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TOPICAL REVIEW

A review on electronic nose for diagnosis and monitoring treatment response in lung cancer

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Abstract

Lung cancer is one of the common malignancies with high mortality rate and a poor prognosis. Most lung cancer cases are diagnosed at an advanced stage either due to limited resources of infrastructure, trained human resources, or delay in clinical suspicion. Low-dose computed tomography has emerged as a screening tool for lung cancer detection but this may not be a feasible option for most developing countries. Electronic nose is a unique non-invasive device that has been developed for lung cancer diagnosis and monitoring response by exhaled breath analysis of volatile organic compounds. The breath-print have been shown to differ not only among lung cancer and other respiratory diseases, but also between various types of lung cancer. Hence, we postulate that the breath-print analysis by electronic nose could be a potential biomarker for the early detection of lung cancer along with monitoring treatment response in a resource-limited setting. In this review, we have consolidated the current published literature suggesting the use of an electronic nose in the diagnosis and monitoring treatment response of lung cancer.

1. Introduction

Lung cancer (LC) is one of the common cancer worldwide with high mortality, accounting for 18.4% of all cancer deaths [1]. Patients are often diagnosed at an advanced stage, thereby limiting curative treatment options. Timely diagnosis and appropriate treatment remain critical for survival and improved outcomes of patients with LC. The long-term prognosis of LC is directly related to the stage of cancer at the time of diagnosis, and 5 year survival rates can range from 5% for stage IV cancers to 80% for stage I cancers [2]. Therefore, improving the detection rate of early-stage LC is essential for improving the prognosis of LC, and prolonging survival.

According to a report published from AIIMS, New Delhi, a vast majority of lower-income Indian patients are staged with advanced disease at the time of diagnosis [3]. It took around 4–5 months to reach the diagnosis of LC, and even longer to start specific therapy. A major cause of this delay was incorrect diagnosis and subsequently inappropriate treatment for TB, especially in low middle income countries. Other challenges may include lag time from symptom onset to the first visit to the primary care physician, delayed investigation procedures, and delay between the diagnosis and start of definitive therapy [4]. LC screening programs using low-dose computed tomogram scans are ongoing in several countries for early diagnosis of LC amongst high-risk individuals [5]. However, these may not be cost-beneficial in resource limited settings. A need is therefore, to develop and use newer, innovative strategies for early detection of LC with the aim of improving survival.

The addition of non-invasively obtained biomarkers could provide much-needed value to these efforts. With an increased understanding of the mechanisms behind LC development and progression, a number of potential biomarkers have been developed and some others are in various stages of

development. The biochemical processes of diseased organs get altered, which in turn results in the production of new chemicals or altered consumption of existing chemicals [6]. These abnormal changes alter the composition of the body fluids resulting in an altered gas mixture of volatile organic compounds (VOCs) that may be analyzed in various specimens. In this context, exhaled breath appears to be an attractive option for non-invasive analysis of these biomarkers. Specific breath signatures can serve as potential biomarkers for individual diseases and can be useful not only for early disease detection but also to understand their pathogenesis [7]. Among these, VOCs and breath-print detection in the exhaled breath of patients have been shown to be effective in respiratory diseases, especially in LC.

2. Volatile organic compounds (VOCs) and electronic nose (eNOSE)

VOCs are small molecular mass compounds having high vapor pressure and a low boiling point [8]. These substances are produced by every living organism and reflect the metabolic processes including inflammation and oxidative stress. They can be measured in several body specimens such as exhaled air, blood, urine, faeces, and pleural fluids. However, most studies have focused on the detection and measurement of VOCs in the exhaled breath. VOCs get produced by different metabolic activities and are associated with different diseases. Interestingly, metabolic pathways like glycolysis, apoptosis, and angiogenesis also get activated during cancer progression. However, there is a lack of evidence on describing interlink between metabolic pathways influencing exhaled breath signatures among the LC patients.

To identify individual VOCs, researchers have used gas chromatography coupled with mass spectrometry (GC-MS) [9]. In this method, the gas sample is transferred into GC-MS where it is analyzed according to the time to elution in the chromatography column and to the mass-to-charge ratio which is an expensive and time-consuming process. However, with the advancement of technology, researchers have looked for new approaches like exhaled breath print through cross-reactive sensors, aiming at defining specific patterns of disease-related VOCs.

