iJRASET
International Journal For Research in Applied Science and Engineering Technology



INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 13 **Issue:** IV **Month of publication:** April 2025

DOI: https://doi.org/10.22214/ijraset.2025.69111

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International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 13 Issue IV Apr 2025- Available at www.ijraset.com

Advances in Early Lung Cancer Detection: A Systematic Review

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Abstract: ***The diagnosis of most lung cancer patients happen only when it is advanced, where the curative therapy is not any more a choice. Lung cancer has more death rates than other prevalent cancers like prostate, breast and skin around the globe. Its mortality rate can be reduced to a certain extend by the earlier detection. It is also very important to know the different types of detection methods and its effectiveness. This review centers upon the likelihood of diagnosing lung cancer at its earlier stage by utilizing different biomarkers like protein biomarkers and exhaled breath analysis and imaging procedures like CT scan imaging.***

Keywords: VOC; biomarkers; image processing; lung cancer; noninvasive.

I. INTRODUCTION

Cancer is a disease characterized by unregulated cell growth and spread of abnormal cells. Uncontrollable spread can cause death to the cancer patient. The second most prevalent disease in the world is cancer after heart diseases. Lung cancer is the leading cause of cancer death for both men and women and is the second most common cancer[1,2,3].

The majority of lung cancer (80% -90%) cases are believed to be related to cigarette smoking. Although active cigarette smoking is the primary cause for the lung cancer; passive smoking, cigar smoking, occupational exposure to nickel, asbestos and chromium, exposure to radon gas in homes and mines also can cause lung cancer [2].

In 2018, an estimated 234,030 Americans will be diagnosed with, and 154,050 deaths will occur from lung cancer. It is estimated that 121,680 males and 112,350 females will be diagnosed with lung cancer. Estimated deaths are 83,550 males and 70,500 females [1]. Five-year survival rates for lung cancer is only 18% (15% for men and 21% for women). In US the lung cancer death rate has declined by 45% since 1990 in men and by 19% since 2002 in women due to reductions in smoking, with the pace of decline quickening over the past decade; from 2011 to 2015, the rate decreased by 3.8% per year in men and by 2.3% per year in women. The incidence rate of lung cancer rely on the geographical area of the world. The highest rates of lung cancer is in Northern America and Europe; and the lowest rate in Africa and Latin America. Hungary has the highest rate of lung cancer followed by Serbia and North Korea. The incidence rates of lung cancer for males and females are shown in the figure 1 and 2 [1, 3].

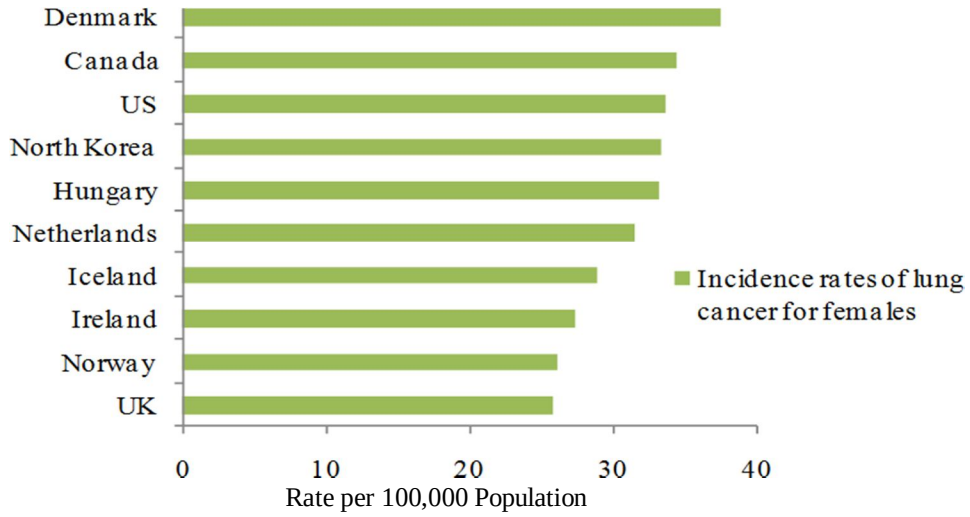


Fig.1. Incidence rates of lung cancer for females depending on geographical areas

