ECRONICON OPEN ACCESS

EC PULMONOLOGY AND RESPIRATORY MEDICINE

Review Article

Screening for Lung Cancer in Primary Care

Maram Omar Shakir[1]*, Khleel Adnan Alowyed[2], Alaa Adel Shabekni[3], Afnan Sultan Alotaibi[4], Wejdan Ariman Alosaimi[5], Wail Mohammad Naji Alanazi[6], Bader Nawaf Alharbi[7], Hanan Mohammed Alghamdi[8], Hamed Faisal Ghabashi[9], Ibrahim Abdullah Albakri[10], Hamza Yahya Khogah[11], Safaa M AlHasani[11] and Mohammad Noor Qadrouh[12]

[1]Almajed Primary Health Care Center, Saudi Arabia

[2]Omran General Hospital, Saudi Arabia

[3]Hera General Hospital, Saudi Arabia

[4]Almaarefa University, Saudi Arabia

[5]Queen Alia Military Hospital, Saudi Arabia

[6]Prince Mutaib Bin Abdulaziz, Saudi Arabia

[7]Al-Imam Muhammad Ibn Saud Islamic University, Saudi Arabia

[8]Ibn Sina National College, Saudi Arabia

[9]King Abdulaziz University, Saudi Arabia

[10]Najran University, Saudi Arabia

[11]Batterjee Medical College, Saudi Arabia

[12]Alnoor Specialist Hospital, Saudi Arabia

***Corresponding Author:** Maram Omar Shakir, Almajed Primary Health Care Center, Saudi Arabia.

Received: January 03, 2019; **Published:** January 09, 2020

Abstract

Introduction: Lung cancer is one of the leading causes of death in the United States of America. It is prevalent both in men and women. The 5-year survival rate, even after so many advances in the diagnostic and management approach, has been constant and has not increased more than 14.

Screening of lung cancer at an early stage has been of interest by many practitioners as they are smaller and are more curable compared to later stages. Chest Radiography and examination of sputum by cytological means have been used as methods for screening of cancer in early stages but to date, the ultimate goal for the screening of the disease has not been achieved; that is the decrease in disease-specific mortality.

Aim of Work: This review highlights lung cancer and the different screening procedures and trials done over the years for lung cancer.

Methodology: The review is a comprehensive research of PUBMED from the year 1979 to 2019.

Conclusion: The leading cause of death in a huge population around the globe is lung cancer. Various screening trials have been started to detect the disease in an earlier stage and start treatment in the preclinical stage of the disease. Sputum Cytology, Low dose Ct scans and radiographs are the main diagnostic tests done for screening trials. Even though there is a lot of pressure from the public to make the screening of lung cancer based only on low dose CT, there should be no short cuts when it comes to rigorous scientific procedures required to diagnose the disease. Well organized randomized studies should be conducted for a better screening program which should be started only after the success of these studies.

Keywords: *Screening; Lung Cancer; Primary Care*

Introduction

Lung cancer is one of the main causes of death in the United States of America. It is prevalent both in men and women. The incidence rate of death is higher from lung cancer compared to any other form of cancer like breast, colon or prostate. The 5-year survival rate, even after so many advances in the diagnostic and management approach has been constant and has not increased more than 14 [1].

Screening of lung cancer at an early stage has been of interest by many practitioners as they are smaller and are more curable compared to later stages. Chest Radiography and examination of sputum by cytological means have been used as methods for screening of cancer in early stages but to date, the ultimate goal for the screening of the disease has not been achieved. That is the decrease in disease-specific mortality. In previous studies, the groups that were screened and the control both had an almost equal number of death rate and hence screening was not done thereafter. Because of the increased rise in technology, they're a lot of developments in the area of screening and patients have an increased awareness due to media and hence demand screening at early stages. The amount of data that has been obtained from various studies has revealed that various screening procedures like low dose CT can be used for screening of cancer at an early stage, thus reducing the mortality rate with that disease. Because of the high number of studies that have been done, there is a huge compilation of data that has now become very confusing and hence before any screening trial is started a detailed study of the screening procedure, the morbidity and mortality rate of the study and cost-benefit relationship is studied [1].

Screening of lung cancer

What is screening?