Recent evidence also suggests the role of VOCs in cell-to-cell communication. Serasanambati and his colleagues have reported that cancer cells can change the phenotype of neighboring cells through the up-regulation of VOCs [10]. The concentration of VOCs in the LC cell culture was significantly augmented in physically connected cells in comparison to physically unconnected cells. Hence, the authors concluded that analyzing these VOCs would serve as a potential tool for LC diagnosis. New, highly sensitive nano-array sensors for exhaled VOCs have been developed using electronic nose technology which is coupled with powerful statistical programs [11]. An eNOSE device consists of an array of gas/VOC sensors integrated with artificial neural networks that has been a promising non-invasive technology for detecting and delineating targeted VOCs from the exhaled breath resulting in early diagnosis of several diseases. These sensors range from conducting polymers, metal oxide semiconductors (MOS), piezoelectric, optical fluorescence, quartz crystal microbalance and amperometric gas sensors [12]. It has been designed to function as human nose and brain. The human nose and brain are trained to detect several volatile compounds, which interact with neuron cell receptors and then send back signals to the brain for further processing. Similarly, electronic nose detects the presence of these volatile compounds by sensor signals and processes them to detect various chemicals in vapor form by artificial intelligence. Since the last decade, researchers have focused on developing sensors which are highly sensitive and specific. These sensors have been developed to detect VOCs which could possibly differentiate LC from healthy subjects and from other respiratory diseases. After signal processing and feature extraction, the output of the sensors is coupled with pattern recognition algorithm for training and testing. This review highlights the published literature suggesting the utility of an electronic nose in the diagnosis and monitoring treatment response of LC.

3. Diagnosis of LC using eNOSE

Various electronic nose devices have been used and developed for detecting LC and discriminating from healthy controls since the early 2000. Over the last two decades several studies which have evaluated the diagnostic utility of eNOSE device. With the use of newer technology devices coupled with better machine learning algorithms, the diagnostic accuracy has improved. McWilliams and his colleagues collected breath samples from LC patients and high-risk smokers without cancer using the cyranose 320 device [13] and were able to discriminate LC from non-LC with 80% accuracy. Subsequently, Rocco and his colleagues validated an artificial olfactory electronic nose system-bionote to detect LC with a sensitivity and specificity of 86% and 95% respectively in high-risk individuals [14]. Shlomi and his colleagues reported that they could discriminate LC from benign pulmonary nodules with a sensitivity, specificity, and accuracy of 75%, 93%, and 87%, respectively [15]. Rodriguez Aguilar and colleagues have recently shown the diagnostic accuracy of cyranose 320 devices in chronic obstructive pulmonary disease (COPD) and LC patients. Despite the different causes of disease development like smoking and household pollution, there was no difference in the breath-prints between COPD-smokers and COPD-household pollution cohort [16]. Furthermore, the authors have shown that they could discriminate between healthy

COPD, LC and breast cancer groups with an accuracy of 91.35% [17]. Another study by Kort and her colleagues have shown that non-small cell LC (NSCLC) could be differentiated from suspected LC by using different electronic nose device-Aeonose which had a better sensitivity (94.4%) but lower specificity (32.9%) [18]. Recently, the same authors have published a multicenter validation study concluding that by combining exhaled breath data with clinical variables, they could discriminate between NSCLC from non cancer subjects [19]. Marzorati and colleagues have developed an artificial neural network-based classification tool which could discriminate healthy controls from LC with a sensitivity of 85.7%, specificity of 100%, and accuracy of 93.8% [20]. Furthermore, Cai and colleagues used zNOSE4200 device to differentiate LC from non-LC with an accuracy of 82.8%, a sensitivity of 76.0%, and a specificity of 94.0% [21]. The details of the studies which looked at LC diagnosis using electronic nose device have been summarized in table 1.

4. Discriminating LC from other chronic respiratory diseases using eNOSE

The ability of eNOSE to differentiate LC from other respiratory diseases including COPD, idiopathic pulmonary fibrosis (IPF) and pulmonary arterial hypertension (PAH) has also been studied. In majority of the studies, eNOSE demonstrated greater than 80% accuracy in discriminating LC from other diseases. In one study Mazonne and his colleagues [22] included 49 patients of NSCLC, 18-COPD, 15-IPF, 20-PAH, and 20 patients of Sarcoidosis along with 21 healthy controls and found that eNOSE could discriminate LC from these respiratory diseases with a sensitivity of 73.3% and a specificity of 72.4% ($p = 0.01$).

