. Oncogenesis. 2014;3(4):e99. https://doi.org/10.1038/oncsis.2014.12
36. Ribas J, Ni X, Haffner M, Wentzel EA, Salmasi AH, Chowdhury WH, et al. miR-21: An androgen receptor regulated microRNA which promotes hormone dependent and independent prostate cancer growth. Cancer Res. 2009;69(18):7165–9. https://doi.org/10.1158/0008-5472.CAN-09-1448
37. Li T, Li R-S, Li Y-H, Zhong S, Chen Y-Y, Zhang C-M, et al. miR-21 as an independent biochemical recurrence predictor and potential therapeutic target for prostate cancer. J Urol. 2012;187(4):1466–72. https://doi.org/10.1016/j.juro.2011.11.082
38. Li T, Li D, Sha J, Sun P, Huang Y. MicroRNA-21 directly targets MARCKS and promotes apoptosis resistance and invasion in prostate cancer cells. Biochem Biophys Res Commun. 2009;383(3):280–5. https://doi.org/10.1016/j.bbrc.2009.03.077
39. Latonen L, Scaravilli M, Gillen A, Hartikainen S, Zhang F-P, Ruusuvuori P, et al. In Vivo Expression of miR-32 Induces Proliferation in Prostate Epithelium. Am J Pathol. 2017;187(11):2546–57. https://doi.org/10.1016/j.ajpath.2017.07.012
40. Jalava SE, Urbanucci A, Latonen L, Waltering KK, Sahu B, Jänne OA, et al. Androgen-regulated miR-32 targets BTG2 and is overexpressed in castration-resistant prostate cancer. Oncogene. 2012;31(41):4460–71. https://doi.org/10.1038/onc.2011.624
41. Zhiping C, Shijun T, Linhui W, Yapei W, Lianxi Q, Qiang D. MiR-181a promotes epithelial to mesenchymal transition of prostate cancer cells by targeting TGIF2. Eur Rev Med Pharmacol Sci. 2017;21(21):4835–43.
42. Liang J, Li X, Li Y, Wei J, Daniels G, Zhong X, et al. LEF1 targeting EMT in prostate cancer invasion is mediated by miR-181a. Am J Cancer Res. 2015;5(3):1124–32.
43. Ouyang Y, Gao P, Zhu B, Chen X, Lin F, Wang X, et al. Downregulation of microRNA-429 inhibits cell proliferation by targeting p27Kip1 in human prostate cancer cells. Mol Med Rep. 2015;11(2):1435–41. https://doi.org/10.3892/mmr.2014.2782
44. Fu Q, Gao Y, Yang F, Mao T, Sun Z, Wang H, et al. Suppression of microRNA-454 impedes the proliferation and invasion of prostate cancer cells by promoting N-myc downstream-regulated gene 2 and inhibiting WNT/β-catenin signaling. Biomed Pharmacother. 2018;97:120–7. https://doi.org/10.1016/j.biopha.2017.10.115
45. Zhu Z, Luo L, Xiang Q, Wang J, Liu Y, Deng Y, et al. MiRNA-671-5p Promotes prostate cancer development and metastasis by targeting NFIA/CRYAB axis. Cell Death Dis. 2020;11(11):949. https://doi.org/10.1038/s41419-020-03138-w

46. Liu Y, Zhao S, Wang J, Zhu Z, Luo L, Xiang Q, et al. MiR-629-5p Promotes Prostate Cancer Development and Metastasis by Targeting AKAP13. Front Oncol. 2021;11:754353. https://doi.org/10.3389/fonc.2021.754353
47. Huang S, Wa Q, Pan J, Peng X, Ren D, Huang Y, et al. Downregulation of miR-141-3p promotes bone metastasis via activating NF-κB signaling in prostate cancer. J Exp Clin Cancer Res. 2017;36:173. https://doi.org/10.1186/s13046-017-0645-7
48. Xu S, Ge J, Zhang Z, Zhou W. miR-141 inhibits prostatic cancer cell proliferation and migration, and induces cell apoptosis via targeting of RUNX1. Oncology Reports. 2018;39(3):1454–60. https://doi.org/10.3892/or.2018.6209
49. Karatas OF, Wang J, Shao L, Ozen M, Zhang Y, Creighton CJ, et al. miR-33a is a tumor suppressor microRNA that is decreased in prostate cancer. Oncotarget. 2017;8(36):60243–56. https://doi.org/10.18632/oncotarget.19521
50. Li Q, Lu S, Li X, Hou G, Yan L, Zhang W, et al. Biological function and mechanism of miR-33a in prostate cancer survival and metastasis: via downregulating Engrailed-2. Clin Transl Oncol. 2017;19(5):562–70. https://doi.org/10.1007/s12094-016-1564-3
51. Fu W, Tao T, Qi M, Wang L, Hu J, Li X, et al. MicroRNA-132/212 Upregulation Inhibits TGF-β-Mediated Epithelial-Mesenchymal Transition of Prostate Cancer Cells by Targeting SOX4. Prostate. 2016;76(16):1560–70. https://doi.org/10.1002/pros.23241
52. Qu H-W, Jin Y, Cui Z-L, Jin X-B. MicroRNA-212 participates in the development of prostate cancer by upregulating BMI1 via NF-κB pathway. European review for medical and pharmacological sciences. 2018;22:3348–56.
