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Pathology e-gazette
Volume 1 Issue 1 JANUARY 2024

Bird's eye view of pulmonary tumors

INTRODUCTION AND EPIDEMIOLOGY

- **Lung cancer is the leading cause of cancer-related deaths worldwide, accounting for the highest mortality rates among both men and women.**
- **Age : 40-70 yrs with peak incidence in 50s and 60s**
- **2% of cases appear before the age of 40 years**
  Sex: Males>Females
- **Smoking is the leading cause of lung cancer, responsible for approximately 85% of all cases.**
- **Lung cancer is often diagnosed at advanced stages when treatment options are limited.**
- **Screening high risk individuals has the potential to allow early detection and to dramatically improve survival rates.**
- **Primary prevention (such as tobacco control measures and reducing exposure to environmental risk factors) can reduce the incidence of lung cancer and save lives.**

Why is lung cancer so deadly, & why are we hopeful that we can control it better in the future?

Because typically patients present when it is already so advanced in its course
Lung Cancer has a long latency period -> window of opportunity for screening where early cancer may be detected and virtually cured
-Also only tends to affect middle aged and elderly

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- Lung cancer mortality is declining due to improved patient outcomes with the help of diagnostic accuracy and better therapeutic strategies through more efficient molecular and biomarker testing.
- Regarding systemic therapy, mortality from NSCLC decreased due to the timing of approval of targeted therapy.
- This reflects the impact of clinical implementation of EGFR- and ALK-inhibiting agents in patients whose tumors harbor specific genomic abnormalities.
- In addition, the impact of newly discovered druggable genetic drivers, such as ROS1, RET, NTRK1-3, BRAF, MET, and ERBB2, and that of immunotherapy and the implementation of early detection techniques are expected to further improve the 5-year survival rate of NSCLC in the next few years.

ETIOPATHOGENESIS

Smoking tobacco (including cigarettes, cigars, and pipes) is the primary risk factor for lung cancer but it can also affect non-smokers. Other risk factors include exposure to secondhand smoke, occupational hazards (such as asbestos, radon and certain chemicals), air pollution, hereditary cancer syndromes, and previous chronic lung diseases.

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MOLECULAR PATHOGENESIS OF LUNG CANCER

SQUAMOUS CELL CARCINOMA

- ASSOCIATED WITH SMOKING
- CHROMOSOMAL DELETION - 3p, 9p (site of CDKN2A gene) and 17p (Site of TP53 gene)
- LOSS OF EXPRESSION of Rb tumor suppressor gene
- AMPLIFICATION of FGFR1
- INACTIVATION of cyclin dependent kinase inhibitor gene - pl6 protein lost

SMALL CELL CARCINOMA

- STRONGLY ASSOCIATED WITH SMOKING
- LOSS OF FUNCTION ABERRATIONS involving TP53 and Rb gene
- Chromosome 3p deletions
- AMPLIFICATION of genes of Myc family