D'Amico and his colleagues were able to differentiate LC from other lung diseases like interstitial lung diseases, COPD, bronchitis, and pleurisy with a global rate of success of 85.7% and sensitivity and specificity of 93% and 73% respectively [23]. Wang and his team used surface acoustic wave (SAW) gas sensors to separate chronic bronchitis patients as well as healthy controls with high accuracy [24].

This technology has also been used to distinguish LC from other cancers, such as colon, breast, and prostate with reasonable degree of success. Moreover, the nano-sensor array could distinguish between the breath patterns of different cancers irrespective of age, gender, lifestyle, and other confounding factors.

Similarly, Hakim and his colleagues have analyzed the three binary data sets of LC, head and neck cancer and healthy controls using NA-NOSE developed by HAICK and were able to differentiate between these groups with sensitivity of 100% and specificity of 92% [25]. De Vries and his colleagues were able to discriminate LC from asthma, COPD, healthy controls with an accuracy of 87%, 68%, and 88% respectively [26]. Rodriguez Aguilar and colleagues have recently shown have shown that they could discriminate between healthy COPD, LC and breast cancer groups with an accuracy of 91.35% [17]. The summary of these studies is depicted in table 2.

5. Discriminating various LC morphological types using eNOSE

Few investigators have also looked into distinguishing various types of LC cases based on breath-print signatures analyzed by eNOSE device. Barash and his colleagues could discriminate adenocarcinoma from squamous cell carcinoma lung using gold nanoparticle based sensors with an accuracy of 96% [27]. This was further supported by Shlomi *et al*, who showed that eNOSE could discriminate patients of adenocarcinoma lung with and without epidermal growth factor receptor mutation with an accuracy of 83% [15]. Peled and colleagues have reported the use of eNOSE to discriminate LC nodules from benign lung nodules and also to distinguish between adenocarcinoma and squamous cell carcinoma [28]. Although all were single-center studies, preliminary results of eNOSE show encouraging results in diagnosing LC along with its sub types and also distinguishing from other chronic respiratory diseases.

6. Discrimination of various LC stages using eNOSE

Peled and colleagues have also reported the use of eNOSE to distinguish between early stage LC and advanced stage LC [28]. Recently, Ke Chen and his colleagues used eNOSE to differentiate LC from non-LC, as well as between stage III and stage IV LC [29]. The authors used indigenously made electronic nose device containing 11 gas sensors and were able to detect the presence of LC with an accuracy of 93.6%, a sensitivity of 95.6% and a specificity of 91.1%. In the same study this eNOSE system could differentiate stage III and stage IV LC with an accuracy of more than 80%, although attempts to differentiate early stage cancer from advanced cancer were not rewarding due to very few patients with early stage disease.

7. Prognostic value of eNOSE in LC

The prognostic utility of eNOSE in LC has been evaluated in limited studies only. De Vries and colleagues have shown the accuracy of serial estimation of VOC signatures in exhaled breath analysis line for assessing non-responders versus responders to anti-programmed death ligand-1 (anti-PD-1) therapy for three months in NSCLC [30]. Based on the immunohistochemistry analysis of anti-PD-1 antibody, VOC signatures in exhaled breath were able to differentiate non-responders from responders with a specificity of 81%, sensitivity of 50% and

Table 1. Studies on electronic nose for early detection of lung cancer.