Screening of a disease is generally done in initial stages when cure or control of the disease is possible. A series of people who are thought to be at risk are undertaken for screening, and people who have a positive result to screening are further evaluated for the disease. Once the diagnosis is made for the disease, the treatment is started at an early stage hence reducing the death rate caused by the disease. The survival from the time diagnosis is made even though is reported but is not appropriate and can be misleading since it is subjected to lead-time bias. For any screening to be counted as successful, it is important that the effect is shown in the decrease in mortality rate rather than on survival rate. For the success of the screening procedure, it's essential that the treatment for a particular disease is started at the preclinical stage. The cost-benefit ratio, sensitivity and specificity of the screening test should also be taken into regard [2].

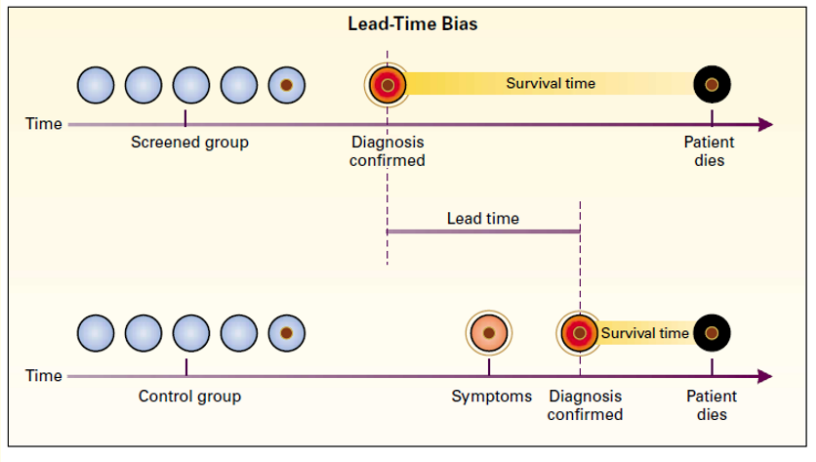

Figure 1: *Lead time Bias in cases of screening. Even though the time of death remains constant in both the groups, the survival time increases in patients in whom screening was done [3].*

Risk factors for lung cancer

The most predominant cause of lung cancer is smoking and it is directly linked to the disease with a higher prevalence in women than in men [4]. Indirect exposure to smoke in the form of secondhand smoke is also a common cause and several thousand people die each year with that [5]. When it comes to occupation-based hazard, the most common cause is exposure to asbestos followed by arsenic, chromium and nickel. Nonmalignant lung conditions like tuberculosis, pulmonary fibrosis and obstructive pulmonary disease also cause increased rates of lung cancer [6].

Pathogenesis of lung cancer

Lung cancer can be classified as small cell and non-small cell carcinoma. The histologic classification of lung cancer is adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma (Table 1). Adenocarcinoma has the tendency to metastasize in the early stages and is seen in patients with lung cancer. Squamous cell carcinoma metastasizes late in the course of the disease. It is aggressive and involves the mediastinum. Even though small cell carcinoma responds to chemotherapy, by the time they get diagnosed, they become very advanced and the patient has a poor prognosis. Large cell carcinoma metastasizes early like adenocarcinoma [7].

	Classification of lung cancer based on histology	
Class	**Prevalence**	**Subclass**
1. Adenocarcinoma	40%	i. Acinar ii. Bronchoalveolar iii. Solid carcinoma iv. Papillary v. Mixed
2. Squamous cell carcinoma	25%	
3. Small cell carcinoma	20%	i. Pure small cell carcinoma ii. Combined small cell carcinoma
4. Large cell Carcinoma	10%	i. Large cell neuroendocrine ii. Large cell with rhabdoid phenotype
5. Adenosquamous Carcinoma	Less than 5%	
6. Bronchial gland Carcinoma	Less than 5%	
7. Carcinoid	Less than 5%	

Table 1: *Classification of lung cancer based on histology [8].*

Clinical presentation of lung cancer

In approximately 10% of the patient's chest, radiographs reveal the disease even when they are asymptomatic. Other nonspecific systematic symptoms that can be seen are anorexia, weight loss, and tiredness. Other symptoms that are caused by the direct manifestation of the tumor can be seen as an intrathoracic and extrathoracic spread. Following is a list of symptoms that can be associated with the disease [9] (Table 2).

