NANOTECHNOLOGY IN LUNG CANCER: ADVANCES IN DIAGNOSIS, IMAGING AND TARGETED THERAPY

[1]Jinal Patel*, [2]Renisha Bhuva, [3]Vrushti Mehta, [4]Tirth Shastri,[5]Nikita Gupta

[1,2,3,4]Student, School of Pharmacy, ITM SLS Baroda University, Vadodara, Gujarat, India
[5]Assistant Professor, School of Pharmacy, ITM SLS Baroda University, Vadodara, Gujarat, India

***Corresponding Author**: jinalpatelh123@gmail.com

- **Abstract**

Background

Lung cancer arises from the malignant growth of respiratory epithelial cells following prolonged exposure to carcinogens such as tobacco smoke, air pollution, and industrial pollutants. Common clinical manifestations include persistent cough, chest pain, and unintended weight loss, often leading to diagnosis at advanced stages. In 2022, approximately 2.48 million new lung cancer cases were reported worldwide, with a higher incidence in males (63.4 percent) compared to females (36.6 percent), underscoring a significant global disease burden. This systematic review distinguishes itself by presenting an integrated and updated overview of how nanotechnology is reshaping lung cancer research, diagnosis, and treatment.

Method

A focused literature search was conducted using Scopus-indexed databases, including Elsevier, Springer Nature, Wiley up to March 2024 were screened based on relevance and scientific quality. Studies addressing nanotechnology-based diagnostic, therapeutic, and monitoring approaches in lung cancer were included.

Result

The results highlight PD-L1 expression, EGFR mutations, KRAS G12C alterations, circulating tumour DNA, and exosome mRNAs as the most prominent biomarkers identified across studies, with nano-enabled platforms showing improved sensitivity and early detection. Clinically, nano-formulated agents such as albumin-bound paclitaxel and polymeric micelle–based paclitaxel represent the most advanced therapeutics and reduced systemic toxicity in NSCLC. Regulatory analysis indicates that approved nanomedicines benefit from well-defined characterization and safety. Overall, nanotechnology consistently outperforms conventional approaches by enabling targeted delivery, improved bioavailability, reduced side effect, and give effect without compromising lungs.

Conclusion

This review consolidates current evidence on lung cancer by integrating disease biology, epidemiology, and therapeutic limitations with recent advances in nanotechnology, highlighting nanomedicine's potential to drive precision diagnosis and treatment while informing future clinical translation.

• **Keywords:** *Pulmonary drug delivery; Nanoparticles; Inhalation therapy; Lung cancer; Targeted drug delivery; Silver nanoparticles; Lycopene; Aerosol drug delivery; Nebulization; Pulmonary deposition*

1. INTRODUCTION

Lung cancer derived as malignant transformation of epithelial cells [2] lining the tracheobronchial tree and peripheral alveolar structures. It develops through a progressive accumulation of genetic mutations, epigenetic alterations, and microenvironmental changes that interruption normal cell regulation, promoting uncontrolled proliferation, impaired tumour cell death, angiogenesis, and invasion into surrounding tissues. [1,2]. Its clinical course is marked by rapid progression, early metastatic spread, and significant challenges in early detection. Although therapeutic science has advanced considerably, lung cancer continues to contribute heavily to global cancer mortality, reflecting both its biological complexity and the limitations of current treatment strategies [3,4].

The histological, molecular and cellular characteristics of lung cancer exhibit tremendous heterogeneity. Each histological subtype (e.g. NSCLC vs. SCLC) demonstrates distinct biological behaviours, response to therapy, and prognosis. The discovery of molecular abnormalities in EGFR, KRAS, ALK and PD-L1 has changed the therapy of lung cancer; but the challenges of resistance to drugs, intratumoral heterogeneity and lack of sufficient drug penetration continue to present major challenges for the effective lung cancer treatment for patients [4,5].

A major obstacle for early diagnosis continues to be the very low rates of early detection. Techniques such as low-dose computed tomography (LDCT) have improved screening outcomes, but false-positive rates, radiation exposure, and accessibility barriers limit widespread application. Many cases are still diagnosed at advanced stages, where curative interventions are no longer feasible [6,7].

The standard elements of clinical care include surgery, radiology, and chemotherapy, yet these modalities do not allow for a significant impact on patients due to several factors including: 1) limitations of systemic side effects; 2) the non-selective nature of drug distribution; and 3) the absence of a method to eliminate resistant variants of cancer cells. Newer approaches such as targeted treatments and immunotherapies have better results for selected patients but are influenced by mutation profiles, tumour microenvironment dynamics, and adaptive resistance mechanisms [4,5].

Nanotechnology has become a viable approach for advancing diagnosis and therapy. Nanocarriers can enhance drug solubility, improve tumour-specific accumulation, and reduce off-target toxicity [8]. Nano biosensors and nanoparticle-enhanced imaging have shown potential for more sensitive and precise detection [8]. Inhalable nano systems open new possibilities for local delivery directly to the lung tissue, achieving higher therapeutic concentrations with reduced systemic exposure [8].

The heterogeneity of lung cancer makes managing it clinically much more complex than many other cancers. For example, not all lung cancer tumours have the same rate of growth, pattern of metastasis, molecular profile, and response to treatment (6, 5). Therefore, using individualised treatment plans is extremely important, and yet in a lot of cases, the tumours still demonstrate resistance to therapies available and/or relapse after an initial response. (1,9)

This review provides a structured overview of lung cancer biology, current therapies, diagnostic challenges, and the expanding role of nanotechnology. It also explores specific nano-based interventions and outlines future directions for clinical translation.

1.1. Historical development of lung cancer research

In 1879, Harting and Hesse verified previous findings that miners were a group that was especially prone to the development of proliferative lesions in the lung tissue based on multiple autopsy exams [10]. The first possible risk factor for lung cancer occupational, prolonged exposure to mine dust was discovered for the first time as a result of the aforementioned research. The list of variables that may cause lung cancer has steadily expanded. Later on, it was complemented by exposure to ionising radiation, which was come radon present in the mines[11].
The advent of molecular biology has contributed to understanding lung cancer on a more basic level. The discovery of the important molecular targets that lead to lung cancer (EGFR mutations, ALK rearrangements, KRAS mutations, and subsequently ROS1 and BRAF mutations) ushered in the era of personalized medicine. This has also facilitated the development of molecular diagnostic tests and targeted treatments that were once unthinkable for certain groups of patients. [1,9]

Advances in immunology added another important dimension to the understanding of lung cancer and the rationale for the type of cure that is most effective. Understanding the mechanisms of immune evasion has caused immune checkpoint inhibitors to be developed. that provide durable long-term responses in selected patients with advanced forms of lung cancer. The use of biomarkers such as PD-L1 expression has allowed for improved patient selection strategies for these patients. [9,12]

1.2. Types of lung cancer, histological and molecular classification [4,13]

Table 1. Histological and Molecular Classification of Lung Cancer

Category	Subtype	Key Features	Molecular Characteristics	Clinical Notes
Non–Small Cell Lung Cancer (NSCLC)	**Adenocarcinoma**	Derived from glandular or alveolar epithelium, peripheral location	EGFR mutations, KRAS mutations, ALK and ROS1 rearrangements, BRAF mutations	Most common subtype, high prevalence in never-smokers, strong relevance in targeted therapy

	Squamous Cell Carcinoma	Arises from bronchial epithelium, central location, keratinization	FGFR1 amplification, PI3K alterations, DDR2 mutations	Strong association with smoking, lower response rates to EGFR/ALK inhibitors
	Large Cell Carcinoma	Poorly differentiated NSCLC lacking glandular or squamous features	Molecular profile overlaps with adenocarcinoma (KRAS, EGFR) or neuroendocrine markers	Diagnosis often relies on exclusion; aggressive clinical course
	Adenosquamous Carcinoma	Contains both glandular and squamous components	Mixed genetic profiles; may share driver mutations of adenocarcinoma	Less common, presents therapeutic challenges due to heterogeneity
	Sarcomatoid Carcinoma	Spindle cell and pleomorphic morphology	alterations, TP53 mutations	Barely but highly aggressive, limited established therapies
Small Cell Lung Cancer (SCLC)	**Classic SCLC**	High-grade neuroendocrine tumor, rapid growth, early metastasis	TP53 and RB1 loss, high mutational burden	Highly chemo-sensitive initially; early relapse common
	Combined SCLC	SCLC with additional NSCLC components	Molecular overlap with classic SCLC; may show EGFR or KRAS changes	Less responsive to standard SCLC regimens

Other Neuroendocrine Tumors	**Typical Carcinoid**	Low-grade neuroendocrine tumor	Mutations in MEN1, low proliferation index	Indolent behavior, surgical management preferred
	Atypical Carcinoid	Intermediate-grade neuroendocrine tumor	MEN1 alterations, chromosomal instability	Higher recurrence risk than typical carcinoid
Molecular Subtypes Across Lung Cancer	**EGFR-mutant tumors**	Increased proliferation signaling	Exon 19 deletions, L858R mutation	Respond well to EGFR TKIs
	ALK-rearranged tumors	Fusion-driven kinase activation	EML4–ALK fusion variants	Sensitive to ALK inhibitors
	KRAS-mutant tumors	Strong driver mutations associated with smoking	KRAS G12C, G12D, G12V	Historically resistant; G12C inhibitors improving outcomes
	PD-L1–high tumors	Immune-evasive phenotype	PD-L1 overexpression; TMB variability	Benefit from immunotherapy monotherapy
	MET-altered tumors	Dysregulated signaling and proliferation	MET amplification, exon 14 skipping	Respond to MET inhibitors in selected cases
	ROS1-rearranged tumors	Fusion gene–driven oncogenesis	CD74–ROS1 and other fusions	Sensitive to ROS1 inhibitors
	BRAF-mutant tumors	MAPK pathway–driven	BRAF V600E and non-V600E	BRAF–MEK inhibition effective in V600E cases

1.4. Epidemiology

Lung cancer presents a significant worldwide public health issue because of its great prevalence and mortality rates worldwide. Its epidemiology involves complex interactions between environmental exposures like tobacco smoke and air pollution, lifestyle factors such as diet, socioeconomic conditions, and genetic susceptibility. [14,15]

- **Global incidence and mortality**

In 2020, GLOBOCAN estimates reported 2.2 million new lung cancer cases globally, accounting for 11.4% of all cancer diagnoses, alongside 1.8 million deaths representing 18% of cancer mortality. Updated 2022 data from GLOBOCAN indicate approximately 2.5 million new cases (12.4% of cancers) and 1.8 million deaths (18.7% of cancer deaths), highlighting a persistently high fatality-to-incidence ratio driven by late-stage diagnoses and limited early detection. [16,17]

- **India-specific trends and patterns**

India exhibits a distinct and steadily increasing epidemiological pattern of lung cancer. [19,20] National cancer statistics indicate that lung cancer accounts for approximately 5.9 percent of all new cancer cases and about 8.1 percent of cancer-related deaths. Broader population-based analyses from 2020 have reported even higher proportions, with lung cancer contributing around 11.4 percent of all new cancer diagnoses and 18 percent of cancer deaths nationwide. Projections suggest a continued upward trajectory, with new cases expected to rise from an estimated 63,708 cases in 2015 to approximately 81,219 cases by 2025. These trends are driven by persistent tobacco consumption in men, environmental and indoor air pollution affecting both genders, and widespread biomass fuel exposure in rural households. [16,19,21]

1.5. Etiological factors

- **Smoking;**

One established risk factor for lung cancer is cigarette smoking [22]. The International Agency for Research on Cancer (IARC) has assessed over 70 carcinogens found in cigarettes as human carcinogens, and IARC monographs have compiled epidemiologic studies showing a link between smoking cigarettes and lung cancer [22, 23].

- **Occupational exposures;**

About 10% of lung cancer cases were caused by known occupational lung carcinogens, with significant geographical differences, such as asbestos, diesel fumes, arsenic, beryllium, cadmium, chromium, nickel, and silica [24]. According to estimates, occupational exposure was responsible for 9.5% of lung cancer fatalities in China in 2005 [25].

- **Radon;**

Based on epidemiologic research showing a strong exposure-response association between occupational exposure to radon and its decay products and risk of lung cancer, the IARC has categorised radon as a Group 1 human carcinogen [26].

- **Air pollution;**

Every 10 μg/m 3 rise in PM 2.5 was associated with a statistically significant higher risk of lung cancer incidence (RR = 1.09, 95% CI: 1.04, 1.14), according to a meta-analysis [27].

- **Dietary factors**

Comparison is difficult because different food frequency questionnaires were employed in this research. Increased intake was linked to a somewhat lower risk of lung cancer, according to meta-analyses of fruits and vegetables [28,29], soy-products [30], and fish [31], as well as a moderately increased risk as- sociated with high intakes of red and processed meat [32,33].