Sr. No.	Author/Year	No. of participants	Device	Sensitivity	Specificity	Accuracy
1	Natale *et al* (2003) [34]	LC ($n = 42$), controls ($n = 18$)	Libranose	—	—	LC—100%, Controls—94%
2	Machado *et al* (2005) [35]	LC ($n = 28$), controls ($n = 135$)	Cyranose 320	71.4%	91.9%	—
3	Chen *et al* (2006) [36]	LC ($n = 24$), other lung disease ($n = 8$), controls ($n = 18$)	SAW based eNOSE	—	—	—
4	Blatt *et al* (2007) [37]	LC ($n = 43$), controls ($n = 58$)	MOS sensors based eNOSE	95.3%	90.5%	92.6%
5	Yu *et al* (2011) [38]	LC ($n = 9$), controls ($n = 9$)	Semiconductor & EC based CN eNOSE	100%	88.9%	94.4%
6	Mazonne *et al* (2012) [39]	LC ($n = 92$), controls ($n = 137$)	Colorimetric sensor array	70%	86%	81.1%
7	Peled *et al* (2012) [40]	LC ($n = 53$), controls ($n = 19$)	Nanoscale NA-NOSE, coupled with GC-MS	—	—	88%
8	Wang *et al* (2012) [24]	LC ($n = 47$), controls ($n = 42$)	MOS SAW based eNOSE	93.62%	83.37%	—
9	Broza *et al* (2013) [41]	LC ($n = 12$), controls ($n = 5$)	Nanomaterial based eNOSE	100%	80%	—
10	Bikov *et al* (2014) [42]	LC ($n = 27$), controls ($n = 37$)	Cyranose 320	63%	78%	72%
11	McWilliams *et al* (2015) [13]	LC ($n = 25$), controls ($n = 166$)	Cyranose 320	88%	81.3%	—
12	Rocco *et al* (2016) [14]	LC ($n = 23$), controls ($n = 77$)	Bionote	86%	95%	—
13	Gasparri *et al* (2016) [43]	LC ($n = 70$), controls ($n = 76$)	Libranose	81%	91%	—
14	Nardi-Agmon *et al* (2016) [44]	LC ($n = 39$)	Nanoscale NA-NOSE coupled with GC-MS	93%	85%	89%
15	Shlomi *et al* (2017) [15]	LC ($n = 89$), Benign patients ($n = 30$)	Nano-material based sensor array	75%	93.3%	87%
16	Cai *et al* (2017) [21]	LC ($n = 57$), controls ($n = 72$)	zNose4200	76%	94%	—
17	Huang *et al* (2018) [45]	LC ($n = 56$), controls ($n = 188$)	Carbon nanotubes sensor array	75%–100%	86.2%–96.6%	85.4%–92.7%
18	Kort *et al* (2018) [18]	LC ($n = 144$), controls ($n = 146$)	Aeonose	94.4%	32.9%	—
19	Van de Goor *et al* (2018) [46]	LC ($n = 52$), controls ($n = 93$)	Aeonose	83%	84%	83%
20	Marzorati *et al* (2019) [20]	LC ($n = 6$), controls ($n = 10$)	MOS Sensor array	85.7%	100%	93.8%
21	Saidi *et al* (2020) [32]	LC ($n = 32$), controls ($n = 12$)	Chemical gas sensor	—	—	98.6%
22	Kort *et al* (2022) [19]	LC ($n = 239$), controls ($n = 253$)	Aeonose	95%	49%	—

an receiver operating characteristic-area under curve (ROC-AUC) of 0.85 (CI, 0.7–0.96). The authors further validated these results in an independent set of patients with advanced stage NSCLC.

Recently, Alessandra Buma and colleagues have also discriminated anti-PD-1 responders from non-responders after 6 weeks of treatment in NSCLC patients using SpiroNose device [31]. At the end

Table 2. Studies on electronic nose for discriminating lung cancer from other chronic lung diseases.

Sr. No.	Author Year	No. of participants	Device used	Sensitivity	Specificity	Accuracy
1	Mazonne *et al* (2007) [47]	NSCLC ($n = 49$), COPD ($n = 18$), IPF ($n = 15$), PAH ($n = 20$), Sarcoidosis ($n = 20$), controls ($n = 21$)	Colorimetric sensor array	73.3%	72.4%	—
2	Wang *et al* (2008) [48]	LC ($n = 15$), other lung disease ($n = 7$), controls ($n = 10$)	SAW based eNOSE	—	—	—
3	Dragonieri *et al* (2009) [49]	LC ($n = 10$), COPD ($n = 10$), controls ($n = 10$)	Cyranose 320	—	—	85%
4	D'Amico *et al* (2010) [23]	LC ($n = 28$), other lung disease ($n = 28$), controls ($n = 36$)	Libranose	93%	79%	85.7%
5	Peng *et al* (2010) [50]	LC ($n = 30$), other cancers ($n = 66$), controls ($n = 81$)	Nanosensors based GNP coupled with GC-MS	—	—	—
6	Tran *et al* (2010) [51]	LC ($n = 16$), other lung disease ($n = 11$), controls ($n = 62$)	ENS-Mk3	—	—	—
7	Peng *et al* (2011) [50]	LC ($n = 25$), HNC ($n = 22$), controls ($n = 40$)	Nanoscale NA Nose	100%	92%	—
8	Capuano *et al* (2014) [52]	LC ($n = 20$), other lung disease ($n = 10$)	QMB based eNOSE coupled with GC-MS	—	—	90%
9	Hubers *et al* (2014) [53]	LC ($n = 38$), COPD ($n = 39$)	Cyranose 320	80%	48%	—
10	De Vries *et al* (2015) [26]	LC ($n = 31$), COPD ($n = 31$), Asthma ($n = 37$), controls ($n = 45$)	Spironose	—	—	87%(a), 68%(b), 88%(c)
11	Tan *et al* (2016) [54]	LC ($n = 12$), COPD ($n = 12$), controls ($n = 13$)	Chemiresistor based alkane eNOSE	83% (a), 86% (b), 80% (c)	88% (a), 80% (b), 93% (c)	—
12	Von Hooren *et al* (2016) [55]	LC ($n = 32$), HNC ($n = 52$),	Aenose	85%	84%	—
13	Li *et al* (2017) [56]	LC ($n = 24$), other lung disease ($n = 5$), controls ($n = 23$)	Different sensors	91.58%	91.72%	—
14	Nakhleh *et al* (2017) [57]	LC ($n = 45$), other cancers ($n = 357$), controls ($n = 411$)	Au Nanoparticles & single walled carbon nanotubes	—	—	86%
15	Tirzite *et al* (2017) [58]	LC ($n = 165$), non-cancer ($n = 91$), controls ($n = 79$)	Cyranose 320	87.3%	71.2%	93%