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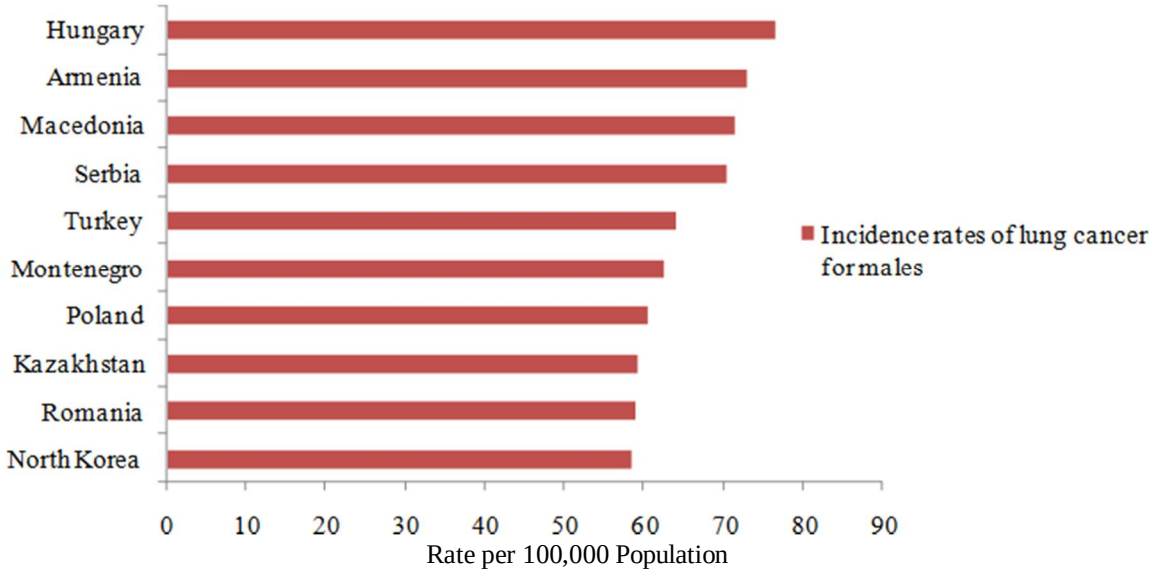


Fig.2. Incidence rates of lung cancer for males depending on geographical areas

The lung cancer treatment requires vast and complex steps and the survival scarcely attains five years. Mostly lung cancers are diagnosed clinically at an advanced stage where the patients show symptoms like pain, persistent cough and weight loss [4,5]. Diagnosing the malignancy at an early stage will greatly improve the result. The death rate from lung cancer can be reduced by effective screening that leads to early detection of the disease and treatment is likely to be more effective. The early detection of lung cancer can be done by many methods such as chest X-ray, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), sputum cytology and breath analysis [6].

II. ADVANCES IN LUNG CANCER DETECTION

The techniques which are currently available for lung cancer detection have certain drawbacks. The demerits like use of radiation, false negative response and high cost is associated with chest X-ray and computed tomography [7]. Even though MRI and positron emission tomography are reliable it is unsuitable for the patients with other complications [8]. A non-invasive and easy method sputum cytology has the disadvantages of false positive results and degradation of biomarkers due to the enzymes in sputum [9]. The detection levels and biomarkers are different for these techniques (Table 1).

A fast and sensitive technique is required for early lung cancer prediction since the present diagnostic methods are time consuming. With this approach, several detection methods are developed and research is going on in the field of medical electronics that provides a bright future in the prediction of numerous major diseases through fast, reliable,

TABLE 1: Current Techniques For The Early Detection Of Lung Cancer

Detection mechanism	Detection Level	Biomarkers
Chest X-Ray	Tissular Level	Neoplastic tissue
CT	Tissular Level	Neoplastic tissue
PET	Tissular Level	Neoplastic tissue
Sputum Test	Cellular or Molecular Level	Abnormal cells and methylated gene promoters
Serum test	Cellular or Molecular Level	Circulating tumor cells, circulating DNA, plasma proteins, telomerase, etc
Breath analysis	Molecular level	Volatile and non-volatile organic compounds
Urine test	Molecular level	Urine volatile odorants

responsive and easy accomplishment. A non -invasive and painless technique is developed for easy and early detection with the use of sensors for the analysis of blood samples to detect the presence of biomarkers. Enzymes, nucleic acids, proteins or small molecules show a change in both body fluids and malignant tumour tissues in cancer patients. By the presence and concentration of cancer biomarkers, detection of certain cancer types can be done effectively at an early stage [10]. Another accessible non-invasive method is analysis of exhaled breath samples which is currently used in the areas of disease diagnosis and monitoring. Early detection of lung cancer is possible with sampled breath analysis. In this method, analysis of volatile organic compounds (VOC) from the sampled breath of humans to identify the existing component related to the particular cancer is carried out.