- **Other than that physical activity, psychological factors, Genetic factors**

2.6 Pathophysiology of lung cancer

The main reason for lung cancer is the gradual changes that occur in the normal structure of cells, mainly because of extended exposure to genetic and environmental risk factors (34,35). In lung tissue, specifically the bronchial and alveolar epithelium there is accumulation of molecular and structural abnormalities as a result, abnormal differentiation and uncontrolled proliferation occurs, due to this the regular cellular mechanism gets fail (34). Genetic instability, dysregulation of important signalling pathways, and interaction between tumour cells and their surrounding Microenvironment all this contribute to disease's progression which would eventually lead to tumour growth, and metastatic spread (35,37).

The epithelial cells present inside the lungs they use strict mechanisms of cell division, differentiation, apoptosis so the normal tissue structure is maintained under physiological conditions (34). Tumour suppressor systems and efficient DNA repair mechanisms they help to preserve the genomic stability and eliminate damaged cells, through programmed cell death, maintaining overall cellular turnover and preventing abnormal cell division (34). However prolonged exposure to environmental carcinogens mainly cigarette smoke and air pollution and occupational agents such as asbestos and radon results in repeated damage to the bronchial and alveolar epithelial cells (35).

This exposure to carcinogens produces reactive oxygen and nitrogen species that damages cellular DNA, in which strand breakage, base alterations, and DNA adduct formation occurs (35,36). The normal mechanism of DNA repair pathways gets hindered due to chronic exposure, due to these mutations accumulate even in morphologically normal cells which increases genetic instability - an early and critical feature for lung carcinogenesis (34,36).

More and more epithelial injury also increases chronic inflammation, characterized by release of cytokines, growth factors, and free radicals (35). These inflammatory signals worsen DNA damage and stimulate cell proliferation, which increases the chances that DNA errors are permanently incorporated into genome (35,36).

As genetic damage accumulates DNA repair systems and tumour suppressor genes stop working properly (34).As the controls are lost, the damaged cells escape programmed cell death because apoptosis signalling and cell cycle check points are disrupted (34).This disruption allows the abnormal cells to multiply, which overall promotes lung cancer (34,35).The molecular drivers such as EGFR , KRAS ,and ALK keep the growth related signalling pathways active at this time, these changes help the epithelial cells of the lung to grow , survive as well as resist cell death, due to which uncontrolled division occurs (34).

Lung epithelial cells slowly lose normal structure and function, due to these genetic disturbances (34). Cells began to focus more on survival and rapid growth, rather than their

normal activity. Hypoxic conditions develop within the tumour as the blood cannot supply oxygen to this rapidly growing cells (36). Hypoxia makes the tumour more aggressive and promote new blood vessels formation by activating signals, help cells adapt their metabolism, and also increase resistance to stress (36).

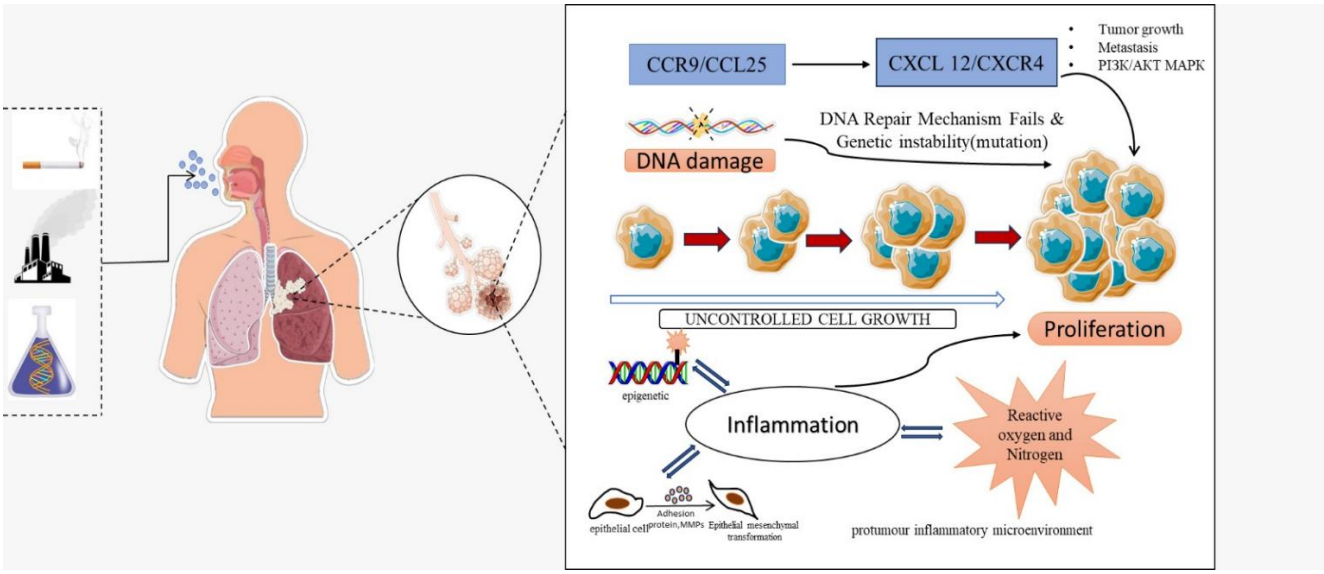
Chronic inflammation is maintained within the tumour microenvironment because of continuous release of cytokines and inflammatory mediators, which further promotes cancer progression (35). The immune attack is also escaped by lung cancer cells by altering surface antigen expression, reducing antigen presentation, and disrupting immune signalling pathways (35). so, the tumour cells continue to grow despite an active immune response (35).

As the tumours increase in size, angiogenesis becomes essential for their continuous growth (37). Lung cancer cells release pro-angiogenic factors that stimulate the formation of new blood vessels which helps in supplying adequate amount of oxygen and nutrients (37).

These blood vessels also help the the tumour cells to enter the bloodstream and spread to other sites (37).Proteolytic enzymes are also secreted by cancer cells at the same time which helps in degrading the basement membrane and extracellular matrix. so this overall reorganization of tissue occurs, which allows tumour cells to invade around the surrounding lung tissue, which causes the progression from local to invasive disease (37).

Early abnormal tissue changes such as squamous metaplasia, atypical adenomatous hyperplasia and carcinoma in situ are often present before invasive lung cancer develops (38).These lesions show abnormal cell behaviour due to disturbed genetic control even though they don't cross the basement membrane (38).The progression turns to invasive lung cancer because of build-up of genetic changes and selection of more aggressive cell populations , which over all accelerates the tumour growth (38).

Lung cancer cells spread via lymphatic and hematogenous routes in the mature stages (4). Lymphatic spread involves lymph nodes, bones, and adrenal glands. Hematogenous spread causes metastasis to distant organs including brain and liver (37). This extensive spread indicates the development of advanced illness and is a significant factor in the morbidity and mortality linked to lung cancer (37).



39. Created from Servier Medical Art

2.6.1 Major Molecular Alterations and Targeted Therapies in Non-Small Cell Lung Cancer (40,41)

Non-small cell lung cancer is considered very complicated disease because of the different genetic changes that occur. Due to this the normal functioning of the cell gets disturbed, and causes uncontrolled growth and proliferation. The important genetic changes that occur which causes cancer mainly includes EGFR, ALK, HER2, ROS1, RET, MET, KRAS, BRAF, NRAS, and AKT1 in such gene's mutations, gene fusions, gene amplification, and splice variations occurs. This changes further leads to the activation of improper control of cell signalling pathways like MAPK, PI3K/AKT, and PLCγ.As a result, cancer cells grow uncontrollably, survive longer, avoid normal cell death, and can spread more easily to other parts of the body. Abnormal signalling also affects how cancer cells differentiate, adapt their metabolism, and interact with the tumour microenvironment, which further supports tumour progression. With the discovery of these molecular drivers, targeted therapies have been developed, including tyrosine kinase inhibitors, monoclonal antibodies, and fusion-specific inhibitors. These therapies specifically block abnormal cancer signalling pathways and help improve treatment outcomes. The table below summarizes the major molecular changes seen in NSCLC, how they work, their biological effects, and the targeted treatments currently available.

Molecular driver	Type of alteration	Pathway Activation	Biological effects	Clinical targeted therapy
EGFR (Epidermal Growth Factor Receptor)	Exon 19 deletions; Exon 21 L858R point mutation; Exon 20 insertions	Constitutive activation of EGFR tyrosine kinase → PI3K/AKT, RAS/MAPK, JAK/STAT	Increased cell proliferation, survival, and also cancer cells survive longer due to prevention of	EGFR Tyrosine Kinsa Inhibitors: gefitinib, erlotinib, afatinib, Osimertinib

		pathways	programmed cell death.	
ALK (Anaplastic Lymphoma Kinase)	Chromosomal rearrangement (most common: EML4-ALK fusion)	ALK protein is permanently switched on which causes the activation of PI3K/AKT, MAPK pathways	cells grow and divide faster and do not die when they are supposed to.	ALK inhibitors: crizotinib, alectinib, brigatinib, lorlatinib
HER2 (Human epidermal growth factor receptor 2) ERBB2 is the gene which produces this protein.	Exon 20 insertion mutations, and extra copies of genes are made inside the cell.	Activation of HER2 signalling → PI3K/AKT and MAPK pathways	Increased tumour growth and rapid progression occur.	Trastuzumab deruxtecan; HER2-targeted TKIs
ROS1	Gene rearrangements (CD74-ROS1, SLC34A2-ROS1, etc.)	Constitutive ROS1 kinase activation → MAPK, PI3K/AKT	Increased proliferation and metastasis	Crizotinib, entrectinib
RET	RET fusion rearrangements (KIF5B-RET, CCDC6-RET, etc.)	Activation of RET tyrosine kinase → MAPK and PI3K pathways	Tumour cell growth and survival	Selpercatinib, pralsetinib
NTRK1 (TrkA)	Gene fusions (e.g., LMNA-NTRK1)	Activation of TRK signaling → MAPK, PI3K/AKT, PLCγ pathways	Oncogenic transformation and proliferation	Larotrectinib (LOXO-101), entrectinib
MET	MET exon 14 skipping mutations occurs which prevents the protein from being broken down, causes	Activation of MET receptor → PI3K/AKT and RAS/MAPK pathways	cancer cells move and spread more easily.	Capmatinib, tepotinib

	continuous cell growth and survival and along with that gene amplification occurs.			
KRAS	Point mutations (most common: G12C)	Constitutive RAS/MAPK pathway activation	Increased proliferation, resistance to EGFR TKIs	KRAS G12C inhibitors: sotorasib, adagrasib
BRAF	V600E mutation (most common)	Activation of MAPK pathway	Enhanced tumor growth	Dabrafenib + trametinib
AKT1	E17K mutation (rare)	Activation of PI3K/AKT pathway	Increased survival and resistance	Investigational AKT inhibitors

3. Conventional therapies and their limitations

Conventional therapies of lung cancer consist of the standard treatment strategies used for treating cancer which includes surgery, chemotherapy, radiotherapy, targeted therapies and immunotherapies. These treatments are the first line strategies used for disease management (42,44,46,48,51,55). The overall effect of these therapies depends on patient's condition, the type of tumour, disease progression and the method chosen for treatment.

The type of treatment chosen for patients to get cured depends upon the stage of disease. Cancer is also of different types such as NSCLC which includes adenocarcinoma and squamous cell carcinoma.

3.1 Chemotherapy, Radiotherapy, surgery: Current status

Management of non-small cell lung cancer depends upon the stage of disease. Surgical resection is the preferred option for patients

diagnosed at early stages, especially for stages 1 and 2 (44). Among the available options, lobectomy is mainly preferred as it provide better therapeutic effects without damaging the lungs. For patients with tiny tumours, segmentectomy is done (44,52). Methods such as thoracoscopic surgery and robotic assisted procedures have been adopted and implemented to improve overall therapeutic effect (44,53). However, surgery still has limitations in advanced cases, in such cases the tumour spreads to nearby organs like lymph nodes, or distant part of

the body, which makes the complete removal difficult. Additionally, surgery can also lead to complications and reduced lung capacity (44).

Radiotherapy is another conventional method chosen to treat cancer. To get cured from cancer, accurate precision of tumours is very important, radiotherapy plays a very important role in that. Stereotactic ablative radiotherapy (SABR) is a method in which there is high radiation due to which tumours get killed easily (45,46). Another preferred method is chemoradiation, it has also good output, as it is combined therapy which gives better efficacy (47). There are also other method such as intensity-modulated radiation therapy (IMRT) and image guided radiation therapy (IGRT) which have improved tumour targeting (46). Even though after this much benefits, radiotherapy still has limitations, radiotherapy is less effective in hypoxic or radio-resistant tumours and also high radiation can damage normal tissues (46).

Chemotherapy is also an important method for both small cell lung cancer as well as non-small cell lung cancer. In Small cell lung cancer (SCLC) chemotherapeutic treatment generally includes using platinum-based drugs, in this method etoposide combined with a platinum drug as this treatment works quickly. In non-small cell lung cancer chemotherapy is generally combined with radiotherapy or immunotherapy to get get maximum results (47,51).

However, chemotherapy still has limitations for small cell lung cancer as the used method give the results quickly, the benefit doesn't last longer as some cancer cells survive and grow again. Another side effects include stomach and intestinal problems, reduced bone marrow activity (leading to low blood cells), overall stress on body, due to this many patients don't continue with this therapy (54,55).

