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## 2.1 Background

Lung carcinoma is one of the lethal diseases afflicting the global population [1]. Tobacco smoking attributes to majority of cases of lung cancer. Despite decades of efforts to improve outcome through multimodality therapy, survival rates have remained dismal. This is partly attributable to relatively ineffective methods for early detection and lack of curative treatment for advanced disease [2, 3].

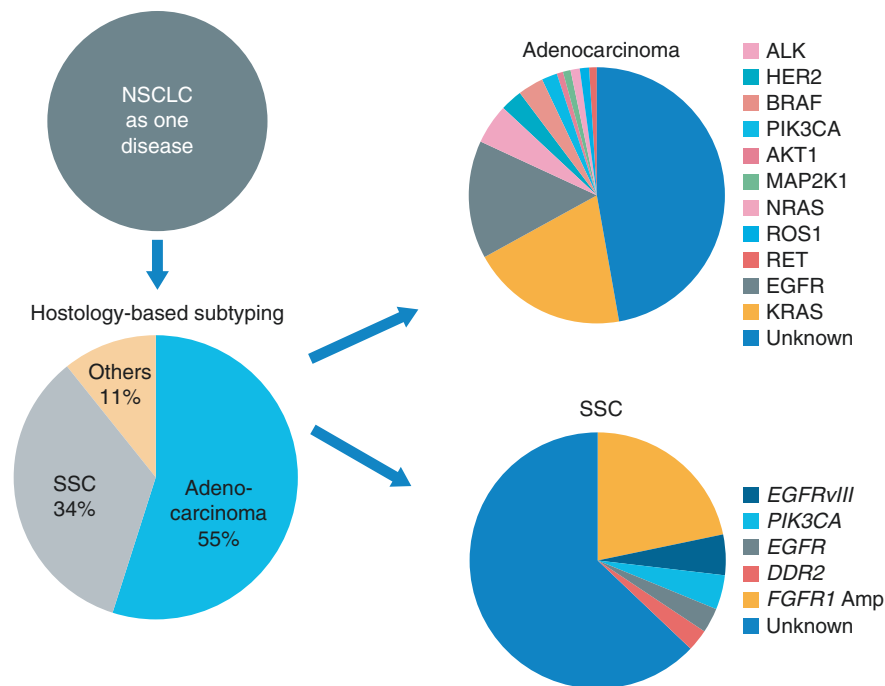
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## 2.2 Role of Pathologist in Today’s Era of Personalized Medicine

Lung cancer has been traditionally perceived as a relentlessly aggressive, and largely incurable disease, for which the surgical pathologist until recently had a marginal role [2, 4]. Historically, lung cancers have been subdivided by histology

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**Fig. 2.1** Evolving genomic classification of non-small-cell lung carcinoma (NSCLC)

into small-cell and non-small-cell lung cancers (NSCLCs), with NSCLC further classified into squamous cell carcinoma (SqCC), adenocarcinoma (ADC), and large-cell carcinoma. Prior to the 2004 WHO classification, there have been no therapeutic implications to classify the NSCLCs tumors further, so little attention was given to the distinction of ADC and SqCC in small tissue samples [2, 4]. The last decade has seen a shift toward molecular-based classification, in which information about genetic alterations and protein expression level is considered alongside histology in order to better understand the pathogenesis of the disease (Fig. 2.1) [5, 6]. Now, the patients with NSCLCs are to be classified into more specific types such as ADC or SqCC, whenever possible, as it is important for therapeutic decision-making for several reasons: (1) ADC histology is a strong predictor for improved outcome with pemetrexed therapy compared with SqCC [7], (2) potential life-threatening hemorrhage may occur in patients with SqCC who receive bevacizumab [8], and (3) ADC or NSCLC-not otherwise specified (NSCLC-NOS) should be tested for epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase [*ALK*] rearrangement as the presence of these mutations is predictive of responsiveness to tyrosine kinase inhibitors [9–13] and crizotinib [14–17].

With the advent of newer predictive biomarkers, tissue is required not only for routine histopathology but also for IHC and molecular analyses [3, 18, 19]. Thus, proper handling of the tissue is the biggest issue in era of personalized medicine, and pathologists' role in the management of lung cancer is becoming more

challenging and demanding, as they are expected to deliver maximal information from these tiny valuable samples. This has resulted in a paradigm shift in the practice of pathologist, who is now holds center stage in the treatment decision process for lung cancer patients [18, 20, 21].