CT scan imaging is one of the effective techniques in lung cancer detection but have the demerits of difficulty in interpretation and identification of the tumour from CT scanned images. The accurate detection of malignant tumours can be done with the help of computer assisted approaches using image processing and artificial intelligence [11].

A. Protein Biomarkers

Cancer cells or the human body itself produces the tumour biomarkers in response to conditions as cancer or some other diseases. The detected level of tumour biomarkers in urine, blood or body tissues of several cancer patients is very high. The tumour markers include hormones, isoenzymes, tissue specific proteins, oncofetal antigens, differentiation antigen, mucin, oncogenes and other glycoproteins and glycolipids. Using medical, genetic or biochemical based methods many genetic biomarkers and proteins have been screened for lung cancer studies that include diagnostic, prognostic and therapeutic development processes [9].

The concentration level and existence of wide variety of protein biomarkers connected with lung cancer can be complex. Depending on the histological types of lung cancer the response ratio and specificity of the protein biomarkers can exhibit changes [12]. For early lung cancer detection several biomarkers are currently used clinically.

The clinically used protein biomarkers such as carcinoembryonic antigen (CEA), cytokeratin fragment (CYFRA 21-1), and Pro-gastrin-releasingpeptide (ProGRP) alone cannot be used for early detection of lung cancer since they have low concentrations in serum [9]. The cancer detection is possible with the combined action of these biomarkers. Adenocarcinoma can be detected with the mixture of CYFRA 21-1 and CEA. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) shows different levels of Neuron specific enolase (NSE). NSE shows low specificity for NSCLC than SCLC; CYFRA 21-1 and CEA are more specific in NSCLC cases according to main histological subtypes . With a combination of Cancer Antigen (CA125), CEA, NY-ESO (cancer-testis antigen) and CYFRA 21-1 the lung cancer patients and healthy individuals can be differentiated.

CEA is a cell adhesion glycoprotein that becomes180 kD molecular weight when glycosylated and 70 kD normally and its level is related to lung cancer [9]. In cancer patients CEA concentration escalates significantly than in healthy people. Lung cancer may be detected for CEA amount higher than 3 $ngmL^{-1}$. Malignant and benign tumours can be effectively differentiated with CEA protein biomarker. NSE located in cell membrane and cytoplasm is a glycolytic enzyme found in adult neurons as the most generous form of the glycolytic enzymes [13]. In lung cancer patients the amount of NSE will be higher than 9 ng mL^{-1}. Another important protein biomarker, Chromogranin A (CgA) is an acidic glycoprotein that belongs to the granin family. The primary structure of CgA consists of 439 amino acids and its molecular weight is 49 kD. The amount of CgA is 50 ng $mL^{-1}$and over in lung cancer cases [14].

B. Exhaled breath analysis

Since long back the breath analysis method for disease recognition is used clinically like diabetes mellitus associated with sweet smell, liver disease with fish-like smell and kidney disease with urine-like smell [15]. Since breath analysis is a simple, non-invasive, sensitive and inexpensive method, early lung cancer detection based on this method is becoming more popular. The exhaled breath contains trace concentrations of various volatile organic compounds (VOCs) in addition to oxygen, nitrogen, water vapour and carbon dioxide [16]. Most VOCs are believed to reflect endogenous metabolic processes at the tissue level, such as inflammation and oxidative stress. VOCs are usually collected from human breath. From human breath around 3000 different VOCs have been identified. They can be categorized into few main groups such as alcohols, hydrocarbons, ketones, aldehydes and aromatic and nitrile VOCs [17]. The VOCs concentrations ranges in volume by parts per million (ppm) to parts per trillion (ppt). Till now it is not clear about the production mechanism of some VOCs whereas some other VOCs can be rationally explained in clinic [18]. However, breath analysis also detects exogenous VOCs, which reflect exposure to carcinogens such as cigarette smoke, pollution and radiation. If the concentrations of reactive oxygen species such as hydrogen peroxide (H2O2), superoxide (O2-) and hydroxyl radical (·OH) increase, part of them can produce certain damages to membrane and DNA of cells [6]. This may further cause lipid peroxidation and protein oxidation, and finally lead to the production of volatile organic compounds that are

secreted into breath and body liquid. The final result may be cellular senescence, inflammation, cancer and apoptosis. In addition to this irradiation, inflammation and pollutants in the air can also produce some VOCs.

The surface of cells emits some chemicals as tumour grows and certain sensors can be used to measure the emitted chemicals in the exhaled breath [19]. The VOCS detected in urine, breath and blood samples provides great information about the human condition. There is a distinguishable change in the patterns of biochemical markers from those of controls and cancer patients.