LUNG CANCER IN NON-SMOKERS

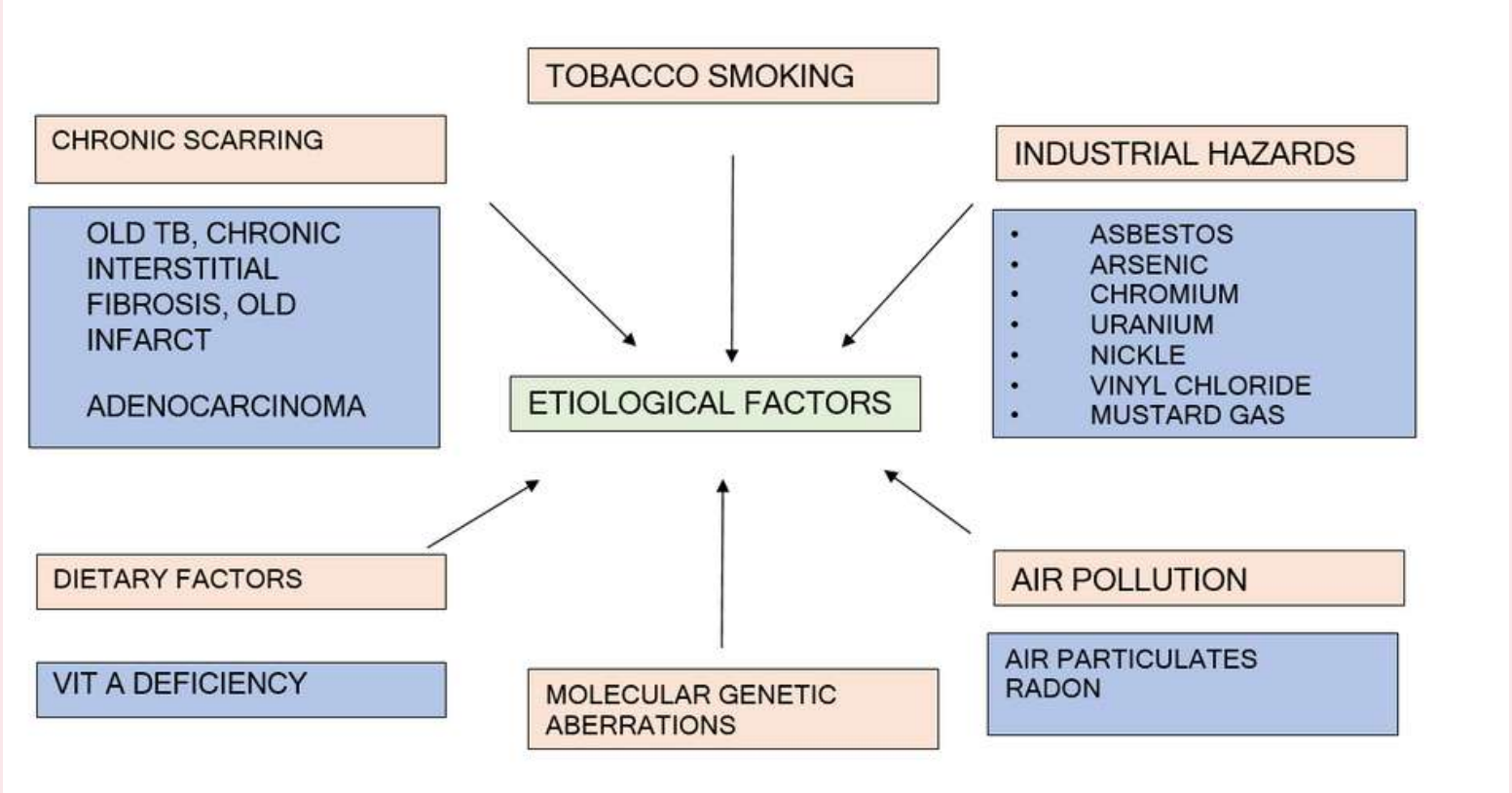
- More common in females and are adenocarcinomas
- Common mutations - EGFR
- TP 53 mutations - not uncommon

ADENOCARCINOMA

- GAIN OF FUNCTION MUTATIONS involving multiple genes encoding tyrosine kinase receptors - EGFR, ALK, ROS, MET and RET
- MUTATIONS in the KRAS gene in tumors without tyrosine kinase gene

INHERITED PREDISPOSITION

- Rare - found in Li-Fraumeni syndrome who inherit p53 mutations
- First degree relatives - 2-3 folds increased risk



WHO RESPONSE

- WHO recognizes the significant impact of lung cancer on global health and has implemented several initiatives to address the disease comprehensively.
- The WHO's response focuses on tobacco control, cancer prevention, early detection, and improving access to quality treatment and care. WHO supports countries in implementing evidence-based tobacco control policies, including increasing tobacco taxes, enforcing comprehensive bans on tobacco advertising, promotion, and sponsorship, and implementing strong graphic health warnings on tobacco products.
- The Organization also promotes cancer prevention strategies by advocating for healthy lifestyles, including regular physical activity, a healthy diet, and minimizing exposure to environmental risk factors.
- Additionally, WHO supports early detection programs and encourages countries to implement screening measures for high-risk populations to detect lung cancer at earlier stages when treatment options are more effective.
- WHO works towards ensuring access to quality treatment and care for lung cancer patients by providing technical guidance to member states, promoting equitable access to essential cancer medicines, and fostering international collaboration to share best practices and improve cancer care outcomes.