### 2.3 New 2015 WHO Classification of Lung Cancer Recommendations

A significant change in classification of lung cancer occurred with the landmark publication by collaborative efforts of International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) in 2011 about new lung adenocarcinoma classification [18]. Many good clinical practice guidelines were proposed in this landmark paper (Table 2.1), which were adopted in new 2015 WHO classification with minor alterations [3, 22]. The major changes adopted in the new classifications as compared to 2004 classification are discussed as follows:

**Table 2.1** Summary of pathology considerations for good practice applicable to small biopsy and cytology specimens

1. Tissue specimens should be managed not only for diagnosis but also to maximize the amount of tissue available for molecular studies
2. To guide therapy for patients with advanced lung ADC, each institution should develop a multidisciplinary team that coordinates the optimal approach to obtaining and processing biopsy/cytology specimens to provide expeditious diagnostic and molecular results
3. When paired cytology and biopsy specimens exist, they should be reviewed together to achieve the most specific and concordant diagnoses. Cell blocks should be prepared from cytology samples including pleural fluids
4. In order to bring uniformity in routine diagnosis as well as future research and clinical trials for the classification of the disease cohorts in relation to tumor subtypes, similar terminologies should be used for categorization
5. For small biopsies and cytology, NSCLC should be further classified into a more specific type, such as adenocarcinoma or squamous cell carcinoma, whenever possible
6. The term NSCLC-NOS be used as little as possible, and we recommend it be applied only when a more specific diagnosis is not possible by morphology and/or special stains
7. 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 based on light microscopy alone or if special stains were required
8. The terms AIS and MIA 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
9. Neuroendocrine immunohistochemical markers should be performed only in cases where there is suspected neuroendocrine morphology. If neuroendocrine morphology is not suspected, neuroendocrine markers should not be performed
10. 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

*ADC* adenocarcinoma, *AIS* adenocarcinoma in situ, *MIA* minimally invasive adenocarcinoma, *NOS* not otherwise specified, *NSCLC* non-small-cell lung carcinoma, *SQCC* squamous cell carcinoma

## (a) Multidisciplinary Approach Is Required for Lung Cancer Diagnosis

One of the central proposals in this new classification is that lung cancer diagnosis is now clearly a multidisciplinary problem [18]. All specialists involved with the diagnosis of lung cancer patients need to work closely together to achieve the correct diagnosis and to obtain appropriate and sufficient tissue for molecular testing [3, 18, 19, 23].

## (b) New Criteria and Terminologies for Small Biopsy and Cytology Specimens

Prior classifications were primarily based on the resection specimens, so there were no proposed guidelines for dealing with small biopsies and cytology which are the only available diagnostic material in advance stage [2]. New WHO classification addresses the standardized terminology and criteria for resection specimens, as well as small biopsies and cytology (summarized in Table 2.2) [3, 24, 25].

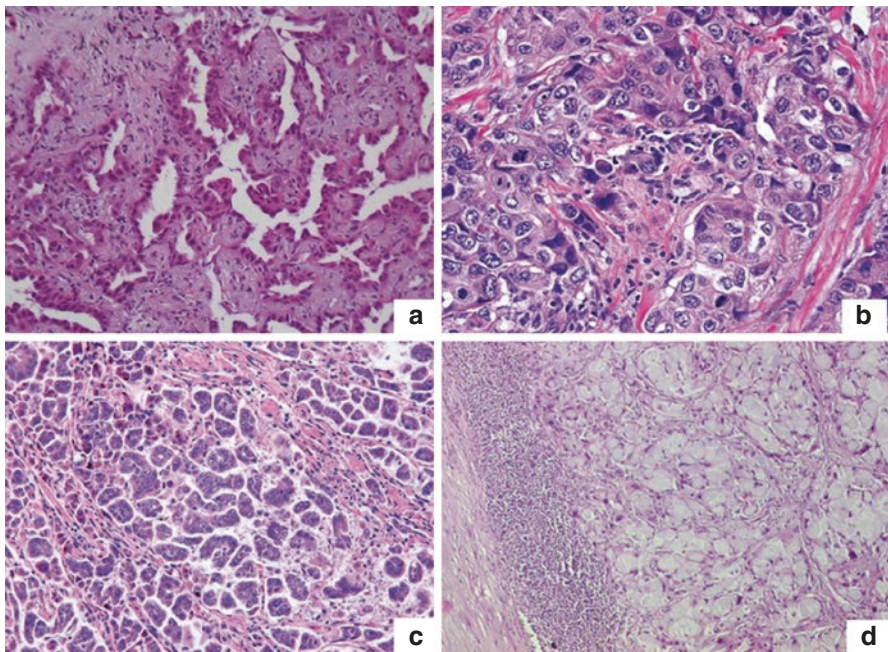
**Table 2.2** Specific terminology and criteria for adenocarcinoma, squamous cell carcinoma, and NSCLC-NOS in small biopsies and cytology

