

# Does Cell Type in Lung Cancer Have any Clinical Importance?

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## ABSTRACT

Lung cancer is the leading cause of deaths from cancer in men (20%), and it has reached 16.5% and started to surpass deaths due to breast cancer in women. Lung tumors include many subtypes according to the classification of the World Health Organization. These tumors are primarily classified as small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) from the aspects of disease presentation, potential of metastasis, clinical presentation, response to treatment and survival time. NSCLC constitutes nearly 80-85% of all lung cancers. NSCLCs are classified in different subtypes. The two predominant NSCLC histological subtypes are adenocarcinoma and squamous cell carcinoma. Adenocarcinomas have become the most commonly seen subtype of lung cancers (40%). The incidence of Squamous cell carcinoma has decreased in the last few decades and it is estimated to constitute 20-30% of all lung cancers today. Subtypes of NSCLC develop due to different factors, exhibit different clinical and radiological presentations, and consequently respond differently to surgical treatment and chemotherapeutic agents.

**Keywords:** Lung cancer, cell type, cancer

## INTRODUCTION

Lung cancer is the leading cause of deaths from cancer in men (20%), and it has reached 16.5% and started to surpass deaths due to breast cancer in women. Smoking, air pollution, genetic factors, occupational exposure, gender, dietary habits and chronic lung diseases are the main risk factors in lung cancer development (1).

Lung cancer can be diagnosed through histopathological examination of tissues or cytology. The specimens necessary for these examinations can be obtained by minimally invasive methods such as bronchoscopy, transthoracic needle biopsy, as well as invasive methods such as incisional biopsy, wedge resection, lobectomy and even pneumonectomy. While light microscopy is enough to diagnose lung cancer in almost all cases, special histochemical or immunohistochemical staining might be necessary to differentiate some histological subtypes.

Lung tumors include many subtypes according to the classification of the World Health Organization (WHO). On the other hand, these tumors are primarily classified as small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) from the aspects of disease presentation, potential of metastasis, clinical presentation, response to treatment and survival time. NSCLC also has some major types such as squamous cell carcinoma, adenocarcinoma, and large cell carcinoma (2).

Lung tumors can be pure tumors originating from a single cell, as well as exhibit histological heterogeneity by originating from

a multifunctional stem cell. Therefore, NSCLC can be diagnosed from small tissue specimens, but it is not always possible to obtain precise information about a subtype (3).

## Genetic and Molecular Alterations in the Oncologic Process

Although oncogenic processes in lung tumors have not been completely revealed, there is important information regarding the development process of some histopathological subtypes and oncogenic factors. The course of the disease and response to treatment differ in each subtype due to the differences in histopathological subtypes.

KRAS, EGFR and ALP mutations play an important role in the oncogenic process in lung adenocarcinomas (4). In patients with adenocarcinoma, KRAS mutations occur almost always in smokers, whereas EGFR mutations mainly develop in nonsmokers and Asian women (5-7). Some lung adenocarcinomas exhibit translocations in the ALK gene and lead to the overexpression of oncogenic ALK protein (8). EGFR and ALK tyrosine kinase inhibitors (gefitinib and erlotinib, crizotinib) developed after these mutations were identified have provided significant progress in the treatment of patients with translocation (9). Therefore, it is recommended to perform EGFR and ALK translocation tests regardless of the clinical features in all lung adenocarcinomas (10).

Other potential factors that have a role in lung tumor development are the mutations in genes such as p53, c-myc, Rb, BRAF, HER2 and FGFR1 (4, 11-13). Clinical studies on agents that have

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an effect on these genes have been continuing to ensure that significant development will be made for targeted treatments in the future.

Some molecular biological markers such as thymidylate synthase (TS) are also used in order to identify patients with lung cancer that have a high possibility of benefiting from molecular therapy and in order to predict their response to treatment. TS is generally found in high levels in SCLC and squamous cell carcinomas, but in low levels in adenocarcinomas. The efficacy of TS-targeted treatments such as pemetrexed is lower in SCLC and squamous cell carcinomas due to high levels of TS in comparison to adenocarcinomas (14).

Today, many genetics and molecular studies like these are continuing to be conducted at full speed. Oncogenic processes in the lungs begin with the addition of some external factors to such genetic and molecular alterations. In this process, most tumors develop after some preneoplastic stages.

