Detection of Prostate Cancer by an Electronic Nose: A Proof of Principle Study

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Abbreviations and Acronyms

BPH = benign prostatic hyperplasia

DRE = digital rectal examination

eNose = electronic nose

G/LC-MS = gas/liquid chromatography-mass spectrometry

LOOCV = leave-one-out cross-validation

NMR = nuclear magnetic resonance spectroscopy

PCa = prostate cancer

PSA = prostate specific antigen

TURP = transurethral resection of prostate

Purpose: We evaluate the ability of an electronic nose to discriminate prostate cancer from benign prostatic hyperplasia using urine headspace, potentially offering a clinically applicable noninvasive and rapid diagnostic method.

Materials and Methods: The ChemPro® 100-eNose was used to discriminate prostate cancer from benign prostatic hyperplasia using urine sample headspace. Its performance was tested with 50 patients with confirmed prostate cancer and 24 samples from 15 patients with benign prostatic hyperplasia (15 patients provided urine preoperatively and 9 patients provided samples 3 months postoperatively) scheduled to undergo robotic assisted laparoscopic radical prostatectomy or transurethral resection of prostate, respectively. The patients provided urine sample preoperatively and those with benign prostatic hyperplasia also provided samples 3 months postoperatively to be used as a pooled control sample population. A discrimination classifier was identified for eNose and subsequently, sensitivity and specificity values were determined. Leave-one-out cross-validation was performed.

Results: Using leave-one-out cross-validation the eNose reached a sensitivity of 78%, a specificity of 67% and AUC 0.77.

Conclusions: The electronic nose is capable of rapidly and noninvasively discriminating prostate cancer and benign prostatic hyperplasia using urine headspace in patients undergoing surgery.

Key Words: prostatic hyperplasia, electronic nose, prostatic neoplasms

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Study received ethical committee approval.

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PROSTATE cancer is the second most common cancer in males and one of the leading causes of cancer mortality.[1] The heterogeneity of PCa makes it difficult to diagnose and to predict tumor progression. Current cornerstones of the diagnosis, ie DRE and plasma PSA,[2] have limited sensitivity and specificity, although free PSA adds to the performance.[3] Histological examination of transrectal ultrasound guided biopsies leads to definitive diagnosis, but is associated with considerable costs, discomfort and risk of infectious complications.[4] In addition, a significant proportion of diagnosed cancers is low grade and will not cause symptoms or disease

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specific mortality. Therefore, aggressive treatment can lead to decreased quality of life without affecting the longevity of the patient.[5] Thus, there is a need for novel diagnostic tools.

The first report on the olfactory detection of cancer was a case study published in *The Lancet*.[6] Since then, experimental studies of the use of trained dogs in the detection of cancer have confirmed the preliminary findings.[7–9] Previous results of PCa detection were discouraging[10] until Cornu et al showed that trained dogs are able to detect PCa using urine with high sensitivity and specificity.[11] This finding sparked considerable attention.[12,13]

The concern with canine olfaction is the heterogeneity of the performance of the dogs between and within studies.[11,14] The eNose is a device that consists of a cluster of nonspecific sensors. When the device is exposed to the sample, it produces a profile or a smell print. eNoses are best suited for qualitative analysis of complex gaseous mixtures of molecules,[15] and are routinely used in food and agricultural quality control and in military applications.[16] eNoses have been studied in various medical applications, including the early detection of cancer,[15] especially from exhaled air.[17,18]

Exhaled air is a problematic sample material since it requires good cooperation and technique from the patient as well as immediate analysis, while urine is simple to attain and store and, therefore, more feasible in clinical practice. Urine has also been used in several metabolomics studies using G/LC-MS or NMR.[19] Preliminary data suggest that the detection of urological malignancies using urine headspace is possible.[20]

Recently we showed that the discrimination of PCa cells and cells from BPH is possible.[21] These results encouraged us to launch a prospective clinical study recruiting patients undergoing robotic assisted laparoscopic radical prostatectomy and symptomatic patients with BPH undergoing TURP. In this study we test the hypothesis that the eNose system is capable of discriminating patients with PCa from those with BPH using urine headspace. We also evaluate potential sources of diagnostic error such as prostate volume and tumor size.

MATERIALS AND METHODS

Patients and Samples

The study population was prospectively formed of consecutive patients referred to a urologist for operative treatment of PCa or BPH at Tampere University Hospital (Tampere, Finland) or Hatanpää City Hospital (Tampere, Finland) between March 2011 and November 2012. Inclusion criteria were operative treatment of PCa or BPH. Exclusion criteria were patient refusal, material insufficient for histopathology, known malignancy other than PCa, persistent urinary infection and urinary catheter in place. Patients were divided into cases and controls, as in patients with biopsy proven PCa scheduled to undergo robotic assisted laparoscopic radical prostatectomy (50) and PCa-free patients (15). The PCa-free group comprised patients with BPH scheduled to undergo TURP, having later confirmed benign histology. Of the patients with BPH 3 had previously had negative prostate biopsies.

The control group consisted of 15 patients who gave a urine sample preoperatively, and of these patients 9 provided another sample 3 months postoperatively, resulting in a total of 24 samples. As the measurement of postoperative prostate volume was not included in the study protocol, we reduced prostate volume 40% from the postoperative results. Subjects provided a standard morning urine sample before the operation and 3 months after the operation. No standardization of diet, hydration status or bladder time was conducted. The samples were stored at −70C until eNose analysis.

Written informed consent was acquired from all subjects. The study was approved by the ethical committee of Tampere University Hospital (code: R10066). The baseline clinical characteristics of the patients are provided in the table.

eNose and Measurement Chamber

The eNose used in this study is a commercially available model (ChemPro® 100, Environics Inc., Mikkeli, Finland) based on the ion mobility spectrometry principle. The device contains an ion mobility cell that consists of 8 electrode strips producing 2-channel output and a metal oxide based semiconductor cell. Together these sensors produce 18-channel measurement data. The sensors do not specify molecules but produce a characteristic smell print of the sample. Ambient air is used as carrier gas. The device is described in detail by Utriainen et al.[22] The device was connected to a Windows® based portable

Baseline clinical and pathological characteristics of study subjects

	Confirmed PCa Group	Control Group
Age:		
Mean	62	66
Median (range)	63.5 (49–73)	67 (53–72)
Total PSA:		
Mean	7	3
Median (range)	6.3 (2–18.2)	1.75 (0.2–9)
Prostate vol:		
Mean	36.7	48.6
Median (range)	33 (15–75)	40.3 (18.2–100)
PSA density (PSA/prostate vol):		
Mean	0.22	0.06
Median (range)	0.18 (0.04–0.69)	0.05 (0.02–0.2)
No. postop Gleason score:		
6	9	Not applicable
7	34	Not applicable
8	1	Not applicable
9	6	Not applicable
No. pT status (%):		
pT2	27 (50)	Not applicable
pT3	23 (50)	Not applicable
No. presence of Gleason 4 or greater (%)	41 (50)	Not applicable