Conventional therapies mainly consist of a trio which is surgery, chemotherapy and radiotherapy. Even though each of these methods have certain limitations, but corrections in them can lead to better outputs. There are new methods developed to overcome such limitations and has new techniques which includes targeted therapies as well as immunotherapies (42).

3.2 Targeted therapies and immunotherapies

Smarter approaches have been developed for the treatment of lung cancer, where better therapeutic effects can be achieved. one such method includes targeted therapies which mainly focuses on molecular changes that are responsible for tumour growth. There are different kind of mutations which are seen such as EGFR, KRAS, etc. and to treat them different drugs are there (48,50). Drugs like erlotinib, gefitinib, afatinib works best for tumours which have EGFR mutations, this drug reduces the overall metastatic spread and improves chances of success (48,50).

similarly, for ALK gene drugs like crizotinib, lorantinib, and alectinib are used. These drugs are often combined with next generation drugs to improve efficacy as well penetration also improves into the central nervous system(48,50). Different mutations have different drugs, and the field of targeted therapy has been expanded by discovering molecular targets like RET fusions, NRTK gene fusions, BRAF V600E and many more, these all mutations are not seen more common (48).

Targeted therapies also have certain limitations they don't work well for all patients. They are applicable to only who have specific gene mutations, and also these mutations can change with

time, they can have new pathways to survive and also change their behaviour. so, the responses to the treatment may stop (48,50).

Immunotherapy is another kind of method which is used for the treatment of cancer. In this method, immune system helps to kill the tumours. The effectiveness of this method depends on the level of PD-L1 expression as well as tumour mutational burden, and the selection of treatments also depends on the level of PD-L1(42,50,51). some patients respond well to these therapies, especially the one who has higher PD-L1 levels. Medicines target PD-L1, helps the immune system to fight against cancer cells, they stop the blocking of T-cells by cancer cells, which helps the immune system to fight against cancer cells (42,50,51). Immunotherapy when combined with chemotherapy, it gives a better response in some patients (51).

Immunotherapy also has some limitations, immune system while attacking the cancer cells may destroy the normal cells and there are also some side effects regarding the immune system that can occur such as pneumonitis, colitis (49,50). Cancer cells also stop responding to the medicines because there are different cancer cells inside the same tumor and thus don't work equally for all different kind of cancer cells. some tumours do not strongly activate the immune system and they have a tumour microenvironment that do not respond well to immunotherapy drugs (49,50). so, all these limitations regarding the therapy need to be kept in mind while choosing immunotherapy as a treatment option.

3.3 Barriers to effective lung cancer therapy

3.3.1 Physiological barriers in the pulmonary system

Once the medicine enters the body, it's therapeutic efficacy depends on several factors, one such factor is physiological barriers. The distribution of drugs inside the lungs gets hindered by several factors such as mucus, pulmonary surfactant, and mucociliary clearance that rapidly eliminate foreign particles, due to which drug residence time reduces in the respiratory tract (56,57). Another factor which lowers drug concentration is phagocytosis of inhaled particles by alveolar macrophages (56,57). These mechanisms are important for preserving lung health, but turns out in reducing drug concentration which ultimately lowers the therapeutic effect (56,57).

3.3.2 Tumour microenvironment related barriers

The tumour microenvironment also reduces drug effectiveness due to certain factors. Hypoxia, acidic PH, and dense extracellular

matrix all of these reduces the drug activity (58,59,61). Tumour cells also get protected from cancer associated fibroblasts (CAFs) which are supportive cells present around the tumour which helps the cancer cells to grow, and immunosuppressive immune cells that supress the body's immune response, which promotes progression of disease (56,57).

3.3.3 Cellular level barriers

cancer cells may take less drug at the cellular level. The drug gets trapped inside the cellular components due to which its amount gets reduced, so the amount of drug which should be reached to targeted cell is not sufficient, which reduces the overall therapeutic effect (58,61) Altered cellular mechanisms and method to take nanoparticles further influences treatment response 61).

3.3.4. Patient related barriers

Therapeutic efficacy of drugs also relies on patient's condition. Patients with certain problems such as smoking habits, they respond differently to drugs, not only this but the effectiveness also depends on the formulation such as unstable aerosols, particle clumping all of this plays a major role in the therapeutic response (57,60). Incorrect inhalation technique and poor adherence to treatment by patient also contributes to this (57,60).

3.3.5 Systemic toxicity and safety related limitations

Systemic toxicity remains a major barrier in treatment of cancer. Many of the therapies which are used for the treatment of lung cancer they lack selectivity and due to this they damage the normal cells also. This situation is explained by chemotherapeutic agents who lacks selectivity. This damaging to normal cells causes problems such as gastrointestinal disturbances, nephrotoxicity and neurotoxicity (58,59). All these problems often reduce the dose concentration as well as lead to treatment discontinuation (59). Targeted therapies and immunotherapies also contribute to this, targeted therapies interfere with normal cellular signalling in organs such as skin, liver, or heart. Immunotherapies they cause immune related side effects which involves lungs and well as endocrine system (58,60).

3.3.6. Pharmacokinetic barriers

Therapeutic efficiency also gets limited by pharmacokinetic parameters. There should be uniform distribution of drugs in the tumour for proper treatment but poor drug absorption, rapid drug clearance doesn't allow this to happen (59,61). Patients age, organ condition and the disease stage also lead to inappropriate treatment. plasma protein binding is another factor which contributes to restricted therapeutic effect (61).

4.0 Nanotechnology in Lung Cancer

The National Cancer Institute (NCI) acknowledges that nanotechnology presents a groundbreaking chance to drive revolutionary progress in lung cancer treatments.

Delivering inhalation nano-medicines to the lung cancer.

Delivering nanomedicines directly to the lungs holds great promise for boosting and sustaining drug levels right where they're needed most, offering a targeted way to fight lung cancer. The pulmonary delivery of nanomedicines capability to increase and regulate site specific drug concentration to cure lung cancer. Targeting the drug right to where it's needed lowers the required dose and cuts down on side effects throughout the body.[62] Plus, it sidesteps issues with oral dosing, like unpredictable absorption from changing stomach conditions [63]. It targets the receptor specific natural and artificial receptor ligand or target specific receptor antibody complex of drug in drug formulation. One of the examples of target drug tumor therapy is Herceptin it is clinically approved monoclonal antibody manufactured by Genentech, Inc., San Francisco, CA, USA. Treatment in the breast cancer [64].

Nanotechnology for the targeting of the lung cancer

There are two types of targeting for the lung cancer: Passive Targeting, Active Targeting

Passive Targeting

Passive targeting enhances the permeability of the tumour tissue. Passive targeting is the commonest to destroy rapidly growing tumour tissues which are leaky and faulty. Preferential concentration of a drug or drug formulation in any one tissue, on the basis of biophysical

properties, is called passive targeting.[65] As an illustration, the accumulation of the differently sized particles or aerosol droplets in the various parts of the lungs depends on the size of the particle or aerosol droplet; this would be referred to as the EPR effect. Drugs may be made in aerosols of drug droplets of relevant size and used in the delivery of drugs [66].

Active Targeting

Active targeting is made to find its way into the tumour tissue, individual cancer cell or even parts within these cells by having the nanoparticles bound to special targeting molecules to find their way in better results. These targeting moieties or ligands are usually antibodies (mAbs), aptamers, small molecules (e.g. folate), and proteins (e.g. transferrin).[67] Active targeting is the term commonly used. instead of molecular or natural targeting; it can. accurately be referred to as any active process used on a formulation that is going to result in localized drug effect.[67] also encompasses techniques of physical targeting where physical target cells are subjected to force on drug formulations and/or target cells to. mediate localized delivery. These are, electroporation, sonoporation and magnetic targeting.

4.1 Rationale for Nano-Drug Delivery in Lung Cancer [68,69]

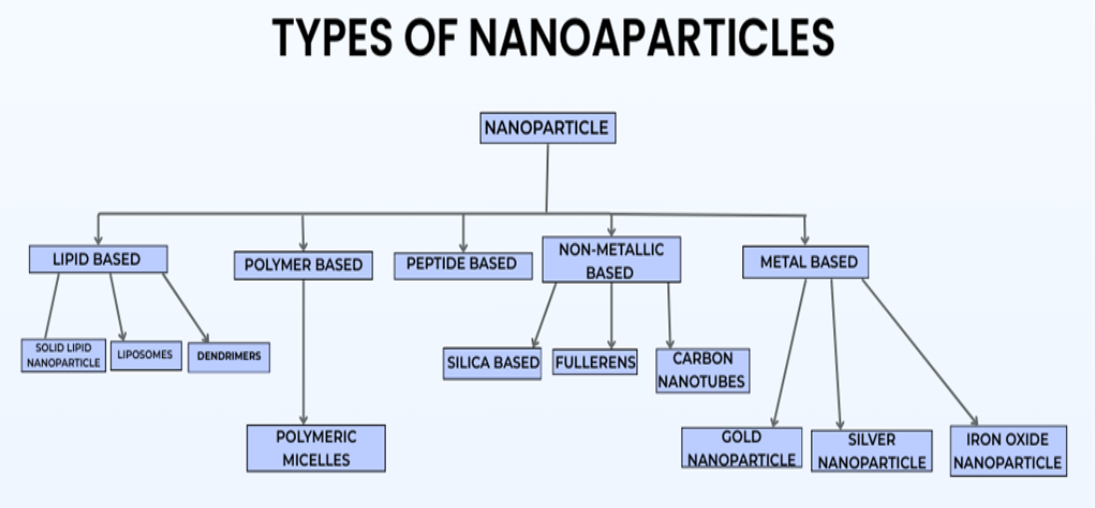
1. **Improved Drug Delivery and Bioavailability**: Some examples of nanocarriers are liposomes, polymers and magnetic particles which protect drugs against degradation, increase drug solubility and release all of which significantly enhance pharmacokinetics and bioavailability**.**
2. **Precision medicine, also known as targeted therapy:** Passive targeting is done by the increases permeability and retention (EPR) effect where tumour tissues aggregate nanoparticles as a consequence of the leaky vasculature. Active targeting It involves the modification of the surface of NPs with ligands (including peptides or antibodies) capable of binding to a particular receptor on lung cancer cells.
3. **Reduced Systemic Toxicity**: Since nanoparticles target tumour cells, the quantity of the drug in simple tissues is decreased significantly, thereby minimizing the adverse effects on the body Nanoparticles
4. **Overcoming Multidrug Resistance (MDR):** Nanoparticles can avoid or prevent efflux pumps in cancer cells to pump out chemotherapeutic drugs and thus reduces MDR.
5. **Enhanced Diagnosis and Imaging:** Nanoparticles (i.e. iron oxide, quantum dots) enhance sensitivity in imaging to yield better tumour visibility to facilitate earlier and more accurate diagnosis.
6. **Improved Routes of Administration**: Nanotechnology enables the use of non-invasive and local therapy, including the use of inhalable nanomedicines to deliver the drug to the direct lung. This improves treatment and reduces exposure to the system.

4.2 Types of Nanoparticles.

Nanoparticles are versatile colloidal platforms, which are built using a variety of materials in a wide range of configurations- such as quantum dots (QDs), polymer-based. nanoparticles, gold nanoparticles (AuNPs), magnetic nanoparticles, and so forth [70].

Nanoparticle Classification Nanoparticles are characterized by their sizes and shapes depending on the material compositions and structures.