#### **Preinvasive Lesions**

It has become possible to diagnose lung cancer in early stages due to the advancements in radiologic imaging modalities and the application of screening programs throughout the world. The interest in preinvasive lesions has increased with the addition of information obtained in studies regarding oncogenic processes (15).

It is known that lung cancer develops as a result of very complex combinations constituted by morphological, molecular and genetic alterations. Different preinvasive lesions may develop during this process depending on the cell of origin.

Although no preinvasive lesions were defined in the 1967 WHO classification of lung cancer, *in situ* squamous dysplasia and carcinoma were defined as preinvasive lesions in the 1981 WHO classification. Today, the main preinvasive lesions such as atypical adenomatous hyperplasia, adenocarcinoma *in situ*, and diffuse idiopathic pulmonary neuroendocrine cell have also been defined (2).

#### **Squamous Dysplasia and Carcinoma *in Situ***

Squamous cell carcinoma (SCC) is rather centrally located, wherein it develops as a result of a continuous transformation involving basal cell hyperplasia of normal bronchial mucosa, squamous metaplasia, dysplasia and carcinoma *in situ* (2, 16).

Squamous dysplasia can be mild, moderate, or severe depending on the abnormal thickness of the bronchial epithelium and the severity of cytologic atypia. Moreover, carcinoma *in situ* corresponds to full-thickness epithelium involvement and distinct cytologic atypia.

#### **Atypical Adenomatous Hyperplasia (AAH) and Adenocarcinoma *in Situ* (AIS)**

Contrary to squamous cell carcinomas, adenocarcinomas are largely peripheral in location and originate from alveolar or bronchial epithelia (pneumocytes or Clara cells). Molecular alterations

in preinvasive lesions, such as AAH and AIS, are not characterized as well as they are in squamous carcinogenesis. However, it is believed that this process proceeds with the changes in epidermal growth factor receptor (EGFR) signal in non-smokers and with the changes in KRAS signaling pathways in smokers (16, 17).

#### **Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH)**

This lesion is thought to be a preneoplastic lesion of carcinoid tumors. Neuroendocrine cell hyperplasia and tumorlets are generally lesions secondary to airway inflammation or fibrosis (17, 18).

A distinct preneoplastic lesion has not been identified for other tumors of the lungs. On the other hand, it has been found that morphologically normal bronchial epithelium neighboring the tumor exhibits genetic changes in SCLC. Therefore, it is thought that SCLC bypasses the traditional multi-stage preneoplastic sequence (17, 18).

#### **Non-Small Cell Lung Carcinoma and Subtypes (NSCLC)**

NSCLC constitutes nearly 80-85% of all lung cancers. Subtypes of NSCLC develop due to different factors, exhibit different clinical and radiological presentations, and consequently respond differently to surgical treatment and chemotherapeutic agents. Therefore, NSCLCs are classified in different subtypes.

#### **Squamous Cell Carcinoma (SCC)**

SCC has the highest association with smoking and it is more commonly seen in men. The incidence of SCC has decreased in the last few decades probably due to the changes in smoking habits in the population, wherein it is estimated to constitute 20-30% of all lung cancers today (19).

Nearly 65% of these tumors are centrally located, whereas the remaining 35% are peripheral in location. SCC generally starts in segmental bronchi and extends to the lobar and main bronchi, and it is the tumor that exhibits cavitation most frequently (19).

Squamous Cell Carcinoma is the tumor type with the highest rate of accurate diagnosis (79%) in preoperative biopsy materials. It exhibits distant metastases later than other types and tends to spread locally. Among lung cancers, this subtype is the one that exhibits p53 mutations most frequently.

It includes various subtypes such as papillary, clear cell, small cell and basaloid. However, the proven clinical or prognostic effects of these subtypes are not clearly known, except for those of the basaloid subtype. Therefore, there are also alternative sub-classification recommendations (19, 20).

#### **Adenocarcinoma (AC)**

The prevalence of adenocarcinoma has increased over recent years, wherein adenocarcinomas have become the most commonly seen subtype of lung cancers, making up nearly 40% of cases. These are less associated with smoking in comparison to other subtypes and more frequently seen in women. ACs are mainly peripheral in location and they can be confused with mesothelioma as they may exhibit extensive pleural involve-

ment. Pulmonary adenocarcinomas often present histological heterogeneity, i.e. they are formed by a combination of other histological subtypes (20).

