Biomedicine & Pharmacotherapy 106 (2018) 1586–1599

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Current trends and emerging diagnostic techniques for lung cancer

Bala Prabhakar, Pravin Shende*, Steffi Augustine

Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM'S NMIMS, V.L. Mehta Road, Vile Parle (W), Mumbai, India

ARTICLE INFO

Keywords:
Biosensors
Quantum dots
Artificial inte
Lligence
Biomarkers
Nanorobots

ABSTRACT

Cancer is one of most fatal forms of disease with rapid, abnormal and uncontrolled division of cells which spreads into different organs in the body. The primary aim of this review is to showcase the current and emerging diagnostic techniques that are used in lung cancer detection. Lung cancer is a leading cause of death among smokers and it has been emerging in non-smokers due to passive smoke inhalation by non-smokers. The mortality rate of patients with lung cancer is very high due to the change in lifestyle and environmental factors. It is often misdiagnosed as tuberculosis in India as tuberculosis is prevalent in India. On the contrary tuberculosis is not prevalent in the western countries Like U.S.A., U.K., Canada, etc. The major setback in lung cancer is that the symptoms of lung cancer occur at very later stages when the tumor has spread profusely. Hence, highly advanced techniques are employed for detection, accurate staging and treatment of lung cancer. The review focuses on the various novel and emerging diagnostic tools like biomarkers and biosensors, radiogenomics and artificial intelligence. This review also gives an insight of the various conventional techniques like CT-imaging, sputum cytology, biopsy and bronchoscopy which have been modified over the years for better sensitivity and accuracy. It also encompasses the regulatory provisions like IDE, CLIA-certification, etc. for manufacturing and sale of diagnostics in India, U.S.A., Japan and Australia.

1. Introduction

Cancer is a leading cause of mortality among the population after cardiovascular diseases [1]. Some of the most fatal types of cancer include lung, colorectal and stomach cancer as they get detected only when the tumor cells have metastasized in other parts of the body. Lung cancer is often misdiagnosed as tuberculosis due to their common symptoms. The main cause of lung cancer is tobacco smoking (direct and passive) and the other risk factors that can lead to lung cancer include radon, asbestos inhalation, genetic factors, race and ethnicity, diet, environmental pollution, and biomass or wood incineration [2]. Two-thirds of the lung cancer cases are detected in the geriatric patients of age over 65 years [3]. The detection and stage finding of lung cancer is very crucial and difficult as the stages can be misinterpreted due to interrelated characteristics of the tumor [4]. Lung cancer is classified into three major classes: NSCLC, SCLC and LCT [5]. In this era, a tremendous development is observed in the field of diagnosis for lung cancer. The basic techniques like Computed Tomography Imaging, biopsy and bronchoscopy underwent modifications [6,7] and this development also involved the introduction of advanced tools and techniques like biosensors, biomarkers, radiogenomics, artificial intelligence, etc. The staging of tumor is characterized on the basis of TNM proposed by Denoix in 1946 [8]. TNM staging is widely used with the screening techniques for effective detection of nature and type of lung carcinoma. The diagnostic techniques used in the detection of lung cancer has associated risks and mishandling of which can cause damage

Abbreviations: NSCLC, Non-Small Cell Lung Carcinoma; SCLC, Small Cell Lung Carcinoma; AC, Adenocarcinoma; LCT, Lung Carcinoid Tumor; LCC, Large Cell Carcinoma; CTC, Circulating Tumor Cells; UICC, The Union for International Cancer Control; CT, Computer-based Tomography; LDCT, Low Dose Computed Tomography; PET, Positron Emission Tomography; SPECT, Single Proton Emission Computed Tomography; WBB, White Balance Bronchoscopy; ELONA, Enzyme Linked Oligo Nucleotide Assay; RG, Radiogenomics; AI, Artificial Intelligence; QD, Quantum dots; PTT, Photo-Thermal Therapy; TNM, Tumor Node Metastasis; EMA, European Medicines Agency; USFDA, United States Food and Drug Administration; WHO, World Health Organization; IALSC, International Association for the Study of Lung Cancer; NCI, National Cancer Institute; NLST, National Lung Screening Trials; NCTN, National Clinical Trials Network; IDE, Investigational Devices Exemption; CLIA, Clinical Laboratory Improvement Amendments; PMDA, Pharmaceuticals and Medical Devices Agency; MHLW, Ministry of Health, Labor and Welfare; TGA, Therapeutic Goods Administration; IVD, *In-vitro* Diagnostics; DoH, Department of Health; CDSCO, Central Drugs Standard Control Organization; ROSE, Rapid Onsite Cytopathology Evaluation; PTEN, Phosphatase and tensin analog; EGFR, Endothelial Growth Factor Receptor; ALK, Anaplastic Lymphoma Kinase; ROS, 1 Proto-oncogene; KRAS, Kristen Rat Sarcoma; HER2, Human Epidermal Growth Factor Receptor 2; mAb, Monoclonal Antibodies

* Corresponding author.
E-mail address: shendepravin94@gmail.com (P. Shende).

https://doi.org/10.1016/j.biopha.2018.07.145
Received 30 April 2018; Received in revised form 24 July 2018; Accepted 25 July 2018

Table 1
USFDA approved companion diagnostics.

Diagnostic test	Company name	Type of cancer	Year of approval
FoundationOne CDx	Foundation medicines, Inc	Solid tumors	2017
Oncomine Dx Target Test	Life Technologies Corporation	NSCLC	2017
Cobas EGFR mutation test v2	Roche molecular systems, California	NSCLC	2016
VENTANA PD-L1 (SP142) Assay	Ventana Medical Systems, Inc.	NSCLC	2016

to the patient. Hence in order to carry out these tests, there are various regulations proposed by EMA, USFDA, JPMA, TGA and CDSCO [9].