1. One Dimension Nanoparticles thin films (or created surfaces) have been used over decades. Solar cell technology has now progressed to monolayers or thin films 1-100 nm, which are used in a variety of applications such as chemical/biological sensors, information storage, magneto-optical/optical devices, and fibre-optic systems.
2. Two-dimension nanoparticles: Carbon nanotubes.
3. These are three-dimension nanoparticles: Dendrimers, Quantum Dots, Fullerenes (Carbon 60), (QDs).[71]



1. **Lipid Based Nanoparticle**

Lipid-based nanocarriers is a type of nanoscale particle comprising of lipid materials that have special characteristics including biodegradability. non-toxicity, drug release capability, penetration of phospholipid membrane of the tumour cells, and possibility of vascular transportation. These nano-carriers can affirmatively increase the delivery of chemotherapeutic drugs, small interfering RNA (siRNA) and other therapeutics through encapsulation or adsorption by using controlled release, targeting and by enhancing bioavailability.[72]

(A) Liposomes

Liposomes are usually made out of phospholipids arranged in the form of bilayer vesicles. Liposomes are classified as multilamellar depending on the size and physical structure. vesicles consisting of multiple phospholipid concentric bi-layers, and large and small uniflagellar vesicles consisting of single bilayer.[71] Liposomes are able to deliver hydrophilic and hydrophobic drugs due to the phospholipid bi-layer and allow drug co-delivery to modify the therapeutic mechanism of chemo-therapeutics. The concentration and area of concentric bilayers determine the amount of medication in the capsule [73]. The surface functionalization of a liposome and its size dictate the duration of a liposome in circulation mediation because lung surfactants and plasma membranes naturally have both.[72] A dual-purpose liposome that is decorated with an altered peptide which consists of "1, 2-distearoyl-sn-glycero-3-phosphoethanolamine" and "2, 3-dimethyl maleic anhydride" to be used in the treatment of lung cancer and overcoming the multidrug resistance. The capability to modify the properties of the liposomes on the surface opens up new possibilities of their development as the effective delivery systems of the medication that will target the cancer in particular.[74]The use of liposomes is becoming an efficient and less hostile pulmonary drug delivery method because it has sustained release properties over a long period of time, it can be administered locally as well as biodegradable properties. Liposomes are hollow, spherical and highly adaptable in composition consisting of a single or more bilayers of phospholipids [74]. Phospholipids consist of hydrophilic head group and hydrophobic tail, which allow stabilization of bilayer structures in aquatic environments [77]. The drugs may be incorporated into the liposomes by dissolving them in either the inner or outer section of the bilayers or by incorporating them into the inner section of the bilayer structure [75]. The liposomes have great tunability due to their ability to change phospholipid composition, stacking, surface charge, and changes, which allows one to control their stability in an in vitro and in

vivo environment. The optimal liposomes to use in pulmonary administration are those with a range of 50 500 nm [74].
The liposomal nanoparticles are further divided into 3 types

- Long circulating PEG
- Targeted PEG liposomes
- pH Sensitive liposomes [77]

1.2 Dendrimers

Dendritic polymers are commonly known as dendrimers and are nanoparticles with one central core whereby several tree-like branches surround it. Surface shell multi-factional with core tree-like with hyper-branches and cavities which enables conjugation or encapsulation of medicinal compounds [76]. Moreover, conjugation of target peptides or delivery of drugs allows the power to alter the active terminal surface with "acylation or PEGylation" to increase dendrimer availability in biological systems [80]. Absorption and retention of dendrimers in the lungs are dependent on their weights and structure. administration of medications. The absorption and retention of dendrimers in the lungs depend on the molecular weight and the composition of the dendrimers. For instance, breathing in the larger molecular weight (78 kDa) of dendrimers compared to the tiny molecular weight (<22 kDa) dendrimers result in reduced rate of absorption and enhanced retention of the drug in the lung tissues [81]. In addition, the administration of doxorubicin-conjugated PEGylated dendrimers by the respiratory system increases the drug in the lung tissues and completely inhibits the burden of lung tumour in rats [82]. Drug delivery can be enhanced through the targeting peptide decoration of dendrimers as shown by generation 4 (G4) dendrimers system conjugated to non-small cell lung cancer targeting peptides (sequence RCPLSHSLICY)[83]. Dendrimers are manmade molecules with larger size and very branching and tiered structures. These consist of a core molecule, terminal functional entities and branch entities. The upper groups of dendrimers can be conjugated with other. functional components which enhance their lung-targeting ability including proteins, peptides and antibodies. Transporter of drugs-dendrimers have the tendency of being 1 to 10nm, this simplifies the process of tumour penetration.[84] Example, developed oral polyamidation dendrimers (G4NH2) complex with siRNA in a metered-dose inhaler, delivering a presurged volume of 50 mg per kilogram in a low-volume inhalation in order to produce stable and biodegradable inhalation dispersions [85].

1.3 Solid Lipid Nanoparticle

Solid lipid nanocarriers (SLNs) are another kind of medication and gene delivery vehicle. SLNs have more stability, larger drug load, improved biocompatibility and can be produced on a large scale in large quantities, unlike their lipid counterparts. Example, transfected p53-Null H1299. SLN-carrier p53 lung cancer cells. As compared to commercially obtained Lipofectin they could demonstrate effective p53 protein production, implying that SLNs could be used as highly effective vectors of gene therapy in lung cancer [85]. In a recent research, researchers had the possibility to co-encapsulate CdSe/ZnS quantum dots to offer optical traceability, and to load SLNs with Bcl-2 siRNA and paclitaxel to use them as a synergistic combination therapy. Combined, the properties of SLNs render them ideal in the molecular imaging of cancer and combined chemotherapy and /or gene therapy [85]. Nanoparticles that are solid lipids in size (range of 50 to 1000 nm) are submicron colloidal carriers fabricated of physiological lipid and dispersed in water, or within an aqueous surfactant solution. Cholesterol, beeswax, cetyl alcohol and triglycerides form the solid lipid nanoparticles.

The SLN in a biological system is much more stable than the liposome. SLN is regarded as a zero-dimensional nanomaterial when its dimensions are within the nanometre's scale [84]. As a colloidal carrier of hydrophobic chemotherapy drugs, the SLN is useful in facilitating longer bloodstream circulation [87]. Cationic SLN is amphiphilic when hydrophobic amino groups are present together with two hydrophobic fatty acid chains and the linker.

2. Polymer Based Nanoparticle

Polymeric based nanoparticle is a colloidal based systems in which the medicinal substances are adsorbed to the upper layer of the nano-particles or embedded in the polymeric matrix. There are 2 kinds of nanoparticles made of polymer-based materials; nano-spheres (in this medication is evenly dispersed) and nano-capsules (in this medication is encased by a polymer-coated chamber). The particular polymer has to contain 1) biocompatible, 2) nonimmunogenic, 3) cheap and easy to synthesize, 4) water-soluble, and 5) biodegradable in vivo to prevent the possibility of toxicity caused by the accumulation of non-metabolised polymeric particles. A linker can sometimes be inserted between the polymer and medicinal substance in order to achieve constancy and avoid release in the bloodstream after the cellular distribution e.g. 90% of doxorubicin and ellagic acid-containing lactoferrin-chondroitin sulphate nanoparticles (192 nm) accumulate in lung tissues, increasing the therapeutic index of the medication. The modes of delivering drugs can utilize natural or synthetic polymers. Natural, biodegradable polymers are chitosan, gelatine, cellulose and alginate. Synthetic biodegradable polymers such as polylactic acid, poly (alkyl cyanoacrylates), polyanhydrides and poly(lactide-co-glycolide) (PLGA) are applied in the preparation of nanoparticles. The polymer nanoparticles are normally delivered into the body in two phases: (a) the polymer nanospheres and (b) the polymer nano-capsules.

2.1Polymeric Micelles

Micelles are colloidal nanoparticles that form under an aqueous medium when the level of synthetic amphiphilic copolymer or surfactant surpasses some threshold which is otherwise known as the critical micelle concentration, or CMC.199200 The reduced size (diameter of less than 100 nm) of polymeric micelles is the factors that make it the most preferable drug delivery system because it actively prevents renal elimination and RES. They even permit themselves to actively surge the barrier of the endothelium penetration in the tumour -affected area. Polymeric micelles are also hydrophobic drug delivery systems and as such they promise a lot. The rapid self-assembly of the amphiphilic block copolymers in aqueous environment provides the unique zones that constitute the structural arrangement of micelles due to the hydrophobic or lipophilic interactions. The hydrophilic barrier and the hydrophobic core of the micelles inhibit protein linkage, particle agglomeration and opsonin linkage. They disintegrate in the blood vessels prior to arriving at the target zone. Liu et al. prepared folic acid, doxorubicin, and contrast-media-loaded micelles formed with the help of the covalent functionalization of b cyclodextrin. Hydrophobic, cytotoxic drugs (including antineoplastic drugs) are effective delivered by micelles. The effects of these drugs entangled in the innermost core area are increased water solubility, reduced toxic profile, tumour cell-specific aggregation, and reversal of treatment resistance. Also, a hydrophilic shell could extend blood circulation time by inhibiting identification through the reticuloendothelial barrier, as well as the diminution of alveolar absorption. Since they selectively accumulate around tumours due to the more restrictive characterization of particle size and long plasma circulation (in vivo), which eventually improves the therapeutic effect and bioavailability of poorly soluble drugs in water.203 The biodegradability of therapeutic delivery systems is one of the key factors that make

the strategy a more favourable option in the creation of anti-cancer and ocular drugs. The use of the drug in micelles significantly reduced toxicity, reduced carcinogenesis, and extended the period of circulation. Due to the inherent elastic architecture, conjugation-based polymeric-micelle based distributions are preferred. The capacity to increases the efficacy, vulnerability, and selectivity of therapeutic and diagnostic approaches through the capability to introduce theragnostic agents to local locations. Also, they can be readily altered to enhance biocompatibility and thermostatic solubility. Micelles are small molecules, which are formed spontaneously in water when there is a hydrophobic reaction with each other. They possess self-assembled amphiphilic core-shell. They are prepared after dissolving individual polymeric chains in aqueous solution at a certain level of concentration (critical micelle concentration; the concentration of surfactant in water that initiates the creation of micelles) and solution temperature (critical micelle temperature; the lowest temperature, at which surfactants create micelles in water). Most of the micelles are made of amphiphilic.

3. **Peptide Based Nanoparticles**

Neurotransmitters are utilized in the human body in a range of physiological activities. These are naturally occurring peptide molecules that have less than thirty amino acids. They are not commonly used in clinical practice due to their low chemical and physical stability, short half-life in systemic circulation because of glomerular filtration and degradation by serum proteins. Nevertheless, due to their easy penetration into cells and discharge of drugs based on tissue pH, small peptide molecules also possess a number of positive attributes as therapeutic agents [78]. As an example, in the tumour extracellular environment (pH =6.8), peptide conjugated liposomes have been able to internalize into mitochondria by altering their surface charge of negative to positive60. This has attracted the attention of peptide-based nanoparticles to be used as medication and gene carriers to the target organs. As an example, cisplatin and methotrexate injected into the veins separately with K16ApoE. Widely, the physicochemical can be changed to increase the half-life of peptides in the bloodstream and decrease enzymatic degradation. and chemical structure of peptide molecules [79]. Examples of techniques previously used include peptide structural modification by conjugation with albumin, albumin-binding antibody, or cell-penetrating peptides, PEGylation to enhance circulation half-life, and binding with nuclear localizing sequences as a way of enhancing targeted drug delivery. Small molecule peptides and proteins readily diffuse across the pulmonary mucosal surface when they are inhaled due to the abundance of anti-protease enzymes.[90] Therefore, nanoparticle delivery through the lungs using peptides can be systemic bioavailability when compared to intravenous or subcutaneous injection.

4. **Non-Metal Based Nanoparticles**

Due to its versatile property, dynamic drug loading capacity, controlled drug release capability and its multifunctional property, mesoporous silica nanoparticles (MSNs) have increasingly become popular in the study of anticancer drug delivery [85]. Silica nanoparticles that are mesoporous and possess numerous functions have been used. In nanomedicine research, intracellular labelling and animal magnetic resonance imaging nanomedicine is currently utilized in treating lung cancer.[88] The MSNs are endocytosed by human lung cancer cells predominantly. A tumour-targeted MSN-based drug delivery system was developed to be used in inhalation therapy of lung cancer. The experiment was successful in targeting anticancer drugs (doxorubicin and cisplatin) inside cancer cells along with two types of siRNA against MRP1 and BCL2 mRNA, respectively in order to prevent pump and non-pump cellular resistance in NSLC [77]**.**

5. **Metal-Based Nanoparticles**

There are three kinds of metal nanoparticles that are formed out of metal compounds such as metal oxides and metal salts, namely pure metals, metal oxides, and metal chalcogenides [77]. Copper (Cu), iron, (Fe), silver (Ag), and gold (Au), and the most critical elements that make metal nanoparticles are platinum (Pt). Metal nanoparticles have widespread application in the diagnosis and treatment of lung cancer with their distinct physicochemical features, namely, magnetic, optical, thermal, and electrochemical ones. Some of these applications include imaging enhancement, biosensors, cancer biomarker detection, drug delivery reinforcement, chemo-sensitization and combination.

5.1 Gold Nanoparticles [80,81,87]

Gold NPs are the most common inorganic NPs that are used in medication delivery as well as cancer diagnosis. Gold is a noble metal. Colloidal gold has the desired properties that make it the ideal choice in targeted treatment. The noble metal NPs have a high surface-volume ratio, broad optical properties, biological inertness, corrosion resistance, low toxicity (when this particle breaks, it is nontoxic and is either eliminated through the renal system or incorporated into the metabolic pathways), and effective antimicrobial properties (even at very low concentrations, against bacteria, viruses, and other eukaryotic microorganisms; in a recent study, GNPs have been shown to destroy DNA or the cell wall of germs and bacteria by shrinking the cytoplasm membrane or detached .microbes proteins and inactivated them). The ability of DNA molecules to reproduce is inhibited as they condense and lose their functionality when covered by GNPs, which could be the main method by which GNPs inhibit bacterial replications [81]. no harm to epidermal cells. Also, GNPs have variable surface functionalization and can be synthesized easily, which means that they are potentially useful in the therapeutic field as well; even GNPs display highly size-tuneable optical properties, including the strong surface plasmon resonance (SPR) effect, thereby producing vivid colours through high absorption and scattering. GNPs' cross section. The SPR effect of GNPs can be simply adjusted to the wavelengths at which is lowest attenuated by blood and tissue i.e. within the biological window. Based on their shape (e.g., nanoparticles, nano-shells, nanorods), (650-900 nm). size (e.g. 1-100 nm), composition (e.g. core/shell or alloy noble metal), and dielectric strength of the surrounding medium. GNPs also are used to deliver different medicinal compounds to the target sites and mainly, the interaction between applied electromagnetic waves and the surface conduction electrons forms the main cause of SPR that is essentially tailored to the needs of our biological systems. Methotrexate (MTX) and DOX are water soluble chemotherapeutic drugs, and in most cases they do not retain well in the tumour, hence reducing efficacy of the drugs drastically.[84] Chen et al proved that in cases where MTX was conjugated with GNPs and targeted at LLC cells of a xenografted mouse, it was found to accumulate in large amounts at the target sites and therefore proved to be very effective when used to treat cancer.

