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## Exosomal microRNAs as Potential Biomarkers in Castration-resistant Prostate Cancer.

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*Published in:*  
European Urology

*DOI:*  
[10.1016/j.eururo.2014.08.067](https://doi.org/10.1016/j.eururo.2014.08.067)

2015

[Link to publication](#)

*Citation for published version (APA):*  
Hafliðadóttir, B., & Ceder, Y. (2015). Exosomal microRNAs as Potential Biomarkers in Castration-resistant Prostate Cancer. *European Urology*, 67(1), 42-43. <https://doi.org/10.1016/j.eururo.2014.08.067>

*Total number of authors:*  
2

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1 **Exosomal microRNAs as potential biomarkers in Castration Resistant**  
2 **Prostate Cancer.**

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9 **3-5 keywords:** microRNA, exosome, CRPC, biomarker

10 **Word count:** 988

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19 **Refers to:** Huang X, Yuan T, Liang M, et al. Exosomal miR-1290 and miR-375 as prognostic  
20 markers in castration-resistant prostate cancer. European Urology (in press).

21 Castration-resistant prostate cancer (CRPC) develops as metastatic prostate cancer patients  
22 inevitably progress and become resistant to treatment targeting the androgen signalling axis; it  
23 represents the final stage of the disease with a median survival of less than two years. Although  
24 CRPC remains incurable, a number of treatment alternatives that gives modest prolongation of life  
25 have been developed and FDA approved during the last few years, *e.g.* selective adrenal inhibitors,  
26 androgen receptor signalling inhibitors, novel immune compounds, and less toxic radio nucleotides.  
27 The progression towards more personalised treatment strategies is however hampered by the lack of  
28 easily implemented reliable biomarkers predicting response to therapy and survival. In this month's  
29 issue of *European Urology*, Huang *et al.*, attempts to address this issue [1]. They have investigated  
30 the prognostic potential of microRNAs (miRNAs) within exosomes in circulation and propose that  
31 two miRNAs, miR-375 and miR-1290, can serve as a prognostic biomarker in CRPC.

32

33 The miRNAs identified here are derived from exosomes in the blood circulation; extensive attention  
34 is now being paid to these vesicles as a source of biomarkers as their content resembles that of the  
35 cell of origin. In 2008, Skog *et al.* showed the miRNA content of extracellular vesicles to be  
36 reflective of the miRNA expression profile of the cells they originate from [5], however, it should  
37 be noted that the miRNA content of the exosomes is not an uncorrupted sampling of the contents in  
38 the parental cells. When investigating the content of the plasma derived exosomes (or extracellular  
39 vesicle) Huang *et al.* found mature miRNAs to be the most common RNA species [1]. This is in  
40 agreement with earlier sequencing of the RNA content in prostatic tissues that also identified  
41 miRNA as the most abundant class, constituting 95% of the RNA pool [2]. The miRNAs are not  
42 only the most abundant, but also technically suitable as biomarkers, as they can be easily and  
43 sensitively detected in small samples sizes by qRT-PCR and are stable in serum and plasma and  
44 resistant to extended storage, freeze-thawing and extreme pH [3]. Over the last decade, miRNAs  
45 have been found to be deregulated in prostate cancer and emerged as key players in cancer

46 progression and many studies highlight their diagnostic and prognostic potential [4]. Nevertheless,  
47 the current study does not confirm that it is the expression of the individual miRNAs that are  
48 changed; it could also be the exosomal content in circulation or the RNA content of the exosomes.  
49 As this also would be of great interest, it would have been informative to combine the evaluation of  
50 individual miRNAs with an evaluation of the amount of extracellular vesicles and their RNA  
51 content. The choice of reference genes is as important as the target genes in these studies, in the  
52 discussed study 192 plasma samples are investigated to identify the endogenous reference control  
53 including men, women, healthy and other types of cancer as well as 23 cases in the screening  
54 cohort. One of the reference genes, miR-30e, have been reported to be highly expressed in blood  
55 cells, particularly in monocytes [6] this could indicate that a difference in exosomal content is  
56 emphasised.

57

58 The first report of miRNAs as potential non-invasive diagnostic markers in a prostate cancer setting  
59 came in 2008. Mitchell *et al.* compared a panel of miRNAs in serum from healthy men to men with  
60 advanced prostate cancer and found that miR-141 was elevated in the cancer samples [7]. Giving  
61 the heterogeneity of prostate cancer it is not surprising that although many miRNAs have since been  
62 implicated as diagnostic and prognostic makers, no single miRNA has been consistently validated  
63 or implemented as a biomarker in clinical management of prostate cancer. In line with this, Huang  
64 *et al.* show that the combination of miR-375 and miR-1290 gives increased significance in  
65 prediction of survival compared to individually. The patients with high levels of both miR-375 and  
66 miR-1290 have significantly higher mortality rate than the patients with low levels of the two  
67 miRNAs at the 20 month follow up. There is also a significant difference in the median overall  
68 survival of patients with high levels of miR-375/1290 compared to the patients with low levels.  
69 Incorporation of miR-1290/-375 into a clinical prognostic factors-based model based on PSA and  
70 ADT failure time, also significantly improved the predictive performance. It would have been very

71 interesting to have a comparison to CellSearch for the exosomal miRNAs as CellSearch is currently  
72 the only FDA approved prognostic biomarker for CRPC. It would also make it easier to compare  
73 with other similar studies *e.g.* a recent study by Danila *al.* that found a 5-gene panel measured in  
74 blood samples from 97 metastatic CRPC patients to be prognostic predictor for survival,  
75 comparable with the CellSearch system. Further, if combining the gene panel and CellSearch the  
76 prognostic powers were enhanced compared to CellSearch alone [8].

77

78 It is evident that CRPC is a heterogeneous disease and given the complexity of the AR signalling  
79 cascade, the idea of a more complex panel of marker is appealing. Investigation if the inclusion of  
80 several miRNAs would give more representative information on the patient status and how much  
81 this could be improved is possible in the Huang *et al.* data set as the data of 375 known miRNAs  
82 and 57 putative miRNAs is available. For example, one of the predicted miRNAs on chromosome  
83 12 seems to have excellent potential. It is however encouraging that one of the miRNAs identified  
84 in this paper, miR-375, has been described previously in several independent studies to be elevated  
85 in metastatic CRPC serum as the authors discuss. Two cohorts are used in this study, a screening  
86 cohort of 23 individuals and a validation cohort constituting 100 men. Hopefully, there will be  
87 future validation of presented biomarkers in larger independent cohorts to establish their reliability  
88 and potential clinical applicability. To conclude, the current paper by Huang *et al.* reinforces the  
89 notion that novel non-invasive prognostic methods for patients with CRPC will soon be a reality.

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## 91 **References**

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120 **Conflict of interest:** The authors have nothing to disclose.