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Guidelines for Good Practice of Small Biopsies and Cytologic Preparations

1. For small biopsies and cytology, NSCC should be further classified into a more specific type, such as ADC or SQCC, whenever possible.
2. The term “non-small cell lung carcinoma-NOS (NSCLC-NOS)” should be used as little as possible, and only when a more specific diagnosis is not possible.
3. When a diagnosis is made in a small biopsy or cytology specimen in conjunction with special studies, it should be clarified whether the diagnosis was established on the basis of light microscopy alone or if special stains were required.
4. The term “non–squamous cell carcinoma (non-SQCC)” should not be used by pathologists in diagnostic reports. This categorization is used by clinicians to define groups of patients whose tumors comprise several histological types and who can be treated in a similar manner; in small biopsies/cytology, pathologists should classify NSCLC as ADC, SQCC, NSCLC-NOS, or other terms
5. The classification of ADC versus other histologies and the terminology should be used in routine diagnosis, future research, and clinical trials, to ensure a uniform classification of disease cohorts in relation to tumor subtypes, stratified according to diagnoses made by light microscopy alone versus diagnoses requiring special stains.
6. When paired cytology and biopsy specimens exist, they should be reviewed together to achieve the most specific and concordant diagnosis.
7. The terms AIS and minimally invasive ADC should not be used for diagnosis of small biopsies or cytology specimens. If a noninvasive pattern is present in a small biopsy, it should be referred to as a lepidic growth pattern. Similarly, if a cytology specimen has the attributes of AIS, then the tumor should be diagnosed as an ADC, possibly with a comment that this may represent, at least in part, AIS.
8. The term large cell carcinoma should not be used for diagnosis in small biopsy or cytology specimens and should be restricted to resection specimens where the tumor is thoroughly sampled to exclude a differentiated component.
9. In biopsies of tumors that reveal sarcomatoid features (marked nuclear pleomorphism, malignant giant cells, or spindle cell morphology), these should be initially classified as mentioned previously in relation to ADC; NSCC, favor ADC; SQCC; or NSCC favor SQCC, as this is apt to influence management, with additional statement that giant and/or spindle cell features (depending on what feature) are present. If such features are not present, the term NSCC-NOS should be used, again with comment on the sarcomatoid features.
• 10. Neuroendocrine immunohistochemical markers should be performed only in cases where there is suspected neuroendocrine morphology•

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WHO 2015	Entity name (changed or new nomenclature)	WHO 2021
	Bronchiolar adenoma/ciliated muconodular papillary tumour	New entity in 2021 WHO classification under the category of adenoma
	Thoracic SMARCA4-deficient undifferentiated tumour	New entity in 2021 WHO classification
	Primary pulmonary hyalinising clear cell carcinoma	New entity in 2021 WHO classification under the category of salivary gland tumour
Lymphoepithelial like carcinoma	Lymphoepithelial carcinoma	Change in nomenclature and catagorise under squamous cell carcinoma
	Spread through the airspaces (STAS)	New term added in WHO 2021 classification

Cytologic features	Pulmonary ADCA	Clear cell tumor	Hamartoma	Granular cell Tumor	Atypical Type II Pneumocytes
Cellularity	Usually hypercellular	May be hypercellular	Usually hypocelluar	May be Hypercellular	Usually hypocellular
Background	Necrotic	Non necrotic Foamy Vacuolated	Non necrotic	Non necrotic Granular	Non necrotic May be inflammatory
Pattern	Clusters /acinar Single cells 3 - dimensional	Clusters Single cells	Sheets of bronchial cells Mesenchymal cells	Loose sheets	Cluster with "knobby" border
Cell type	Cuboidal / columnar Polygonal	Polygonal Spindle	Epithelial and Mesenchymal	Polygonal Fusiform	Cuboidal
Cytoplasm	Scant to moderate Fine to coarse vacuolization	Moderate to abundant Vacuoles	Scant to moderate	Abundant Ill defined Granular	Moderate Vacuolated
Nuclear	Variably sized; round to oval; High N/C ratio. May be eccentric	Round to oval; Low N/C ratio May have inclusions	Round to oval Uniform	Round to oval. Uniform (occasional atypia)	Round to oval; there may be high N/C ratio
Nuclear membrane	Irregular	Smooth	Smooth	Smooth	Usually smooth but may be irregular