5.2 Silver Nanoparticles

Apoptosis and necrosis pathways mediate the cytotoxicity of silver nanoparticles (Ag NPs) to a variety of cell lines, which are promoted by the alteration of membrane shape and the up-regulation of apoptotic signalling molecules [84]. The cytotoxicity of these nanoparticles. Spherical silver nanoparticles and microparticles are almost non-toxic to human alveolar epithelial cells in their varying sizes, shape, surface chemistry, and other properties, and in contrast, silver wires are very cytotoxic. The only drawback of silver nanoparticles is that its low biocompatibility with the in vivo system does not allow its universal application. Recently, in an attempt to solve this problem, it was

established that organically functionalizing silver nanoparticles by capping them using the stem latex of the medicinal plant Euphorbia nivulia had a significant positive effect on the biocompatibility of the latter. These NPs have been found to have dose-dependent cytotoxicity with human lung cancer cells (A549). The terpenoid and peptide contents in the latex facilitate the formation of latex-capped silver nanoparticles (Ly-AgNPs), which may also be used as a biocompatible carrier of the NPs and cross cell membranes. The silver nanoparticles have properties such as Absorbs and scatters light, stable, anti-bacterial, disinfectant [83]. There are many methods to synthesis of nanoparticles such as Mechanical milling, Nanolithography, Laser ablation, Sputtering, Thermal decomposition. it was proved that silver nanoparticles lead to an increase of oxidative stress, membrane fluidity, and apoptotic death of tumour cells. AgNPs possess a radio sensitizing effect. The release of Ag 3 cations is an element of the radio sensitization pathway and they capture electrons and cause an amplification in the oxidative stress in the. cells. Moreover, they reduce the ATP levels in the cells and increase the production of the ROS. Gliomas that were subjected to AgNPs followed by radiation demonstrated an antiproliferative and proapoptotic effect. In vitro studies indicate that AgNPs of different sizes increase radiation induced necrosis in glioma cells. AgNPs do not work as well as they become larger. In terms of radiation sensitivity to U251 cells, AgNPs of 20 nm are superior to those of 50 nm and 100 nm [81]. The same was observed in SHG-44 and C6 cells. The experiments in vivo use C6 glioma cells prepared as rats and exposed to 6 mV X-rays alone and combined with AgNPs. The results of the experiment showed that in case of combination therapy the therapeutic efficacy and killing of tumour potency were enhanced without any evidence of systemic damage [82].

5.3 Iron Oxide Nanoparticles

Due to magnetic and plasmonic properties, iron nanoparticles have found extensive application in cancer diagnostics as well as cancer therapy [80]. In the absence of toxic wavelength radiation, iron oxide nanoparticles, including oscillating MFs or near infrared (NIR), are turned into harmful stimuli of ROS that eventually kills tumour cells. The major advantage of using iron oxide nanoparticles has been given as site-specific targeting as they are covalently bonded to molecular determinants specific to a particular tissue. Due to magnetic characteristics, iron oxide nanoparticles (NPs) translate radiant energy with reduced damage to normal cells into heat or ROS after the delivery of local external MF, thereby decreasing the adverse effects of treating cancer which are rather dangerous. In an effort to improve the therapeutic efficacy of conventional DOX therapy, iron oxide nanoparticles (NPs) are used in conjunction with chemotherapeutic drugs such as DOX since they are magneto sensitive [82]. This increases the anticancer effect because DOX gains the magnetic property of paramagnetic compounds and that electron transfer can be made to the nano-complex with more free radicals due to the presence of external MF. Besides enhancing the synergistic anticancer and antimetastatic effect of the conventional therapy, the integration of the MF nano-complex of iron oxide and DOX as well as moderate radiofrequency-induced hyperthermia will provide a new method of successfully curing cancer in future. The European Union has licensed the EU Spherical iron oxide nanoparticles as a medicinal device when used in conjunction with chemotherapy and radiation treatment in prostate cancer and in causing cerebral hyperthermia [83]. Having been interacted with the extracellular matrix of the tumour it is found that the PEG-coated iron oxide nanotubes kill the matrix under the magnetic stimulus thereby slowing the growth of the tumour by redistributing the NPs in the three-cycle heating process1. To kill cancer cells, heat at temperatures exceeding 40 degrees Celsius is

usually administered in hyperthermic situations. Iron oxide nanoparticles (NPs) are delivered to the site of the tumour and are useful in capturing energy presented by external sources (NIR radiations) and transforming it into heat. The iron oxide nanoparticles are heat generating due to the When exposed to radio frequency oscillating MFs, there is reorientation of the magnetization process. The process of magnetization leads to the aggregations of the NPs. Tumour-targeted SPIO NPs were recently examined in terms of the efficacy of magnetic hyperthermia of lung cancer by Tanmoy et al. The results indicated that SPIO NP tumour retention is enhanced by EGFR targeting. Additionally, targeted SPIO NPs were also applied in the treatment of magnetic hyperthermia, which had a considerable effect on the in vivo growth of lung tumours [90]. In another Delivered to the tumour site, the iron oxide nanoparticles (NPs) are useful in absorbing the energy in the extrinsic sources (NIR radiations) and transforming it into heat. The iron oxide nanoparticles are heat generating since Higher sizes can be selected, although they can only reach to a critical size in which in this case iron oxide nanoparticles are prone to forming ferromagnetic nanoparticles. This limit is also known as the superparamagnetic limit. The aggregation of the NPs into the unwanted particles that influence the magnetic performance of these particles is to be avoided to prevent. In some cases, smaller size is desirable so as to act as a source of heat to a small part of a tumour. In case of the removal of the MF, SPIONs become deprived of their magnetic feature, or magnetization. Iron oxide nanoparticles (NPs) (when treated with X-ray source) serve as radio sensitizing agents in the shape of citrate and malate-coated SPIONs, which facilitates the destruction of cancer cells by the accelerated production of ROS.

4.3 Recent Nano-drug Delivery Strategies for Lung Cancer. [87,88,89,90]

Nanocarrier Type	**Therapeutic Approach**	**Mechanism of action**	**Outcome Reported in Research**
PLGA Polymeric Nanoparticles	Paclitaxel, Docetexal	Controlled release and improve the intracellular uptake.	Enhanced cytotoxicity in NSCLC and decreased systemic toxicity.
Chitosan-modified Polymeric Nanoparticles	siRNA oppose the EGFR	Gene silencing and reduce the tumour causing signalling	Most decrease in KRAS mediated cell proliferation
PEGylated Liposomes	Cisplatin, Doxorubicin	Extend Circulation and improve renal toxicity	More cancer cells growth is control.
Liposomes Nanoparticles	mRNA, siRNA	Effective delivery of nucleic acid.	Hindrance of metastatic pathways and regeneration of tumour suppress miRNA
Solid -Lipid Nanoparticles	Curcumin, Resveratrol	Amended solubility and anti-inflammatory action	Improved apoptosis and abridged cancer cell growth in non-clinical lung model
Gold Nanoparticles (AuNPs)	Chemotherapeutics drug	Photothermal removal and heightened cellular acceptance	Restricted cancer cells heating and importantly tumour reversion with

			minimal damage to healthy tissue
Silver Nanoparticles (AgNPs)	Natural compounds such as (lycopene, quercetin)	Reactive oxygen species cohort and mitochondrial disfunction	Potent cellular toxicity in contradiction of cancer cells. Abridged feasibility
Iron Oxide Nanoparticles (Fe3O4)	Magnetic targeting of drugs	Accretion done by using magnetically guided nanoparticles	Amended restricted accumulation and heightened MRI scans
Mesoporous Silica Nanoparticles	Combination drug therapy Eg: cisplatin + siRNA	Good delivering capacity pH-responsive release	Higher synergistic activity
Polymer Lipid Hybrid Nanoparticles	EGFR inhibitors and immunomodulators combination therapy	Combined delivery of micro molecules	Surges immune activation
Biomimetic Nanoparticles (Cell membrane coated)	Paclitaxel, siRNA	Immune shirking and homotypic targeting	Improved cancer cells specific deposition and reduced macrophages clearance
Inhalable Nano-aerosols	Nano-docetaxel, Nanocurcumin, AgNPs	Pulmonary accumulation directly in lungs	Increased local drug concentration in lung tissues
Stimuli-responsive Nanoparticles	pH, enzyme, ROS-responsive release	Targeted drug release in the tumour cells	Increased specificity and decreased unharmed cell toxicity
Theragnostic Nanoparticles	Drug + imaging techniques	Image scanning with combination of therapy	Initial stages detection

5.Nanotechnology in Early Diagnosis of Lung Cancer

One of the most major aspects of lung cancer management is advanced detection, as there are multiple challenges in this field. Many patients are diagnosed with the disease when there are finite treatment options, and symptoms are detectable, as patient are frequently diagnosed at a later, more advance stage of disease. As for diagnostic tools, usual method such as imaging and tissue biopsy also has restrictions in the area of susceptibility, specificity, accessibility and interference. Under these conditions, field of nanotechnology can provide tools for early disease stage detection due to advanced biomarker diagnostic availability, imaging technologies, and non-invasive liquid biopsy technologies [91].

The novel feature of certain nanomaterials, such as their size and optical, magnetic, and electrical property, are the reason for the highly sensitive diagnosis of the disease. Carcinogenesis in the early stages is the reason for the special nanoscale measurements to detect and interact at the blood and pulmonary level. Some of the circulating molecules, such as tumor DNA, tumor exosomes, and certain volatile and blood proteins, are much more easily identified with these biosensor technologies. Most traditional review have much lower

detection thresholds, allowing for significantly more advanced stages of malignancy to be identified earlier during the detection process [92].

Radiological imaging techniques such as CT, MRI, PET, and other optical imaging method can be further increased in terms of resolution and contrast with the use of imaging-modifying nanoparticle. Certain metalliferous nanoparticle, quantum dot materials, and iron-oxide particulate compounds can act as contrast agents that especially accumulate in malignant lesions. This process helps in the earlier imaging of tumours as well as the accurate boundary representation of malignant lesions. The resulting diagnostic accuracy, improved presentation, and confident discrimination of anatomical tumours allow enhanced staging with ensuing improved treatment plans. [91][93]

Radiology and medical field as a whole can also benefit from the added value of nanotechnology in the conception of liquid biopsies. Detecting and isolating circulating tumor cells, microRNA, and cell free DNA can be archive using nanotechnology, permit for improved efficiencies over traditional methods. The outcome of this significant technological innovation is non-invasive methods that allow real-time effective disease progression and treatment monitoring with the ability to alert caregivers to disease reoccurrence.[94]

Point-of-care diagnostics involved nanotechnology as well as quick and portable nanotechnology-enable diagnostic devices which can evaluate and analyse multifarious patient sample process with some need for manual data entry or processing. Such diagnostic devices can be employed in high-risk and low-resource environments, simplified the patient diagnostic workflow to allow disease-modifying treatment to be employed earlier.[91][95]

Overall, nanotechnology promote early diagnosis of lung cancer with much significant detection, specificity and feasibility. Nano biosensing tools, imaging enhancement, and liquid biopsy technologies enable more systematic early detection along with advanced staging and prognostic evaluations, thereby enhancing clinical outcomes [91][92][94].