In 2011, the IASLC/ATS/ERS proposed a new sub-classification for lung adenocarcinoma. With this new classification, bronchoalveolar carcinoma definition was replaced by the terms adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA). MIA was defined as a lepidic predominant tumor with a diameter smaller than 3cm and with an invasive component of 5mm or smaller. Histologically, these lesions are generally non-mucinous, but they can at rare times be mucinous. In both subtypes, complete resection can provide 5-year survival in nearly 100% of cases (21).

The new classification brings some important changes that reflect the heterogenous nature of these tumors. As the majority of these tumors exhibit mixed histopathological patterns, it is recommended to provide all other sub-patterns listed in the pathology report in percentages and to specify the predominant pattern (lepidic, acinar, papillary, micro-papillary, or solid) (21).

Prognosis can be predicted better with this algorithm proposed for reporting lung adenocarcinoma, as small components of the tumor are also specified. For example, there are studies which report that early stage adenocarcinoma with micro-papillary pattern is associated with poor prognosis (21).

The IASLC/ATS/ERS classification recognizes four adenocarcinoma variants: invasive mucinous (former mucinous BAC), colloid, fetal (low or high grade) and enteric. Invasive mucinous adenocarcinomas are classified as adenocarcinoma variants differing from non-mucinous adenocarcinomas due to their strong combination of KRAS mutations, TTF-1 expression deficiency, and commonly seen multi-centric tumors. Together with the production of mucin, mucinous adenocarcinomas may exhibit a diversity of abundant lepidic, acinar, papillary, or micro-papillary architectural patterns like their nonmucinous analogues (21).

The IASLC/ATS/ERS classification shows that the proposed histological subtypes may help identify patients with a risk of poor clinical outcome. As discussed before, AIS and MIA are associated with excellent prognosis. While prognosis is moderate in histological subtypes that involve predominant papillary or acinar patterns, the presence of invasive mucinous or colloid variants, or predominant solid or micro-papillary variants is associated with a poor prognosis (22).

### Neuroendocrine Tumors

Neuroendocrine tumors constitute nearly 20-25% of all lung cancers. There are morphological, molecular, immunohistochemical (IHC) and ultrastructural features that distinguish these tumors from lung tumors. According to the WHO's classification, neuroendocrine tumors of the lung are divided into four categories, i.e. small cell lung carcinoma (SCLC), large cell neuroendocrine carcinoma (LCNEC), typical carcinoid (TC), and atypical carcinoid (AC) tumors. The main distinctive histological features of these four types of neuroendocrine tumors are the presence or absence of necrosis and their mitotic rate (2).

### Small Cell Lung Carcinoma (SCLC)

Small cell lung carcinoma constitutes nearly 12-15% of all lung cancers and it is more frequently seen in men and smokers between the ages 50-60. It is a very aggressive neuroendocrine tumor and the majority of patients have metastatic disease at the time of diagnosis. Therefore, surgical treatment can only be used occasionally. Only 5-8% of these patients with a very poor survival rate still survive five years after diagnosis (2).

Small Cell Lung Carcinomas have a high mitotic rate, wherein 60-70 mitoses are seen in 10 high power fields (for 10 HPF  $\geq 11$  mitoses) and they generally contain extensive necrosis (2). They are easily recognizable even in small biopsy and cytology specimens due to their distinctive histological appearance. However, immunohistochemical examinations, such as pan cytokeratin and neuroendocrine markers (chromogranin, synaptophysin and CD56) might help confirm the diagnosis in small specimens that are crush artefacts. In pancytokeratin-negative cases, lymphoma, chronic inflammation, and small round cell tumors should be considered in the differential diagnosis (21, 23).

Small Cell Lung Carcinoma can be pure or combined SCLC. The combination of SCLC and large cell carcinoma is present in 4-6% of cases, whereas approximately 1-3% of SCLCs are combined with adenocarcinoma or squamous cell carcinoma. In addition, SCLC may also combine with spindle cell carcinoma, large cell carcinoma and carcinosarcoma. If combined SCLC contains an adenocarcinoma or squamous cell carcinoma, no threshold is necessary for the ratio. However, in order to refer to SCLC as combined SCLC that contains a large cell tumor, the tumor has to have a large cell component of at least 10%. Considering the comparison of pure and combined SCLCs in clinical studies, the differences concerning clinical features, prognosis and response to treatment are not clear (2, 24).

