This is the post print version of the article, which has been published in Gynecologic oncology . 2018, 151 (3), 519-524.https://doi.org/10.1016/j.ygyno.2018.09.016.

FAIMS analysis of urine gaseous headspace is capable of differentiating ovarian cancer

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Abstract

Aim: We hypothesized that field asymmetric waveform ion mobility spectrometry (FAIMS) as a novel artificial olfactory technology could differentiate urine of women with malignant ovarian tumors from controls and women with benign tumors, based on previous findings on the ability of canine olfactory system to "smell" cancer.

Patients and methods: Preoperative urine samples from 51 women with ovarian tumors, both benign and malignant, and from 18 women with genital prolapse, as controls, were collected. The samples were analyzed by FAIMS device. Data analysis was processed by quadratic data analysis (QDA) and linear discriminant analysis (LDA), and cross-validated using 10-fold cross-validation.

Results: Thirty-three women had malignant ovarian tumors, of which 18 were high-grade cancers. FAIMS distinguished controls from malignancies with the accuracy of 81.3 % (sensitivity 91.2 % and specificity 63.1 %), and benign tumors from malignancies with the accuracy of 77.3 % (sensitivity 91.5 % and specificity 51.4 %). Moreover, low grade tumors were also separated from high grade cancers and benign ovarian tumors with accuracies of 88.7 % (sensitivity 87.8 % and specificity 89.6 %) and 83.9 % (sensitivity 73.1 % and specificity 92.9 %), respectively.

Conclusions: This proof of concept-study indicates that the FAIMS from urine has potential to discriminate malignant ovarian tumors from no tumor-bearing controls and benign tumors.

Key words: FAIMS; ovarian neoplasm; ovarian cancer; VOC; Owlstone Lonestar; urine

Introduction

Annually 22,000 new ovarian cancer (OC) cases are diagnosed in the United States, and the survival rates are poor due to the majority of OCs being detected at advanced stages [1]. While early diagnosis and adequate cytoreductive surgery improve prognosis, there is a need for better preoperative diagnostic methods for ovarian tumors.

Various ultrasound-based models have been developed for preoperative evaluation of ovarian masses. These include e.g. Risk of Malignancy Index (RMI) [2] and logistic regression analyses and ultrasound-based rules from the International Ovarian Tumor Analysis (IOTA)-study. Although they have relatively high sensitivity and specificity, they are non-applicable for about 20 % of tumors [3].

Studies on urinary biomarkers for OC are relatively sparse. Urinary protein biomarkers, human epididymis protein 4 (HE4) and mesothelin, have shown to improve the early detection of serous OC compared to serum biomarkers [4]. Metabolite changes related to OC have been discovered as potential biomarkers [5,6], like N^1,N^{12}-diacetylspermine in polyamine analyses [7]. In addition, circulating microRNAs have been shown to be abundant in urine of OC patients [8].

Many diseases are linked to distinct odors caused by volatile organic compounds (VOCs) released into exhaled air, urine, blood and stool [9]. Horvath et al. trained dogs to discriminate OC patients and healthy controls from tissue samples [10] and blood samples from cancer patients [11] with high accuracy. The costly training, limited working capacity and cultural factors have prevented the use of “sniffer dogs” in the clinic. Artificial olfaction with electronic devices could be easier to validate and adopt into clinical practice [9].

Gas chromatography-mass spectrometry (GC-MS) has been used extensively in analysis of VOCs but it involves complex technology and has high costs. Electronic nose (eNose) technology provides a more economical and simpler way to qualitatively analyze VOCs. The technology mimics the working principle of mammalian olfactory system (Figure 1). Ion mobility spectrometry (IMS) works according to the same principles, providing a qualitative VOC spectrum from the sample. Field asymmetric waveform IMS (FAIMS) is a modern and sensitive variant of IMS providing a high sensitivity and stability [12]. The working principle of FAIMS is illustrated in Figure 2.