Symptoms of Lung cancer	
Primary tumour	1. Discomfort in chest 2. Cough 3. Hemoptysis 4. Dyspnea
Intrathoracic Spread	5. Invasion of the chest wall 6. Esophageal Symptoms 7. Pancoast's tumor 8. Paralysis of phrenic nerve 9. Paralysis of pharyngeal nerve 10. Obstruction of Superior Vena Cava
Extrathoracic spread	11. Pain in bone and fracture 12. Confusion and change in personality 13. Seizure 14. Weight loss 15. Weakness 16. Palpable lymphadenopathy

Table 2: *Clinical Manifestations of Lung cancer [9].*

Tissue diagnosis for lung cancer

The diagnosis of lung cancer is a combined effort of the Pulmonologist, radiologist, and a thoracic surgeon. When a non-small cell carcinoma is detected, the patient has advised a thoracotomy for good tissue diagnosis and appropriate staging. When the patient has a condition of small cell or metastatic non-small cell carcinoma, diagnosis is made by non-invasive methods like pleural effusion, a biopsy of any node inaccessible areas, transthoracic needle aspiration. In patients where the stage and type of cancer id not very clear other diagnostic tests can be done like Sputum Cytology, Bronchoscopy, and transthoracic needle aspiration [10].

Sputum cytology

During lung cancer, there are a lot of molecular events that take place which can act as markers for the disease and should be checked in patients with the high-risk category. Molecular changes are seen in bronchial epithelium in the form of squamous metaplasia and p53 expression. Sputum cytology is a non-invasive technique that involves the identification of tumors that are located centrally. Sputum cytology can detect centrally as well as peripherally located tumors [11].

The sputum collected for cytology can either be induced or collected as and when produced spontaneously by the patient. A fixative solution by Saccomanno can be used for the collection, fixing and transportation of the sputum [12]. A sputum sample is only checked for markers if epithelial cells from the bronchial lining are seen in the sample because that shows that the sample is originated from deeper layers in the lung. Only a minor portion of the sputum is tested for macrophages, amongst which an even lesser number is reflective of tumor cells. The macrophage quantity ranges from as low as 5 to 150 in number. Sputum sample can be used to detect the presence or absence of tumor and can also classify the stage of the lesion (Figure 2-4). A lot of studies have shown that sputum cytology has a very limited role in the screening of lung cancer but studies comparing x-ray to cytology show that sputum cytology had a higher chance of

revealing cancer compared to radiographs. In a study done in Japan, out of 36 cases that were studied, 4 cases could only be detected by sputum and 8 cases were detected both by sputum and Xray. All this data emphasizes the use of sputum cytology in the screening of lung cancer [13].

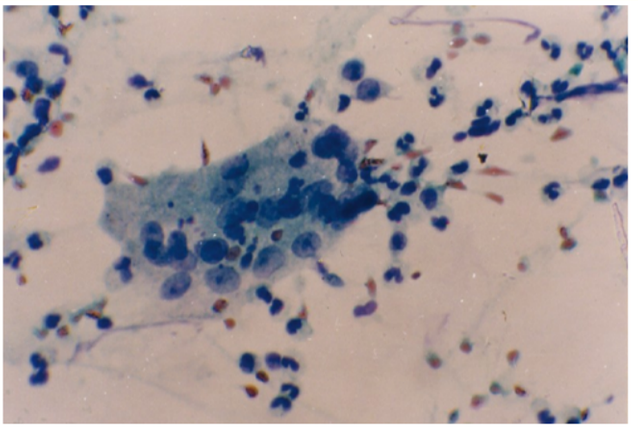

Figure 2: *Sputum cytology: PAP stain of the patient showing Langhans giant cell [14].*