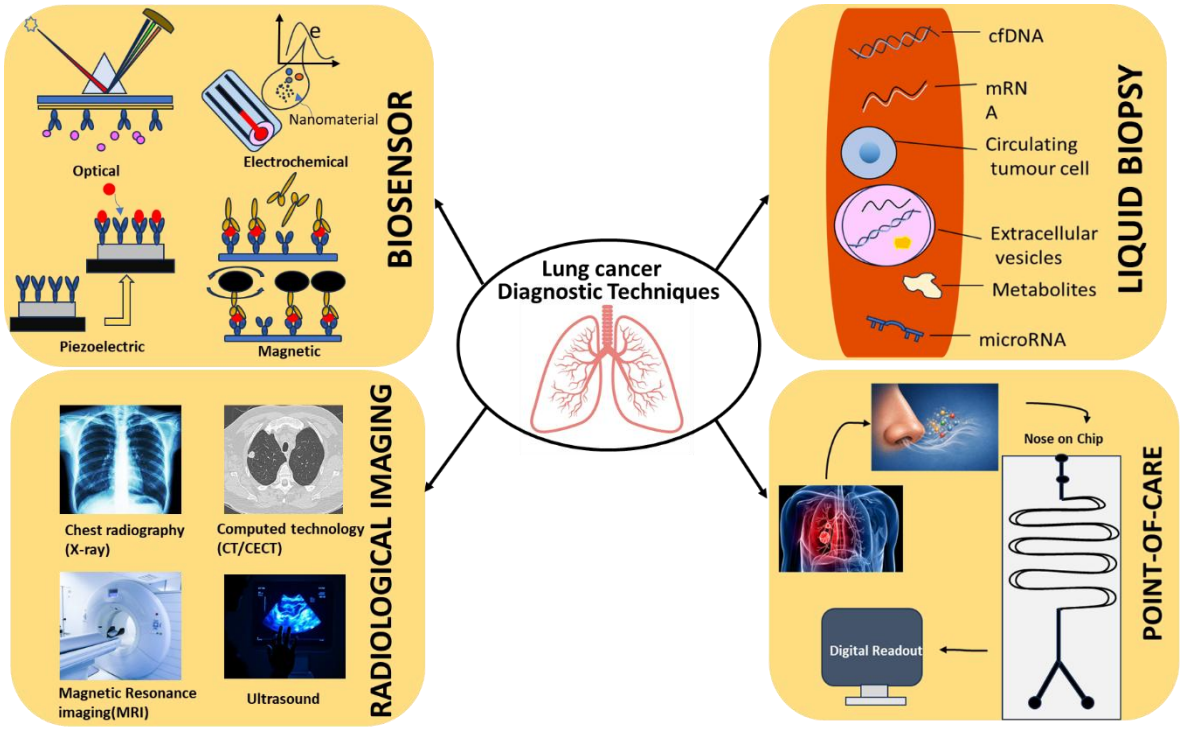


Figure 1. Schematic Representation of Diverse Lung Cancer Diagnostic Techniques

The various lung cancer diagnostic methods shown in this diagram include molecular liquid biopsies that analyse ctDNA, mRNA, exosomes, and metabolites; advanced biosensors such as optical, electrochemical, and magnetic types; traditional imaging methods like chest X-rays, CT, MRI, and ultrasound; and cutting-edge non-invasive tools like digital breath analysis and point-of-care chips. It highlights a shift toward real-time, minimally intrusive techniques for early identification and monitoring.

5.1. Nano-biosensors for biomarker detection

As there are few technologies for early detection of lung cancer, nano-biosensors are among the most advanced and promising tools using nanotechnology for this purpose. They are rapid, ultra-sensitive, and able for detecting molecular changes at the early stages of a disease when other technologies are blind. Nano-biosensor consist of nanomaterial and biomolecule that can diagnose and capture lung cancer related biomarker, Including circulating tumour DNA, microRNAs, proteins, exosomes, and volatile organic compound.[92][96]

Different type of nanomaterial, like gold nanoparticle, carbon nanotubes, graphene, quantum dots, magnetic nanoparticle, and metal-oxide nanostructures, all boots the efficacy of biosensors, and this is due to their particular catalytic, mechanical, optical, and electrical properties. Among their unique properties is high surface-to-volume ratio that facilitate enough target molecule interaction, which improve binding efficacy and decrease the detection limit. This results in the detection of biomarkers that exist in very small amount in blood, sputum, or breath expiration.[92][96]

When it comes to identification of genetic and epigenetic changes, electrochemical nano-biosensor are important. Incorporation of conductive nanomaterial in the system, these biosensors get to benefits of high signal amplification and fast electron transfer, which facilitates the detection of mutation in circulating tumor DNA, methylation patterns, and even

oncogenic microRNAs. This level of detection accuracy makes it possible to diagnose and even choose treatment options in real-time throughout the progression of the disease. [91][97]

A special type of optical nano-biosensor that implement plasmonic nanoparticles or quantum dots also assist the enhanced fluorescence or colorimetric signals in the presence of specific biomarkers. They have a unique characteristic of optical properties, which enhances the detection of several proteins like carcinoembryonic antigen, cytokeratin fragment, and exosome-associated proteins. These are applicable for laboratory and point-of-care settings since they allow for speedy and precise identification.[91][92]

Iron oxide nanoparticle is biosensor that are able to separate and identify circulating tumor cells and exosomes very efficiently. Because they are magnetically responsive, they can quickly isolate from complex biological fluids, enhancing sensitivity and efficiency of the process. [94][98]

5.2. Using nanoparticles for imaging

The introduction of a variety of nanoparticles has transformed the imaging of lung cancer. Their ability to improve sensitivity, contrast, and specificity of various imaging modalities has been unprecedented. Their specific optical, magnetic, and radioactive properties make them suitable candidates for contrast agents and therefore imaging. In the context of lung cancer, where early lesions are small, heterogeneous, and can be in poorly visible areas, enhanced imaging via nanoparticles can result in improved detection, precise disease staging, and optimal monitoring of the disease and response to treatments [91][93].

In computed tomography imaging, augmentation is greatly aided by the presence of gold and silver nanostructures that belong to the metal-based nanoparticles**.** They have very high X-ray attenuation coefficients. Among the gold nanoparticles, a stronger contrast is provided compared to iodine-based agents, and they have a longer circulation time, which is beneficial for clearer visualization. As far as the edges of the tumor and the tiny nodules within it all undergo some degree of profiling, and the outer surfaces of the nodules can be functionalized so that they can accumulate in some malignant tissues, and even diagnose malignancy more accurately.[93]

Magnetic resonance imaging benefits greatly from the contribution of the iron oxide nanoparticles. In the case where the iron oxide nanoparticles are superparamagnetic, they would produce a strong T2-weighted contrast to facilitate the outlining/tumor delineation, detection of even small metastases, and the determination of the involvement of the lymph nodes. In addition, the nanoparticles function as delivery systems where the imaging and the therapy would be used in a single system. These nanoparticles are valuable in theragnostic applications due to their biocompatibility and incorporation of therapeutic agents.[93]

Sensitive imaging of cancerous cells and early lesions can be done on the basis of the quantum dots, and this is because they produce strong fluorescence with narrow spectra, and they also have a high level of photostability. The quantum dots also have tunable properties that can support multiplexed imaging, which is where more than a single biomarker is detected at a time. Even with no clinical approval, some of the quantum dots can be used for molecular-level visualization. There are, however, merits for zero clinical approval, like in the case of the quantum dots, which are documented.[93]

Nanoparticles are good for improving positron emission tomography (PET) and photoacoustic imaging. Radiolabelled nanoparticles are stable PET tracers that get stuck in tumors and allow for extended imaging. In photoacoustic systems, nanoparticles turn the absorbed light into sound, which creates clear images of deep tissues and blood vessels that grow around tumour. [91,93]

Nanoparticles are also serving as imaging and therapeutic agents at the same time. This simultaneous therapy and diagnostics tool allow for the tracking of therapeutic agents in real time as they provide information about how the tumor responds and where the drugs are within the tumor. Such agents improve the efficiency of treatment by identifying the different tumor types, blood flow, and conditions of the tumor, such as low oxygen. [91,93]

5.3. Circulating tumor cells and liquid biopsy nanoplatforms

The introduction of liquid biopsy as a method for diagnosing and monitoring lung cancer has changed the field. It allows for the detection of tumors through non-invasive collection of blood and other biological fluids. Nanotechnology improves liquid biopsy by capturing and isolating circulating tumor cells and DNA (ctDNA), tumor-containing exosomes, and some microRNAs in the bloodstream.[94][99]

The presence of circulating tumor cells (CTCs) in blood samples suggests metastatic disease and indicates a more aggressive form of illness. Traditional methods struggle to isolate them, even though they are present in the blood sample. CTCs can be enriched from blood samples using magnetized nanoparticles coated with antibodies. These antibodies are designed to attach to epithelial cell adhesion molecules (ECAMs) found on tumor cells. Enriching CTCs from blood samples improves downstream molecular analyses and enables earlier identification of metastases.[94][99]

The identification of microRNAs (miRNAs) and circulating tumour DNA (ctDNA) in the blood of lung cancer patients advances our knowledge of the illness. They disclose the genetic characteristics of the tumour, show its current state, and provide crucial information about resistance mechanisms. Femtomolar probe hybridisation, plasmonic nanoparticles, graphene-based systems, and electrochemical sensors are all used in nano diagnostic detection technologies to make fast and precise diagnoses. Early detection of several important EGFR mutations, ALK rearrangements, and other mutations is possible with these technologies. Each patient can receive individualised care thanks to this capability.[94][99]

Exosomes are tiny vesicles that get released by tumors, and they reflect their microenvironment through their proteins, lipids, and nucleic acids. The use of nanoparticle systems like immunomagnetic beads and nano plasmonic sensors facilitates the increased exosome separation and characterization. These systems allow for the quantitative measurement of exosomal PD-L1 and other predictive biomarkers along with tumor microRNA [94][99].

Liquid biopsy tools based on nanotechnology have a number of benefits that include faster processing times of the samples, lower thresholds for biomarker detection, reduced volumes of the samples, and improved accuracy. They also allow for long-term monitoring of the disease, the effects of therapy on the disease, and the appearance of resistant mutations and their monitoring without needing additional tissue biopsies [94][99].

5.4 Point-of-Care Nano Diagnostics

The use of point-of-care nano-diagnostics allows for a quick, convenient, and cheap way to detect lung cancer markers without advanced laboratory setups. These systems use portable diagnostic devices and nanomaterials to provide accurate diagnostics in minutes. These systems are helpful in settings with limited resources and large population screenings [91][95].

To improve sensitivity and detect biomolecules in lower concentrations, point-of-care devices use nanomaterials to improve biomarker detection. Some of the nanomaterials used are gold nanoparticles, carbon nanotubes, graphene derivatives, quantum dots, and metal-oxide nanostructures. These nanomaterials improve marker detection through signal amplification, biomarker detection, and surface reactivity. Some of the markers these devices can detect include proteins, microRNAs, circulating tumor DNA, and exosomal elements that are indicative of early-stage lung cancer [92][95].

Point-of-care diagnostics that use enhanced lateral flow assays represent a widely studied format. These assays use gold nanoparticles to detect proteins and other biomarkers through a colour change and can be quantitated using an optical reader. These diagnostic assays can conduct rapid screenings at a lower cost.[95]

Another key platform is the electrochemical nanoscale diagnostic devices. The use of conductive nanomaterials like graphene and metal nanocomposites provide these devices with the highest levels of sensitivity and the fastest response times. These devices are able to detect genetic changes and methylation and protein biomarkers in minutes, making them valuable in real time clinical settings. Accessible electrochemical chips are portable and integrate digitally with smartphones.[91][95]

Recently, breath-based diagnostic devices have also been getting a lot of interest as the fully non-invasive alternatives. These devices have nanostructured sensors specifically designed to analyse and detect volatile organic compounds and can perform an analysis linked to the metabolism of lung cancer. They are portable which is of great benefit when screening large high-risk groups.[96]

Nanotechnology in point-of-care diagnostics further lessens the reliance on specialized diagnostic apparatus and prevents the time-lag in diagnostics thus preventing delays needed for timely clinical intervention. Rapid detection of malignant signatures improves patient stratification in patient screening and improves the speed of initiation for radical therapy along with the overall improvement in large-scale screening.[91][95]

6. Therapeutic Potential and Safety Aspects

Lung cancer treatment through nanomedicine is encouraging due to its ability to improve migration to target tissues, greater selectivity of the tumours, and less overall toxicity to the body.[100] But the prospects of nanoscale materials in the clinic raise safety, biodistribution, regulations, and biological concerns. Still, these factors will help characterize the potential of nano formulations in propelling the current experimental therapies towards the clinic and being the first inhalable therapies to cap the nanomedicine field.[102]

6.1. Toxicity considerations of nanomedicines

While nanocarrier technology has improved how we deliver chemotherapeutics and reduced their toxicity, nanocarriers have their own toxicity issue as well.[103] These are associated

mainly with the characteristics of the nanoparticles, including their size, surface charge, surface shape, coating, and the use of anchor and sensor polymers.[103] Small nanoparticles are more likely to cross biological membranes and barriers and interact with subcellular organelles, which may result in adverse biological consequences.[104]

Increased surface reactivity increases the potential toxicity of a nanomaterial. For example, silver and gold nanoparticles may produce reactive oxygen species and exacerbate oxidative stress, which can produce mitochondrial dysfunction and even remove segments of cells via apoptosis, and/or damage the DNA. Polymeric nanoparticles and lipidic nanoparticles are generally more biocompatible, but we are still missing information as to how the non-volatile reaction solvents and the inorganic fillers might initiate inflammation or activate immune responses. From a toxicity perspective, it is more worrisome that inhalable nanomaterials are likely to be directly in contact with the respiratory mucosa, which may cause inflammation, deactivation of enzymes that reduce surface tension of the alveoli, and the activation of macrophages in the lung.[104][103][105]

Another problem is immunogenicity resulting from possible activation of complement pathways by the nanoparticles and resulting hypersensitivity reactions induced by cytokine release.[104] Any changes to immune behaviour or chronic inflammatory responses resulting from repeated dosing are also a problem.[104] For all these reasons, the need for detailed in silico studies, in vivo biodistribution studies, and long-term safety studies also has to be accounted for when making a toxicity assessment.[101][103]

6.2. Regulatory guidelines for inhalable nanomedicines.

The situation is slowly improving for inhalable nanomedicines with the FDA and EMA requesting careful characterization of nano formulations [100]. Regulatory requirements include a comprehensive investigation of the size distribution, morphology, surface chemistry, and polydispersity and stability of the nanoparticles.[102] Producers must show reproducible synthesis, controlled drug release, and consistent performance of the drug during inhalation.[106]

Further specifications apply for pulmonary delivery. For instance, there needs to be an assessment of the aerodynamic particle size and the deposition efficiency for all regions of the respiratory tract, as well as potential airway irritation/vesicular injury.[105] Interactions that need to be studied include pulmonary surfactant, mucociliary, and macrophage uptake.[105][108] However, there has to be stability for the drug during the process of nebulization or aerosolization, as nanoparticles may aggregate or degrade.[106]

Acute, sub-chronic, and chronic exposure studies as well as assessments of oxidative stress, fibrosis, inflammation, and altered lung function are required by toxicology guidelines [104]. Regulators need proof of minimal long-term accumulation for metallic nanoparticles [104]. Immune-modulating or gene-delivery nano formulations need to show that they don't cause genotoxicity or unexpected immunological reactions [101]. The safety and uniformity required for inhalable nanomedicines to be used in clinical settings are guaranteed by these stringent regulatory requirements [100].