There is mounting evidence of the potential of eNose devices in detection of cancer from various sample media [12]. FAIMS specifically has previously been shown to detect colorectal and pancreatic cancers from urine [13,14]. Detection of OC has been only attempted from cancer tissue [15]. Urine is a promising sampling method since it can be obtained non-invasively.

We hypothesized that FAIMS would be capable of differentiating the urine of women with OC from benign ovarian tumors and controls.

Materials and methods

Subjects and study design

Between May 2013 and March 2016, 60 women with an adnexal tumor scheduled for surgery gave a morning urine sample in the operation day at the Department of Obstetrics and Gynecology of Tampere University Hospital. They were all postmenopausal, and none of them had an ongoing treatment for cancer. After operation nine tumors were excluded due to their non-ovarian origin or a concurrent malignant tumor. The final sample size after exclusions was 51. Eighteen women scheduled for urinary incontinence or genital prolapse surgery were recruited as controls. The samples were stored at -70°C until analysis. Because of the proof-of-concept nature of the study, no power calculations could be done. The size of the study population was based on the experience from previous studies with similar technology [16].

The samples were defrosted and analyzed using Owlstone Lonestar (Owlstone Inc, Cambridge, United Kingdom) device which uses FAIMS technique. The sensor was coupled with ATLAS sampling unit (Owlstone Inc, Cambridge, United Kingdom) that standardizes the analytical conditions by controlling the temperature and dilution of the VOCs evaporated from the sample.

Protocol of FAIMS

For FAIMS analysis, we used settings previously described by Arasaradnam et al [13]. The step-by-step analysis protocol was as follows:

1) Urine samples were first thawed at room temperature and analyzed in random order.
2) A 5 ml urine sample was aliquoted to a 30 ml glass vial and warmed to 40°C.
3) Once the sample achieved the target temperature, three consecutive scans were conducted to minimize the effect of scan-to-scan variation.

4) After the analysis, the sample vial was removed from the sampling unit and a vial of 5 ml of purified water was placed in to the chamber.
5) The vapour released from the purified water acts as a cleaning agent that removes the carry-over effect of trace VOCs from the urine sample that are retained in the sensor. Five consecutive scans with purified water were conducted.

The next urine sample was placed to the sampling chamber and the process was repeated. To ensure stable and clean carrier gas for the system, we utilized standard pressurized clean air that was cleaned from residual humidity with a silica gel filter and from residual VOCs with activated charcoal filter before entering the system. We used the flow settings recommended by the manufacturer for urine samples: The flow rate over the sample was 500 ml/min, which was mixed to 2000 ml/min stream of clean air for a total flow of 2500 ml/min for the sensor. The FAIMS scanning settings used were also ones provided by the manufacturer: Dispersion field from 0 to 90 % was scanned in 51 steps and compensation voltage from -6 to +6 V was scanned in 512 steps. Each scan contains two ion windows, one for negative and one for positive ions. One window is produced by the negative ions that collide the positive detector and the other is produced by the positive ions that collide the negative detector, respectively. The detectors are illustrated in Figure 2.

The ion window is a spectrum that has compensation voltage on the X axis and dispersion field on the Y axis as seen in Figure 3. The compensation voltage is the base voltage between the electric plates in the separation part of the FAIMS sensor. This biases the ion flow either towards negative or positive plate. The dispersion field strength represents the strength of the electrical field between the plates as a percentage of the maximum field that can be created by the system. The ion window is compiled by adjusting the dispersion field strength stepwise and on each step scanning the selected compensation voltage range at each step. The scans were saved on the hard drive of the Lonestar system from which they were transferred to an USB drive for statistical analysis.

Statistical methods

The last of the three scans from the urine sample was found to be equal in performance when compared to the average of three scans, and was taken for analysis. One scan consists of a matrix of 52,200 measurement values, including both positive and negative ion window. The areas with no response were removed and the remaining signal was downsampled, selecting every other line and column of the scan, leaving 1,536 points for each measurement.