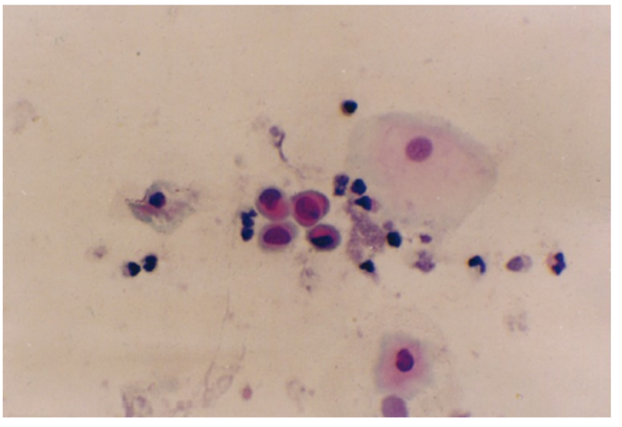

Figure 3: *PAP stain of sputum revealing metaplasia of squamous cell [14].*

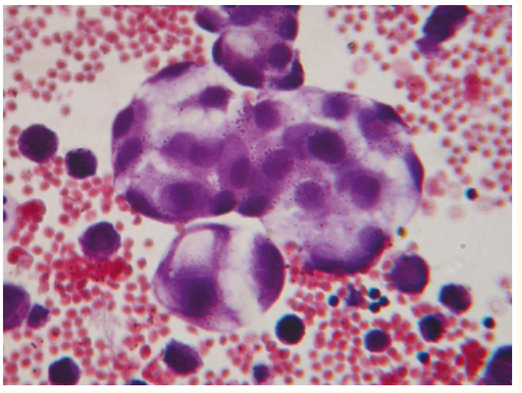

Figure 4: *PAP stain showing adenocarcinoma [14].*

Imaging studies for the screening of lung cancer

The screening tests that were done earlier are not regarded high anymore and are questioned due to varying study design, analysis, bias and older technology. The development of new radiation technologies have now increased awareness and raised the need for new imaging detection trials. Various comparative studies have been done comparing the use of cytology and imaging or radiographs and computed tomography scans (CT Scans). The Early lung cancer project compared low dose CT scans with chest radiographs in patients who were high-risk smokers and were over the age of 60 [15]. These trials have shown that Ct scans are more useful when compared with radiography in the detection of nodules in the lung and in some cases, these nodules have evolved into cancer (Figure 5). when the data from recent low dose CT scans are compared with older studies it shows that CT has diagnosed more cases of lung cancer compared to other imaging techniques [16].

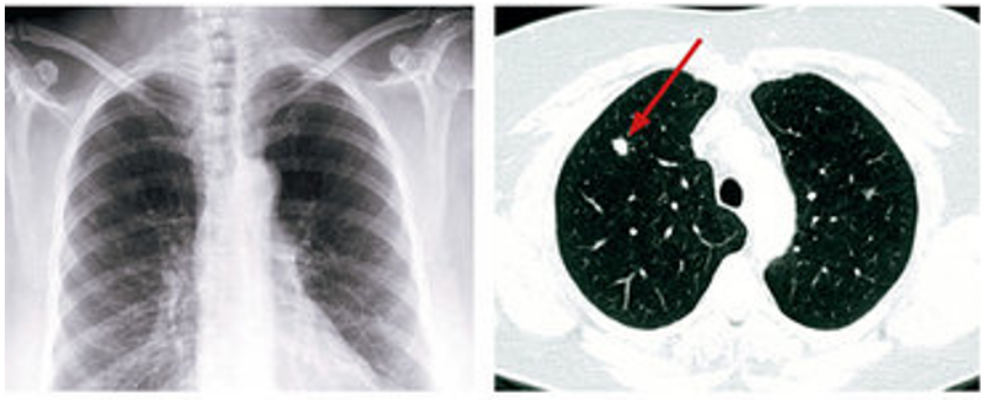

Figure 5: *The chest X-ray and Ct Scan of the same patient, X-ray did not reveal any lesion because of the overlapping 2D image but when CT Scan was taken a small malignant nodule was observed (red arrow) [16].*

Significance of the small tumors that are diagnosed via screening is not known, and their effect on mortality is yet to be investigated. Low dose Ct scans also reveal an intermediate nodule in one of 23 patients that are scanned. Several studies are done but only a few preexisting data for screening are present. Mayo clinic in 1999 conducted a study where they enrolled around 1500 patients who were current or had been a smoker previously; all the patients underwent low dose CT and Sputum cytology examination. The patients were kept under follow up and the results were 15 patients had lung cancer out of which 60% had early-stage disease. 51% of the patients were kept under follow up due to small nodules being present. The trials using low dose CT are showing to have good results and several groups are now proposing that randomized clinical trials that are prospective in nature should now be conducted to increase the sensitivity of the trials [16].