### Clinical features and prognosis in Small Cell Lung Carcinoma

Small Cell Lung Carcinomas are very aggressive and approximately two thirds thereof develop as a perihilar mass. These tumors are typically seen in a peribronchial area with the infiltration of bronchial submucosa and peribronchial tissue. Bronchial obstruction is generally due to peripheral compression, however, endobronchial lesions may develop occasionally. Diagnosis is generally based on transbronchial biopsy and cytologic examination. Symptoms of paraneoplastic syndrome and generalized lymph node metastasis are frequently seen at the time of diagnosis, whereas 5% of cases present with a single solid lesion (25).

In Small Cell Lung Carcinoma, whether single lesion or advanced, survival is limited to a few months unless a treatment is administered. In early SCLC cases receiving combined KRT, median survival may be 10-16 months, whereas in advanced SCLC cases, median survival can be 6-11 months.

### Differential diagnosis in Small Cell Lung Carcinoma

In order to differentiate between SCLC and large cell carcinoma or large cell neuroendocrine carcinoma (LCNEC), certain criteria such as cell size, nucleotide, nuclear-cytoplasmic ratio, nuclear chromatin, nuclear molding and cell shape should be applied.

The most useful markers for SCLC in formalin-fixed, paraffin-embedded tissue sections are chromogranin A, synaptophysin and neural cell adhesion molecule. Although neuron specific enolase (NSE) is claimed to be a useful marker for neuroendocrine differentiation, it is relatively nonspecific as it also stains 60% of NSCLCs. If keratin staining is negative in suspected SCLC, the clinician should pay attention to excluding other possibilities, such as chronic inflammation, lymphoma, primitive neuroectodermal tumor, or small round cell sarcoma (22, 23).

#### Large Cell Neuroendocrine Carcinoma (LCNEC)

Large Cell Neuroendocrine Carcinoma is another aggressive neuroendocrine tumor that exhibits the cytologic features of NSCLC. It constitutes nearly 3-9% of all lung cancers and is generally peripheral in location. However, it can also be centrally located (23).

Differentiation between LCNEC and other NSCLC is based on the presence of positive IHC and neuroendocrine morphology for at least one neuroendocrine marker. In other words, the diagnosis is actually made by showing histopathologically that the tumor is not adenocarcinoma, squamous cell carcinoma, or SCLC. Like SCLC, these tumors also exhibit necrosis and high mitotic activity (more than 10 mitoses in 10 high power fields [ $\geq 11$  mitoses per HPF]). LCNEC can be pure, as well as combined with other NSCLC types (2).

As Large Cell Neuroendocrine Carcinoma is essentially a diagnosis of exclusion, the entire tumor should be examined histopathologically in order to reveal this. Therefore, the final decision is generally made by examining surgical resection specimens. Large cell carcinoma cannot be diagnosed from small biopsy or cytology specimens and as per the new IASLC/ATS/ERS recommendations, these cases should be classified as NSCLC as long as otherwise stated. According to the 2004 WHO classification, large cell carcinoma subtypes consist of large cell neuroendocrine carcinoma (LCNEC), basaloid carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, and large cell carcinoma with rhabdoid phenotype (21, 23).

#### Clinical features

Large Cell Neuroendocrine Carcinoma is closely associated with smoking and has a poor prognosis. Travis et al. (25) reported 27% and 11% five-year and ten-year survival rates for LCNEC respectively. Iyoda et al. (26) reported 35.3% and 31.7% five-year and ten-year survival rates for LCNEC respectively. Iyoda et al. (26) found the prognosis for LCNEC to be worse in comparison to large cell carcinoma, whereas Jiang et al. (27) reported better survival rates for LCNEC in comparison to non-small cell carcinoma. Surgical resection should be performed if possible. However, the efficacy of adjuvant radiation therapy or chemotherapy needs to be proven. Iyoda et al. (26) did not find any significant differences between patients with large cell carcinoma with neuroendocrine morphology and LCNEC patients in terms of age, gender, smoking history, tumor size and survival, although the mitotic rate was higher (28).