1.Squamous cell carcinoma
-Polyhedral cells
-Eosinophilic cytoplasm
-Intracellular keratin orange cytoplasm
-Moderate nuclear pleomorphism & Hyperchromatic nuclei, Inconspicuous nucleoli
-Fiber or Tadpole cells
-Squamous cell ghost
-Keratin pearls
-Tumor diathesis (debris & necrosis)

2.Adenocarcinoma Lung (Gland forming tumour)
-Cluster or glandular pattern
-Honeycomb pattern
-Moderate vacuolated cytoplasm
-Central to eccentric nucleus
-Prominent nucleoli seen

3.Small cell carcinoma
-Dissociated cells
-Cells are small look like lymphocytes
-Scanty cytoplasm
-Hyperchromatic nuclei with inconspicuous nucleoli
-Nuclear molding

4.Undifferentiated Large cell carcinoma
-Large cells & marked pleomorphism
-Moderate to abundant cytoplasm
-Ill-defined cytoplasm
-Bizarre cells
-Tumour giant cells
-Prominent nucleoli

5.Carcinoid
-Rosettes seen
-Monomorphic cells
-Moderate cytoplasm
-Round monomorphic nucleus
-Salt & pepper chromatin
-Mitosis uncommon

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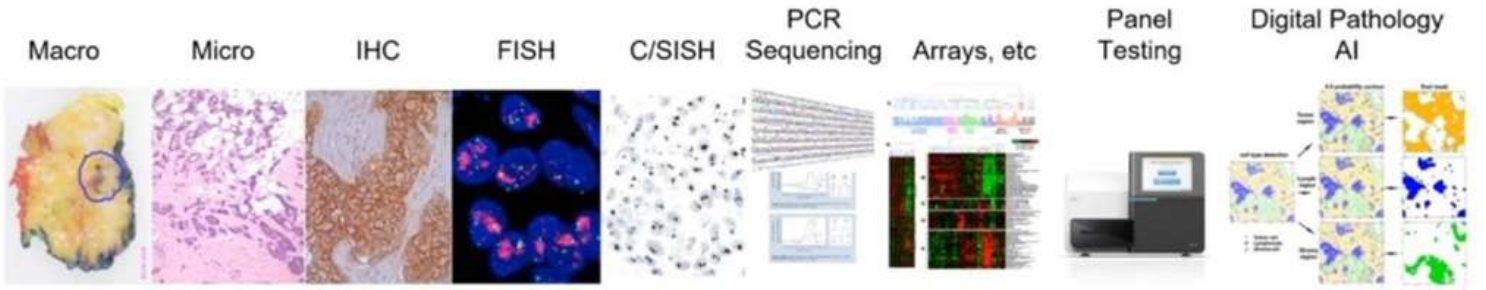
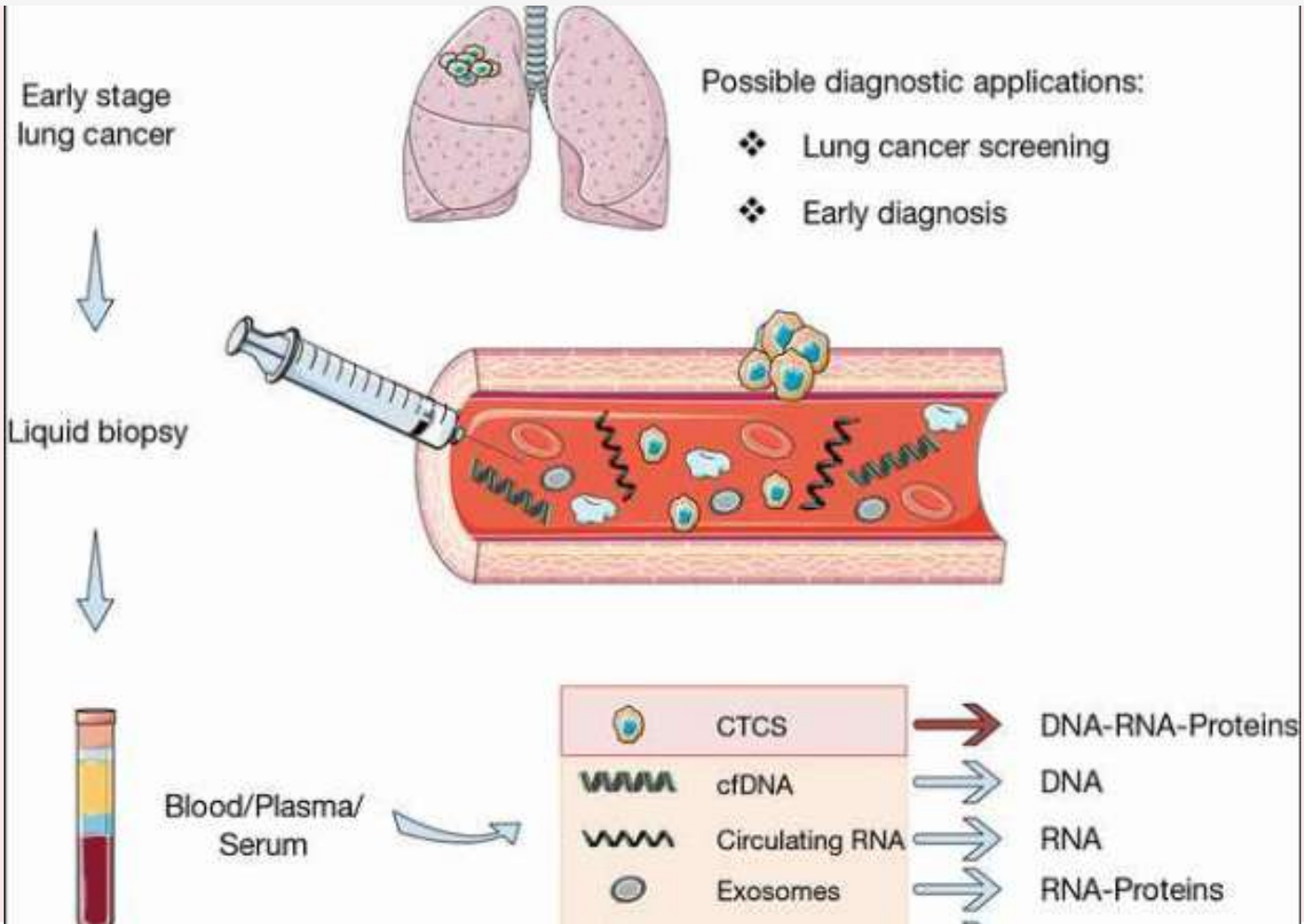
The Expanding Tool Kit of Pathologists for Lung Cancer Diagnostics[1-9]



AI, artificial intelligence; ALK, anaplastic lymphoma kinase; CISH, chromogenic in situ hybridization; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NTRK, neurotrophic tyrosine receptor kinase; PCR, polymerase chain reaction; PD-L1, programmed cell death ligand 1; ROS1, c-ros oncogene 1; SISH, silver in situ hybridization.

1. Hajdu SI, et al. *Cancer*. 2012;118:1155-1168. 2. Hajdu SI, et al. *Cancer*. 2015;121:2480-2513. 3. Bishop R. *Bio Horizons*. 2010;3:85-95. 4. Isola J, et al. *Methods Mol Med*. 2004;97:133-144. 5. Dziadziuszko R, et al. *J Thorac Oncol*. 2012;7:340-347. 6. Mardis ER, et al. *Hum Mol Genet*. 2009;18:R163-R168. 7. Hsiao SJ, et al. *JCO Precis Oncol*. 2020;4:1038-1048. 8. Niazi MK, et al. *Lancet Oncol*. 2019;20:e253-e261. 9. Planchard D, et al. *Ann Oncol*. 2018;29(suppl 4):iv192-iv237.