New small biopsy/ cytology terminology	Morphology/stains	2015 WHO classification
Adenocarcinoma (describe identifiable patterns present)	Adenocarcinoma Morphologic adenocarcinoma patterns clearly present	Adenocarcinoma Predominant pattern <ul style="list-style-type: none"> <li>• Lepidic</li> <li>• Acinar</li> <li>• Papillary</li> <li>• Solid</li> <li>• Micropapillary</li> </ul>
Adenocarcinoma with lepidic pattern (if pure, add note: an invasive component cannot be excluded)		Minimally invasive adenocarcinoma, adenocarcinoma in situ, or invasive adenocarcinoma with lepidic component
Invasive mucinous adenocarcinoma (describe patterns present; use term mucinous adenocarcinoma with lepidic pattern if pure lepidic pattern)		Invasive mucinous adenocarcinoma
Adenocarcinoma with colloid /fetal/enteric features		Colloid /fetal/enteric adenocarcinoma
Non-small-cell carcinoma, favor adenocarcinoma	Morphologic adenocarcinoma patterns not present (supported by special stains, i.e., TTF-1)	Adenocarcinoma(solid component may be just one component of tumor)
Squamous cell carcinoma	Morphologic squamous cell patterns clearly present	Squamous cell carcinoma
Non-small-cell carcinoma, favor squamous cell carcinoma	Morphologic squamous cell patterns not present (supported by stains, i.e., p40)	Squamous cell carcinoma (non-keratinizing component may be component of tumor)
Non-small-cell carcinoma, not otherwise specified	No clear adenocarcinoma, squamous or neuroendocrine morphology or staining pattern	Large-cell carcinoma (in resection)
Non-small-cell carcinoma with spindle cell or giant cell carcinoma		Pleomorphic, spindle cell, or giant cell carcinoma

The major changes were focused on the terminology and introduction of new entities for classification of ADC. These include the discontinuation of the terms bronchioloalveolar carcinoma (BAC) and adenocarcinoma, mixed subtype, as well as the introduction of micropapillary as a new histologic subtype, the term adenocarcinoma with lepidic pattern for the former BAC growth pattern and invasive mucinous adenocarcinoma for overtly invasive tumors previously classified as mucinous BAC [3, 18, 22, 24].

For resection specimens, new concepts are introduced such as adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) for small solitary adenocarcinomas ( $\leq 3$  cm), with either pure lepidic growth (AIS) or predominant lepidic growth with  $\leq 5$  mm invasion (MIA) to define patients who, if they undergo complete resection, will have 100% or near 100% disease-free survival, respectively. The invasive component in MIA is defined as follows: (1) histological subtypes other than a lepidic pattern or (2) tumor cells infiltrating myofibroblastic stroma. AIS and MIA terminologies are never to be used in the biopsy specimens [3, 18, 25].

More than 90% of invasive lung adenocarcinomas fall into the mixed subtype in 2004 WHO classification, so it has been proposed to use comprehensive histologic subtyping to make a semiquantitative assessment of percentages (in 5% increments) of the various histologic components: acinar, papillary, micropapillary, lepidic, and solid (Fig. 2.2). Individual tumors are then classified according to the predominant pattern, and the percentages of the subtypes are also reported [18, 25]. This has demonstrated an improved ability to address the complex histologic heterogeneity of lung adenocarcinomas and to improve molecular and prognostic correlations [3, 26].