Forward feature selection with linear discriminant analysis (LDA) and quadratic discriminant analysis (QDA) were utilized to find discriminating features from each group. Both LDA and QDA seek a classifier that is optimal for discrimination of the groups. LDA is a special case of QDA where the covariance of each group is assumed to be equal which results in a linear discriminator whereas QDA allows the covariances to differ which also enables quadratic, parable-shaped discriminators. Because LDA is a simpler method, it is preferred as the first option to test. The results were cross-validated by 10-fold cross-validation to avoid overfitting. In this method, the dataset is divided into 10 groups. One group is then excluded from the dataset and the remaining nine groups are used to create the classification parameters as the training set. The excluded group is then classified using these parameters. Since, due to random division for the cross validation, the classification parameters change to a certain extend in every run, the process was repeated 100 times to reduce the effect of variation and to calculate averages and standard deviations for classification results. The analysis was conducted with MATLAB R2017b (MathWorks Inc, Natick, MA, USA).

Results

Characteristics of the final study population are presented in Table 1. The averages and standard deviations of the 100 runs of QDA and LDA analysis are given in Table 2. The performances of QDA and LDA seem to be mostly equal yet there is a notable difference in comparisons of benign tumors

with low grade vs. high grade malignant tumors, respectively. The data produced by FAIMS is nonlinear by nature [17], and it is likely that nonlinear methods such as QDA yield better results in most cases, especially when the differences between groups are less distinct. By QDA analysis, benign ovarian tumors were distinguished from malignant tumors with sensitivity and specificity of 91.5 % and 51.4 %, respectively. However, the specificity improved to 79.7 % when they were compared only to high-grade ovarian cancers. Even low grade ovarian malignancies were discriminated from high grade ovarian cancers with sensitivity of 87.8 % and specificity of 89.6 %, and from benign ovarian tumors with sensitivity of 73.1 % and specificity of 92.9 %, respectively. Figure 3 shows average FAIMS outputs from urine sample of a control and of a woman with ovarian cancer.

Discussion

This study provides preliminary evidence that FAIMS analysis of VOCs can discriminate urine samples from OC patients, patients with non-malignant tumors and healthy controls. High grade ovarian cancers seem to be separated from low grade ovarian cancers, benign ovarian tumors and controls.

The study further demonstrates that OC is associated with distinct odor [18-20]. The fact that this phenomenon is apparent in urine suggests that a systemic process is involved. It is apparent that metastatic, systemic cancer may elicit profound changes in urine composition that may be an indication of decreasing renal function. However, in the case of colorectal cancer, even early stage cancers could be detected [13]. There is in fact mounting body of evidence that cancer releases VOCs to systemic circulation that consequently are released through alveoli to breath and via glomerular filtration to urine [21]. This suggests that breath and urine can be considered alternative sampling methods for same VOCs. The feasibility of FAIMS/IMS has been demonstrated in both sampling

sources [13,22]. Reliable sampling from exhaled breath is challenging [23] and the performance of breath VOC analysis in OC seems to be inferior to our results obtained from urine [18,24]. Since urine can be obtained non-invasively, we consider it as a more promising sampling source for VOC analysis in OC.

VOCs in different sample mediums and cancers seem to have common features, which are related to oxidation such as benzene derivates [13,18,21]. The metabolic origin and function of most of these VOCs are unclear. They can originate from endogenous and exogenous sources and may thus be a result also from environmental exposure instead of the cancer [21]. In this study we achieved a good discrimination of high grade and low grade cancers. It has been suggested that KRAS and TP3 mutations play a role as a watershed in development of high or low grade serous OC, i.e. type I and II OCs [25]. These single mutations have resulted in VOC changes in cellular model [26] that reflect those found in urine in other cancers [13]. We speculate that the VOC alterations concerning various mutations should be studied in future also in ovarian cancer.