Positive immunohistochemical staining can be observed in 10-20% of NSCLC cases without neuroendocrine morphology. Similarly, neuroendocrine granules may be found in 10% of cases using an

electron microscope. These types of tumors are called non-small cell carcinomas with neuroendocrine differentiation (NSCLC-NED). The clinical importance of NSCLC-NED diagnosis is unknown. Iyoda et al. (26) found that the size of large cell carcinoma tumor with neuroendocrine differentiation is bigger in comparison to LCNEC, whereas survival was not different from that of LCNEC patients. It has not been clearly revealed whether these tumors respond to SCLC chemotherapy regimens, or if neuroendocrine marker expression could be a negative prognostic factor (29, 30).

#### Typical Carcinoid (TC) and Atypical Carcinoid (AC) Tumors

Carcinoid tumors constitute 1-2% of all invasive lung tumors. They are low or intermediate-grade neuroendocrine tumors that originate from neuroendocrine cells located in normal airways. Fifty percent of patients do not have any symptoms at the time of diagnosis. Symptomatic patients may exhibit hemoptysis, post-obstructive pneumonia, and dyspnea. Paraneoplastic syndromes include carcinoid syndrome, Cushing's syndrome, and acromegaly. These tumors are equally distributed between two genders and are frequently found in the 4<sup>th</sup>-5<sup>th</sup> decades (20, 31).

The primary approach in the treatment of pulmonary carcinoids is surgical resection. Patients with TC have an excellent prognosis after surgical treatment and rarely die due to the tumor (32).

In comparison to TC, AC involves a larger tumor size and higher rate of metastasis with lower survival rates. Studies have shown that the 5-year survival rate is 50-70% and 10-year survival rate is 30-50% in AC cases (32).

Carcinoid tumors are generally centrally located, wherein bronchoscopy reveals a polypoid endobronchial lesion in approximately 75% of cases. Peripheral carcinoids are generally located in the subpleural parenchyma. Both TC and AC are characterized by organoid growth pattern and regular cytologic features. The nucleoli are not recognized in most TCs, whereas they can be more apparent in AC. Various histological patterns may be seen in AC and TC, including spindle cell, trabecular, rosette-like, papillary, sclerosing papillary, glandular and follicular patterns (33).

Atypical Carcinoid is defined as the carcinoid tumor of the live tumor that contains high mitosis and necrosis. Pleomorphism, vascular invasion and increased cellularity are not useful for differentiating between TC and AC. On the contrary, TC can exhibit focal cytologic pleomorphism, but it does not have necrosis and the number of mitotic areas is low. Necrosis in AC generally consists of small foci located centrally within organoid nests of tumor cells (23).

The diagnosis criteria for differentiating between TC and AC are the mitotic rate and presence or absence of necrosis. TC exhibits less than 2 mitoses in 10 high power fields (for 10 HPF <2 mitoses) and it does not contain necrosis. On the other hand, AC exhibits 2-10 mitoses in 10 high power fields (2-10 mitoses for 10 HPF) (2).

#### Carcinoma with pleomorphic, sarcomatoid or sarcomatous elements

Differentiating this lung carcinoma group is very challenging and it implies a pleomorphic, sarcomatoid and sarcomatous ele-

ment spectrum. Pleomorphic carcinomas are peripheral tumors, wherein they generally have a poor prognosis and chest wall involvement. Due to the distinct heterogeneity of this tumor, it is important to perform sufficient sampling. Pleomorphic carcinomas should contain at least 10% spindle cells or giant cells and they should also contain other histological types, such as adenocarcinoma or squamous cell carcinoma (33).

If the tumor contains pure giant cell or spindle cell model systems, the terms giant cell or spindle cell carcinoma may be used respectively. Giant cell carcinoma consists of pleomorphic and multinucleated giant tumor cells. Cells are generally adhesive and inflammatory cells are infiltrated by neutrophils in particular. This tumor is defined using light microscopy. However, immunohistochemistry might help confirm epithelium differentiation for epithelium markers, especially for those such as keratin (33).

#### **Carcinosarcoma and pulmonary blastoma**

Carcinosarcoma is a tumor that contains carcinoma and sarcoma components and which has to exhibit heterologous elements, such as cartilage, bone and skeletal muscle, according to WHO/IASLC classification (23).