Ethane, pentane, acetone, isoprene, dimethylamine, ethanol, isobutene etc are the main VOCs present in the exhaled breath from humans [20]. Usually an array of sensors is used for the detection of VOCs which is cost effective and reduces the required processing power whereas a single sensor is difficult to achieve and in terms of required processing power and cost, it is impractical. The array of sensors used in this method is able to distinguish between cancerous and healthy breath and it can also differentiate across the breath patterns of variety of cancers in exactly similar statistical investigation, regardless of gender, lifestyle, age and other astonishing elements [19]. The main elements of e-Nose (electronic nose) based VOC analysis are sampling space, array of sensors, microcontroller and a pattern recognition system. A common power supply unit provides required power to the system. The block diagram depiction of the e-Nose system is shown in the figure 3.

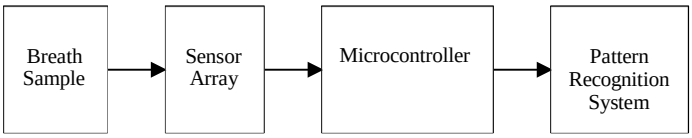


Fig. 3. Block Diagram of e-Nose System

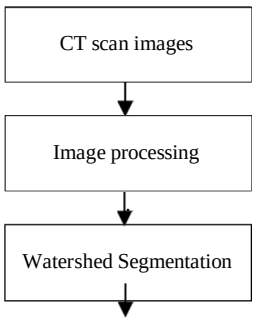
The two main components of an e-Nose System are the sensor array and the automated pattern recognition system. In an array of VOC gas sensors each sensor measures a different property of the sensed odour or the array with overlapped sensitivity response to a complex odour. As a result the sensor array produces a pattern or characteristic signature. The signals obtained from sensor arrays are converted into digital signal using a microcontroller. The pattern recognition system used is Backpropagation Neural Network. Feature extraction is done and the features extracted are used to train the Neural Network. The designed algorithm calculates the content of gases present and the percentage of gases present is depicted as a graph. The healthy individuals and lung cancer patients can be differentiated from analyzing the output of the e-nose system [20].

A. CT Scan Imaging

CT scan imaging is a reliable technique for lung cancer detection since it can reveal every cancer nodules suspected and unsuspected [21]. Even though it is a reliable technique, intensity variation in computer tomography scanned images and errors in the judgment of structural anatomy by clinicians and radiologists may cause trouble in labeling the cancerous cell. Computer aided diagnosis is nowadays common and is a promising tool for the accurate detection of early lung cancer [22, 23].

Lung cancer detection using CT scan images is shown in figure 4. CT scan images are first pre-processed with the implementation of Median filter and Gaussian filter. The salt and pepper noise is removed by the action of Median filter whereas smoothening and removal of speckle noise from image is carried out by Gaussian filter. Cancer nodules are detected in the next stage where the watershed segmentation is applied to the processed image [21]. The watershed segmentation can segregate and spot the touching object in the images which support in actual segmentation of cancer nodule if that touches other false nodule.

In the feature extraction stage features like perimeter, area, eccentricity, diameter, centroid etc are extracted for the detected tumour nodules. Support Vector Machine is used to classify the tumours as benign or malignant [21,24]. A trained prediction model is produced by using extracted features as training features. Finally the trained prediction model can help the classification of unknown detected cancer nodule.



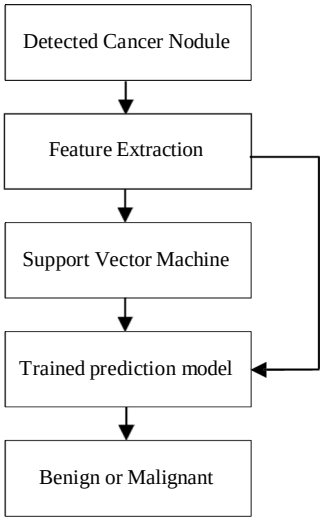


Fig. 4. Lung cancer detection using CT scan images

III. CONCLUSION

The quick invasion and short survival time of the malignant tumours causes the lung cancer to be the mostly deadly of all types of cancers. A significant reduction in lung cancer disease and death rate is possible by the early detection. Standard diagnostic procedures are not always acceptable for the early prediction of lung cancer as they detect abnormalities at the later stages.

Biomarkers, the application of biosensor technology can provide a reliable detection technique for the early prediction of lung cancer. With the recent advancements in biosensing systems, detecting the normal range of protein biomarkers of ng mL^{-1} by using nanomaterials amplification, surface chemistries and bioassay format is possible. Biosensor systems with microfluidics and nanomaterials can greatly improve the efficiency and reliability.