**Fig. 2.2** Histological patterns of adenocarcinoma including lepidic (a), solid (b), micropapillary (c), and signet ring cell (d) as predominant patterns (hematoxylin-eosin, original magnification  $\times 20$ )

(c) Diagnostic Approach to Lung Carcinoma with Judicious Use of Immunohistochemistry

In prior WHO classification, lung cancer diagnosis was based mainly on the light microscopy, and role of immunohistochemistry (IHC) was limited to large-cell neuroendocrine tumors and sarcomatoid carcinomas, with no consideration in biopsies [2]. However, a new approach is introduced by recommending limited and judicious use of IHC and/or mucin stains for NSCLC-NOS cases that cannot be categorized definitively on morphological grounds [3, 18, 22]. In the recent past, many algorithms and recommendations to standardize the morphological and IHC classification of lung cancers have been proposed with the aim to optimally preserve the maximum tissue for the molecular testing (Fig. 2.3) [27–29]. The new WHO classification recommended the use of IHC, whenever possible, not only for small biopsies/cytology but also for resected specimens in certain settings such as solid ADC, non-keratinizing SqCC, large-cell carcinoma, neuroendocrine tumors, and sarcomatoid carcinomas [3, 22].

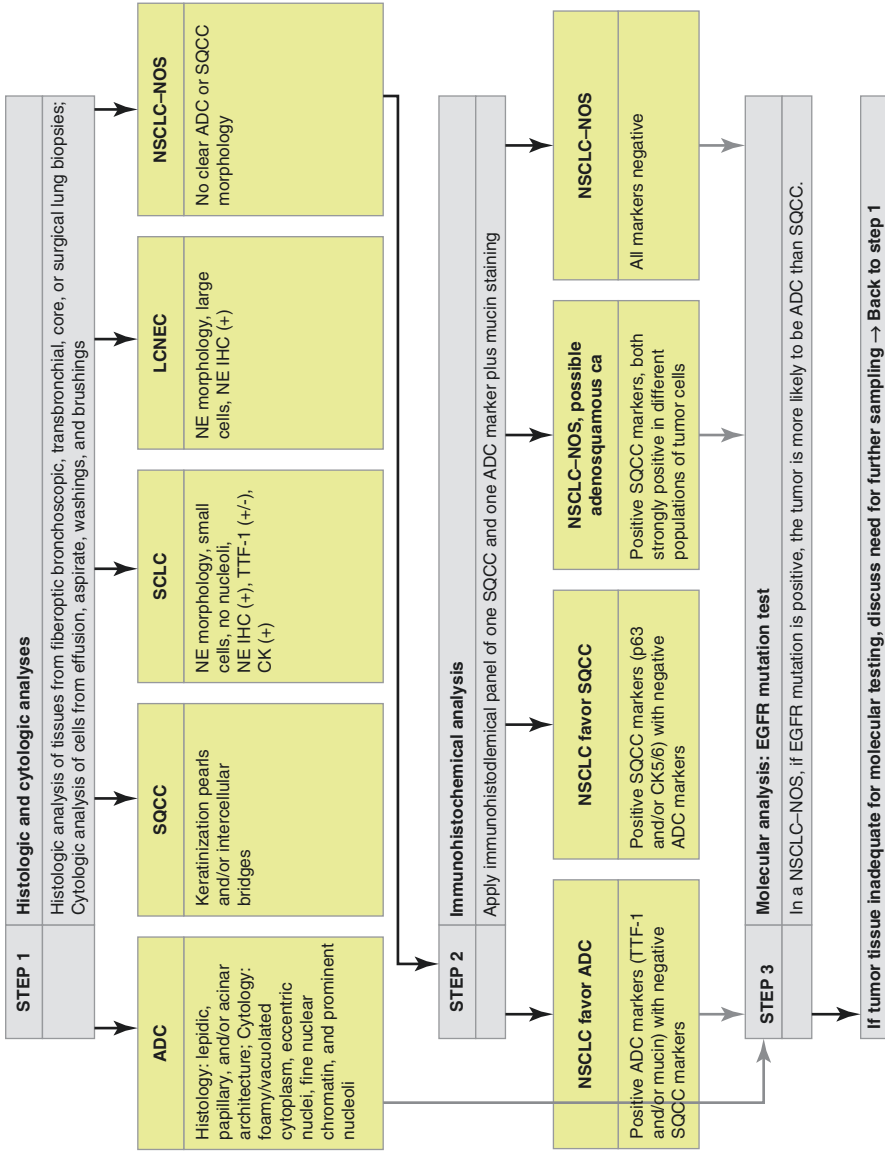
It is recommended to reduce use of the term NSCLC-NOS as minimal as possible using IHC judiciously and classify tumors according to their specific histologic subtype. Tumors that have clear morphologic patterns of ADC (acinar, papillary, lepidic, micropapillary) or SqCC (unequivocal keratinization, well-formed bridges) can be diagnosed, without IHC (Fig. 2.4) [3, 18, 24]. Based on the sensitivity and specificity, the markers which had emerged as preferred classifier of NSCLC include TTF-1 and napsin (for ADC) and p40, p63, and CK5/CK6 (for SqCC) [28, 29]. The reasonable recommendation is that, when IHC is deemed necessary, at least one antibody each for squamous and glandular differentiation, but no more than two antibodies, should be used for an initial work-up (e.g., TTF-1 or napsin and P40 or P63) (Fig. 2.5) [3, 18, 22]. Of these TTF-1 and p40 are viewed as most useful, and a simple panel of these two markers may be able to classify most NSCC, NOS cases [30–32]. Table 2.3 summarized the various terminologies used, while IHC is used for the categorizing of lung tumors.

