



LUND UNIVERSITY

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

Haflidadottir, Benedikta; Ceder, Yvonne

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):

Haflidadottir, 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

General rights

Unless other specific re-use rights are stated the following general rights apply:

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

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

3 Benedikta S. Haflidadóttir¹ and Yvonne Ceder².

4 ¹Institute of Biosciences and Medical Technology, University of Tampere and Tampere University
5 Hospital, Tampere, Finland.

6 ²Department of Laboratory Medicine, Lund, Division of Translational Cancer Research, Lund
7 University, Lund, Sweden.

8

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

10 **Word count:** 988

11 **Corresponding author:**

12 Dr. Yvonne Ceder

13 Department of Laboratory Medicine, Lund,

14 Division of Translational Cancer Research,

15 Medicon Village, Building 404:A3

16 223 81 Lund, Sweden

17 Email: Yvonne.Ceder@med.lu.se

18 Phone: +46 46 2226452

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.

90

91 **References**

- 92 [1] Huang X, Yuan T, Liang M, et al. Exosomal miR-1290 and miR-375 as prognostic markers in
93 castration-resistant prostate cancer. *European Urology* (in press).
- 94 [2] Martens-Uzunova ES, Jalava SE, Dits NF, al. Diagnostic and prognostic signatures from the
95 small non-coding RNA transcriptome in prostate cancer. *Oncogene* 2012; 31: 978–991.

- 96 [3] Sita-Lumsden A, Dart DA, Waxman J, and Bevan CL. Circulating microRNAs as potential new
97 biomarkers for prostate cancer. *Br. J. Cancer* 2013; 108:1925–1930.
- 98 [4] Fang Y-X, and Gao W-Q. Roles of microRNAs during prostatic tumorigenesis and tumor
99 progression. *Oncogene* 2014; 33: 135–147.
- 100 [5] Skog J, Würdinger T, van Rijn, S, et al. Glioblastoma microvesicles transport RNA and proteins
101 that promote tumour growth and provide diagnostic biomarkers. *Nat. Cell Biol.* 2008; 10: 1470–
102 1476.
- 103 [6] Pritchard CC, Kroh E, Wood B, et al. Blood cell origin of circulating microRNAs: A cautionary
104 note for cancer biomarker studies. *Cancer Prev. Res.* 2012; 5: 492–497.
- 105 [7] Mitchell PS, Parkin RK, Kroh EM, et al. Circulating microRNAs as stable blood-based markers
106 for cancer detection. *Proc. Natl. Acad. Sci. U. S. A.* 2008; 105: 10513–10518.
- 107 [8] Danila DC, Anand A, Schultz N et al. Analytic and clinical validation of a prostate cancer-
108 enhanced messenger RNA detection assay in whole blood as a prognostic biomarker for survival.
109 *Eur. Urol.* 2014; 65: 1191–1197.

110

111

112

113

114

115

116

117

118

119

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