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Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Technical Note	1500	No abstract	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.
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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the

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References

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Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

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Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

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Contents

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From the Guest Editor

Lung cancer is still a detrimental problem for physicians and surgeons. Because of having no standard treatment and poor survival, enforces us to find new approaches for its eradication. However, we have a so long way to this purpose. Genetic and cell researches to find out its real etiology and pathway are developing. But today, patients with lung cancer are waiting for some treatment methods which ease and give hope themselves immediately. Surgery is the most hopeful way for radical solution of lung cancer. Recently, new anesthetic and surgical technics give us some important advantages that were very frightfully before.

In this issue, we aimed to emphasize the new researches, interventions and experimental studies about pulmonary carcinoma. All authors worked hard for this purpose. I appreciate all of them and the editor in chief Prof. Murat Sucu. I hope all articles will help us thinking and researching lung cancer in all ways.

Prof. A. Feridun Işık

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The Philosophy of Staging in Lung Cancer: Prognosis or Treatment Planning?

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ABSTRACT

Tumor staging is one of the cornerstones of oncology. The purpose of staging is to provide a universal terminology regarding the anatomical extent of cancer without causing incomprehensibility. This allows for reliable communication between clinicians without room for doubt, a common language in clinical studies, and the evaluation of the results of planned treatment strategies. Although it is critical to represent staging with a terminology that is used consistently and coherently, periodic revisions are also necessary. The terminology is also improved in parallel with the obtainment of new data regarding the definition of the anatomical extent of tumors with developments in technology. Although the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) are institutions that define and periodically review the classification systems and work together in order to ensure the universal consistency of staging, staging in thorax malignancies has been regulated under the lead of the International Association for the Study of Lung Cancer (IASLC) for the last two decades. The aim of this review is to summarize and discuss the philosophy of staging in lung cancer.

Keywords: Lung cancer, staging, philosophy.

INTRODUCTION

Survival rate in cancer patients is higher in cases with localized disease in comparison to cases when the disease has spread outside the organ. In the light of this fact, cancer cases have been divided into groups called stages. Selection of the treatment to be administered in accordance with objective data obtained from patient groups that are at a stage similar to the cancer stage at the time of diagnosis is the key factor that determines the prognosis. There are many staging systems used throughout the world. The difference between these systems stems from the differences in the purpose and needs of clinicians, as well as in population screening. The most commonly used staging system throughout the world is the tumor-node-metastasis (TNM) staging system developed by the AJCC and UICC jointly due to its clinical practicality (1). With the TNM staging system, cancers are classified with the help of anatomical variables, such as the size and extent of the primary tumor (T), regional lymph node involvement (N), and presence or otherwise of distant metastases (M), as well as some non-anatomical variables for some cancer types in recent years. Numbers next to these three components indicate the grading of cancer extent and are expressed as T0, T1 (mi, a-c), T2 (a, b), T3, T4, N0, N1, N2, N3, M0, M1 (a-c). The AJCC and UICC meticulously revise the TNM classification based on evidence periodically due to the changes in clinical data, developments in cancer biology, and better understanding of the prognostic factors. TNM staging is revised every 6-8 years. The most up-to-date version of the TNM staging for lung cancer is the 8th edition that has been in use since January 1, 2017. Unlike previous stagings, the last two revisions of lung cancer staging were made by the IASLC using multinational data. The IASLC database was created by analyzing more than 100,000 cases from four continents and nearly twenty countries. Despite this data diversity, it was shown that staging could be performed successfully. Data from cases that received non-surgical treatment were also included, as well as cases that received surgical treatment. The success of clinical staging was investigated by analyzing data from cases that were administered non-surgical treatment (cases that received only chemotherapy or only radiotherapy or chemoradiotherapy) (2).

The TNM System's Philosophy of Classification and Staging

A simple classification scheme that can be applied universally is the main goal of the TNM system proposed by the AJCC and UICC. A useful staging system should include the characteristics that define the biological behavior of the tumor. AJCC classification is based on the premise that cancers in the same anatomical region with the same histology share similar patterns of growth and have similar outcomes. In other words, criteria that define the anatomical extent of the disease will differ for tumors of different histological type and for tumors in different anatomical regions. There are two defined classifications for each region; a) Clinical classification denoted as cTNM is the basis of treatment choice

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and evaluation. It is an evidence-based classification obtained from physical examination, biopsy, bronchoscopy, endoscopy, and such examinations. b) Pathological classification denoted as pTNM. This is the classification based on the examination of a surgically resected case that has sufficient tissue for evaluating T, N or M classification. It provides the most accurate data for reaching a final outcome and predicting the prognosis. Most of the time, cancer spreads to regional lymph nodes and/or has distant metastases before it is noticed in the clinical examination. Therefore, the examination during surgical procedure and the histological examination of surgically resected tissues may result in a difference between surgical stage and clinical stage. The post-treatment stage (yTNM) documents the spread of the disease in cases that have received chemotherapy or radiotherapy before surgery, or in cases that will not have surgery and continue the primary treatment with chemotherapy or radiotherapy. Post-treatment recurrent cancers are assessed according to a similar criteria to those used in clinical staging before treatment. "Restage" classification (rTNM) for recurrent cancer provides therapeutic guidance and helps predict the prognosis under the recently emerging conditions (3).

It is important to evaluate the anatomical extent of cancer clinically and develop a treatment strategy in accordance with this evaluation before starting treatment. The anatomical extent of cancer is determined by the presence of local tumor growth, spreading to regional lymph nodes, and distant organ metastasis. This anatomical extent (TNM) is the shortest and simplest way of expressing the cancer grade or disease severity within a certain time period. As the extent of untreated cancer increases, the possibility of regional lymph node involvement and/or developing distant metastases will increase, leading to a worse prognosis. A different staging system that employs descriptive criteria other than T, N and M is used in order to determine the prognosis in some tumor types such as Hodgkin's disease and lymphomas as an exception. Although staging recommendations for most cancer types relate to disease extent from an anatomical aspect, non-anatomical factors that significantly affect prognosis such as histological "grade" (soft tissue sarcoma) and age (thyroid carcinoma) have also been included in staging as necessary (1). Lung cancer has not been included in the staging for non-anatomical prognostic factors in the 8th edition of TNM staging (4).

Prognostic factors include many heterogenous variables to help understand the natural course of cancer. Although, it is exciting to predict the course of cancer and other diseases, it is not possible to make an exact prediction for each patient and only possibilities can be mentioned. This is because studies in this field are conducted on patient groups, rather than individuals. Therefore, only a connection can be made between data obtained from patient groups and a single patient. Hence, it is not possible to make a critical prediction for cancer patients on an individual basis. TNM classification is a universal system that records the anatomical extent of the disease. However, there is no optimal system similar to TNM for the classification of prognostic factors. On the other hand, prognostic factors are frequently used in cancer practice. These factors are included in all phases of decision making about the disease and in treatment planning, i.e. briefly in the broadest management scheme of the cancer patient. For example, the efficacy of targeted therapy administered to a case with Stage 4 lung adenocarcinoma in the presence of the epidermal growth factor receptor gene (EGFR) mutation would be higher in comparison to standard chemotherapy. Knowing the EGFR mutation status increases the capacity for prognosis, as well as for treatment selection. However, when these molecular prognostic parameters will be included in staging is a question that is frequently asked. TNM staging is an anatomical staging. Therefore, the answer actually lies within. Nonetheless, multidisciplinary prognostic grouping studies that include a reasonable number of prognostic factors based on TNM and molecular classification are ongoing today. This is one of the most important duties of the IASLC Staging and Prognostic Factors Committee during the third phase of the IASLC staging study being conducted between 2017-2024 (4).

In the future, it may be possible to make additions to anatomical indicators in cancer classification when the importance of tumor-associated (tumor histology, invasion pattern, histological grade, tumor markers, genetic mutations), patient-associated (age, gender, comorbidity, performance status) and environmental (socioeconomic status) prognostic factors are proven (5).

DISCUSSION

In medicine, the prediction of prognosis has always been necessary and important. In the early 20th century, Halsted et al. (6) believed that solid tumors could gradually spread from the primary tumor zone to distant organs via the lymphatic system and that the patient would have a gradually worsening prognosis at each stage. As a result of this opinion and other following studies that were supported, it was thought that clinical and pathological T, N, and M factors could provide information regarding the spread of the disease and prognosis. In 1953, French surgeon Pierre Denoix proposed to the UICC that these three factors should be standardized and integrated into a prognostic system that could be used in all solid tumors. This suggestion of having a common language of prognosis in solid tumors is considered as the beginning of the TNM staging system that is now used throughout the world (7). The TNM system has been revised eight times so far under the guidance of the AJCC founded in 1959 in the United States.

The TNM staging system is a "box model". Patients are separated according to T-N-M prognostic factors and each patient is placed in a box. These boxes are grouped in order to create a more extensive, larger box called a stage. The average survival of the patients in a box is used in order to predict the prognosis of a new patient placed in a box. For instance, when a new patient is placed in a box, it is predicted that the disease-specific 5-year survival of that patient will be the same as the average survival of all patients placed in that box 5 years ago (8). It is possible to select suitable patients for optimal treatment and provide prognosis predictions for patients with this system. However, staging is comprised of data from patients who have received specific treatment. Therefore, it is important to remember that staging is not a treatment guide but a tool that can provide suggestions for treatment.

It is important to understand the relationship between stage classification and prognosis. In the 8th edition of TNM staging for lung cancer, it is primarily seen that for a tumor up to 5 cm in size, every cm is redefined (T1a-c and T2a,b) and in this way, the emphasis is put on the importance of tumor size in terms of prognosis. It is observed that minimally invasive adenocarcinoma was included as T1mi, partial or total atelectasis were included in the same group (T2) without differentiating, and diaphragm invasion was moved to a higher category (T4) as it exhibits poor prognosis. Proximal tumors were moved to a lower category (T2), as it was determined that the distance of tumor from the carina did not affect the prognosis. No changes for N descriptors were proposed. For metastases, redefinition of the number of organs and metastases (M1a-c) can be summarized as the new TNM changes. In the new version, differences in prognosis between corrected multi-variable regression analyses and multiple subgroups were calculated in order to divide tumors into sufficiently well and homogenous groups. Five-year survival probabilities for Stage IA, IA2, IA3, IB, IIA, IIB, IIIA, IIIB, IIIC, IVA, and IVB were calculated as 92%, 83%, 77%, 60%, 53%, 36% in clinical staging and 90%, 85%, 80%, 65%, 56%, 41% in pathological staging, respectively (9-11). However, lung cancer belongs to a heterogenous disease group that involves genomic differences. Therefore, it is possible to state that the new version is also insufficient, despite anatomical variables being more detailed.