This study must be considered as preliminary, and the results should be verified in larger patient cohorts with this repeatable method. However, there is urgent need for early detection of especially aggressive type II OCs, with an ultimate goal to improve the prognosis of this devastating disease [25]. An important topic in future FAIMS research is to examine if cytoreductive surgery and immunosuppressive therapy have influences on VOC emissions of urine samples. FAIMS technology itself has advantages compared to GC-MS- and eNose implications; the technology by nature is sensitive to trace concentrations of molecules, is considerably more economical than MS-based methods, and does not suffer stability problems of other eNose technologies [27]. In contrast to canine studies, FAIMS is standardized and repeatable, whereas it is almost impossible to replicate research settings of canine studies because of variation in dogs.

Our study has also limitations. First, the present results cannot as such be generalized to unselected populations, but rather should be considered valid in the setting of tertiary hospitals, as part of the diagnostic work-up of adnexal tumors. Second, the number of analyzed urine samples was quite small. However, the proportions of three patient groups (controls, benign and malignant tumors) were balanced. Third, the considerable number of low malignant potential and borderline ovarian tumors in our study certainly has an influence on our results comparing benign and malignant ovarian tumors, and may have contributed to the rather great deviation seen between comparisons of benign tumors and all or low-grade malignant tumors. However, the comparisons between benign ovarian tumors or controls and high grade ovarian tumors are more accurate and specific. Fourth, the storage time of our samples was several years, which may have reduced the VOC emissions and thus differences between groups, as has been shown in a recent study examining the effect of storage on VOC profiles of urine [28]. In addition, the effects of the diet and possible medications may have had influence on the concentration and composition of urine although the samples were collected in the morning after at least four hours fasting. The fact that the highest discrimination rate was achieved for benign tumors and controls suggests that there is a degree of bias between patient groups. This may also result from the larger and more heterogenous nature of cancer group.

Conclusion

According to our results, we propose that the VOC signature of urine of ovarian cancer patients can be recognized by FAIMS and that it has potential for being a non-invasive method in the detection of ovarian malignancy. Our novel study encourages us to examine further possibilities of FAIMS for diagnostics and follow-up of gynecological malignancies.

Funding

The study was supported by the Finnish Cancer Foundation (J.M. Grant MS738), Competitive Research Funding of Tampere University Hospital (J.M. Grant 9U036, N.O. Grants 150618, 9S045, 9T044, 9V044, 151B03 and 9U042), Tampere Tuberculosis Foundation (N.O. Grant) and Emil Aaltonen foundation (N.O. Grant).

Role of the Funding Source

Researchers received funding for governmental bodies and non-profit organizations. These parties had no role in planning and execution of the study or in in the analysis and writing process of the article.

Conflict of interest statement

RJN, EE and JUM declare no conflicts of interest. NO, PSK and ANR are shareholders of Olfactomics Ltd. which is about to commercialize proprietary technology for the detection of diseases by ion mobility spectrometry.

Ethical conduct of research

All participants gave their informed consent to the study, and the investigation was approved by the Ethic committee of Tampere University Hospital.

Acknowledgements

The authors thank medical student Elina Jokiniitty for technical assistance.

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Table 1. Demographic data of study population

	Malignant tumors		**Benign tumors**	**Controls**
n	33		18	18
Age (years) Median (range)	64 (51-82)		64 (51-73)	71 (55-83)
Diagnosis (n)	Low grade cancers (15) - mucinous adenocarcinoma Stage IA and IC (1+1) - endometrioid adenocarcinoma Stage IA (1) - mucinous borderline Stage IA (5) - serous borderline Stage IA (4) - Sertoli-Leydig cell tumor Stage IIIC (1) - Granulosa cell tumor Stage IA (2)	High grade cancers (18) - carcinosarcoma Stage IIIC (1) - high grade serous adenocarcinoma • Stage IC (1) • Stage IIC (1) • Stage III/IV (15)	Serous cystadenoma (9) Mucinous cystadenoma (1) Fibroma (2) Simple cyst (3) Endometriotic cyst (2) Necrotized cyst (1)	Genital prolapse or urinary incontinence (18)