53. Zhou Y, Ji Z, Yan W, Zhou Z, Li H. The biological functions and mechanism of miR-212 in prostate cancer proliferation, migration and invasion via targeting Engrailed-2. Oncol Rep. 2017;38(3):1411–9. https://doi.org/10.3892/or.2017.5805
54. Guan H, You Z, Wang C, Fang F, Peng R, Mao L, et al. MicroRNA-200a suppresses prostate cancer progression through BRD4/AR signaling pathway. Cancer Med. 2019;8(4):1474–85. https://doi.org/10.1002/cam4.2029
55. Williams LV, Veliceasa D, Vinokour E, Volpert OV. miR-200b Inhibits Prostate Cancer EMT, Growth and Metastasis. PLoS One. 2013;8(12):e83991. https://doi.org/10.1371/journal.pone.0083991
56. Shi R, Xiao H, Yang T, Chang L, Tian Y, Wu B, et al. Effects of miR-200c on the migration and invasion abilities of human prostate cancer Du145 cells and the corresponding mechanism. Front Med. 2014;8(4):456–63. https://doi.org/10.1007/s11684-014-0353-z
57. Wa Q, Huang S, Pan J, Tang Y, He S, Fu X, et al. miR-204-5p Represses Bone Metastasis via Inactivating NF-κB Signaling in Prostate Cancer. Mol Ther Nucleic Acids. 2019;18:567–79. https://doi.org/10.1016/j.omtn.2019.09.008
58. Lin Y-C, Lin J-F, Tsai T-F, Chou K-Y, Chen H-E, Hwang TI-S. Tumor suppressor miRNA-204-5p promotes apoptosis by targeting BCL2 in prostate cancer cells. Asian J Surg. 2017;40(5):396–406. https://doi.org/10.1016/j.asjsur.2016.07.001
59. Wa Q, Zou C, Lin Z, Huang S, Peng X, Yang C, et al. Ectopic Expression of miR-532-3p Suppresses Bone Metastasis of Prostate Cancer Cells via Inactivating NF-κB Signaling. Mol Ther Oncolytics. 2020;17:267–77. https://doi.org/10.1016/j.omto.2020.03.024
60. Moghbeli M, Zangouei AS, Nasrpour Navaii Z, Taghehchian N. Molecular mechanisms of the microRNA-132 during tumor progressions. Cancer Cell Int. 2021;21:439. https://doi.org/10.1186/s12935-021-02149-7
61. Chakravarthi BVSK, Chandrashekar DS, Agarwal S, Balasubramanya SAH, Pathi SS, Goswami MT, et al. miR-34a Regulates Expression of the Stathmin-1 Oncoprotein and Prostate Cancer Progression. Mol Cancer Res. 2018;16(7):1125–37. https://doi.org/10.1158/1541-7786.MCR-17-0230
62. Fang L, Sun B, Huang L, Yuan H, Zhang S, Chen J, et al. Potent Inhibition of miR-34b on Migration and Invasion in Metastatic Prostate Cancer Cells by Regulating the TGF-β Pathway. Int J Mol Sci. 2017;18(12):2762. https://doi.org/10.3390/ijms18122762
63. Wa Q, Li L, Lin H, Peng X, Ren D, Huang Y, et al. Downregulation of miR-19a-3p promotes invasion, migration and bone metastasis via activating TGF-β signaling in prostate cancer. Oncol Rep. 2018;39(1):81–90. https://doi.org/10.3892/or.2017.6096

64. Liu C, Kelnar K, Liu B, Chen X, Calhoun-Davis T, Li H, et al. The microRNA miR-34a inhibits prostate cancer stem cells and metastasis by directly repressing CD44. Nat Med. 2011;17(2):211–5. https://doi.org/10.1038/nm.2284
65. Liang J, Li Y, Daniels G, Sfanos K, De Marzo A, Wei J, et al. LEF1 Targeting EMT in Prostate Cancer Invasion is Regulated by miR-34a. Mol Cancer Res. 2015;13(4):681–8. https://doi.org/10.1158/1541-7786.MCR-14-0503