6.3. Clearance, biodistribution, and long-term safety

Long-term safety assessment is important for nanomedicines, especially those meant for repeated use [101]. Biodistribution studies indicate that nanoparticles act differently than traditional drugs [103]. Based on their size and composition, nanoparticles can gather in the liver, spleen, lungs, or kidneys [104]. Ongoing accumulation may heighten the risk of chronic toxicity, inflammation, or reduced organ function [104].

Disparate multifunctional carriers have respective clearance metabolic pathways. It is known that the polymeric nanocarriers undergo degradation into non-toxic, metabolizable products that the liver or kidney can eliminate [104]. The lipid-based carriers, as well, can be metabolized through the natural lipid-processing pathways [103]. The metallic nanocarriers, which can be of concern due to their capability in tissue retention, require a thorough assessment of long-term oxidative stress, protein fold interaction, and potential thermal cellular functional ruptures [104].

Specific to the lung, there exist unique biodistribution challenges. The amplified therapeutic retention even in long-term, though presents increased exposure risks, is due to the possibility of inhaled nanoparticles remaining in the alveolar space for long durations, and not getting untaken by macrophages [104, 105]. These abusive exposure risks can include, but are not limited to, delayed hypersensitivity reaction, subclinical inflammatory response, and airway tissue remodelling [107]. Thus, the need to study the prolonged physiologic effect of the lung, the resiliency of the nanoparticles, and clearance potential via mucociliary and phagocytic pathways [105][108].

For complete safety assessments chronic toxicity profiles and immune response analysis have to be integrated with histopathological evaluation and pharmacokinetic data [101][103]. In order to bring inhalable nanomedicine platforms to the clinic it will be important to ensure there is foreseeable clearance and no long-term negative effects [102]

Reference

1. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small-cell lung cancer. Nature. 2018;553(7689):446-454. doi:10.1038/nature25183
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249. doi:10.3322/caac.21660
3. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small-cell lung cancer. Nature. 2018;553(7689):446–454. doi:10.1038/nature25183
4. 4 Skoulidis F, Heymach JV. Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. Nat Rev Cancer. 2019;19(9):495–509. doi:10.1038/s41568-019-0179-8
5. Hirsch FR, Scagliotti GV, Mulshine JL, et al. Lung cancer: current therapies and new targeted treatments. Lancet. 2017;389(10066):299–311. doi:10.1016/S0140-6736(16)30958-8
6. Bade BC, Dela Cruz CS. Lung cancer 2020: epidemiology, etiology, and prevention. Clin Chest Med. 2020;41(1):1–24. doi: 10.1016/j.ccm.2019.10.001

7. de Koning HJ, van der Aalst C, de Jong PA, et al. Reduced lung cancer mortality with volume CT screening in a randomized trial. N Engl J Med. 2020;382(6):503–513. doi:10.1056/NEJMoa1911793
8. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer. 2017;17(1):20–37. doi:10.1038/nrc.2016.108
9. Skoulidis F, Heymach JV. Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. Nat Rev Cancer. 2019;19(9):495-509. doi:10.1038/s41568-019-0179-8
10. Greenberg, M.; Selikoff, I.J. Lung cancer in the Schneeberg mines: A reappraisal of the data reported by Harting and Hesse in 1879. Ann. Occup. Hyg. 1993, 37, 5–14. [PubMed]
11. Riudavets, M.; Garcia de Herreros, M.; Besse, B.; Mezquita, L. Radon and Lung Cancer: Current Trends and Future Perspectives. Cancers 2022, 14, 3142. [CrossRef]
12. Garon EB, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372(21):2018-2028. doi:10.1056/NEJMoa1501824
13. National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409. doi:10.1056/NEJMoa1102873
14. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small-cell lung cancer. Nature. 2018;553(7689):446-454. doi:10.1038/nature25183
15. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc. 2019;94(8):1551-1565. doi: 10.1016/j.mayocp.2019.01.013
16. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-249. doi:10.3322/caac.21660
17. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-263. doi:10.3322/caac.21834
18. Zhou J, Ward ZJ, Xu W, et al. Global burden of lung cancer in 2022 and projections to 2050. Cancer Treat Rev. 2024; 132:102833. doi: 10.1016/j.ctrv.2024.102833
19. Mallath MK, Taylor DG, Badwe RA, et al. The growing burden of cancer in India: epidemiology and social context. Lancet Oncol. 2014;15(6):e205-e212. doi:10.1016/S1470-2045(14)70115-9
20. Pramesh CS, Badwe RA, Borthakur BB, et al. State of cancer care in India and opportunities for innovation. Future Oncol. 2024;20(2):93-104. doi:10.2217/fon-2023-0586
21. Balmes JR, Eisen EA, et al. Ambient and household air pollution and lung cancer in low- and middle-income countries, including India. Int J Cancer. 2020;146(11):3028-3039. doi:10.1002/ijc.32627IARC Working Group on the Evaluation of Carcinogenic Risks to HumansTo- bacco smoke and involuntary smoking.
22. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risk to humans: tobacco smoke and involuntary smoking. InIARC

monographs on the evaluation of carcinogenic risk to humans: tobacco smoke and involuntary smoking 2004 (pp. 1452-1452).

23. IARC Working Group on the Evaluation of Carcinogenic Risks to HumansPersonal habits and indoor combustions. Volume 100 E. A review of human carcinogens. IARC Monogr Eval Carcinog Risks Hum . 2012;100(Pt E):1–538 .
24. Veglia F, Vineis P, Overvad K, et al. Occupational exposures, environ- mental tobacco smoke, and lung cancer. Epidemiology . 2007;18(6):769–775. doi: 10.1097/ede.0b013e318142c8a1 .
25. Wang JB, Fan YG, Jiang Y, et al. Attributable causes of lung cancer incidence and mortality in China. Thorac Cancer . 2011;2(4):156–163. doi: 10.1111/j.1759-7714.2011.00067.
26. Man-made mineral fibres. IARC Monographs Eval Carcinogenic Risks Humans . 1988;43:39–171.
27. Hamra GB, Guha N, Cohen A, et al. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. Environ Health Perspect . 2014;122(9):906–911. doi: 10.1289/ehp.1408092.
28. Wang C, Yang T, Guo XF, et al. The associations of fruit and vegetable intake with lung cancer risk in participants with different smoking status: a meta-analysis of prospective cohort studies. Nutrients . 2019;11(8):1791. doi: 10.3390/nu11081791 .
29. Wang Y, Li F, Wang Z, et al. Fruit and vegetable consumption and risk of lung cancer: a dose-response meta-analysis of prospective cohort studies. Lung cancer. 2015;88(2):124–130. doi: 10.1016/j.lungcan.2015.02.015.
30. Yang WS, Va P, Wong MY, et al. Soy intake is associated with lower lung can- cer risk: results from a meta-analysis of epidemiologic studies. Am J Clin Nutr . 2011;94(6):1575–1583. doi: 10.3945/ajcn.111.020966.
31. Song J, Su H, Wang BL, et al. Fish consumption and lung cancer risk: systematic review and meta-analysis. Nutr Cancer. 2014;66(4):539–549. doi: 10.1080/01635581.2014.894102.
32. Farvid MS, Sidahmed E, Spence ND, et al. Consumption of red meat and processed meat and cancer incidence: a systematic review and meta-analysis of prospective studies. Eur J Epidemiol. 2021;36(9):937–951. doi: 10.1007/s10654-021-00741-9.
33. Xue XJ, Gao Q, Qiao JH, et al. Red and processed meat consumption and the risk of lung cancer: a dose-response meta-analysis of 33 published studies. Int J Clin Exp Med. 2014;7(6):1542–1553
34. Huang Q, Zhang H, Li Y, et al. Advances in molecular pathology and therapy of non-small cell lung cancer. Signal Transduct Target Ther. 2025;10(1):1–22. doi:10.1038/s41392-025-02243-6.
35. Smolarz B, Romanowicz H, Madej-Czerwonka B, et al. Lung cancer—epidemiology, pathogenesis, treatment. Int J Mol Sci. 2025;26(5):2049. doi:10.3390/ijms26052049.
36. Zhou S, Zhang Y, Wang L, et al. Hypoxia studies in non-small cell lung cancer. Oncol Rep. 2024;51(3):1–14. doi:10.3892/or.2024.8862.
37. Ngaha TYS, Ghuwalewala S, Lwin Z, et al. Angiogenesis in lung cancer: understanding tumor growth, invasion and metastasis. Front Oncol. 2023;13:1184579. doi:10.3389/fonc.2023.1184579

38. Moghaddam SJ, Li H, Cho SN, et al. Premalignant progression in the lung: knowledge gaps. Am J Respir Crit Care Med. 2024;209(5):545–556. doi:10.1164/rccm.202406-1168ST.
39. Servier Medical Art. SMART: Servier Medical Art [Internet]. Paris: Servier; [cited 2026 Mar 21]
40. Friedlaender A, Perol M, Banna GL, Parikh K, Addeo A. Oncogenic alterations in advanced NSCLC: a molecular super-highway. Biomark Res. 2024;12:24. doi:10.1186/s40364-024-00566-0.
41. Wang Z, Xing Y, Li B, Li X, Liu B, Wang Y. Molecular pathways, resistance mechanisms and targeted interventions in non-small-cell lung cancer. Mol Biomed. 2022;3:42. doi:10.1186/s43556-022-00107-x.
42. Jeon H, Wang S, Song J, Gill H, Cheng H. Update 2025: Management of non-small-cell lung cancer. Lung. 2025;203:53. doi:10.1007/s00408-025-00801-x.
43. Kariri YA. Update on the treatment of non-small cell lung carcinoma (NSCLC). J Clin Med. 2025;14:6960. doi:10.3390/jcm14196960.
44. Montagne F, Guisier F, Venissac N, Baste JM. The role of surgery in lung cancer treatment: present indications and future perspectives—state of the art. Cancers (Basel). 2021;13:3711. doi:10.3390/cancers13153711.
45. mBin Sumaida A, Shanbhag NM, Pervez N, AlKaabi K, Balaraj K. Surgery versus stereotactic body radiotherapy for early-stage non-small cell lung cancer (NSCLC): a comprehensive review of survival and local control outcomes. Cureus. 2025;17:e84440. doi:10.7759/cureus.84440.
46. Brown S, Banfill K, Aznar MC, Whitehurst P, Faivre Finn C. The evolving role of radiotherapy in non-small cell lung cancer. Br J Radiol. 2019;92:20190524.
47. Yeghiaian-Alvandi R, Hau E. A systematic review and meta-analysis of treatment-related toxicities of curative and palliative radiation therapy in non-small cell lung cancer. Sci Rep. 2021;11:5939. doi:10.1038/s41598-021-85131-7.
48. Li S, de Camargo Correia GS, Wang J, Manochakian R, Zhao Y, Lou Y. Emerging targeted therapies in advanced non-small-cell lung cancer. Cancers (Basel). 2023;15:2899. doi:10.3390/cancers15112899.
49. Wang H, Niu X, Jin Z, Zhang S, Fan R, Xiao H, Hu SS. Immunotherapy resistance in non-small cell lung cancer: from mechanisms to therapeutic opportunities. J Exp Clin Cancer Res. 2025;44:250. doi:10.1186/s13046-025-03519-z.
50. Li MSC, Mok KKS, Mok TSK. Developments in targeted therapy & immunotherapy — how non-small cell lung cancer management will change in the next decade: a narrative review. Ann Transl Med. 2023;11(10):358. doi:10.21037/atm-22-4444.
51. Lahiri A, Maji A, Potdar PD, Singh N, Parikh P, Bisht B, Mukherjee A, Paul MK. Lung cancer immunotherapy: progress, pitfalls, and promises. Mol Cancer. 2023;22:40. doi:10.1186/s12943-023-01740-y.
52. Li T, He W, Zhang X, Zhou Y, Wang D, Huang S, Li X, Fu Y. Survival outcomes of segmentectomy and lobectomy for early stage non-small cell lung cancer: a systematic review and meta-analysis. J Cardiothorac Surg. 2024;19:353. doi:10.1186/s13019-024-02832-6.
53. Malik Z, Zhou Y, Zhang C. Minimally invasive segmentectomy for non-small cell lung cancer (NSCLC): a comparative analysis of robotic and thoracoscopic

approaches. BMC Surg. 2025. Epub ahead of print. doi:10.1186/s12893-025-03421-7.