If both TTF-1 and p40 are negative in a tumor that lacks clear squamous or glandular morphology, one may consider performing a cytokeratin stain to confirm that the tumor is a carcinoma. If a keratin stain is negative, further stains (S100, CD45, or CD31) may be needed to exclude other tumors [3, 27, 29, 32].

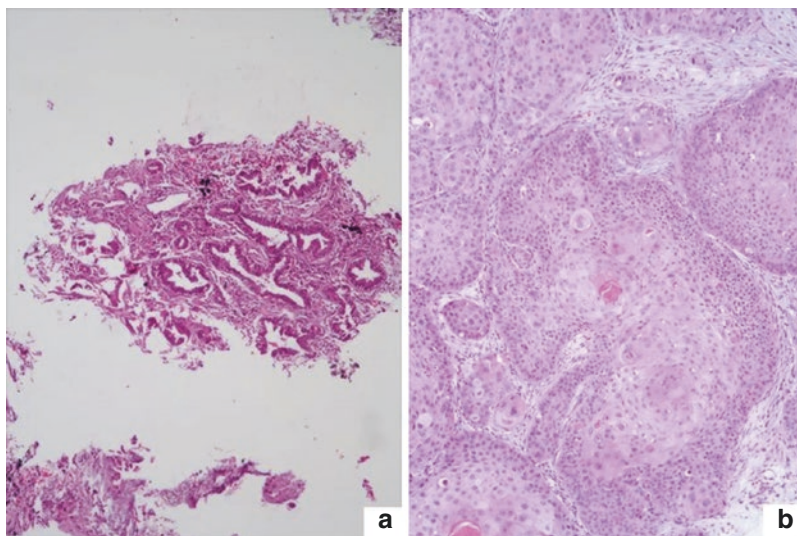
Although primary lung adenocarcinomas can be TTF-1 negative (e.g., mucinous adenocarcinomas), in this setting, one may perform additional IHC markers or suggest clinical evaluation to exclude a metastasis from other sites such as colon or breast. [3, 22, 27]

Even after applying this algorithm, there will remain a minority of specimens where the diagnosis remains NSCLC-NOS, as no clear differentiation can be established by routine morphology and IHC [22, 24].

