The diagnostic potential of tumor derived extracellular vesicles (tdEVs) in plasma and urine of prostate cancer patients and healthy volunteers: pilot study.

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Determination of the number of tdEVs in plasma and urine in PCa patients at different stages, together with appropriate controls. This will be determined by the use of different EV enumeration and molecular techniques. For comparison, some sample...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Observational invasive

Summary

ID

NL-OMON46711

Source
ToetsingOnline

Brief title
The diagnostic potential of tumor derived extracellular vesicles.

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Prostate cancer - Prostate carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: NWO,Exosomics,IZON Science,Merus,Universiteit van Twente,VyCAP

Intervention

Keyword: diagnosis, extracellular vesicles, prostate cancer

Outcome measures

Primary outcome

The main study parameter is the number of tdEVs, the ctDNA, and the unique mRNA reads in plasma and urine from PCa patients, measured once without follow-up for all participants except the prostatectomy patients where it will be measured at most three times (confirmation of elevated PSA, before and after prostatectomy).

Secondary outcome

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Study description

Background summary

Prostate cancer (PCa) is the second most frequently diagnosed cancer and the sixth cause of cancer-related death in men worldwide [1]. Prognosis and monitoring of therapy efficacy in metastatic castrate resistant prostate cancer (PCa) is possible using circulating tumor cells (CTCs) in whole blood [1-3]. In castration resistant PCa patients (CRPC) the median concentration is 5 CTC*s/ 7.5 mL whole blood [2]. This low number results in a large uncertainty on the actual concentration of CTCs, which in turn limits the application of CTCs in clinical practice. To detect more CTCs one would either require substantially larger blood samples, or the adjustment of the CTC definition to also include CTC derived particles [4]. A larger blood volume is undesirable due to the burden for the patient. Large (2-4 µm) tumor derived extracellular vesicles (tdEVs) are equally prognostic to CTC, with a 30-fold higher concentration [5]. This result is remarkable because these tdEVs were measured in the cell fraction (red blood cell + buffy coat), while we expect to find the majority in blood plasma. Furthermore, we also expect to find tdEVs in urine. At present,

the concentration of tdEVs in plasma and urine are unknown.
Furthermore, the presence of at least one CTC/30 mL blood was prognostic for reduced survival in early stage breast and colorectal cancer [6, 7]. A low number of CTC*s were found in locally advanced PCa patients, but not evaluated for prognostic value [10]. Because the number of CTC*s correlates to disease stage, and tdEVs are more numerous, we expect to find tdEVs in earlier stage PCa patients, albeit at a lower concentration than in mCRPC patients. Thus, the concentration of tdEVs might be a prognostic indicator for all stages of PCa.
A radical prostatectomy is expected to greatly reduce the number of tdEVs, and thus is expected to prove that the detected tdEVs are prostate specific.
The composition of the selected population is aimed at a first determination of the number of tdEVs in plasma and urine in PCa patients at different stages, together with appropriate controls.

1. de Bono, J.S., et al., Circulating Tumor Cells Predict Survival Benefit from Treatment in Metastatic Castration-Resistant Prostate Cancer. Clinical Cancer Research, 2008. 14(19): p. 6302-6309.
2. Scher, H.I., et al., Circulating tumour cells as prognostic markers in progressive, castration-resistant prostate cancer: a reanalysis of IMMC38 trial data. Lancet Oncology, 2009. 10(3): p. 233-239.
3. Coumans, F.A., S.T. Ligthart, and L.W. Terstappen, Interpretation of changes in circulating tumor cell counts. Translational oncology, 2012. 5(6): p. 486.
4. Coumans, F.A., et al., Challenges in the Enumeration and Phenotyping of CTC. Clinical Cancer Research, 2012.
5. Coumans, F.A.W., et al., All circulating EpCAM+CK+CD45- objects predict overall survival in castration-resistant prostate cancer. Annals of Oncology, 2010. 21(9): p. 1851-1857.
6. Franken, B., et al., Circulating tumor cells, disease recurrence and survival in newly diagnosed breast cancer. Breast Cancer Research, 2012. 14(5): p. R133.
7. van Dalum, G., et al., Importance of circulating tumor cells in newly diagnosed colorectal cancer. International Journal of Oncology, 2015. 46(3): p. 1361-1368.
8. Cristofanilli, M., et al., Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med, 2004. 351(8): p. 781-91.
9. Cohen, S.J., et al., Prognostic significance of circulating tumor cells in patients with metastatic colorectal cancer. Annals of Oncology, 2009. 20(7): p. 1223-1229.
10. Thalgott, M., et al., Detection of circulating tumor cells in different stages of prostate cancer. Journal of cancer research and clinical oncology, 2013. 139(5): p. 755-763.

Study objective

Determination of the number of tdEVs in plasma and urine in PCa patients at different stages, together with appropriate controls. This will be determined by the use of different EV enumeration and molecular techniques. For

comparison, some sample will be analysed for circulating tumor DNA (ctDNA). The applied techniques include, but are not limited to, immunogold electron microscopy, scanning electron microscopy, flow cytometry, (superresolution) confocal microscopy, Raman microspectroscopy, long and short read mRNA sequencing, PCR (with mutation specific probes).

Study design

This is a human, ex-vivo pilot study without follow-up.

Study burden and risks

The burden is limited to approximately 18 mL of blood, and 40 mL of urine. Adverse events are not expected. Standard of care as stated by the AMC protocols will not be affected by the choice regarding participation in this study. The results of this study do not influence the clinical decision making for the optimal treatment modality. There are no direct benefits for patients participating in this study. The results of this study are important for future patients. In conclusion, we believe that the burden and risk associated with participation in this study are neglectable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Healthy volunteers (N=10):
Adult male not related to the Urology department <= 40 years old.
Informed consent signed.;Elevated PSA level (N=40):
Patients presenting with a PSA level >= 3.0 ng/mL.
Informed consent signed.;Before/after prostatectomy (N=10):
Patients with localized PCa after prostate biopsy, who are planned for radical prostatectomy.
Informed consent signed.;mCRPC (N=10):
Patients with histologically confirmed prostate cancer that is metastatic and progressing despite castrate levels of testosterone (<50 ng/mL).
Informed consent signed.

Exclusion criteria

Healthy volunteers:
Clinical signs of prostate diseases, no medical or surgical therapy for prostate disease.;Elevated PSA level:
Patients with a history or presence of other cancers, or non-prostate urological disorders.;Before/after prostatectomy:
None. ;mCRPC:
None.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-10-2018
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	26-06-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 28556
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL64623.018.18
OMON	NL-OMON28556