66. Gaur S, Wen Y, Song JH, Parikh NU, Mangala LS, Blessing AM, et al. Chitosan nanoparticle-mediated delivery of miRNA-34a decreases prostate tumor growth in the bone and its expression induces non-canonical autophagy. Oncotarget. 2015;6(30):29161–77. https://doi.org/10.18632/oncotarget.4971
67. Guo W, Ren D, Chen X, Tu X, Huang S, Wang M, et al. HEF1 promotes epithelial mesenchymal transition and bone invasion in prostate cancer under the regulation of microRNA-145. J Cell Biochem. 2013;114(7):1606–15. https://doi.org/10.1002/jcb.24502
68. Huang S, Guo W, Tang Y, Ren D, Zou X, Peng X. miR-143 and miR-145 inhibit stem cell characteristics of PC-3 prostate cancer cells. Oncology Reports. 2012;28(5):1831–7. https://doi.org/10.3892/or.2012.2015
69. Peng X, Guo W, Liu T, Wang X, Tu X, Xiong D, et al. Identification of miRs-143 and -145 that Is Associated with Bone Metastasis of Prostate Cancer and Involved in the Regulation of EMT. PLoS One. 2011;6(5):e20341. https://doi.org/10.1371/journal.pone.0020341
70. Rajabi F, Liu-Bordes W-Y, Pinskaya M, Dominika F, Kratassiouk G, Pinna G, et al. CPEB1 orchestrates a fine-tuning of miR-145-5p tumor-suppressive activity on TWIST1 translation in prostate cancer cells. Oncotarget. 2020;11(45):4155–68. https://doi.org/10.18632/oncotarget.27806
71. Sun J, Deng L, Gong Y. MiR-145-5p Inhibits the Invasion of Prostate Cancer and Induces Apoptosis by Inhibiting WIP1. J Oncol. 2021;2021:4412705. https://doi.org/10.1155/2021/4412705
72. Sengupta D, Deb M, Patra SK. Antagonistic activities of miR-148a and DNMT1: Ectopic expression of miR-148a impairs DNMT1 mRNA and dwindle cell proliferation and survival. Gene. 2018;660:68–79. https://doi.org/10.1016/j.gene.2018.03.075
73. Rana S, Valbuena GN, Curry E, Bevan CL, Keun HC. MicroRNAs as biomarkers for prostate cancer prognosis: a systematic review and a systematic reanalysis of public data. Br J Cancer. 2022;1–12. https://doi.org/10.1038/s41416-021-01677-3
74. Ramalho-Carvalho J, Gonçalves CS, Graça I, Bidarra D, Pereira-Silva E, Salta S, et al. A multiplatform approach identifies miR-152-3p as a common epigenetically regulated onco-suppressor in prostate cancer targeting TMEM97. Clin Epigenetics. 2018;10:40. https://doi.org/10.1186/s13148-018-0475-2
75. Wu J, Ji A, Wang X, Zhu Y, Yu Y, Lin Y, et al. MicroRNA-195-5p, a new regulator of Fra-1, suppresses the migration and invasion of prostate cancer cells. J Transl Med. 2015;13:289. https://doi.org/10.1186/s12967-015-0650-6
76. Yaman Agaoglu F, Kovancilar M, Dizdar Y, Darendeliler E, Holdenrieder S, Dalay N, et al. Investigation of miR-21, miR-141, and miR-221 in blood circulation of patients with prostate cancer. Tumor Biol. 2011;32(3):583–8. https://doi.org/10.1007/s13277-011-0154-9
77. Sun T, Yang M, Chen S, Balk S, Pomerantz M, Hsieh C-L, et al. The Altered Expression of MiR-221/-222 and MiR-23b/-27b Is Associated With the Development of Human Castration Resistant Prostate Cancer. Prostate. 2012;72(10). https://doi.org/10.1002/pros.22456