#### **Adenosquamous Carcinoma**

Adenosquamous carcinoma constitutes 0.6-2.3% of all lung cancers and is defined as the lung carcinoma that contains at least 10% squamous cells and adenocarcinoma. Similar to LCC, the diagnosis should be based on histology rather than immunophenotype. In addition, further guidelines and definitions are necessary for characterization using immunohistochemistry. Adenosquamous carcinoma can only be diagnosed definitively by surgical resection. However, it may be suspected in case of small biopsy or cytology specimens that exhibit both squamous and glandular differentiation features (21).

#### **Sarcomatoid carcinoma**

Sarcomatoid carcinoma is a poorly differentiated NSCLC that exhibits the morphological features of sarcoma, or ones that are similar. It constitutes nearly 1% of all lung cancers and has five subtypes; pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma. These highly aggressive tumors are thought to represent epithelium malignancies that have been differentiated in different ways. These tumors should not be diagnosed from small biopsy or cytology specimens as they are heterogeneous (2, 21).

#### **Salivary gland-type carcinomas**

Salivary gland tumors originating from bronchial glands are rare and constitute less than 1% of all lung cancers. They have three known subtypes, including mucoepidermoid carcinoma, adenoid cystic carcinoma and epithelial-myoeplithelial carcinoma (2, 21).

#### **Challenges in Diagnosis**

As can be seen, the subtypes of lung cancer develop due to different factors, exhibit different clinical and radiological presentations, differ in terms of clinical presentation and metastatic potential, and consequently respond differently to surgical treatment and chemotherapeutic agents. Although the differ-

entiation of SCLC and NSCLC remains important today, it is not deemed sufficient. The determination of subtypes is preferred in order to plan treatment and predict the prognosis.

Another important problem in the process of making a diagnosis and determining the treatment is the presence of multiple tumors. This is because, in the presence of multiple tumors, it is of the utmost importance to differentiate between synchronous tumor or metastasis in terms of treatment planning.

When multiple tumors are present, synchronous tumors and metastatic lung cancers can generally be differentiated with extensive histologic and cytologic examination. However, it might be impossible to differentiate between multiple primary lung cancer and metastatic lung cancer in some of these cases, despite careful histopathological examination and IHC profiling. Detailed clinical history and multidisciplinary case examination are required for differentiation. It is thought that genetic studies and molecular analyses will provide higher diagnosis accuracy in the future (34).

Another problem that poses a challenge for diagnosis is the differentiation of primary lung cancers and lung metastases. It is not always possible to differentiate between them, especially in small biopsy and cytology specimens. Unless primary lung malignancy is clearly observed in the histologic examination of preparations, metastatic disease should be considered.

For example, in the case of enteric differentiation in primary adenocarcinoma of the lungs, it may be hard to distinguish from colorectal carcinoma metastasis (35).

Also, it may not always be possible to differentiate between metastatic head and neck SCCs and primary pulmonary SCC, which shows a similar morphology and stems from similar etiologic factors. Although several immunohistochemical examinations are performed for this differentiation, there is no reliable marker. Therefore, in the case of suspected metastatic lesions, it is very important to conduct a detailed clinical evaluation.

#### **Treatment Planning**

The prevailing opinion is that the primary treatment should be surgical resection in lung cancers without metastasis and non-surgical treatments should be considered primarily in the case of patients with regional or distant metastases. Therefore, assessing the presence or absence of metastases in patients diagnosed with lung cancer seems to be the most important factor in determining the treatment process today. Furthermore, it is known that some lung cancer patients who exhibit only regional spreading or solitary distant metastases benefit from other treatment methods combined with surgical treatment. Based on this information and observations, there are recommendations to perform surgical treatment also in some advanced tumors.

As a result of observing that response to treatment varies between patients and enhancing our knowledge of complex tumor biology in recent years, personalized treatment methods that also include surgical treatment are starting to be considered.

Therefore, making a malignancy diagnosis and differentiating between SCLC/NSCLC is not enough anymore, and it is now significantly important to conduct histological subtyping and molecular testing.

Diagnosis, staging and management of lung cancer is a dynamic process that evolves continuously. The emergence of personalized medicine for lung cancer has brought about important changes, as well as new challenges. It is clear that in order to plan modern treatment methods for lung cancer, cooperation between surgeons, oncologists and pathologists should be increased, and geneticists and biologists should also be included in this team with whom cooperation should also be further increased.

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