(Continued.)

Table 2. (Continued.)

Sr. No.	Author Year	No. of participants	Device used	Sensitivity	Specificity	Accuracy
16	Tirzite *et al* (2019) [59]	LC ($n = 252$), controls ($n = 223$)	Cyranose 320	95.8%	92.3%	—
17	Binson *et al* (2021) [33]	LC ($n = 40$), COPD ($n = 48$), controls ($n = 90$)	MOS Sensor array	91.3%	84.4%	94.4%
18	Rodriguez Aguilar *et al* (2021) [17]	LC ($n = 30$), Breast Ca ($n = 50$) COPD ($n = 50$), controls ($n = 50$)	Cyranose 320	—	—	91.35%

of sixth week of treatment, patients with partial response showed a distinct clustering of prediction scores towards higher probabilities of an objective response, while the patients with progressive disease showed a distinct clustering towards lower probabilities of an objective response. However, the patients with stable disease showed an increased spread in prediction scores, with the majority of scores falling back to low probabilities of an objective response.

Authors from both the above studies concluded that exhaled breath analysis by eNOSE could be used in classifying responders and non-responders. Electronic nose based on cross-reactive non-specific sensor arrays could accurately identify true responders to anti-PD-1 therapy.

8. Use of eNOSE in LC patients in developing countries

Most of the studies on eNOSE have been performed in developed countries. However, few studies describe the application of eNOSE in LC patients in developing low and middle income countries as well. Tarik Saidi and his team observed differentiation of LC patients from healthy controls using UV-irradiated WO_3 sensor array. Further, the authors could discriminate between the NSCLC and small cell LC with the accuracy of 84.5% and between squamous cell carcinoma and adenocarcinoma with 77.5% [32]. Recently, Rodriguez Aguilar and his colleagues could discriminate LC from breast cancer and COPD patients with the accuracy of more than 90% in Mexican subjects [17]. The problem of air pollution is of concern in developing countries which could influence disease development and outcome. Rodriguez Aguilar and his colleagues have shown that the breath-prints between COPD-smokers and COPD-household pollution cohorts were similar [16]. V A Binson and his colleagues from India have used MOS sensor based eNOSE to discriminate of LC from healthy control with an accuracy, sensitivity and specificity of 91.3%, 84.4% and 94.4% respectively [33].

Exhaled breath analysis shows promising results as regards to diagnosing and monitoring treatment response in LC patients. The main confounding factors in breath-print analysis were related to the type of device used, validation of the device, population studied, age and ethnicity, smoking status and sample size. However, in the resource limited settings or areas with a high burden for endemic diseases like Tuberculosis, the clinical use of eNOSE technology is yet to be investigated further.

9. Conclusion

Electronic nose is emerging as a promising tool for non-invasive diagnosis of LC and for differentiating various LC sub-types. Currently, however, it remains primarily a research tool since evidence in insufficient to qualify it as a point-of-care diagnostic test for routine clinical practice. The available databases on breath signatures are not universal due to either lack of sensitivity, specificity, reproducibility and validity of various eNOSE devices. Thus, there is a need of large scale validation studies in both developed and developing countries which could help develop eNOSE device as a potential non-invasive diagnostic and prognostic tool for LC

Data availability statement

No new data were created or analyzed in this study.

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Conflict of interest

No conflict relevant to this work

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