78. Kiener M, Chen L, Krebs M, Grosjean J, Klima I, Kalogirou C, et al. miR-221-5p regulates proliferation and migration in human prostate cancer cells and reduces tumor growth in vivo. BMC Cancer. 2019;19:627. https://doi.org/10.1186/s12885-019-5819-6
79. Krebs M, Solimando AG, Kalogirou C, Marquardt A, Frank T, Sokolakis I, et al. miR-221-3p Regulates VEGFR2 Expression in High-Risk Prostate Cancer and Represents an Escape Mechanism from Sunitinib In Vitro. J Clin Med. 2020;9(3):670. https://doi.org/10.3390/jcm9030670
80. Gan B-L, Zhang L-J, Gao L, Ma F-C, He R-Q, Chen G, et al. Downregulation of miR-224-5p in prostate cancer and its relevant molecular mechanism via TCGA, GEO database and in silico analyses. Oncol Rep. 2018;40(6):3171–88. https://doi.org/10.3892/or.2018.6766
81. Mavridis K, Stravodimos K, Scorilas A. Downregulation and Prognostic Performance of MicroRNA 224 Expression in Prostate Cancer. Clin Chem. 2013;59(1):261–9. https://doi.org/10.1373/clinchem.2012.191502

82. Xiong S, Lin T, Xu K, Dong W, Ling X, Jiang F, et al. MicroRNA-335 Acts as a Candidate Tumor Suppressor in Prostate Cancer. Pathol Oncol Res. 2013;19(3):529–37. https://doi.org/10.1007/s12253-013-9613-5
83. Zhang P, Yang X, Wang L, Zhang D, Luo Q, Wang B. Overexpressing miR-335 inhibits DU145 cell proliferation by targeting early growth response 3 in prostate cancer. Int J Oncol. 2019;54(6):1981–94. https://doi.org/10.3892/ijo.2019.4778
84. Fu Q, Liu X, Liu Y, Yang J, Lv G, Dong S. MicroRNA-335 and -543 suppress bone metastasis in prostate cancer via targeting endothelial nitric oxide synthase. Int J Mol Med. 2015;36(5):1417–25. https://doi.org/10.3892/ijmm.2015.2355
85. Tang Y, Wu B, Huang S, Peng X, Li X, Huang X, et al. Downregulation of miR-505-3p predicts poor bone metastasis-free survival in prostate cancer. Oncol Rep. 2019;41(1):57–66. https://doi.org/10.3892/or.2018.6826
86. Du Y, Zhu H, Liu X, Wang L, Ning J, Xiao C. MiR-543 Promotes Proliferation and Epithelial-Mesenchymal Transition in Prostate Cancer via Targeting RKIP. CPB. 2017;41(3):1135–46. https://doi.org/10.1159/000464120
87. Wang D, Lu G, Shao Y, Xu D. microRNA-802 inhibits epithelial-mesenchymal transition through targeting flotillin-2 in human prostate cancer. Biosci Rep. 2017;37(2):BSR20160521. https://doi.org/10.1042/BSR20160521
88. Gao T, Zou M, Shen T, Duan S. Dysfunction of miR-802 in tumors. J Clin Lab Anal. 2021;35(11):e23989. https://doi.org/10.1002/jcla.23989
89. Li H, Li Y, Tian D, Zhang J, Duan S. miR-940 is a new biomarker with tumor diagnostic and prognostic value. Mol Ther Nucleic Acids. 2021;25:53–66. https://doi.org/10.1016/j.omtn.2021.05.003
90. Rajendiran S, Parwani AV, Hare RJ, Dasgupta S, Roby RK, Vishwanatha JK. MicroRNA-940 suppresses prostate cancer migration and invasion by regulating MIEN1. Mol Cancer. 2014;13:250. https://doi.org/10.1186/1476-4598-13-250