Table 2. Results of FAIMS signal data and QDA and LDA classification

Classification pairs	**QDA**			**LDA**		
	Accuracy (%) (±2 Std)	Sensitivity (%) (±2 Std)	Specificity (%) (±2 Std)	Accuracy (%) (±2 Std)	Sensitivity (%) (±2 Std)	Specificity (%) (±2 Std)
Benign ovarian tumors vs. controls	91.9 (±9.8)	93.4 (±11.4)	90.4 (±14.4)	86.1 (±9.6)	86.0 (±11.2)	86.1 (±12.2)
Controls vs. malignant ovarian tumors	81.3 (±8.2)	91.2 (±7.2)	63.1 (±16.0)	81.2 (±5.8)	90.4 (±5.2)	64.3 (±12.8)
Controls vs. high grade ovarian cancers	81.9 (±5.2)	89.1 (±2.8)	74.6 (±9.6)	82.1 (±6.0)	88.7 (±3.2)	75.6 (±11.8)
Benign vs. malignant ovarian tumors	77.3 (±13.8)	91.5 (±6.4)	51.4 (±32.0)	65.9 (±13.8)	87.1 (±9.0)	27.1 (±38.6)
Benign ovarian tumors vs. low grade ovarian cancers	83.9 (±23.4)	73.1 (±41.4)	92.9 (±11.4)	59.3 (±7.0)	35.9 (±14.0)	78.8 (±5.8)
Benign ovarian tumors vs. high grade ovarian cancers	82.5 (±10.0)	85.3 (±15.0)	79.7 (±12.0)	82.5 (±9.6)	85.0 (±15.0)	79.9 (±11.2)
Low grade vs. high grade ovarian cancers	88.7 (±11.2)	87.8 (±12.8)	89.6 (±16.6)	82.0 (±10.8)	84.3 (±16.0)	79.7 (±13.4)

Figure 1. The working principle of mammary and eNose compared

A) VOCs enter a sampling unit where the humidity, the temperature and the concentration of the sample are optimized.

B) Optimized sample enters the sensor unit where different VOCs attach to different areas of the sensor and produce electrical currents.

C) Electrical currents are referred to a computing system for analysis where they are associated with previously gathered information.

D) A result of the analysis is produced.