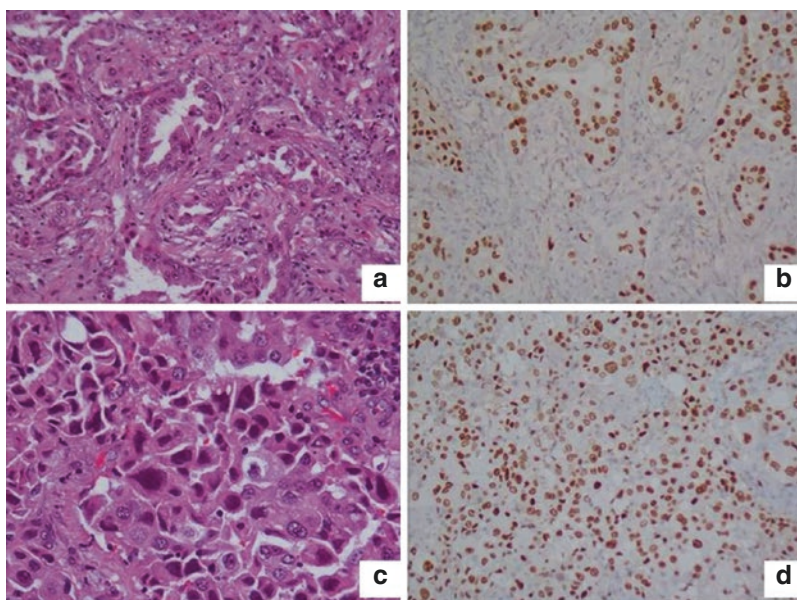
Recently, the role of EGFR mutation-specific antibodies [32] and ALK [33–35] has been explored. Now, ALK IHC can be used as good screening tool for ALK testing.



**Fig. 2.3** Algorithm for work-up of lung cancer diagnosis in small biopsies and cytology samples. *ADC* adenocarcinoma, *CK* cytokeratin, *IHC* immunohistochemistry, *LCNEC* large-cell neuroendocrine carcinoma, *NE* neuroendocrine, *NSCLC-NOS* non-small-cell lung carcinoma-not otherwise specified, *SCLC* small-cell carcinoma, *SQCC* squamous cell carcinoma, *TTF-1* thyroid transcription factor-1



**Fig. 2.4** The small biopsy showed fragments of adenocarcinoma with acinar configuration (a, hematoxylin-eosin, original magnification  $\times 40$ ) and another case of squamous cell carcinoma with nests of tumor cells that have keratinization and pearls (b, hematoxylin-eosin, original magnification  $\times 40$ ). These cases can be diagnosed without immunohistochemistry



**Fig. 2.5** A case of adenocarcinoma with acinar predominant pattern, exhibiting TTF-1 and confirming the primary pulmonary origin (a, b). Another case of non-small-cell lung carcinoma revealing solid pattern of growth with no clear acinar, papillary, or lepidic growth and no intracytoplasmic mucin. The tumor was thought to have a squamoid morphology and was initially diagnosed as a squamous cell carcinoma (c), however, thyroid transcription factor-1 (TTF-1) stain revealed positive immunostaining, favoring adenocarcinoma (d) (hematoxylin-eosin, original magnification  $\times 20$  (a); immunohistochemistry for TTF-1, original magnification  $\times 40$  (b))



**Table 2.3** Algorithm for subtyping of poorly differentiated non-small-cell lung carcinomas according to immunohistochemical staining

TTF-1/ Napsin	P63	P40	CK5/CK6	Diagnosis (Resection)	Diagnosis (Biopsy/ Cytology)
Positive (focal or diffuse)	Negative	Negative	Negative	Adenocarcinoma	NSCLC, favor adenocarcinoma
Positive (focal or diffuse)	Positive (focal or diffuse)	Negative	Negative	Adenocarcinoma	NSCLC, favor adenocarcinoma
Positive (focal or diffuse)	Positive (focal or diffuse)	Positive (focal)	Negative	Adenocarcinoma	NSCLC, favor adenocarcinoma
Positive (focal or diffuse)	Negative	Negative	Positive (focal)	Adenocarcinoma	NSCLC, favor adenocarcinoma
Positive in different areas	Any one of the above positive in different population as compare to TTF1			Adenosquamous carcinoma(>10% of each component)	NSCLC, possibly adenosquamous carcinoma
Negative	Any one of the above diffusely positive			Squamous cell carcinoma	NSCLC, favor squamous cell carcinoma
Negative	Any one of the above focally positive			Large-cell carcinoma, unclear	NSCLC, NOS
Negative	Negative	Negative	Negative	Large-cell carcinoma	NSCLC, NOS
No stains available	No stains available	No stains available	No stains available	Large-cell carcinoma with no additional stains	NSCLC, NOS

NSCLC non-small-cell lung carcinoma, NOS not otherwise specified

## 2.4 Molecular Work-Up for the Lung

The identification and characterization of molecular targets are having a growing impact on the management of patients with lung cancer [36–38]. Due to these developments, lung cancer has now emerged as the role model for the precision cancer medicine for solid tumors [6]. Within the family of lung carcinomas, the molecular underpinnings of lung ADC are best understood at this time (Table 2.4 and Fig. 2.1) [3, 22, 23]. *EGFR* and *ALK* are now widely recognized as therapeutic targets, and thus routine testing for alterations in these genes is a standard of care for advanced lung ADC [9–17].