91. Rajendiran S, Maji S, Haddad A, Lotan Y, Nandy RR, Vishwanatha JK, et al. MicroRNA-940 as a Potential Serum Biomarker for Prostate Cancer. Front Oncol. 2021;11:628094. https://doi.org/10.3389/fonc.2021.628094
92. Bucay N, Bhagirath D, Sekhon K, Yang T, Fukuhara S, Majid S, et al. A novel microRNA regulator of prostate cancer epithelial-mesenchymal transition. Cell Death Differ. 2017;24(7):1263–74. https://doi.org/10.1038/cdd.2017.69
93. Duffy MJ. Biomarkers for prostate cancer: prostate-specific antigen and beyond. Clinical Chemistry and Laboratory Medicine (CCLM). 2020;58(3):326–39. https://doi.org/10.1515/cclm-2019-0693
94. Cucchiara V, Cooperberg MR, Dall'Era M, Lin DW, Montorsi F, Schalken JA, et al. Genomic Markers in Prostate Cancer Decision Making. European Urology. 2018;73(4):572–82. https://doi.org/10.1016/j.eururo.2017.10.036
95. Eggener SE, Rumble RB, Armstrong AJ, Morgan TM, Crispino T, Cornford P, et al. Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline. JCO. 2020;38(13):1474–94. https://doi.org/10.1200/JCO.19.02768
96. Carneiro A, Kayano PP, Gomes Barbosa ÁR, Wroclawski ML, Ko Chen C, Cavlini GC, et al. Are localized prostate cancer biomarkers useful in the clinical practice? Tumour Biol. 2018;40(9):1010428318799255. https://doi.org/10.1177/1010428318799255
97. Ladjevardi S, Berglund A, Varenhorst E, Bratt O, Widmark A, Sandblom G. Treatment with curative intent and survival in men with high-risk prostate cancer. A population-based study of 11 380 men with serum PSA level 20-100 ng/mL. BJU International. 2013;111(3):381–8. https://doi.org/10.1111/j.1464-410X.2012.11320.x
98. Izumi K, Lin W-J, Miyamoto H, Huang C-K, Maolake A, Kitagawa Y, et al. Outcomes and predictive factors of prostate cancer patients with extremely high prostate-specific antigen level. J Cancer Res Clin Oncol. 2014;140(8):1413–9. https://doi.org/10.1007/s00432-014-1681-8
99. Karnes RJ, Choeurng V, Ross AE, Schaeffer EM, Klein EA, Freedland SJ, et al. Validation of a Genomic Risk Classifier to Predict Prostate Cancer-specific Mortality in Men with Adverse Pathologic Features. Eur Urol. 2018;73(2):168–75. https://doi.org/10.1016/j.eururo.2017.03.036

100. Moreira Leite KR, Camara-Lopes LH, Dall'Oglio MF, Cury J, Antunes AA, Sañudo A, Srougi M. Upgrading the Gleason score in extended prostate biopsy: implications for treatment choice. Int J Radiat Oncol Biol Phys. 2009;73(2):353–6. https://doi.org/10.1016/j.ijrobp.2008.04.039
101. Fabris L, Ceder Y, Chinnaiyan AM, Jenster GW, Sorensen KD, Tomlins S, et al. The Potential of MicroRNAs as Prostate Cancer Biomarkers. Eur Urol. 2016;70(2):312–22. https://doi.org/10.1016/j.eururo.2015.12.054
102. Vanacore D, Boccellino M, Rossetti S, Cavaliere C, D'Aniello C, Di Franco R, et al. Micrornas in prostate cancer: an overview. Oncotarget. 2017;8(30):50240–51. https://doi.org/10.18632/oncotarget.16933
103. Moltzahn F, Olshen AB, Baehner L, Peek A, Fong L, Stöppler H, et al. Microfluidic based multiplex qRT-PCR identifies diagnostic and prognostic microRNA signatures in sera of prostate cancer patients. Cancer Res. 2011;71(2):550–60. https://doi.org/10.1158/0008-5472.CAN-10-1229