1.1. USFDA approved companion diagnostics

Companion diagnostics are *in-vitro* medical devices which give essential information about effective use of drugs. These devices detect specific genes in the body and their response to anti-cancer drugs. These have made the development of personalized medicine easy and these are essential post-diagnosis for effective monitoring of the disease. The sensitivity of these companion diagnostics are above 95% but the cost of these tests are relatively higher which limits its use among the poorer population.

The various USFDA approved companion diagnostics for LC are listed in Table 1.

1.2. Misdiagnosis of lung cancer (LC)

LC is often misdiagnosed as TB in countries like India where TB is prevalent because both the diseases show common symptoms at the initial stages like coughing up blood, loss of appetite, weight loss and fever [10]. The misdiagnosis of LC as TB is very rare in western countries like U.S.A., U.K., etc. as TB is not a prevalent disease in these countries. TB is caused by *Mycobacterium tuberculosis* infection and LC is primarily caused by inhalation of hazardous smoke. One of the distinguishing points between TB and LC is that TB can occur in non-smokers whereas LC is caused by smoking and it rarely occurs in non-smokers unless there is excessive passive smoke inhalation [11]. Various evidence showed that the scar caused due to TB in the lung can act as a starting point for LC [12]. Although TB and LC show common symptoms they can be clearly distinguished by careful examination of the patient's medical history. The use of diagnostic tests specific to LC during the examination of patient is also helpful in distinguishing between the two diseases. The various differentiable parameters between TB and LC which can help medical professionals in avoiding misdiagnosis of LC for medical professionals are listed in Table 2 [13].

Table 2
Distinguishing TB and LC.

Sr.No.	Symptoms and indications	LC	TB
1.	Fever	Non-specific occurrence	Low-grade fever with rising in the evening
2.	Weight loss	Sudden	Gradual
3.	Dyspnea	Present	Absent or present
4.	Clubbed nails	Present	Not often
5.	Response to anti-tubercular drugs	No	Yes and immediate
6.	Specific detection technique	Biopsy	CT

2. Types of lung cancer and their classification for diagnosis

Lung cancer is broadly classified as NSCLC, SCLC and LCT among which NSCLC accounts for about 85% of LC cases, SCLC accounts for 10–15% and LCT accounts for 5% of LC cases respectively and LCT occurs rarely as compared to the other types of LC [5]. The classification of lung cancer is shown in Fig. 1.

2.1. Histological classification of lung cancer

SCLC is also known as oat cell carcinoma due to the size of the cells present in the tumor as a small lesion which is completely isolated. SCLC when present with some components of NSCLC it is termed as combined small cell carcinoma [14]. Histologically the cells are small in size, fusiform, with little or no cytoplasm, fine chromatin, small or no nucleus and show nuclear molding. The rate of mitosis of SCLC cells is as high as 80 mitoses per 2 mm^2 of the area [15]. NSCLC is classified into three types (Fig. 1) among which squamous cell carcinoma involves intercellular, bridging and squamous cell spheronization. Squamous cell carcinoma occurs in the central region of the lung and rarely in the peripheral area. Adenocarcinoma (AC) can be distinguished as invasive or non-invasive type with a lepidic type of growth observed in the cells. The size of cells involved in tumor formation in AC is usually larger than oat cell carcinoma cells [14]. A depiction of histology of SCLC and NSCLC is illustrated in Fig. 2. A schematic view of important categories of lung cancer is shown in Fig. 3.

A schematic view of important categories of lung cancer is shown in Fig. 3 and these are the most prevalent types of LC.

2.2. TNM classification

The TNM classification is the most widely used classification system used by medical practitioners around the world. This staging system was first proposed by Dr. Pierre Denoix in the 1940's and it was further developed by UICC under the guidance of Dr. Denoix. It categorizes lung cancer on basis of the type of tumor, the degree of metastasis and the number of nodes as shown in Fig. 1 [16].

2.3. Classification-based on biological fluids

According to cancer research UK, on the basis of the spread of tumor cells in the biological fluids and compartments, lung cancer is classified into four stages as shown in Fig. 1. Stage 1 (1 A and 1B) indicates that the tumor is confined to the lungs and not entered into other biological fluid compartments. Stage 1 A indicates the tumor size is 3 cm or less and it is similar to TNM stage T1, N0, M0 and stage 1B indicates the tumor size is between 3 cm–4 cm and it is similar to T2,N0,M0. Stage 2 (2 A and 2B) indicates metastasis in the nearby lymphatic fluid compartment and it is similar to TNM stages T1, N1, M0; T2a-b, N1, M0 or T3, N0, M0. Similarly stage 3(3 A, 3B and 3C) depicts that the cancer cells have spread to more number of lymphatic tissue and stage 4 indicates proliferation and metastasis into nearby organs like liver, spleen, pancreas, gut and into the blood [17].

3. Diagnostic techniques for lung cancer

The ideal technique used in screening of any disease especially cancer requires some ideal characteristics mentioned in Fig. 4 [18].

The drawbacks associated with conventional techniques is that they involve poor patient compliance and higher cost hence the focus of research is shifting towards developing convenient and cheaper methods for detection of cancer. The various diagnostic techniques for LC are shown in Fig. 5.

A summary of advantages and disadvantages of the diagnostic techniques for LC are given in
Table 3.