CONCLUSION

Although staging is a well-defined universal terminology, which is comprised of the anatomical aspects of cancer with clear boundaries, the stage of the disease at the time of diagnosis might not only be a reflection of tumor growth and spread rate, but also of tumor type and tumor-patient relation. Therefore, it would be wrong to separate prognostic factors from purely anatomical tumor staging. It should be noted that tumor stage, which is the most important indicator of cancer, is only one of the broad prognostic factor pools that contain multiple heterogenous variables. Hence, considering these factors in the selection of a specific treatment method will affect the success of treatment.

The TNM staging system will continue to be useful in the future as long as it makes improvements as a result of the increase in cancer population screenings for finding new targeted therapies and for the use of new molecular biological indicators.

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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 preneoplasic 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 nonmucinous, 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 ≥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 [≥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 in 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^{th}-5^{th} 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 heterogenous (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-myoepithelial 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 differentiation 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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What Lung Cancer Guidelines Tell Us: Are they Life Savers or Delimiting?

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ABSTRACT
It is considered that the individual is now being ignored due to the scientific and technological developments that have been made in recent years. Medicine is conversion of scientific evidence-based knowledge to beneficial work at the hands of conscientious and experienced clinicians. The concepts forming a basis for the term "evidence based medicine" have been known for centuries and became much clearer in the seventeenth century with the publication of individual works and books. Clinical Practice Guidelines (CPGs) have become very common in medical practice. CPGs offers a serious contribution to the diagnosis, treatment and prevention of diseases. However, CPGs also have limiting aspects. Reading and assimilating a CPG is difficult, in addition to the fact that guidelines can damage the doctor's critical approach as they do not take clinical experience into consideration. Bedside decisions, operational rules of hospitals and clinics, and governments and insurance companies' expenses are all influenced by guidelines. The patient's personality, social status, economic status, and reactions to the disease should definitely be taken into consideration during the application of lung cancer guidelines. It should be keep in mind that diseases can be cured in a shorter time when the doctor-patient relationship is based on respect and love, rather than simple mathematical and technological level and customer satisfaction. It is considered that the need for guidelines can be decreased with the help of individual personalities, experience, science/technology and social sciences based on ethical values and social identifiers.
Keywords: Lung cancer, guideline, limitations

INTRODUCTION

When clinical practices were carried out based on the view "Treat the patient, not just the disease", the individual's anamnesis, history and physical examination were at the forefront. However, it is considered that the individual is now being ignored due to the scientific and technological developments that have been made in recent years.

Medicine is conversion of scientific evidence-based knowledge to beneficial work at the hands of conscientious and experienced clinicians (1). Knowledge and empathy are required for patient care at the same degree. The art of medicine starts where standards end (1).

The concepts forming a basis for the term "evidence-based medicine" (EBM) have been known for centuries and became much clearer in the seventeenth century with the publication of individual works and books. In the 1990s, EBM became identified as "a systematic approach towards analyzing studies published on the basis of clinical decisions" (2). Then in 1996, Sacket et al. (3) defined EBM as "making conscientious, clear and reasonable decisions for the management of individual patients". Evidence per se is not enough for the clinical decision process (4).

CLINICAL AND RESEARCH CONSEQUENCES

Clinical Practice Guidelines (CPGs) have become very common in medical practice. Many of the medical specialty associations have published similar guidelines. The best designed CPGs are those constructed according to EBM principles and those whose agreed recommendations are established by a group of specialists (5-7).

Clinical Practice Guidelines provide significant benefits to patients in terms of diagnosis and prevention of diseases. Especially in homogenous societies, recommendations are very beneficial in cases such as preventive vaccine application, preventive colonoscopy application, and preventive cholesterol and serum glucose monitoring for children and other age groups (8).

However, CPGs also have limiting aspects. The likelihood of studies with negative results being published is much lower than that of studies with positive results being published (especially studies supported by the biomedical industry, making up 60% of all studies). Therefore, studies with negative results are not included in the meta-analysis and studies are unable to reflect the reality (8). Individuals working in guideline committees also have a role on the boards of scientific associations; however, they are short of time and travel a lot, meaning that they do not have enough time to maintain daily contact with patients, which is required for maintaining clinical experience (8). Also, at least some committee members have a close relationship with the biomedical industry (8). This relationship can be on a subconscious level; yet, it can potentially influence recommendations and guidelines (8).

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Reading and assimilating a CPG is difficult, in addition to the fact that guidelines can damage the doctor's critical approach as they do not take clinical experience into consideration (8). Experienced doctors who are taking care of their patients and who have knowledge of physiopathology can decide on a different treatment method accompanied with guidelines. CPGs are for diseases, not for specific patients.

The diagnosis, treatment and prognosis processes cannot be conducted solely based on the guidelines. However, CPGs have been a significant part of clinical practice for the past 20-25 years. Bedside decisions, operational rules of hospitals and clinics, and governments and insurance companies' expenses are all influenced by guidelines (7, 9). A guideline can provide short instructions about conducting a diagnosis or scanning tests, how medical or surgical services are configured, how much time the patient should stay at the hospital, or other details of clinical practice (9). Nevertheless, guidelines carry the risk of causing harm to patients. Recommendations that are not fully completed can confuse the patient and harm the doctor-patient relationship (9).

Guidelines prepared for lung cancers are router; they are beneficial for the application of the diagnosis, treatment and monitoring process at certain standards. However, the patient's personality, social status, economic status, and reactions to the disease should definitely be taken into consideration during the application of these guidelines (Figure 1).

Lung cancer can essentially be divided into two main categories [(small cell carcinoma (SCLC) and non-small cell carcinoma (NSCLC)]. That said, the development of targeted treatment as a result of the identification of the specific molecules in tumors necessitates sub-divisions for NSCLC. Identified molecules other than squamous cell carcinoma (SCC) have been seen frequently in NSCLCs. Therefore immunohistochemical (IHC) indicators should be applied in case haematoxylon eosin dye preparations are insufficient for differentiate between adenocarcinoma (AC), large cell carcinoma, NCLSC-NOS and SCCs particularly in small biopsies.

In the current WHO guidelines, it is emphasized that 3 immunohistochemical indicators (TTF-1, Napsin-A, p40) are sufficient for sub-type differentiation of NSCLC, especially when the protection of tissues in small biopsies is considered (10). In the majority of cases, these indicators can differentiate between AC and SCC. However, when examining practical applications, p40 positivity can also accompany TTF-1 positivity even though it is pale. In this case, clinical experience and other research findings should also be used (lesion's locus, histopathological findings, presence of mucin, IHC marker sensitivity).

Solitary pulmonary nodules have been separately assessed in the guideline entitled "Early and Locally Advanced Non-Small Cell Lung Cancer (NSCLC): ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up" published by the European Society of Medical Oncology (ESMO) (11). It was stated that the majority of diagnostic algorithms validated for solitary pulmonary nodules are not suitable for all societies (11). The guideline developed by the British Thoracic Society and Fleischner Society has focused on Western societies, as previous guidelines have. There are granulomatous and other infectious diseases that cause pulmonary nodules in other regions, such as Asia. Therefore, it is emphasized that it would be more appropriate for Asians to use guidelines published specifically for them (11). However, no statement was given about what guideline should be used for Asians living in Western countries.

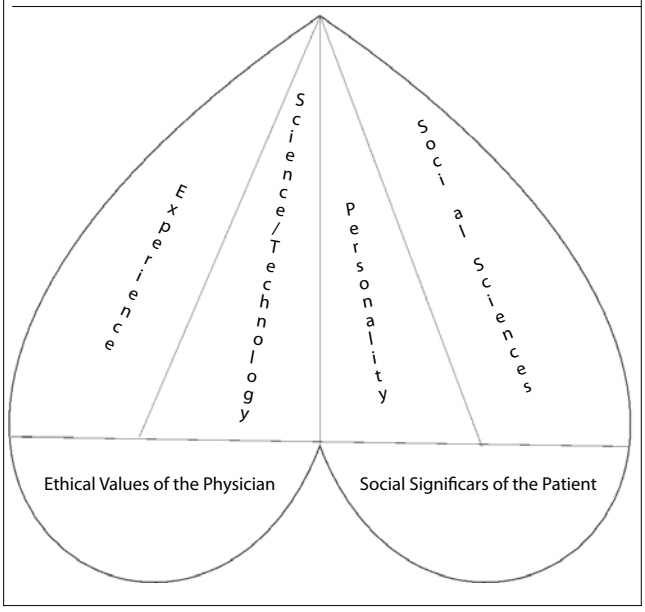
Guidelines prepared using studies covering the majority of the population should include other communities living in that area. Whether the recommendation prepared for Asians is applicable for people who have moved or immigrated to other regions is debatable. It is observed that immigrant communities can be influenced by environmental factors after a while and have similar diseases/have neoplasms or gain immunity. Depending on the duration of time since they migrated, sometimes they can encounter with different results from the society they come from or the society in which they live. When the above example is considered, it should be noted that for first generation Asian immigrants, the guideline used in their country can be applicable, while after 3-4 generations, the guideline used in the West can be applicable. For the intermediate generations, the physician's clinical experience and ethical approach and their knowledge of the individual's social habits, economic status, and the hygienic conditions of the social environment in which they live, will be determinative.

When the National Comprehensive Cancer Network (NCCN) Guideline NSCLC Version 1.2017 is reviewed, it is considered that some recommendations specified under different titles are debatable. Under the title, "The Principles of Diagnostic Assessment", it is stated that co-staging is beneficial for the protection from additional biopsies and processes (12). Therefore, it is recommended that a biopsy is carried out on the suspected metastasis area and the mediastinal lymphatic node to show the highest stage in the patient (12). In this case, it is considered that the tissue taken from metastasis and the primary tumor have the same properties. However, it is emphasized that the majority of NSCLCs are mixed; and moreover, that sub-types of adenocarcinomas should be specified according to the dominant pattern in WHO classification (13). It should be noted that histopathological properties can be different in biopsies taken from combined small cell carcinomas and their metastases as well.