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Recent updates in diagnosis and treatment

- Advances in biomarkers, targeted therapies, and immuno-oncology have transformed the clinical management of patients with advanced NSCLC.
- For oncogene-driven tumors, there are highly effective targeted therapies against EGFR, ALK, ROS1, BRAF, TRK, RET, and MET.
- In addition, investigational therapies for KRAS, NRG1, and HER2 have shown promising results and may become standard-of-care in the near future.
- In parallel, immune-checkpoint therapy has emerged as an indispensable treatment modality, especially for patients lacking actionable oncogenic drivers.

- While PD-L1 expression has shown modest predictive utility, biomarkers for immune-checkpoint inhibition in NSCLC have remained elusive and represent an area of active investigation.

- Given the growing importance of biomarkers, optimal utilization of small tissue biopsies and alternative genotyping methods using circulating cell-free DNA have become increasingly integrated into clinical practice.

- Next generation sequencing(NGS) platforms will become routine in future NGS panels are preferred over multiple single assays

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Emerging Molecular Targets:

- The RET is capable of oncogenic activation via mutation or rearrangement. Rearranged RET occurs in 1%-2% of unselected instances of NSCLC.
- These mutations are frequently observed in non smokers' adenocarcinomas.
- When it comes to NSCLC, Kinesin Family Member 5B (KIF5B) is RET's upstream fusion partner of choice.
- In 3% of non squamous NSCLC, MET exon 14 mutations are another emerging target genetic change. These mutations are more likely to be found in non smokers, and clinical trials are necessary to evaluate how well MET inhibitors work, because only a small number of case reports and restricted series have shown positive results.

PD-L1 is an Essential Biomarker for PD-1/PD-L1 Inhibitors

Treatment with PD-1/PD-L1 inhibitors offers the promise of better outcomes for a growing community of patients in multiple indications.

PD-L1 IHC 22C3 pharmDx was the one PD-L1 assay used to assess PD-L1 status across KEYTRUDA® (pembrolizumab) clinical trials and is FDA-approved for use in every KEYTRUDA indication that requires PD-L1 testing:

For countries outside of the United States, see the local KEYTRUDA product label for approved indications and expression cutoff values to guide therapy
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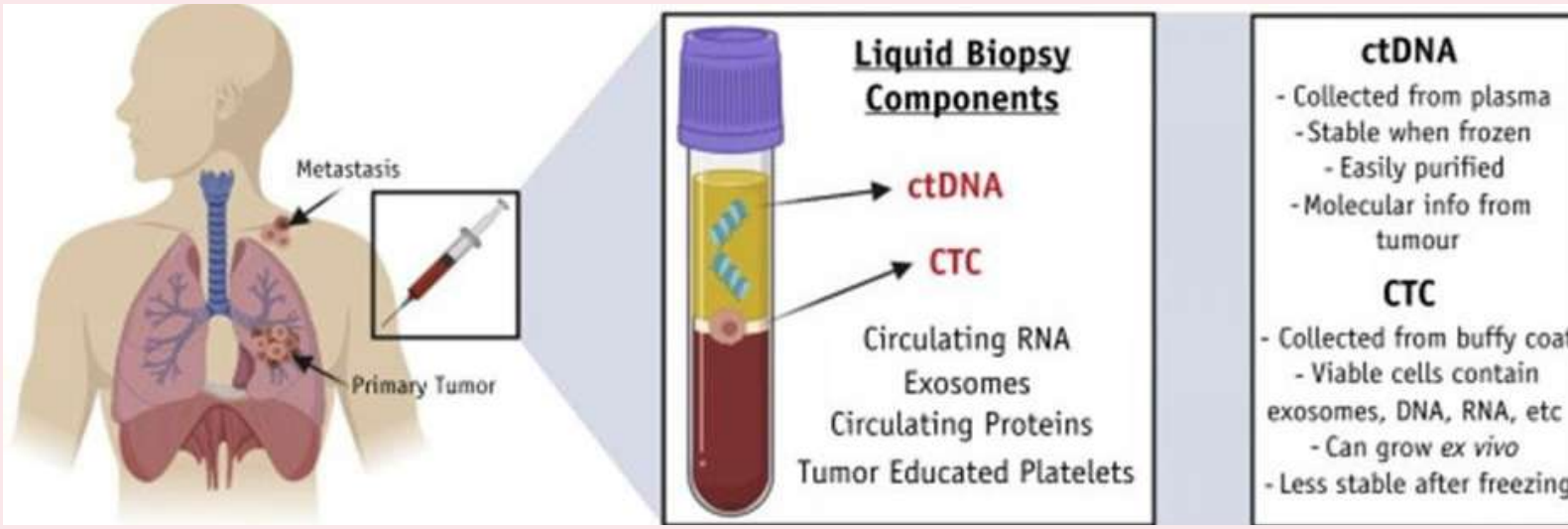