104. Bryant RJ, Pawlowski T, Catto JWF, Marsden G, Vessella RL, Rhees B, et al. Changes in circulating microRNA levels associated with prostate cancer. Br J Cancer. 2012;106(4):768–74. https://doi.org/10.1038/bjc.2011.595
105. Chen Z-H, Zhang G-L, Li H-R, Luo J-D, Li Z-X, Chen G-M, et al. A panel of five circulating microRNAs as potential biomarkers for prostate cancer. The Prostate. 2012;72(13):1443–52. https://doi.org/10.1002/pros.22495
106. Kachakova D, Mitkova A, Popov E, Popov I, Vlahova A, Dikov T, et al. Combinations of Serum Prostate-Specific Antigen and Plasma Expression Levels of let-7c, miR-30c, miR-141, and miR-375 as Potential Better Diagnostic Biomarkers for Prostate Cancer. DNA Cell Biol. 2015;34(3):189–200. https://doi.org/10.1089/dna.2014.2663
107. Tong AW, Fulgham P, Jay C, Chen P, Khalil I, Liu S, et al. MicroRNA profile analysis of human prostate cancers. Cancer Gene Ther. 2009;16(3):206–16. https://doi.org/10.1038/cgt.2008.77
108. Schaefer A, Jung M, Mollenkopf H-J, Wagner I, Stephan C, Jentzmik F, et al. Diagnostic and prognostic implications of microRNA profiling in prostate carcinoma. Int J Cancer. 2010;126(5):1166–76.
109. Haflidadóttir BS, Larne O, Martin M, Persson M, Edsjö A, Bjartell A, et al. Upregulation of miR-96 Enhances Cellular Proliferation of Prostate Cancer Cells through FOXO1. PLoS One. 2013;8(8):e72400. https://doi.org/10.1371/journal.pone.0072400
110. Mortensen MM, Høyer S, Ørntoft TF, Sørensen KD, Dyrskjøt L, Borre M. High miR-449b expression in prostate cancer is associated with biochemical recurrence after radical prostatectomy. BMC Cancer. 2014;14:859. https://doi.org/10.1186/1471-2407-14-859
111. Leite KRM, Reis ST, Viana N, Morais DR, Moura CM, Silva IA, et al. Controlling RECK miR21 Promotes Tumor Cell Invasion and Is Related to Biochemical Recurrence in Prostate Cancer. J Cancer. 2015;6(3):292–301. https://doi.org/10.7150/jca.11038
112. Melbø-Jørgensen C, Ness N, Andersen S, Valkov A, Dønnem T, Al-Saad S, et al. Stromal Expression of MiR-21 Predicts Biochemical Failure in Prostate Cancer Patients with Gleason Score 6. PLoS One. 2014;9(11):e113039. https://doi.org/10.1371/journal.pone.0113039
113. Selcuklu SD, Donoghue MTA, Spillane C. miR-21 as a key regulator of oncogenic processes. Biochemical Society Transactions. 2009;37(4):918–25. https://doi.org/10.1042/BST0370918
114. Bell EH, Kirste S, Fleming JL, Stegmaier P, Drendel V, Mo X, et al. A Novel MiRNA-Based Predictive Model for Biochemical Failure Following Post-Prostatectomy Salvage Radiation Therapy. PLoS One. 2015;10(3):e0118745. https://doi.org/10.1371/journal.pone.0118745
115. Larne O, Martens-Uzunova E, Hagman Z, Edsjö A, Lippolis G, den Berg MSV, et al. miQ-A novel microRNA based diagnostic and prognostic tool for prostate cancer. Int J Cancer. 2013;132(12):2867–75. https://doi.org/10.1002/ijc.27973