Under the guideline's title "The Principles of Surgical Treatment", it is stated that CT and PET used for staging before surgical assessment should be carried out within 60 days (12). Even if the decision to operate should be made after monitoring the progression of neoplasia, the patient's and the country's economic conditions should be taken into consideration. For example, when the period is 61-62 days, should these procedures be repeated? Or should the patient's overall condition, disease progression, the country's needs and social identifiers be taken into consideration?

Under the title, "The Principles of Surgical Treatment", it is stated that surgical treatment is controversial in N2 positive patients and that the role of surgery was investigated in two randomized studies. It is stated that the community is heterogeneous, that

Figure 1. Doctor-patient relationship established according to physician's ethical values and patient's social identifiers (changes have been made according to source no: 8)



differences cannot be evaluated with these studies, and that possible surgery can be beneficial in specific conditions (12). If the result is N2 positive in VATS conducted in the presence of occult mediastinal lymphatic nodes, it is stated that the procedure may or may not be continued (12).

CONCLUSION

When all these are considered together, it should be noted that guidelines can suppress the critical thinking ability of physicians as they do not take clinical experience into consideration (8).

Also, evidence per se is not enough during the clinical decision process (14). Evidence never directly determines the treatment (15). Diagnosis, treatment and prognosis processes cannot be conducted solely based on the guideline, either. Today, doctors who are educated on physiopathology and molecular mechanisms not with CPG are needed more than ever (8). Students of medicine should be interrogator instead of memorizing (8).

Diseases can easily be eradicated in societies when the causes of disease are investigated and assessed. In addition, it should be keep in mind that diseases can be cured in a shorter time when the doctor-patient relationship is based on respect and love, rather than simple mathematical and technological level and customer satisfaction. It is considered that the need for guidelines can be decreased with the help of individual personalities, experience, science/technology and social sciences based on ethical values and social identifiers.

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Molecular Genetic Testing and Liquid Biopsy in Lung Cancer: Present and Future

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ABSTRACT
The genetic landscape of lung cancer has been expanded over decades with advancements in molecular genetic technologies. Despite improvements, the survival rate of lung cancer is still low. When diagnosed at an early stage, resection of tumor or lobectomy is possible, survival rate increases accordingly. Therefore it is crucial to identify diagnostic or predictive biomarkers and develop new technologies which can efficiently analyze these biomarkers. Since lung tumor tissue is difficult for sampling and requires invasive procedures, identification of non-invasive blood-based tumor biomarkers has become attractive recently. This review will summarize clinically significant key genetic biomarkers and focus on liquid biopsy which means analyzing of noninvasive biomarkers such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), circulating miRNAs and exosomes.
Keywords: Lung cancer, genetic biomarkers, liquid biopsy

INTRODUCTION

Lung cancer is the second most common cancer type in the world, and its leading cause of cancer-related deaths in both sex. There are two main types of lung cancer. Small cell lung cancer (SCLC) accounts for about 10-15% of all lung cancers whereas non-small cell lung cancer (NSCLC) accounts for about 80-85%. It is estimated that 85% of all lung cancers are responsible for smoking. The survival rate is approximately 5 years despite medical care. Surgery, radiotherapy, chemotherapy and targeted therapy are the main therapeutic strategies. These treatments can reduce tumor growth but usually, relapse occurs. Genetic heterogeneity and tumor plasticity contribute to drug resistance and metastasis which both are responsible for mortality.

The survival rate of lung cancer is low; 5 years. This mainly because early diagnosis rate is still low, most cases are diagnosed with an advanced-stage when there is no effective curative treatment. Survival rate increases, when diagnosed at an early stage (Stage I and II) since resection of tumor or lobectomy, are possible at an early stage. Hence early diagnosis is very crucial. Currently available methodologies for using diagnosis have several limitations. Chest X-rays, for example, are not enough sensitive for lung cancer detection. More detailed type of chest x-ray, computed tomography (CT) is highly sensitive but specificity is low (1). It is therefore important to develop minimally-invasive or non-invasive methods for screening lung cancer.

Recent advances in molecular genetics technologies provide deeply understanding of tumor biology, response to treatment and identification of diagnostic/prognostic biomarkers. Since lung tumor tissue is difficult for sampling and requires invasive procedures, identification of non- or minimally-invasive blood-based tumor biomarkers has become attractive recently. This review will summarize clinically significant genetic biomarkers and focus on liquid biopsy which means analyzing of noninvasive biomarkers such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), circulating miRNAs and exosomes.

Key Diagnostic and Prognostic Genetic Biomarkers in Lung Cancer

Correlation between tumorigenesis and genetic alterations was first proposed by Nowell In 1976. Later on, progresses in the field of cytogenetics, molecular genetics and innovations in genomics technologies have demonstrated that cancer is driven by diverse genomic alterations. Especially, advances in sequencing technologies have revealed a genomic landscape of cancer. The first revolution began with first-generation sequencing era, which was used in Human Genome Project. The complete sequence of nucleotide base pairs of human DNA and mapping all of the genes were established by this project. By using first-generation sequencing technologies protooncogenes and 'driver' mutations have been identified. Driver mutations usually occur in genes of signaling proteins which are critical for the proliferation and survival of the cell and as a result, they cause a normal cell to transform into cancer. KRAS and TP53 mutations were earliest identified mutations in non-small cell lung cancers (NSCLC). However, first clinically significant mutations were identified in 2004 in epidermal growth factor receptor (EGFR). These mutations were

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detected specifically in tumor tissues of lung cancer patients who responded to tyrosine kinase inhibitor (TKI) treatment (2). EGFR mutation is the second most common mutation after KRAS in lung adenocarcinoma in America (about 15% of African Americans and Caucasians) and in Asian populations (nearly 60%). EGFR mutations usually occur in exon21 (L858R) and exon 19 (small insertions and deletions) and these mutations cause an activation of the oncogenic signaling pathway (3). Furthermore, these mutations cause tumor cells to be sensitive to EGFR TKIs such as first generation inhibitors gefitinib and erlotinib (4).

ALK and ROS1 rearrangements are less commonly seen, <5% of lung cancers, firstly described in 2007 in lung adenocarcinomas (5-6). It was shown that Crizotinib, an inhibitor designed for a proto-oncogene receptor tyrosine kinase, Met, was found to respond in patients with ALK and *ROS1* rearrangements in NSCLC as their ATP-binding sites share 77% amino acid identity. Although these genomic alterations are rare, they are commonly seen among non-smokers and seen almost solely in adenocarcinomas (7-8). Therefore, it is suggested that all patients with advanced lung adenocarcinoma should be assessed for ALK-ROS1 rearrangements and EGFR mutations regardless their smoking status (9).

Despite responded targeted therapy, relapse usually occurs after about one year following EGFR TKIs treatment, and a median of 8 and 19 months following after first-line targeted therapy with ALK and ROS1 alterations, respectively (8, 10). EGFR mutation (T790M) is the main cause of resistance. At the time of relapse, around 50-60% of patients acquire EGFR mutation. Other resistance mechanisms are activation of PIK3CA pathway, Met amplification and transformation of NSCLC to SCLC (small cell transformation) (11). Crizotinib resistance in ALK-rearranged patients mostly causes secondary ALK mutations. Mechanism of Crizotinib resistance in ROS1-rearranged patients is less well defined. However, there are some individual cases have been reported with ROS1 mutations (12-13).

Immune checkpoint blockade, in other words, immunotherapy, has great attention recently. Immunotherapeutic agents target proteins which keep T cell response under control during inflammation. It's well known that tumor cells can evade immune response by using several mechanisms, for example, upregulation of surface programmed death ligand-1 (PD-L1) which enables them to evade T cell-mediated response. There are approved immunotherapeutic agents for lung cancer treatment which include anti-PD-L1 and anti-programmed death-1 (PD-1) (14). Taube JM showed that tumor cell surface PD-L1 expression is associated with responsiveness to PD-1 blockade and there is a correlation between PD-L1 expression level and therapy response in patients with upregulated PD-L1 expression (15). Pembrolizumab was an approved therapy for only use in patients with 50% or more PD-L1 expression level based on randomized controlled trials (16). On the other hand, according to retrospective analyses, patients with EGFR mutations or ALK alterations demonstrate a low response to immunotherapy. Therefore, Pembrolizumab is approved only for ALK- or EGFR-negative patients. Efficacy of immunotherapy in ROS1-rearranged patients is less known.

Other significant oncogenic mutations are seen in BRAF, ERBB2, MET, RET and KRAS. These targetable alterations are still under clinical investigation in lung adenocarcinoma (12, 17-20). In addition, tumor suppressor mutations are suggested to have prognostic value. TP53 and RB1 mutations are suggested to have predictive roles for small cell transformation after EGFR TKI treatment in adenocarcinoma.

Blood-Based Biomarkers

Circulating tumor cells (CTCs)

Circulating tumor cells (CTCs) have been identified in blood circulation from cancer patients. Some tumor cells are thought to have left the tumor and joined into the vasculature or lymphatics. Therefore it is important to isolate them to have an information about their origin non-invasively. CTCs are extremely rare in the circulation, only between 5 and 50 CTCs per 5 ml of cancer patients' blood sample (21). Although they are rare, they have a potential to be used as a biomarker for tumor characterization, prognosis, monitoring cancer status and detection of recurrent (22). The presence of CTCs has been found to be related to poor outcome in metastatic NSCLC patients. A study showed that CTC number has a predictive role of overall survival (OS) in NSCLC. CTCs were collected before and after treatment of one cycle standard chemotherapy from 101 patients. The number of CTCs was higher in patients with stage IV NSCLC compared to stage IIIB or IIIA and number of over 5 CTCs per 7,5 mL were associated with shorter progression-free survival (PFS) and overall survival (OS) in patients with NSCLC (23). There is also a meta-analysis comprising 20 trials with 1,576 patients assessed the prognostic relevance of CTCs. CTCs were found to be associated with tumor stage and lymph node metastasis. Furthermore, there was a significant association between CTCs and shorter overall and progression-free survival (24).