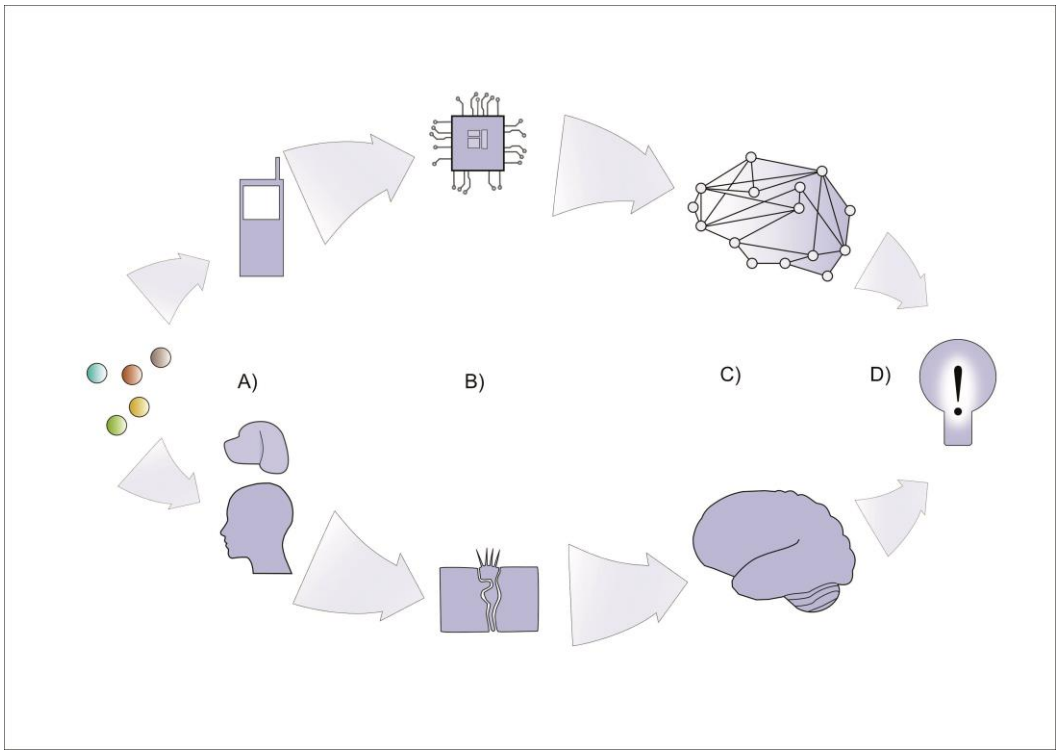

Figure 2. Illustration on the working principle of FAIMS

A) Sample vial is placed in to the sampling chamber where VOCs are released from the sample. VOCs are then transferred to the analyzer by clean air flow.

B) In the analyzer, VOCs are first ionized by a radioactive isotope and gain electrical charge.

C) Ionized VOCs enter separation area where they are alternately exposed to high and low electric fields between the electric plates. The plates also have a baseline compensation voltage that is periodically adjusted. The different properties of VOCs cause them to travel at different speed in the separation chamber and behave differently in high and low electric fields. This results in separation of the VOCs according to their charge, shape and mass.

D) At the last stage of the analysis, VOCs collide with detectors, creating electric currents that create a unique spectrum for each molecular mixture.

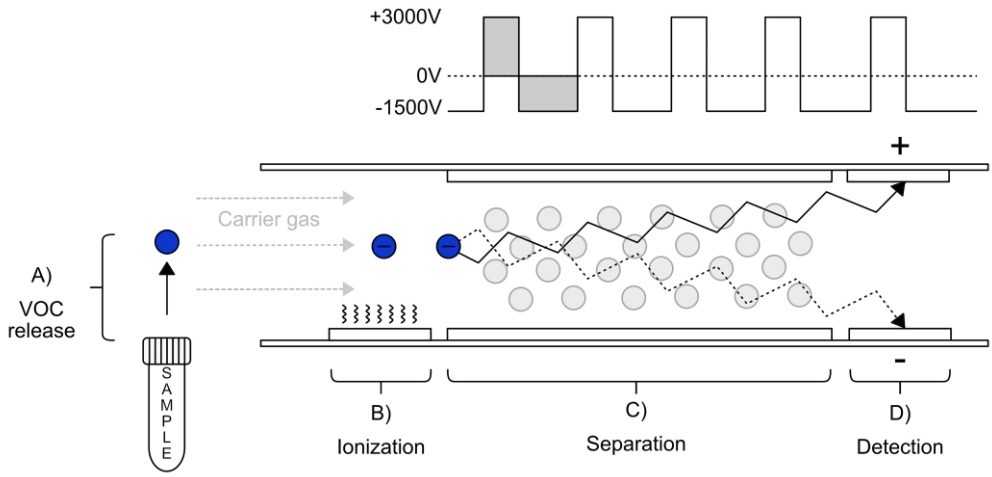

Figure 3. Average FAIMS spectrum from a patient with ovarian cancer and from a control

Stars indicate the areas of the spectrum that yielded optimum discrimination of the two groups. Compensation voltage is on X-axis and dispersion field strength is on Y-axis.