116. Östling P, Leivonen S-K, Aakula A, Kohonen P, Mäkelä R, Hagman Z, et al. Systematic analysis of microRNAs targeting the androgen receptor in prostate cancer cells. Cancer Res. 2011;71(5):1956–67. https://doi.org/10.1158/0008-5472.CAN-10-2421
117. ChunJiao S, Huan C, ChaoYang X, GuoMei R. Uncovering the Roles of miRNAs and Their Relationship with Androgen Receptor in Prostate Cancer. IUBMB Life. 2014;66(6):379–86. https://doi.org/10.1002/iub.1281
118. Thieu W, Tilki D, de Vere White R, Evans CP. The role of MicroRNA in castration resistant prostate cancer. Urol Oncol. 2014;32(5):517–23. https://doi.org/10.1016/j.urolonc.2013.11.004

119. Shen J, Hruby GW, McKiernan JM, Gurvich I, Lipsky MJ, Benson MC, et al. Dysregulation of Circulating MicroRNAs and Prediction of Aggressive Prostate Cancer. Prostate. 2012;72(13):1469–77. https://doi.org/10.1002/pros.22499
120. Josson S, Sung S-Y, Lao K, Chung LWK, Johnstone PAS. Radiation modulation of microRNA in prostate cancer cell lines. Prostate. 2008;68(15):1599–606. https://doi.org/10.1002/pros.20827
121. Li B, Shi X-B, Nori D, Chao CKS, Chen AM, Valicenti R, et al. Down-regulation of microRNA 106b is involved in p21-mediated cell cycle arrest in response to radiation in prostate cancer cells. The Prostate. 2011;71(6):567–74. https://doi.org/10.1002/pros.21272
122. Hatano K, Kumar B, Zhang Y, Coulter JB, Hedayati M, Mears B, et al. A functional screen identifies miRNAs that inhibit DNA repair and sensitize prostate cancer cells to ionizing radiation. Nucleic Acids Res. 2015;43(8):4075–86. https://doi.org/10.1093/nar/gkv273
123. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. N Engl J Med. 2004;351(15):1502–12. http://dx.doi.org/10.1056/NEJMoa040720.
124. Zhang H-L, Yang L-F, Zhu Y, Yao X-D, Zhang S-L, Dai B, et al. Serum miRNA-21: Elevated levels in patients with metastatic hormone-refractory prostate cancer and potential predictive factor for the efficacy of docetaxel-based chemotherapy. Prostate. 2011;71(3):326–31. https://doi.org/10.1002/pros.21246
125. Lin H-M, Castillo L, Mahon KL, Chiam K, Lee BY, Nguyen Q, et al. Circulating microRNAs are associated with docetaxel chemotherapy outcome in castration-resistant prostate cancer. Br J Cancer. 2014;110(10):2462–71. https://doi.org/10.1038/bjc.2014.181
126. Kojima K, Fujita Y, Nozawa Y, Deguchi T, Ito M. MiR-34a attenuates paclitaxel-resistance of hormone-refractory prostate cancer PC3 cells through direct and indirect mechanisms. The Prostate. 2010;70(14):1501–12. https://doi.org/10.1002/pros.21185
127. Konoshenko M, Laktionov P. The miRNAs involved in prostate cancer chemotherapy response as chemoresistance and chemosensitivity predictors. Andrology. 2022;10(1):51–71. https://doi.org/10.1111/andr.13086
128. Culig Z. miRNA as Regulators of Prostate Carcinogenesis and Endocrine and Chemoresistance. Curr Cancer Drug Targets. 2021;21(4):283–8. https://doi.org/10.2174/1568009620666210108103134
129. Wu Y, Hu L, Qin Z, Wang X. MicroRNA302-a upregulation mediates chemo-resistance in prostate cancer cells. Mol Med Rep. 2019;19(5):4433–40.