A study of 56 patients showed that CTCs might be a predictor of recurrence after surgery in early-stage NSCLC. For CTC analysis, blood samples were collected before and one month after surgery. The mean number of CTCs was 3.16/10 mL before surgery and the number decreased to a mean number of 0.66 one month after the surgery. There was a significant association between the presence of CTCs after the surgery and early recurrence and a shorter disease-free survival (DFS) (25).

There is a study presented in 2017 Multidisciplinary Thoracic Cancers Symposium. Blood samples of 48 patients were collected before, during, and after concurrent chemoradiation. 15 of 48 patients had a recurrence. No CTCs were detected in all patients following treatment but the number of CTCs increased in subsequent tests. This increase became detectable an average of 6 months before radiographically validation of recurrence. Although these results are promising they need further validation in larger patient cohorts.

Circulating tumor DNA (ctDNA)

Circulating tumor DNA (ctDNA) was first identified in 1977 but gained attention only recently as sequencing technologies have been advanced in the last decade. Researchers should be aware

of ctDNA is a different term from cell-free DNA (cfDNA). cfDNA compromises all cell-free DNA in circulation irrespective of their origin. However, ctDNA describes tumor-derived freely circulating DNA.

Cell-free DNA can be detected in all individuals at some level but tumor cell-derived ctDNA is proportional to the overall disease burden and therefore it is not always detectable (26). The amount of plasma ctDNA can vary from 0,01% to 90% of all cfDNA (27). The less the ctDNA ratio is, the more difficult it is to detect. A genotyping of cell-free DNA study showed that known EGFR and KRAS mutations are detectable in 100% of lung cancer patients with four or more metastatic sites and about 60% of those with a single metastatic site (28). Current technologies cannot detect ctDNA levels efficiently in early-stage disease (29). Therefore sensitive and reliable detection methods are required for clinical use. For lung cancer, EGFR activating mutations and EGFR TKI resistance mutation T790M are most studied mutations in ctDNA. Real-time PCR, digital droplet PCR (ddPCR) and NGS are methods currently used in routine, however, FDA approved plasma EGFR mutation test is cobas EGFR mutation test v2 (Roche Diagnostics, Indianapolis, IN, USA). Clinicians should be aware of false negative results. Because of the limited sensitivity of ctDNA mutation test, the FDA approval suggested a routine tissue biopsy and repeating the test in tumor tissue when a plasma assay is negative. Detection of either plasma or tissue EGFR mutations has the same degree of EGFR TKI response (9).

Studies showed that there is a high mutation concordance between ctDNA and tumor tissue. Therefore ctDNA is suggested to serve as a biomarker. A phase IV, open-label, single-arm study NCT01203917, evaluating first-line gefitinib, showed that *EGFR* mutation can be accurately detected with high concordance, specificity, and sensitivity by using ctDNA in advanced-stage NSCLC patients. Mutation concordance rate was 94.3% with a 95% confidence interval between 652 matched plasma and tumor samples in *EGFR*-positive NSCLC before treatment (30).

Another study found that EGFR mutation concordance rate was 92.9% with a sensitivity of 85.7% in matched serum and tumor samples obtained from 42 patients with advanced-stage NSCLC treated with gefitinib (31).

Two independent meta-analyses assessed the diagnostic accuracy of EGFR mutations in cfDNA and they found the sensitivity of 67.4% and 61% and specificity of 93.5% and 90% and respectively (32-33).

The ctDNA levels have been found higher in NSCLC patients compared to healthy subjects. (34-35). There was also an association between ctDNA levels and prognosis according to the study of Catarino et al. (6) High pretreatment ctDNA levels presented a lower mean survival time in NSCLC patients who received a first-line platin-based doublet chemotherapy in combination with a third-generation cytotoxic agent (36). Another study demonstrated a significant correlation between the increased concentration of plasma ctDNA and tumor progression following chemotherapy, advanced stage of the tumor and poor survival (37).

Newman et al. (23) introduced a sensitive technique for ctDNA quantifying. It is called cancer personalized profiling deep sequencing (CAPP-Seq). ctDNA was detectable in 100% of patients with stage II-IV and in 50% of patients with stage I NSCLC with a specificity of 96%, indicating its prognostic value. There was a significant association between ctDNA levels and tumor volume and discriminated between treatment-related and residual disease imaging changes. ctDNA levels provided an earlier predictive response than radiographic techniques (38).

The ctDNA analysis gives a clinician opportunity of monitoring minimal residual disease, possible tumor recurrence, and drug resistance. By regular ctDNA analysis during progression or tumor recurrence, new mutation can be earlier detected which cause resistance to first-generation inhibitors. However, therethere is some limitations need to be overcome. For example, a priori knowledge of the target gene of interest is required in most cases. Not all tissue-derived DNA mutations are expressed in ctDNA. Detection is difficult because of a high background of non-tumor cfDNA. Despite challenges, it's promising to be widely recognized in clinical practice in future.

Circulating microRNAs

There is growing attention to identifying non-invasive biomarkers as well as circulating microRNAs (miRNAs) for diagnosis, monitoring response to treatment. miRNAs are small non-coding RNAs, 19-22 nucleotides in length. They regulate gene expression in a negative manner through binding their target mRNAs. Dysregulation of miRNA expression was reported in several cancer types as well as lung cancer. miRNAs serve not only as a diagnostic biomarker but also as potential prognostic markers. Altered miRNA levels contribute to cancer formation and resistance to cancer treatment. Expression levels of miRNAs among lung cancer patients and healthy individuals were found significantly different in various studies. For example, in one study plasma samples from 100 early stage (I to IIIA) NSCLC patients and 100 healthy controls were screened for 754 plasma microRNAs and they identified a 24-miRNA expression panel which could distinguish lung cancer patients from healthy controls. When adding age, sex, and smoking status into this model, diagnostic power can be further enhanced (39). Another 6-miRNA expression panel has been shown to discriminate NSCLC patients from healthy individuals.

Serum or plasma miRNAs might be useful biomarkers not only for diagnosis but also for prognosis. A genome-wide serum miRNA expression analysis found 4 miRNAs (miR-1, miR-486, miR-499, and miR30d) have potential to be a predictor of overall survival in NSCLC patients. Patients harboring two or more high-risk miRNAs showed decreased survival compared to patients with one or no high-risk miRNA (40). Another study found that serum *miR-125b* expression was significantly associated with NSCLC stage and the high miR-125b level was a predictor of poor survival in a screening of 193 NSCLC patients (41). Although the studies are suggesting a potential role of circulating miRNAs as novel biomarkers, further validation is necessary for quantification of these miRNAs.

Circulating exosomes

Exosomes are nano-sized vesicles with a diameter of 30-150 nm. Exosomes are released from any cell and they can be found in various body fluids such as blood, urine, ascites or semen. It has been shown that tumor cells release higher amounts of exosomes than normal cells (42). Exosomes have different roles such as contributing tumor growth), metastasis, drug resistance and immunomodulation () through their cargo; DNA, proteins, lipids, mRNA, microRNA and other non-coding RNAs (43-46). These nanovesicles are stable in circulation, they are not degraded by Rnase or proteinases which makes them suitable biomarker for clinical applications.

A study was carried out to elucidate potential roles of exosomes and their content in lung adenocarcinoma. This study showed that there is a significant difference in the level of total circulating exosome and miRNA levels between lung adenocarcinoma patients and healthy controls. It was also suggested that circulating exosomal miRNA have a potential to be a screening test for lung cancer since the patterns of tumor-derived miRNA and circulating exosomal miRNA were similar. However, there was no correlation between exosomal miRNA levels and the stage of disease (47)

Exosomal miRNAs are the most studied molecules. Unlike circulating plasma miRNAs, exosomal miRNAs are stable and protected from RNAse degradation. the mir-21 level was found significantly high in NSCLC patients compared to healthy individuals (48).

Exosomes are not utilized in clinical practice currently, however, preliminary results demonstrated that there is a correlation between tissue and exosomal biomarkers. For example, a clinical case report of Taverna et al.(43) showed that plasma exosomes isolated from a chemo-naive 70 years old stage IV NSCLC patient harbor an EGFR activating mutation by a deletion in exon 19 (49).

CONCLUSION

Circulating tumor biomarkers, liquid biopsy, in other words, might be a useful test for diagnosis, predicting outcomes, monitoring disease status and treatment response in lung cancer patients. It is well known that lung cancer is most frequently diagnosed in an advanced stage. This is mainly because of a lacking screening test for the disease and therefore liquid biopsy can be a useful tool. Some of circulating biomarkers have already been recognized in routine clinical practice, for example, plasma EGFR mutation test. However present evidence for other biomarkers are not still sufficient to be included in routine tests. Further validation is needed with a larger cohort of patients in randomized clinical trials and longer monitoring. Combined assessment of these biomarkers could be a strategy to monitor dynamic changes during therapy.

There are still limitations of technologies to detect circulating biomarkers but there is a great effort in developing new sensitive and specific technologies. Advances in methodologies will provide not only identify and validate new biomarkers but also a new dimension to personalized care.

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Point Reached in Targeted Therapy; Where are we?

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ABSTRACT
Lung cancer is a very important public health problem. Identification of new molecular targets and development of novel therapies related to activated immune cytotoxic cells are significant steps in achieving the goal of personalized therapy in lung cancer.
Keywords: Epidermal growth factor receptor (EGFR), Anaplastic lymphoma kinase (ALK), immunotherapy, lung cancer

INTRODUCTION

Lung cancer is a major health problem all over the world and Turkey. Today, lung cancer is the leading cause of cancer-related deaths all over the world. It is a very important public health problem in terms of mortality and morbidity burden. There are 1.8 million new cases per year in the world. According to Turkey Cancer Institute Department of Public Health of 2014 cancer statistics, lung cancer was first place with 21.1% in men and fifth with 5.0% in women with all cancers (1).

Lung cancer is divided into two main subgroups as small cell lung cancer and non-small cell lung cancer (NSCLC). NSCLC constitutes approximately 85% of all lung cancer cases (2).