Biological limitations of screening

CT scans can diagnose even smaller nodules, and hence more interest has been taken in this technique but the size of the nodule does not always correlate with the clinical picture. There are currently no studies that can confirm that a smaller nodule says 5mm will have a better prognosis than a bigger 10 mm nodule. Any lesion that occurs is only seen once the disease is in a more developed state [17]. The assumption that the behaviors of the lesion correlate with the size of the lesion has not been confirmed yet. By the time tumors are visible on the CT scan, they would have already metastasized. This shows that a very large group of patients would have already had the disease by the time it is seen in the screening trials [18]. An experiment conducted in the recent past has shown that a tumor as small as 1 - 2 mm would have already metastasized as the tumors have the tendency to coopt adjacent normal blood vessels [19].

Conclusion

The leading cause of death in a huge population around the globe is lung cancer. Various screening trials have been started to detect the disease in an earlier stage and start treatment in the preclinical stage of the disease. Sputum Cytology, Low dose Ct scans and radiographs are the main diagnostic tests done for screening trials. Even though there is a lot of pressure from the public to make the screening of lung cancer based only on low dose CT, there should be no short cuts when it comes to rigorous scientific procedures required to diagnose the disease. Well organized randomized studies should be conducted for a better screening program which should be started only after the success of these studies.

Bibliography

1. Landis SH., *et al*. "Cancer statistics, 1998". *CA: A Cancer Journal for Clinicians* 48.1 (1998): 6-29.
2. Vachani A., *et al*. "Adherence to Annual Lung Cancer Screening". In C30. Lung cancer screening: lessons from the front-line. American Thoracic Society (2019): A4488.
3. Patz Jr E F., *et al*. "Screening for lung cancer". *New England Journal of Medicine* 343.22 (2000): 1627-1633.
4. Bilello KS., *et al*. "Epidemiology, etiology, and prevention of lung cancer". *Clinics in Chest Medicine* 23.1 (2002): 1-25.
5. Bayard SP and Jinot J. "Respiratory Health Effects of Passive Smoking: Lung Cancer & Other Disorders". Diane Publishing (1993).
6. Selikoff IJ., *et al*. "Mortality experience of insulation workers in the United States and Canada, 1943-1976". *Annals of the New York Academy of Sciences* 330.1 (1979): 91-116.
7. Patz Jr E F. "Imaging bronchogenic carcinoma". *Chest* 117.4 (2000): 90S-95S.
8. Travis WD. "Pathology of lung cancer". *Clinics in Chest Medicine* 23 (2002): 65-81.
9. Beckles MA., *et al*. "Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes". *Chest* 123.1 (2003): 97S-104S.
10. Tockman MS., *et al*. "Prospective detection of preclinical lung cancer: results from two studies of heterogeneous nuclear ribonucleoprotein A2/B1 overexpression". *Clinical Cancer Research* 3.12 (1997): 2237-2246.
11. Woolner LB., *et al*. "Roentgenographically occult lung cancer: pathologic findings and frequency of multicentricity during a 10-year period". *Mayo Clinic Proceedings* 59.7 (1984): 453-466.
12. Field JK., *et al*. "Consensus statements from the Second International Lung Cancer Molecular Biomarkers Workshop: a European strategy for developing lung cancer molecular diagnostics in high risk populations". *International Journal of Oncology* 21.2 (2002): 369-373.
13. Sobue T., *et al*. "Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project". *Journal of Clinical Oncology* 20.4 (2002): 911-920.
14. Ammanagi A S., *et al*. "Sputum cytology in suspected cases of carcinoma of lung (Sputum cytology a poor man's bronchoscopy!)". *Lung India: Official Organ of Indian Chest Society* 29.1 (2012): 19.
15. Henschke C I., *et al*. "Early Lung Cancer Action Project: overall design and findings from baseline screening". *The Lancet* 354.9173 (1999): 99-105.

16. Doo K W., *et al*. "Comparison of chest radiography, chest digital tomosynthesis and low dose MDCT to detect small ground-glass opacity nodules: an anthropomorphic chest phantom study". *European Radiology* 24.12 (2014): 3269-3276.

17. Patz Jr E F., *et al*. "Correlation of tumor size and survival in patients with stage IA non-small cell lung cancer". *Chest* 117.6 (2000): 1568-1571.

18. Hermanek P., *et al*. "Classification of isolated tumor cells and micrometastasis". *Cancer: Interdisciplinary International Journal of the American Cancer Society* 86.12 (1999): 2668-2673.

19. Yang M., *et al*. "Widespread skeletal metastatic potential of human lung cancer revealed by green fluorescent protein expression". *Cancer Research* 58.19 (1998): 4217-4221.

Volume 9 Issue 2 February 2020