Breath analysis is a multidisciplinary field comprising of analytical chemistry, clinical, data processing and metabolomics expertise. Breath VOC analysis is a practicable and reliable technique for the early prediction of lung cancer. Nowadays, E-nose based VOC analysis is showing optimistic prospects in clinical practices.

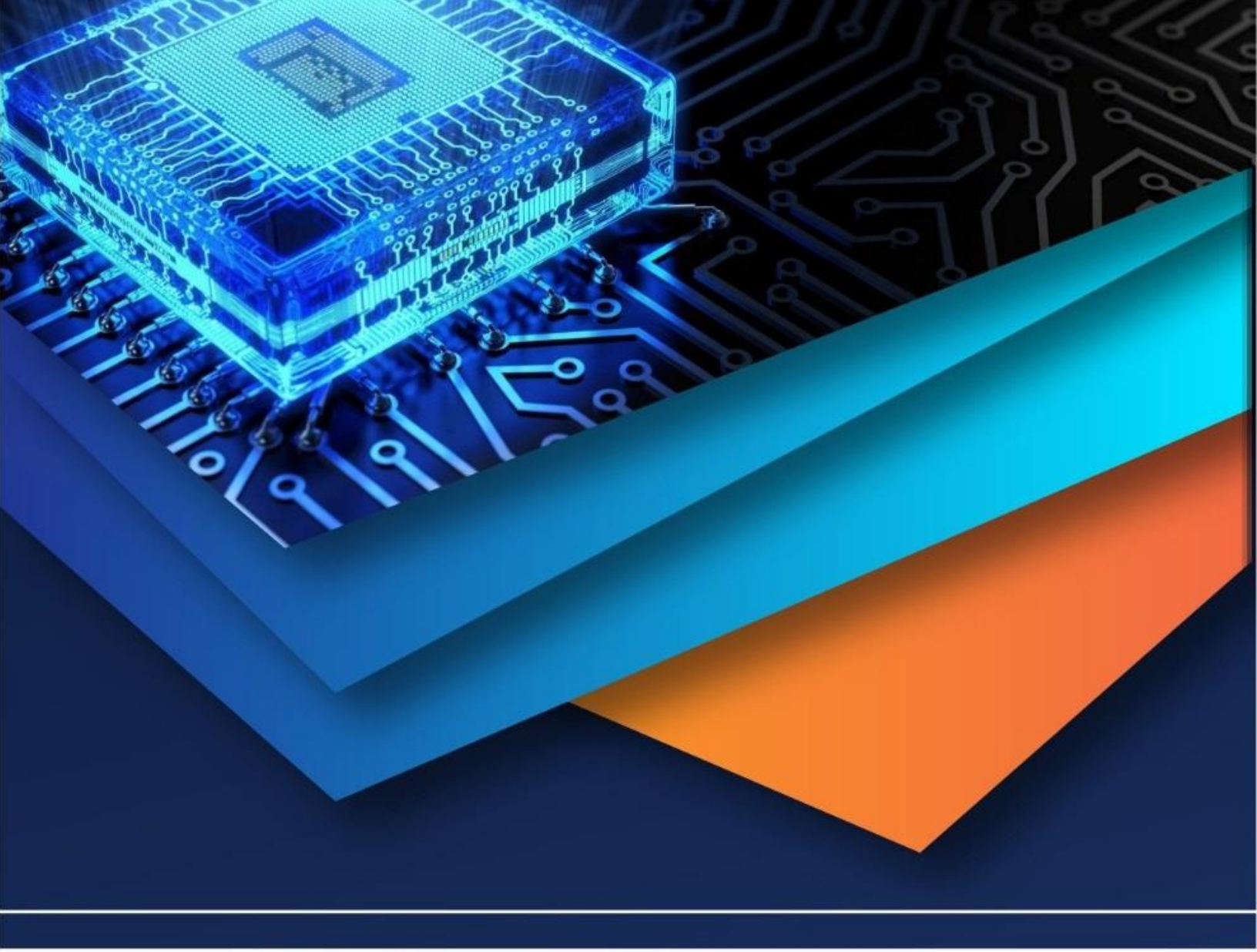
In several medical situations image processing is broadly used for image magnification in the diagnosis stage to assist the prior medical therapy. The early lung cancer detection based on watershed image segmentation, feature extraction and Support Vector Machine algorithm (supervised learning) has high accuracy and robustness.

The methods of early detection of lung cancers explained in our literature provides economical, non-invasive, sensitive, and user-friendly diagnosis tool with highly reliable, specific and sensitive for cancer markers.

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