Histologically, NSCLC has several subtypes, including adenocarcinoma, squamous cell carcinoma, large cell carcinoma and mixed histology. Genotyping studies have revealed genetic/molecular abnormalities in the various subtypes of lung cancer (3). The result of genetic changes, tumors can become dependent for proliferation and survival, on a single oncogene, known as "driver oncogene" (4). Some studies have also shown that these genetic changes may not only be necessary for development or progression of a tumor but are also required for tumor survival, being referred to as "oncogene addiction" (5). This is a rational reason for the development of targeted therapies. In lung cancer cases, the discovery of a number of driver mutations and the therapeutic use of interactions between the immune system and tumor cells in the tumor microenvironment leading to longer survival outcomes (6). The frequency of these mutations and possible therapeutic agents used for these mutations are shown in Table 1. Identification of new molecular targets and development of novel therapies related to activate immune cytotoxic cells are significant steps in achieving the goal of personalized therapy in lung cancer.

In this review, activity and safety data of targeted therapies, biological agents and immunotherapy which used in lung cancer were presented.

CLINICAL AND RESEARCH CONSEQUENCES

Epidermal Growth Factor Receptor (EGFR)

Epidermal growth factor receptor is a growth signal receptor that controls cell proliferation and survival. It is a member of a family of cell surface receptors that dimerize on ligand binding and then activate the intracellular tyrosine kinase domain and trigger downstream pathways that lead to cell proliferation, angiogenesis, and metastases. Targeting the EGFR pathway represents a novel approach to treating NSCLC (7).

Epidermal growth factor receptor mutation frequency is higher in Far East countries (30-40%) than European and American societies (8). The frequency of EGFR mutation can change according to smoking status. While 40-60% patients with EGFR mutation consisted of nonsmokers, mutation frequency is decreasing in the smoking population with older age (9). This mutation is also more frequent in women and young patients. Although many EGFR mutations identified at different locations, the most common mutations are exon 19 deletions (45%) and exon 21 L858R point mutations (10). These two mutations are activating mutations and patients with this mutation are more likely to have to benefit from EGFR tyrosine kinase inhibitors (TKIs). Along with that, another activating mutation is exon 18 mutation. However, because of the low frequency of this mutation due to lack of a sufficient number of patients in clinical trials activity has not been evaluated. Resistance mutations associated with treatment other than activating mutations is monitored. Among these mutations, the best described the T790M mutation in exon 20. In recent years, the new generation of EGFR TKIs is also used effectively in treatment. The first-generation TKIs targeting the EGFR mutation is erlotinib and gefitinib (competitive inhibitors); the second generation is afatinib (non-competitive inhibitor) and the third generation is osimertinib. The clinical studies and their results of EGFR mutation-positive metastatic non-small cell lung cancer (mNSCLC) are presented in Table 2.

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Table 1. Molecular targets and treatment agents in non–small cell lung cancer

	Frequency		
Target molecule	**Adenocarcinoma**	**Squamoz cell carcinoma**	**Drugs**
KRAS	15–33	0	Selumetinib
EGFR	15	0	Erlotinib, Gefitinib, Afatinib, Osimertinib, Dacotinib
ALK	3–13	–	Crizotinib, Alectinib, Ceritinib, Brigatinib, Lorlatinib, Ensartinib
ROS1	1–2	–	Crizotinib, Lorlatinib
BRAF	1–3	0	Dabrafenib, Vemurafenib
MET amplification	3–4	–	Crizotinib, Cabozantinib
Her2	1–3		Afatinib, Trastuzumab, Neratinib, Temsirolimus
MEK	<1	<1	Cobimetinib, Trametinib
RET	1–2	–	Cabozantinib, Vandetanib, Sunitinib, Alectinib
PTEN	2	8	Buparsilib
NTRK1	<1–3	0	Entrectinib
RB1	3–4	7	Palbosiklib
FGFR1	1	20	Dovitinib, nindetanib

Table 2. Anti–EGFR treatments and results used in the treatment of mNSCLC

Study	**Drug**	**Patient number**	**Response Rate (%)**	**Median PFS (month)**	**Median OS (month)**
EURTAC	Erlotinib vs Cisplatin/Docetaxel	173	58 vs 15	9.7 vs 5.2	19.3 vs 19.5
OPTIMAL	Erlotinib vs Gemcitabine/Carboplatin	154	83 vs 36	13.7 vs 4.6	22.7 vs 28.9
ENSURE	Erlotinib vs Cisplatin/Docetaxel	217	63 vs 34	11.0 vs 5.5	26.3 vs 25.5
IPASS	Gefitinib vs Gemcitabine/Paclitaxel	261	71 vs 47	9.5 vs 6.3	21.6 vs 21.9
WJTOG	Gefitinib vs Cisplatin/Docetaxel	172	62 vs 32	9.2 vs 6.3	34.8 vs 34.3
NEJGS002	Gefitinib vs Carboplatin/Paclitaxel	224	74 vs 31	10.8 vs 5.4	30.5 vs 23.6
LUX–Lung 3	Afatinib vs Cisplatin/Pemetrexed	345	56 vs 23	11.1 vs 6.9	28.2 vs 28.2
LUX–Lung 6	Afatinib vs Gemcitabine/Cisplatin	364	67 vs 23	11.0 vs 5.6	23.1 vs 23.5
LUX–Lung 7	Afatinib vs Gefitinib	319	70 vs 56	11.0 vs 10.9	27.9 vs 24.5
FLAURA	Osimertinib vs Erlotinib/Gefitinib	556	80 vs 76	18.9 vs 10.2	Unreached

OPTİMAL was a phase 3 study that comparing erlotinib versus carboplatin/gemcitabine in the first line treatment of EGFR exon 19 and 21 mutant mNSCLC. In this study, a longer progression-free survival advantage was observed in the erlotinib arm (13.6 vs 10.1 months). The event was more prominent in patients with exon 19 deletions (11).

The European Tarceva vs Chemotherapy (EURTAC) trial randomized Europian and American patients with advanced NSCLC with EGFR mutations (exon 19 deletions or L858R mutation in exon 21) to receive erlotinib or cisplatin/docetaxel chemotherapy regimen. The primary endpoint of the study was progression-free survival (PFS). Median PFS was 9.7 months vs 5.2 months favoring erlotinib (HR 0.37; 95% CI 0.25-0.54; p<0.0001) (12).

Another study published in 2015 was the ENSURE. In Asian, EGFR mutant patients, erlotinib and gemcitabine/cisplatin treatments were compared in first-line treatment. Median PFS for erlotinib and chemotherapy were 11.0 and 5.5 months (13).

In all these studies, the PFS benefit was favorable for EGFR TKI and the overall survival (OS) difference could not be shown in any study. The main reason for this situation is that all the studies have been allowed to cross over and thus the patients in the chemotherapy arm have also been used erlotinib. Similar results with erlotinib have been found in studies with gefitinib. The IPASS trial was the first study to compare gefitinib with chemotherapy. When analyzed according to EGFR mutation, gefitinib was found superior to chemotherapy in terms of PFS and response rate (PFS 9.5 vs 6.3 months) (14).

Table 3. ALK inhibitors in the treatment of mNSCLC

Study	Drug	Patient number	Response ratio (%)	Median PFS (month)
PROFILE 1014	Crizotinib vs Platin/Pemetrexed	343	74 vs 45	10.9 vs 7.0
ALEX	Alectinib vs Crizotinib	303	83 vs 75	Unreached vs 11.1
J–ALEX	Alectinib vs Crizotinib	207	92 vs 78	25.9 vs 10.2
ALUR	Alectinib vs Chemotherapy	107	37.5 vs 2.9	7.1 vs 1.6
ASCEND	Ceritinib vs Chemotherapy		73 vs 27	16.6 vs 8.1

Gefitinib was found to be superior to combined chemotherapy regimens in WJTOG and NEJGS-002 studies in Far East patients (15, 16). In the case of studies with gefitinib, the advantage of OS was not revealed due to the similar crossing. Afatinib is the second generation EGFR TKI. It is a more potent EGFR inhibitor when compared to other TKIs and irreversibly binds to Erb2, Erb3, and Erb4 receptors.

LUX-Lung 3 study is an international multicenter study comparing afatinib with cisplatin/pemetrexet. In this study, the duration of PFS was higher in the afatinib arm (11.1 vs 6.9 months) (17). The LUX-Lung 6 study was conducted in the Far East Asian population and the cisplatin/gemcitabine regimen was chosen as the regimen for chemotherapy. In this study, median PFS duration was found to be 5.6 months compared to 11 months of favoring afatinib (18). Although individual studies of these two studies did not reveal overall survival, the combined analysis showed that overall survival could be as high as HR 0.81 in favor of afatinib (19). The LUX-Lung 7 study was phase 2b and afatinib was compared with another EGFR TKI, gefitinib. In this study, PFS was similar in both treatment arms (11.0 vs 10.9 months).The study was not published for the reason that the overall survival data had not completed (20).

Osimertinib is a third generation inhibitor of EGFR and is also effective in patients with the T790M mutation. In the FLAURA trial, the platinum-based chemotherapy regimen and osimertinib efficacy were compared in EGFR mutant patients (21). In this study, osimertinib was shown to provide longer PFS than chemotherapy (18.9 vs 10.1 months). The main problem with patients treated with EGFR TKI is the development of resistance after a while. Drug resistance is developed approximately in 11-12 months (22).

The most common resistance mechanism is exon 20 T790M mutation, which is responsible for about 50% of patients. Other resistance mechanisms include MET amplification, small cell carcinoma transformation and PI3K pathway activation (23). In the case of resistance, a re-biopsy or liquid biopsy should be performed for showing T790M mutation and in this situation, osimertinib is a new treatment option. In patients with the T790M mutation who received first-line EGFR tyrosine kinase inhibitor treatment in the AURA study, median PFS was 10.1 months on the osimertinib arm and 4.4 months on the control arm (24). In this study, it is observed that patients with the T790M mutation have similar median PFS benefit, even for second-line treatment of osimertinib.