54. Muthu V, Mylliemngap B, Prasad KT, Behera D, Singh N. Adverse effects observed in lung cancer patients undergoing first-line chemotherapy and effectiveness of supportive care drugs in a resource-limited setting. Lung India. 2019;36:32-7.
55. Lee SH. Chemotherapy for lung cancer in the era of personalized medicine. Tuberc Respir Dis. 2019;82(3):179–189. doi:10.4046/trd.2018.0068.
56. Fernández-García R, Fraguas-Sánchez AI. Nanomedicines for pulmonary drug delivery: overcoming barriers in the treatment of respiratory infections and lung cancer. Pharmaceutics. 2024;16(12):1584. doi:10.3390/pharmaceutics16121584.
57. Sakkal M, Abdelmoteleb RWA, Al Ali A, et al. Inhalable nanoparticle-based drug delivery system for non-small cell lung cancer therapy: promises and challenges. Saudi Pharm J. 2025;33:50-65. doi:10.1016/j.jsps.2024.11.012.
58. Zhang J, Li Y, Guo S, et al. Moving beyond traditional therapies: the role of nanomedicines in lung cancer. Front Pharmacol. 2024;15:1363346. doi:10.3389/fphar.2024.1363346.
59. Fu J, Yu L, Wang Z, et al. Advances in controlled release drug delivery systems based on nanomaterials in lung cancer therapy: a review. Medicine (Baltimore). 2025;104:e41415. doi:10.1097/MD.0000000000041415.
60. Aryal S, Park S, Park H, Park C, Kim WC, Thakur D, et al. Clinical trials for oral, inhaled and intravenous drug delivery system for lung cancer and emerging nanomedicine-based approaches. Int J Nanomedicine. 2023;18:7865-7888. doi:10.2147/IJN.S432839.
61. Yuan L, Li X, Chen Y, et al. Pharmacokinetics and tumor delivery of nanoparticles: mechanisms and challenges. J Nanobiotechnol. 2023;21:408. doi:10.1186/s12951-023-02152-3.
62. **Ara N, Hafeez A.** Nanocarrier-mediated drug delivery via inhalational route for lung cancer therapy: a systematic and updated review. *AAPS PharmSciTech.* 2024;25:Article 58. doi:10.1208/s12249-024-02758-1.
63. Xie L, Xie D, Du Z, Xue S, Wang K, Yu X, Liu X, Peng Q, Fang C. A novel therapeutic outlook: Classification, applications and challenges of inhalable micron/nanoparticle drug delivery systems in lung cancer. International Journal of Oncology. 2024 Feb 21;64(4):38.
64. Barash O, Peled N, Tisch U, Bunn PA, Hirsch FR, Haick H. Classification of lung cancer histology by gold nanoparticle sensors. In Nanomedicine in Cancer 2017 Sep 1 (pp. 713-735). Jenny Stanford Publishing.
65. Sivarajakumar R, Mallukaraj D, Kadavakollu M, Neelakandan N, Chandran S, Bhojraj S, Karri VV. Nanoparticles for the treatment of lung cancers. Journal of Young Pharmacists. 2018 Jul 1;10(3):276.
66. Ankush Sharma, Amit K. Goyal, Goutam Rath. "Recent advances in metal nanoparticles in cancer therapy", Journal of Drug Targeting, 2017.
67. Sharma A, Shambhwani D, Pandey S, Singh J, Lalhlenmawia H, Kumarasamy M, Singh SK, Chellappan DK, Gupta G, Prasher P, Dua K. Advances in lung cancer treatment using nanomedicines. ACS omega. 2022 Dec 29;8(1):10-41.
68. Plank C. Nanomagnet tools : magnetism opens up new perspectives for targeted aerosol delivery to the lung. Trends in biotechnology. 2008 Feb 1;26(2):59-63.

69. Juillerat-Jeanneret L. Critical analysis of cancer therapy using nanomaterials. Nanotechnologies for the Life Sciences: Online. 2007 Sep 15.
70. Sukumar UK, Bhushan B, Dubey P, Matai I, Sachdev A, Packirisamy G. Emerging applications of nanoparticles for lung cancer diagnosis and therapy. International Nano Letters. 2013 Dec;3(1):45.
71. Bhatia S. Nanoparticles types, classification, characterization, fabrication methods and drug delivery applications. In Natural polymer drug delivery systems: Nanoparticles, plants, and algae 2016 Sep 24 (pp. 33-93). Cham: Springer International Publishing.
72. Min SH, Lei W, Jun CJ, Yan ZS, Guang YX, Tong Z, Yong ZP, Hui LZ, Xing H. Design strategy and research progress of multifunctional nanoparticles in lung cancer therapy. Expert opinion on investigational drugs. 2023 Aug 3;32(8):723-39.
73. Parmar K, Patel J. Metallic Nanoparticles: Technology Overview and Drug Delivery Applications in Lung Cancer. Handbook of Lung Targeted Drug Delivery Systems. 2021 Oct 17:433-41.
74. Girigoswami A, Girigoswami K. Potential applications of nanoparticles in improving the outcome of lung cancer treatment. Genes. 2023 Jun 28;14(7):1370.
75. In GK, Nieva J. Emerging chemotherapy agents in lung cancer: nanoparticles therapeutics for non-small cell lung cancer. Translational Cancer Research. 2015 Aug;4(4).
76. Gopalan B, Ito I, Branch CD, Stephens C, Roth JA, Ramesh R. Nanoparticle based systemic gene therapy for lung cancer: molecular mechanisms and strategies to suppress nanoparticle-mediated inflammatory response. Technology in cancer research & treatment. 2004 Dec;3(6):647-57.
77. Ahmad J, Akhter S, Rizwanullah M, Amin S, Rahman M, Ahmad MZ, Rizvi MA, Kamal MA, Ahmad FJ. Nanotechnology-based inhalation treatments for lung cancer: state of the art. Nanotechnology, science and applications. 2015 Nov 19:55-66.
78. Lee WH, Loo CY, Traini D, Young PM. Inhalation of nanoparticle-based drug for lung cancer treatment: Advantages and challenges. Asian journal of pharmaceutical sciences. 2015 Dec 1;10(6):481-9.
79. Feng J, Zhang P, Wang D, Li Y, Tan J. New strategies for lung cancer diagnosis and treatment: applications and advances in nanotechnology. Biomarker Research. 2024 Nov 13;12(1):136.
80. Yadav KS, Upadhya A, Misra A. Targeted drug therapy in non small cell lung cancer: clinical significance and possible solutions-part II (role of nanocarriers). Expert Opinion on Drug Delivery. 2021 Jan 2;18(1):103-18.
81. Cryer AM, Thorley AJ. Nanotechnology in the diagnosis and treatment of lung cancer. Pharmacology & therapeutics. 2019 Jun 1;198:189-205.
82. Sarkar S, Osama K, Mohammad Sajid Jamal Q, Amjad Kamal M, Sayeed U, Kalim A. Khan M, Haris Siddiqui M, Akhtar S. Advances and implications in nanotechnology for lung cancer management. Current drug metabolism. 2017 Jan 1;18(1):30-8.
83. Li S, Xu S, Liang X, Xue Y, Mei J, Ma Y, Liu Y, Liu Y. Nanotechnology: breaking the current treatment limits of lung cancer. Advanced Healthcare Materials. 2021 Jun;10(12):2100078.

84. Duan Y, Shen C, Zhang Y, Luo Y. Advanced diagnostic and therapeutic strategies in nanotechnology for lung cancer. Frontiers in oncology. 2022 Dec 7;12:1031000.
85. Garbuzenko OB, Kuzmov A, Taratula O, Pine SR, Minko T. Strategy to enhance lung cancer treatment by five essential elements: inhalation delivery, nanotechnology, tumour-receptor targeting, chemo-and gene therapy. 2019 Oct 22;9(26):8362.
86. Koutu V, Gupta M, Das S, Rawat DK, Kharade V, Pasricha RK, Pasricha R. Nanotechnology in lung cancer therapeutics: a narrative review. Cureus. 2023 Jan 26;15(1).
87. Kesharwani P, editor. Nanotechnology-based targeted drug delivery systems for lung cancer. Academic Press; 2019 Jan 26.
88. Kong J, Cai M, Zhu R, Zhang Y, Du Y, Jing X, Sun Y, Chang R, Qu C, Dong X, Ni J. The utilization of metal-organic frameworks in tumour-targeted drug delivery systems. Journal of Science: Advanced Materials and Devices. 2024 Sep 1;9(3):100770.
89. Imran M, Chaudhary A, Ali M, Jha SK, Mohammed Y. Effect of environment of the respiratory tract on nanomedicine drug delivery. In Lipids in Pulmonary Drug Delivery 2025 Jan 1 (pp. 49-68). Academic Press.
90. Garbuzenko OB, Saad M, Pozharov VP, Reuhl KR, Mainelis G, Minko T. Inhibition of lung tumour growth by complex pulmonary delivery of drugs with oligonucleotides as suppressors of cellular resistance. Proceedings of the national academy of sciences. 2010 Jun 8;107(23):10737-42.
91. Wang B, Hu S, Teng Y, Chen J, Liu X, Liu Y, et al. Current advances of nanotechnology in diagnosis and treatment of malignant tumors. **Signal Transduct Target Ther.** 2024;9:200. doi:10.1038/s41392-024-01889-y.
92. Khazaei M, Rashidi MR, Omidi Y. Nanosensors and their applications in early diagnosis of cancer. **Sens Actuators B Chem.** 2023;380:132283. doi:10.1016/j.snb.2023.132283.
93. Pelaz B, Alexiou C, Alvarez-Puebla RA, et al. Diverse applications of nanomedicine. ACS Nano. 2017;11(3):2313–2381. doi:10.1021/acsnano.
94. Li H, Cui Y, Luan X, et al. Nanotechnology in emerging liquid biopsy applications. Nanomedicine (Lond). 2021;16(14):1219–1241. doi:10.2217/nnm-2021-0007.[14]
95. Yetisen AK, Akram MS, Lowe CR. Paper-based point-of-care diagnostics. Lab Chip. 2013;13(12):2210–2251. doi:10.1039/c3lc50169h.
96. Guerrini L, Graham D. Molecularly mediated assemblies of plasmonic nanoparticles for Surface-Enhanced Raman Spectroscopy applications. Chem Soc Rev. 2021;50(22):13712–13736. doi:10.1039/d1cs00433a
97. Tabrizi MA, Ferré-Borrull J, Marsal LF. Electrochemical biosensors for cancer biomarkers detection: from nanomaterials to clinical applications. Biosens Bioelectron. 2020;168:112568. doi:10.1016/j.bios.2020.112568,.
98. Al-Salman HNK, Abdullah AA, Saleh GM. Graphene oxide-based biosensors for lung cancer detection: recent advances. **Talanta.** 2024;265:124843. doi:10.1016/j.talanta.2023.124843.

99. Huang X, Li Y, Zhang H, et al. Optical nanomaterial-based liquid biopsy for cancer diagnosis and monitoring. **J Hematol Oncol.** 2024;17:10. doi:10.1186/s13045-024-01531-y.

100. Fadeel B, Farcal L, Hardy B, Vázquez-Campos S, et al. Advanced tools for the safety assessment of nanomaterials. *Nat Nanotechnol. 2018;13(7):537–543..* doi:10.1038/s41565-023-01409-2.

101. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: Progress, challenges and opportunities. *Nat Rev Cancer. 2017;17(1):20–37.doi:10.1038/nrc.2016.108.*

102. Patil JS, Sarasija S. Pulmonary drug delivery strategies: A concise, systematic review. *Lung.* 2023;201:1–15. doi:10.1007/s00408-022-00580-7.

103. Nel A, Xia T, Mädler L, Li N. Toxic potential of materials at the nanolevel. *Science.* 2006;311(5761):622–627.* doi:10.1126/science.1114397.

104. Oberdörster G, Stone V, Donaldson K. Toxicology of nanoparticles. *Nat Nanotechnol.* 2023;18:130–140. doi:10.1038/s41565-022-01256-9.

105. Geiser M, Kreyling WG. Deposition and biokinetics of inhaled nanoparticles. *Part Fibre Toxicol. 2010;7:2.* doi:10.1186/1743-8977-7-2.*

106. Ventola CL. The nanomedicine revolution: part 1: emerging concepts. P T. 2012;37(9):512–525

107. Donaldson K, Poland CA. Nanotoxicology: new insights into nanotube lung hazard. Nat Nanotechnol. 2013;8(3):179–180. doi:10.1038/nnano.2013.32.[21]

108. Yu CP, Xu GB. The transport and deposition of nanoparticles in respiratory system by inhalation. Inhal Toxicol. 2015;27(6):273–284. doi:10.3109/08958378.2015.1049177