130. Borghesi M, Ahmed H, Nam R, Schaeffer E, Schiavina R, Taneja S, et al. Complications After Systematic, Random, and Image-guided Prostate Biopsy. Eur Urol. 2017;71(3):353–65. https://doi.org/10.1016/j.eururo.2016.08.004
131. Gross MD, Alshak MN, Shoag JE, Laviana AA, Gorin MA, Sedrakyan A, et al. Healthcare Costs of Post-Prostate Biopsy Sepsis. Urology. 2019;133:11–5. https://doi.org/10.1016/j.urology.2019.06.011
132. Mowatt G, Scotland G, Boachie C, Cruickshank M, Ford JA, Fraser C, et al. The diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy: a systematic review and economic evaluation. Health Technol Assess. 2013;17(20):vii-xix, 1-281. https://doi.org/10.3310/hta17200
133. Minervini A, Vittori G, Siena G, Carini M. Morbidity and psychological impact of prostate biopsy: the future calls for a change. Asian J Androl. 2014;16(3):415–7. https://doi.org/10.4103/1008-682X.126388
134. Conte R, Valentino A, Di Cristo F, Peluso G, Cerruti P, Di Salle A, et al. Cationic Polymer Nanoparticles-Mediated Delivery of miR-124 Impairs Tumorigenicity of Prostate Cancer Cells. Int J Mol Sci. 2020;21(3):869. https://doi.org/10.3390/ijms21030869
135. Kim K, Kim HH, Lee C-H, Kim S, Cheon GJ, Kang KW, et al. Therapeutic efficacy of modified anti-miR21 in metastatic prostate cancer. Biochemical and Biophysical Research Communications. 2020;529(3):707–13. https://doi.org/10.1016/j.bbrc.2020.05.215
136. Takahashi R-U, Prieto-Vila M, Kohama I, Ochiya T. Development of miRNA-based therapeutic approaches for cancer patients. Cancer Sci. 2019;110(4):1140–7. https://doi.org/10.1111/cas.13965

137. Kunz M, Brandl M, Bhattacharya A, Nobereit-Siegel L, Ewe A, Weirauch U, et al. Nanoparticle-complexed antimiRs for inhibiting tumor growth and metastasis in prostate carcinoma and melanoma. J Nanobiotechnology. 2020;18:173. https://doi.org/10.1186/s12951-020-00728-w
138. Ma D, Liu H, Zhao P, Ye L, Zou H, Zhao X, et al. Programing Assembling/Releasing Multifunctional miRNA Nanomedicine to Treat Prostate Cancer. ACS Appl Mater Interfaces. 2020;12(8):9032–40. https://doi.org/10.1021/acsami.9b21707
139. Nagesh PKB, Chowdhury P, Hatami E, Boya VKN, Kashyap VK, Khan S, et al. miRNA-205 Nanoformulation Sensitizes Prostate Cancer Cells to Chemotherapy. Cancers (Basel). 2018;10(9):289. https://doi.org/10.3390/cancers10090289
140. Farina NH, Zingiryan A, Vrolijk MA, Perrapato SD, Ades S, Stein GS, et al. Nanoparticle-based targeted cancer strategies for non-invasive prostate cancer intervention. J Cell Physiol. 2018;233(9):6408–17. https://doi.org/10.1002/jcp.26593
141. Hong DS, Kang Y-K, Borad M, Sachdev J, Ejadi S, Lim HY, et al. Phase 1 study of MRX34, a liposomal miR-34a mimic, in patients with advanced solid tumours. Br J Cancer. 2020;122(11):1630–7. https://doi.org/10.1038/s41416-020-0802-1
142. Bhan A, Soleimani M, Mandal SS. Long Noncoding RNA and Cancer: A New Paradigm. Cancer Res. 2017;77(15):3965–81. https://doi.org/10.1158/0008-5472.CAN-16-2634
143. Chan JJ, Tay Y. Noncoding RNA:RNA Regulatory Networks in Cancer. Int J Mol Sci. 2018;19(5):E1310. https://doi.org/10.3390/ijms19051310
144. Schmitz SU, Grote P, Herrmann BG. Mechanisms of long noncoding RNA function in development and disease. Cell Mol Life Sci. 2016;73(13):2491–509. https://doi.org/10.1007/s00018-016-2174-5
145. Huang G, Guo X, Yang H. Long noncoding RNA SNHG1 promotes human prostate cancer progression by sponging miR-383-5p. Anticancer Drugs. 2021;32(3):286–95. https://doi.org/10.1097/CAD.0000000000000916