Anaplastic Lymphoma Kinase (ALK)

Anaplastic Lymphoma Kinase is a transmembrane tyrosine kinase receptor that is normally expressed in the small intestine, testes, and brain. ALK signaling is activated in NSCLC by the creation of oncogenic fusions of the ALK gene on chromosome 2 with an upstream partner, the echinoderm microtubule-associated protein-like 4 (EML4) (25). The chimeric protein is a potent oncogenic driver. EML4/ALK rearrangements occur in 2-7% of NSCLC patients, usually in non-smokers with adenocarcinoma (26). There are many treatment agents in patients with ALK gene rearrangement positive. Crizotinib, Ceritinib, Alectinib, Brigatinib, and Lorlatinib are molecules that differ from one another with different properties. ALK inhibitor treatments and results were presented in Table 3.

A randomized phase III trial, PROFILE 1007, compared crizotinib with a single agent chemotherapy (pemetrexed or docetaxel) who had received one prior platinum-based regimen (27). The median PFS was 7.7 versus 3.0 months for crizotinib versus chemotherapy (HR 0.49, 95% CI 0.37-0.64). In PROFILE 1014, pemetrexed/cisplatin chemotherapy and crizotinib were compared in the first-line treatment of ALK mutation-positive patients. In this study, PFS benefit was obtained in favor of crizotinib (7.0 vs 10.9 months) (28). The response rate was 74% in the crizotinib arm, 45% in the chemotherapy arm. The most common side effects were visual disturbances, diarrhea, nausea and edema in the crizotinib arm and nausea, vomiting, weakness, and loss of appetite were on the chemotherapy arm. Despite these positive results, the median overall survival was not reached in the two groups due to the 70% ratio of crossover.

The ceritinib and alectinib, which are the second-generation TKI, are used in the crizotinib-resistant ALK-positive patient group. In the ASCEND 2 trial, ceritinib activity was proved to be statistically significant in the group of patients who had progressed after both chemotherapy and first line crizotinib (29). ASCEND 3 study showed that median PFS was increased to 11.1 months in untreated patients. In this study, the response rate was 36.3% (30). The second generation of ALK TKIs was found to be more effective in the central nervous system. The ASCEND-3 study also reported 58.8% central nervous system response rates of ceritinib (30).

In a study evaluating the efficacy and safety of alectinib, the systemic response rate was 50.8% and the central nervous system response rate was 58.8%. 20.6% of this response rate was composed of complete response patients (31). Likewise, in the North American study, the central nervous system response rate was

75% in a patient population with a 25% complete response in the central nervous system (31).

ALEX and J-ALEX studies compared the efficacy of crizotinib with alectinib in the first-line treatment of ALK-positive patients (32). The main difference between these two studies was that the patient population was different and alectinib was used at different doses such as 300 mg and 600 mg. Alectinib was superior to crizotinib in both two studies. PFS, which was about 11 months with crizotinib, was over 25 months in the alectinib arm. Therefore, alectinib was approved by FDA for the first line treatment of m NSCLC with ALK mutation (32).

In patients treated with an ALK inhibitor, the drug resistance and the associated progression are a considerable concern. There are 3 different resistance mutations in patients who develop treatment resistance. These are classified as ALK amplification, on-target genetic mutations (35%) such as ALK mutations, or the occurrence of by-pass pathways (EGFR, IGF1R, c-KIT, SRC) (35%). The cause of resistance at 30% probability is not known (33).

Other Mutations

ROS1 is a receptor tyrosine kinase with homology to the insulin receptor superfamily (7). Its frequency is approximately 1-2%. It tends to be more common in young, women and never or mild smokers. ROS1 rearrangements are typically mutually exclusive with EGFR, ALK, or KRAS alterations. In PROFILE 1001 study, crizotinib demonstrated 56% response rate in ROS1 positive tumors (34).

Activating BRAF mutations occur in 1-3% of mNSCLC cases. Adenocarcinoma subtype and smokers have a higher frequency. V600E mutation is more frequent than other mutations but less frequent in melanoma patients. Response rates were found to be 42% with BRAF inhibitors alone and 63% with combinations of BRAF and MEK inhibitors (6).

The mesenchymal-epidermal transition (MET) proto-oncogene codes for a transmembrane tyrosine kinase heterodimer receptor. Binding of MET to its ligand, the hepatocyte growth factor (HGF) activates multiple signaling pathways leading to cancer cell migration, invasion, proliferation, metastases, and neoangiogenesis (35). Several pathways can lead to dysregulation of the MET/HGF pathway in a variety of tumors including NSCLC. These include rare MET mutations; high MET gene copy number seen in 1-11% of cases, which is associated with high MET protein expression and poor prognosis; and MET amplifications seen in about 20% cases which are linked to secondary resistance to EGFR TKIs in patients with EGFR mutated NSCLC (7).

RET is a receptor tyrosine kinase coded by a gene on chromosome 10 (10q11). It is involved in cell proliferation, migration, differentiation and neuronal migration. These fusion genes have been identified in about 1.7% of adenocarcinomas with young non-smokers having solid subtype pathology (7). In these patients, it may be beneficial to use cabozantinib, vandetanib, sunitinib and alectinib. Response rates range from 16 to 53% (6).

KRAS mutations are detected on chromosome 12 in approximately 20% of NSCLC. They are more frequently in adenocarcinoma, smokers with Caucasian ethnicity (35).These mutations are mutually exclusive with EGFR, HER2, or BRAF mutations and ALK rearrangements. KRAS-mutated tumors are intrinsically resistant to EGFR-directed therapies (36). The inhibition of effector protein of the MAPK pathway (MEK1 and MEK2 kinases) is a potential strategy. Selumetinib is a selective inhibitor of the MEK1/MEK2 kinase. In the second line treatment, a significant improvement is observed in PFS (5.3 vs 2.1 months, p=0.014), though OS was not different (9.4 vs 5.2 months, p=0.21) (37).

HER-2 gene mutation is also seen in 1-3% of NSCLC. It is more common in non-smokers with adenocarcinoma. The studies with neratinib, trastuzumab and temsirolimus are continuing. However, response rates are quite low and range from 10-20% (7).

Fibroblast growth factor receptor 1 (FGFR1) is a member of the FGFR family. Its activation leads to downstream signaling through PI3K/AKT, RAS/MAPK pathways, leading to tumor growth, migration and angiogenesis (38). FGFR1 amplification is seen more commonly in SCC (21%) than adenocarcinoma (3%). Several small molecule FGFR TKIs such as ponatinib and dovitinib are currently under clinical development in Phase I/II studies (35).

Biological Agents and Angiogenesis İnhibitors

The vascular endothelial growth factor (VEGF) pathway is one of the best characterized proangiogenic pathways. It comprises six growth factor ligands (VEGF A-E and placental growth factor) and three receptors (VEGFR 1-3). The prominent role of VEGF signaling pathway has prompted the development of antiangiogenic strategies that include Mabs that block the function of the ligand or the receptor and small molecule TKIs that directly inhibit VEGFRs and their signaling pathways (7). Bevacizumab, an antibody against VEGF ligand A, is the only approved agent in the first-line treatment of advanced nonsquamous histology of NSCLC. Since squamous cell histology, tumor necrosis and cavitation were associated with major hemoptysis in patients in a phase 2 study, squamous mNSCLC patients were not included in the subsequent phase 3 trials (39).

In the ECOG 4599 study, nonsquamous NSCLC were randomized to receive paclitaxel and carboplatin with or without bevacizumab (15 mg/kg). Bevacizumab was associated with significant prolongation of both OS (12.3 vs. 10.3 months; $P = 0.0003$) and PFS (6.2 vs 4.5 months; $P < 0.001$). In the AVAiL study, 1043 patients with nonsquamous NSCLC were randomized to receive gemcitabine and cisplatin with or without bevacizumab (7.5 or 15 mg/kg). PFS was significantly prolonged with both doses of bevacizumab (6.7 vs. 6.1 months for 7.5 mg/kg, P= 0.003 and 6.5 vs. 6.1 months for 15 mg/kg for 15 mg/kg, $P = 0.03$). OS was however not prolonged (40).

Ramucirumab, which is also used in recurrent stomach cancer, was used in combination with docetaxel in second treatment in mNSCLC. When combined with docetaxel in the phase 3 REVEL study, it was shown that the response rate, PFS, and OS were statistically significant compared to chemotherapy (6).

Table 4. PD and PDL–1 antibodies in the first and second line treatment of mNSCLC

Study	Drugs	Response Rate (%)	PFS (Month)	OS (Month)
CheckMate 017	Nivolumab 2 mg/kg vs Docetaxel 75 mg/m^2	20 vs 9	3.5 vs 2.8	9.2 vs 6.0
CheckMate 057	Nivolumab 2 mg/kg vs Docetaxel 75 mg/m^2	19 vs 12	2.3 vs 4.2	12.2 vs 9.4
KeyNote–010	Pembrolizumab 2 mg/kg vs Pembrolizumab 10 mg/kg vs Docetaxel 75 mg/m^2	18 vs 9 18 vs 9	3.9 vs 4.0 4.0 vs 4.0	10.4 vs 8.5 12.7 vs 8.5
POPLAR	Atezolizumab 1200 mg vs Docetaxel 75 mg/m^2	15 vs 15	2.7 vs 3.0	12.6 vs 9.7
OAK	Atezolizumab 1200 mg vs Docetaxel 75 mg/m^2	14 vs 13	2.8 vs 4.0	13.8 vs 9.6
KeyNote–024	Pembrolizumab 200 mg vs Platinum–based chemotherapy	45 vs 28	10.3 vs 6.0	Unreached vs Unreached
CheckMate 026	Nivolumab 3 mg/kg vs Chemotherapy	26 vs 33	4.2 vs 5.9	14.4 vs 13.2

In LUME-Lung studies 1 and 2, in the second line treatment, docetaxel and pemetrexed versus nintedanib were used in combination but the response rates were found to be low. While PFS was favored for combination in both trials, OS advantage was not shown (6). Antiangiogenic agents are associated with class-specific adverse events, including hypertension, hemorrhage and venous thromboembolism, which may preclude treatment in some patients.