Guidelines for lung molecular testing recommend that all lung ADCs, regardless of clinical characteristics, undergo molecular testing for *EGFR* mutation and *ALK gene rearrangement* [23]. Other potential driver “events” in NSCLC include *ROS1*, *KRAS*, *BRAF*, *HER2*, and *FGFR1* and may be tested as recommended by the revised guidelines [5, 6, 22, 38]. The current guidelines recommend to prioritize the tissue for *EGFR*, *ALK*, and *ROS* testing. Molecular testing of other molecular markers is not indicated as a routine stand-alone assay in diagnostic laboratory [6, 38].

**Table 2.4** Recurrent molecular alterations in lung adenocarcinoma, squamous cell carcinoma, and small-cell carcinoma

Type of alteration	Adenocarcinoma (%)	Squamous cell carcinoma (%)	Small-cell carcinoma (%)
<b>Mutations</b>			
TP53	30–40	50–80	>90
RB	5–15	5–15	>90
<b>EGFR</b>			
– Caucasian	10–20	<1	<1
– Asian	25–45	<5	<5
<b>KRAS</b>			
– Caucasian	15–35	<5	<1
– Asian	5–10	<5	<1
ERBB2/Her2	<5	0	0
BRAF	<5	0	0
PIK3CA	<5	5–15	<5
<b>Amplifications</b>			
EGFR	5–10	10	<1
ERBB2/Her2	<5	<1	<1
Met	<5	<5	<1
Myc	5–10	5–10	20–30
FGFR1	<5	15–25	<1
<b>Gene rearrangements</b>			
ALK	5	<1	0
ROS	1–2	0	0
RET	1–2	0	0
NTRK1 and NRG1	<1	0	0

However, with the advent of many more potential molecular targets, and the challenges associated with obtaining tissue, there is a growing need to develop and utilize molecular technologies that can determine the expression or mutation status of several genes simultaneously, so-called multiplex testing, in order to obtain the maximum diagnostic information from the limited tumor tissue available. Multiplex PCR assays and high-throughput technologies such as Next Generation Sequencing (NGS) will play an important role in lung carcinoma management and rational therapy selection, but there are many challenges ahead [39]. Further, the role of liquid biopsy in lung cancer is evolving and as per current recommendation can be used to track the disease progression (e.g., EGFR T790M mutational analysis), but not for establishing the diagnosis of malignancy [40].

To conclude, it is now a well-established fact that multidisciplinary approach is essential for establishing a diagnosis of lung cancer and pathologist plays a pivotal role in the lung cancer management in today's era. Modern treatment strategies focus on the pathological classification of NSCLC, which includes assessment of protein expression by IHC as well as the detection of molecular predictive markers.

### Key Points

- Lung cancers are subdivided by histology into small-cell and non-small-cell lung cancers (NSCLCs).
- NSCLC are classified into squamous cell carcinoma (SqCC), adenocarcinoma (ADC), and large-cell carcinoma.
- ADC histology is a strong predictor for improved outcome with pemetrexed therapy.
- ADC or NSCLC-not otherwise specified (NSCLC-NOS) should be tested for epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase [ALK] rearrangement.
- New WHO classification addresses the use of standardized terminology and criteria for resection specimens, as well as small biopsies and cytology.
- Currently, terms such as bronchioloalveolar carcinoma (BAC) and adenocarcinoma, mixed subtype, are discontinued.
- Limited and judicious use of immunohistochemistry and/or mucin stains for NSCLC-NOS cases is recommended.
- The identification and characterization of molecular targets play an important role in the management of patients with lung cancer.
- Multiplex PCR assays and high-throughput technologies such as NGS may play important roles in lung carcinoma management and therapy selection.
- The role of liquid biopsy in lung cancer is evolving and is currently recommended to track the disease progression but not for establishing the diagnosis of malignancy.
- Multidisciplinary approach is essential for establishing a diagnosis of lung cancer, and pathologist plays a pivotal role in the lung cancer management in today's era.

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