Molecular markers as per 2015 WHO	Author's name, year, reference number	Inference of the study
EGFR	Cortes-Funes H et al., 2005 [30] Tokumo M et al., 2005 [31]	EGFR mutations were found in 10 of 83 (12%) of patients EGFR mutations were present in 38 cases out of 120 (32%) and the majority of mutations were in-frame deletions of exon 19 (19 cases) and a missense mutation in exon 21 (18 cases).
ALK	Kwak EL 2010 [32]	Identified 82 patients with advanced ALK-positive disease
ROS1	Bergethon K 2012 [33]	A total of 1,073 tumours screened, 18 (1.7%) were ROS1 rearranged by FISH, and 31 (2.9%) were ALK rearranged
RET rearrangement	Wang R et al., 2012 [34] Saito M et al., 2014 [35]	A total of 936 patients with NSCLC, the RET fusion gene was exclusively detected in 13 patients Results suggest that the RET fusion functions as a driver for the development of thoracic tumours, whose growth is inhibited by RET tyrosine kinase inhibitors

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MET Exon 14 mutations	Awad MM et al., 2016 [36] Schrock AB et al., 2016 [37]	MET exon 14 mutations were identified in 28 of 933 non squamous NSCLCs (3.0%) A total of 11,205 lung cancers profiled by comprehensive genomic profiling, 298 (2.7%) carcinomas harbored alterations predicted to cause METex14
ERBB2-HER2	Mazières J et al., 2013 [38] Arcila ME et al., 2012 [39]	HER2 mutation was identified in 65 (1.7%) of 3,800 patients tested and was almost an exclusive driver, except for one single case with a concomitant KRAS mutation Identified 25 cases with HER2 mutations, representing 6% of EGFR/KRAS/ALK-negative specimens.
BRAF mutations	Barlesi F et al., 2016 [40]	EGFR mutations were reported in 1947 (11%) of 17,706 analyses for which data were available, HER2 mutations in 98 (1%) of 11,723, KRAS mutations in 4894 (29%) of 17,001, BRAF mutations in 262 (2%) of 13,906, and PIK3CA mutations in 252 (2%) of 10,678; ALK rearrangements were reported in 388 (5%) of 8134 analyses

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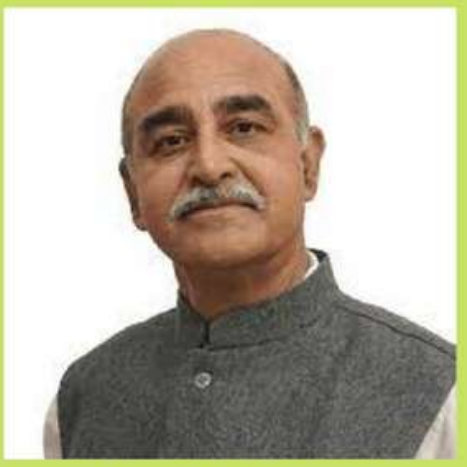

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