Immunotherapy

Responses obtained from acceptable and controllable toxicities in phase 1 trials in previously treated patients have led to the majority of investigations with immunotherapy. Until recently, immunotherapy in cancer treatment has been limited to the treatment of immunogenic tumors such as melanoma and renal cell tumors, while immunotherapeutic approaches in lung cancer are becoming increasingly popular. A large number of phase 1 to 3 studies involving in particular against programmed cell death protein-1 and its ligands against monoclonal antibodies, cytotoxic T lymphocyte-associated protein 4 (CTLA-4), and their combinations, continue throughout the world.

Various PD-1/PD-L1 antibodies (immune check point inhibitors) are already approved for the first- and second-line setting, with manageable toxicity profiles, improved efficacy and longer duration of response compared to standard chemotherapy. Numerous studies have also been conducted on activating or inhibitory receptors that play a role in T cell activation and inhibition. PD-1 and PD-L1 antibodies in the first and second line treatment of mNSCLC are shown in Table 4. The PACIFIC study is a phase 3 study in which immunotherapy was used in the treatment of locally advanced NSCLC. Patients treated with chemoradiotherapy were randomized to placebo and 10 mg/kg durvalumab every 2 weeks for 12 months after treatment. PFS was 16.8 months in the durvalumab arm while 5.6 months in the placebo arm. The objective response rate was 28% in the durvalumab arm while this rate was 16% in the placebo arm (41).

A key Note-24 study comparing pembrolizumab (200 mg/day, 3 weeks) with chemotherapy in primary mNSCLC showed that patients with PD-L1 levels of 50% and over provided PFS (10.3 months, 6.0 months) and OS (unreachable) advantages (42). In the direction of this data, pembrolizumab has been approved by the FDA for first-line treatment in advanced stage NSCLC. In this study objective response rate (ORR) was 45% with pembrolizumab and 28% with chemotherapy. However, in cases with a PD-L1 level> 50%, the ORR was found 80%.

Another study in first-line treatment was KeyNote-21 study. In this study, Pembrolizumab was compared with pemetrexet/carboplatin combination chemotherapy. The patient who developed progression on the chemotherapy arm was continued with pembrolizumab. Overall survival in this study has not yet been reached. PFS was significantly higher in the pembrolizumab arm (13.0 versus 8.9 months) (43).

Check Mate 026 study was another study evaluating the efficacy of chemotherapy with nivolumab in first-line treatment. The ORR in this study was 26% with nivolumab, while 33% with chemotherapy. PFS was found higher in the chemotherapy arm (4.2 versus 5.9 months). OS was found similar in both treatment arms (14.4 vs. 13.2 months) (44). In the squamous cell lung can-

cer, nivolumab, a PD-1 antibody efficiency was compared with docetaxel in Checkmate 017. In this study, the median OS was 9.2 months in nivolumab group and 6.0 months chemotherapy group. Approximately 41% reduction in risk of death was observed. However, in this study, PS was found similar. Treatment-related grade 3 side effects were lower in the immunotherapy arm (7% to 55%).

Following the demonstration that treatment efficacy is independent of PD-L1 level in this study, FDA approved nivolumab on progressed squamous cell lung cancer after platinum-based treatment (45). Another PD-1 antibody, pembrolizumab activity has been evaluated in many studies in the treatment of metastatic NSCLC. In one of these studies, Keynote-010, patients with a PD-L1 level of at least 1% were taken. Survival was significantly superior for the PD-L1 ≥ 50% according to stratification of <1%, 1-49%, and ≥ 50% levels. Atezolizumab is a PDL-1 antibody, unlike the other two drugs. The drug efficacy was shown in POPLAR (phase 2) and OAK (phase 3) studies. OS benefit was demonstrated in the atezolizumab arm in both studies (46).

The patient population in which immunotherapy agents are most effective has not yet been identified. PD-L1 level other determinants that may predict treatment response research continues. One of these was the tumor mutation load. Treatment efficacy was significantly higher in patients with high tumor burden. Another determinant was the immunomodulatory adverse events seen in patients. Both PFS and OS were higher in this group (46).

CONCLUSION

In recent years, the progression-free survival and overall survival in patients with non-small cell lung cancer have improved because of the use of new therapeutic agents. Targeted therapies, immunotherapeutic agents and biological agents developed by the discovery of novel tumor pathways and mutations are used alone or in combination.

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Which is the Best in Early Lung Cancer; Surgery or Stereotactic Body Radiation Therapy?

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ABSTRACT
Despite all improvements in surgical treatment of lung cancer, 25% of early-stage lung cancer patients can either still not undergo safe resection due to medical comorbidities, or they reject surgical treatment. Even though sublober resections were approached with suspicion and even garnered strong reactions in the beginning, it was shown in many studies that results like lobectomy were obtained, and today it has now become a common and safe practice. Based upon the successful results achieved with stereotactic radiosurgery in primary and metastatic brain tumors, due to the technologic advancements, stereotactic body radiation therapy–stereotactic ablative body radiotherapy (SBRT-SABR) practices started to be used at the beginning of the 2000s, which are based on delivering a few fractions of an extremely high radiation dose to a single target. The aim of this study is to evaluate and to discuss the results of clinical interventions in literature about early lung cancer resections and SBRT. The medical literature in the thoracic and cardiovascular surgery and oncology network was reviewed, and studies, cases, and meta-analysis articles that provided early lung cancer treatment even surgical or SBRT outcomes were examined. A discussion was made by also analyzing the survival data in the light of the available guidelines. Surgery is the standard treatment for early-stage lung cancer. SABR is the suitable treatment option in patients that cannot or refuse to undergo surgery. There is no evidence that SABR can be an alternative to surgical treatment in early-stage lung cancer cases with a medically fit condition that do not refuse surgery.
Keywords: Early stage lung cancer, surgery, stereotactic body radiation therapy

INTRODUCTION

About 1.8 million people are diagnosed with lung cancer across the world every year. Despite the increase in smoking cessation programs, scanning programs with low dose CT, and advancements in the field of treatment, it remains as the most prevalent cause of cancer-related deaths, and 1.6 million people die every year due to lung cancer (1, 2).

Due to the developments in imaging methods, and accordingly the increased rate in the application of scanning programs, early-stage lung cancer diagnosis rates have risen to 15%, and long-term survival expectations have increased (1).

Surgical treatment of lung cancer first started in 1933 with pneumonectomy, and lobectomy operations have encouraged the surgery from the 1950s until today. Minimal invasive VATS practices that began in the 1990s due to the advancements in technology were precursors to the VATS lobectomy lung cancer operations that started at the beginning of the 2000s and have begun to be used commonly around the world today with increasing momentum. Along with the imaging methods that are also related with technologic developments, the rates of early-stage lung cancer detection have increased, and sublober resections have started to be performed in peripherally localized tumors smaller than 3cm. Even though sublober resections were approached with suspicion and even garnered strong reactions in the beginning, it was shown in many studies that results similar to lobectomy were obtained, and today it has now become a common and safe practice. Thoracic surgeons have come a long way in the reduction of operative morbidity and mortality during the last decade, surgical mortality has dropped down to rates of lower than 1% today, and patients with medically high risk now have the chance of undergoing surgical treatment (2). During this period, lobectomy rates have decreased from 55% to 50%, whereas pneumonectomy rates have reduced from 3.4% to 1.1%, which, in parallel, has led to an increase in sublober resection rates from 12% to 17% (3).

Despite all these improvements, 25% of early-stage lung cancer patients can either still not undergo safe resection due to medical comorbidities, or they reject surgical treatment (3). The long-term survival results obtained with conventional RT in these cases are extremely bad, and adverse effects related to treatment toxicity are very high. Based upon the successful results achieved with stereotactic radiosurgery in primary and metastatic brain tumors, due to the technologic advancements, sterotactic body radiation therapy – stereotactic ablative body radiotherapy (SBRT-SABR) practices started to be used at the beginning of the 2000s, which are based on delivering a few fractions of an extremely high radiation dose to a single target (4).

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The first phase II study on this subject was performed by RTOG, and 3-year primary tumor control rate, locoregional control rate and survival rate were reported as 97.6%, 87.2% and 55.8%, respectively, with 54 Gy SBRT in three fractions. Excellent and provocative results obtained in medically inoperable patients led the specialized field of radiation oncology to perform investigations on SBRT practice in operable early-stage patients. The patient group that were medically suitable for surgical treatment but refused it constituted the basis of these investigations. In the first study performed on this patient group with 45-72.5 Gy SBRT practice in 7-10 fractions, 5 year local control rate was reported as 92% and 73% in T1 tumors and T2 tumors, respectively, and the survival rate was reported as 72% and 62% in Stage IA and Stage IB, respectively, with the results being claimed to be similar to those in surgical series (1).

The emergence of successful results obtained with SBRT both in medically inoperable and operable patients gave rise to an interest in surgery-SBRT comparison studies. It was seen that a healthy comparison could not be made from studies that were conducted on a retrospective series and population basis (1). Two prospective studies were commenced for this purpose.

1. STARS (StereoTActic Radiotherapy vs Surgery):
Group 1. Patients with clinical Stage I ≤4 cm tumor whose mediastinal lymphatic gland sampling was performed with surgical resection

Group 2. 54Gy SABR practice in 3 fractions on peripheral tumors
50Gy SABR practice in 4 fractions on central tumors

Histologic diagnosis was established in all patients in this study

2. ROSEL (Radiosurgery Or Surgery for operable Early stage Lung cancer)

Group 1. Surgical resection (lobectomy or sublober) on patients with Clinical Stage I ≤ 3cm tumor

Group 2. 54Gy SABR in 3 fractions on peripheral tumors
60Gy SABR in 5 fractions on tumors in contact with the central or thoracic wall

There was no histologic diagnosis condition in this study.

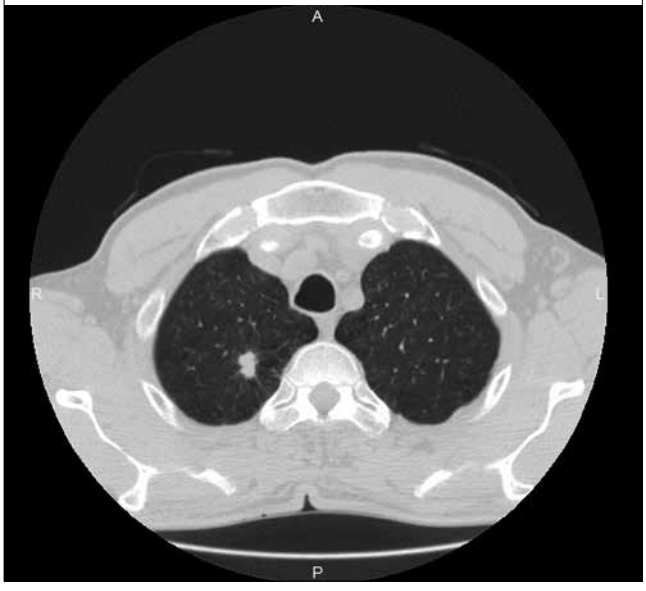
These two prospective studies were terminated early due to the lack of sufficient number of patients. STARS and ROSEL studies were terminated on 36 and 22 patients, respectively. An assessment attempt was made based on these 58 patients, and it was reported that toxicity in SABR was less and results were not worse than surgery; however, no evidence could be presented.

The reason for non-performance of surgery could be determined in only 25% of the patients that decided to take non-surgical treatment. It is not known why surgery could not be performed in 75% of the patients that received non-surgical treatment. While surgically high-risk definitions have been made with various evaluation and scoring systems, the definition of the difference between surgically high risk and medically inoperable concepts is not clear (3). In order to decide that a lung cancer patient is medically inoperable, a thoracic surgeon must be present within the multidisciplinary team.

Comparison of SABR with surgery using the retrospective series involves highly important restrictions. The significant differences between the patient populations of the two groups are quite clear. On the other hand, the two methods applied are very different from each other. While real pathological staging is performed with surgical resections, and hilar mediastinal lymphatic gland dissection or sampling, staging can be made only for the T stage with SABR, and histological diagnosis of the tumor is not often seen as a criterion. An SPN that is evaluated as malignant can be benign or a carcinoid tumor, and these cases are included in the long-term survival rates in the SABR series (Figure 1). Occult lymph node metastasis is identified at a rate of 15-20% in early-stage lung cancer. As lymph node condition cannot be determined in SABR, patients lose the chance of adjuvant treatment. Considering the evaluation of post-treatment relapse, definition of relapse is also quite different between the two methods. Residual parenchyma scar and tumors cannot be distinguished precisely in the computerized tomography during the follow-up of SABR patients. Post-treatment relapse is considered a relapse not only for those in the same lobe, but also for those in different lobes, and the definition of local follow-up varies between these two methods (4).

The low rate of adverse effects and complications in SABR is often emphasized as the advantage of this method. However, studies showing that the method might have some severe complications have also been published. Complications might be seen

Figure 1. A lesion with a spiculated contour of 16x9 mm in the right upper lobe, wedge resection with SUV max 3.2 in PET CT Pathology: Rheumatoid nodule+coal workers' pneumoconiosis (Caplan Syndrome) (From the archive of Department of Thoracic Surgery, Ankara University School of Medicine)



such as esophageal stenosis and fistula, brachial plexus neuropathy, large vascular aneurysm, stenosis or fistula in the trachea or main bronchi, skin ulcerations, rib fracture, and pneumonitis (5). In terms of early adverse effects and mortality, SABR seems to be superior to surgery in elderly patients that are believed not to be able to tolerate surgery, however when considered in the long-term, late complications may arise two years later, and surgery might become superior to SABR in terms of survival (6). On the other hand, a remarkable decrease has been seen in the surgical complication rates with the common administration of minimal invasive surgery and sublober resections starting from the beginning of the 2000s, and it has been determined through many studies that there are effective methods that are suited to oncologic surgery principles. The fact that the lobectomy results were better in the surgical series than those in SABR was identified as statistically significant (7, 8). Apart from that, it has been suggested that the results of segmentectomy, or even wedge resection, are better than those of SABR in a statistically significant way (9-11).

Survival depends on the stage of disease in lung cancer. Therefore, both tissue diagnosis and metastasis studies are very important. Computerized tomography and PET are extremely valuable in this evaluation; however, the false negativity ratio is 5-15% while false positivity ratio is about 50% in staging. Therefore, it is required to use invasive mediastinal staging methods such as TBNA, mediastinoscopy, and VATS. To make a healthy comparison between the two methods, the non-surgical treatment branch must also follow this strategy in the future (2).

Stereotactic ablative body radiotherapy is a suitable treatment method in medically inoperable Stage I lung cancer cases. In patients whose medical condition is fit for surgical treatment, mediastinal lymph node dissection or sampling together with lobectomy is the standard treatment method. This allows patients to obtain a local control and annual survival chance of over 90% and 80.5%, respectively. In patients with medical comorbidities, minimal invasive surgery methods and sublober resections can be administered, and patients thus have the chance to undergo effective treatment. Naturally, there must be a thoracic surgeon in the team to make the decision regarding medical operability.

CONCLUSION

Today, the appropriate approach in identifying the most suitable treatment option is believed to include the presence of a multidisciplinary cooperation, and a discussion carried out between a thoracic surgeon and radiation oncology specialist on the advantages and disadvantages of the treatment method to decide for each patient. Such cooperation will contribute to the studies to be conducted in the future.

To conclude, surgery is the standard treatment for early-stage lung cancer. SABR is the suitable treatment option in patients that cannot or refuse to undergo surgery. There is no evidence that SABR can be an alternative to surgical treatment in early-stage lung cancer cases with a medically fit condition that do not refuse surgery.

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The Role of Sublobar Resections in the Treatment of Small Cell Lung Cancer

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ABSTRACT
Lobectomy is the standard treatment in the early stages of non-small cell lung cancer. Today, however, it is questioned whether lobectomy should be performed in all early diagnosed patients. Sublobar resection remains a treatment option in elderly patients with low cardiopulmonary reserve who cannot tolerate sublobar resection lobectomy. In small tumors measuring 2 cm in diameter, sublobar resections can provide local recurrence rates and long survival rates equivalent to lobectomy when performed with the appropriate techniques in eligible patients. The addition of brachytherapy can further improve the results.
Keywords: Sublobar resection, segmentectomy, wedge resection, brachytherapy

INTRODUCTION

In a randomized study in 1995, a lung cancer study group showed that local recurrence rate was higher in sublobar resection surgery than in lobectomy in patients with stage-I non-small cell lung cancer (NSCLC) (1). Lobectomy is the preferred surgical treatment for stage I NSCLC patients, whereas sublobar resections are only performed in high-risk patients who cannot tolerate lobectomy. Today, some factors make sublobar resections an acceptable technique, especially in the surgical treatment of peripherally located early stage NSCLC. These factors include the recognition of very small-sized NSCLC in high-risk patients with evolving tomography techniques and devices, increase in the literature showing the success of segmentectomy, especially in small peripheral NSCLC cases who cannot tolerate lobectomy, low perioperative morbidity and mortality rates in sublobar resections compared to lobectomy, and superiority in preserving pulmonary functions (2, 3).

Sublobar Resections in High Risk Patients

Several studies have shown that sublobar resections can be performed for lobectomy with moderate morbidity and mortality, recurrence, and survival rates in high-risk patients (4, 5). In a meta-analysis by Hou et al. (6), they reported that segmentectomy reduced mortality in patients with stage IA NSCLC compared to larger resections and provided better survival rates compared to wedge resection, but that wedge resection and segmentectomy provided equal survival rates in sub-group analyzes of T1a cases.

The Effect of Age

The incidence of lung cancer increases with age. There is an increase in the number of elderly patients with diagnosed lung cancer in direct proportion to the aging of society. Database surveys indicate that 70% of newly diagnosed lung cancer cases are over 70 years old (7).

Although age is not a contraindication alone, there is a reduction in the number of patients who can tolerate standard lobectomy in the elderly population compared to the younger population. With increasing age, operative mortality and complication rates increase in lobectomy. In the data reported by Mayo Clinic, these rates are 6.3% and 48%, respectively. In addition, co-morbidity-related mortality rates in elderly patients with early-stage NSCLC were found to be higher than cancer-related mortality rates. The literature review showed that cardiovascular disease-related mortality was higher than cancer-related mortality rates in cancer patients aged 70-79 years over the five-year period (8). Furthermore, SEER (Surveillance, Epidemiology and End Results) data indicates that 31% of these patients have not undergone lobectomy (9). Studies have shown that sublobar resections are effective and beneficial in patients over 75 years old with stage I NSCLC. In a study by Kilic et al. (10), lobectomy was compared to anatomic segmentectomy in patients older than 75 years with stage 1 NSCLC, and it was shown that segmentectomy had lower morbidity and mortality rates, whereas there was no significant difference in local recurrence and long-term survival rates.

Tumor Size, Histology and Location

Tumor size is a prognostic factor in NSCLC cases. Sublobar resections have similar oncologic outcomes as lobectomy in small-sized tumors. There was no difference in the survival rate between sublobar resection (anatomic segmentectomy) and lobectomy for peripheral tumors smaller than 2 cm (11). However, lobectomy provides superior results when the size exceeds 2 cm (12).

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Tumor histology also leads to the decision to perform sublobar resection. The prognosis after sublobar resection is associated with the histological type. Patients with adenocarcinoma in situ (AIS), minimal invasive adenocarcinoma (MIA), and adenocarcinoma with lepidic growth pattern have a good prognosis after sublobar resection. Tumors exhibiting ground-glass opacification are often considered as AIS, MIA or lepidic adenocarcinomas (13).

Tumor localization is also important in the decision to perform sublobar resection in small-sized NSCLC cases. Peripheral tumors constitute the majority of tumors undergoing sublobar resection.

Surgical Approach and Technical Features

The decision to administer a sublobar resection (wedge resection or anatomic segmentectomy) is usually made by evaluating the patient's performance, the tumor's character, and the surgeon's preference. For example, wedge resection is preferred for peripheral small tumors in patients with poor performance and poor self-care, whereas anatomic segmentectomy is preferred for larger tumors confined within the segment. For intersegmental tumors, extended segmentectomy or wedge resection with a surgical margin of at least 1 cm is performed as a sublobar resection (14). Many factors can influence the decision regarding which surgical technique to use. For example, lobectomy will be preferred to segmentectomy in lesions that have exceeded the limits of the segment, the majority of which form deep lesions. This is most frequently encountered in the lower lobe superior segment and basilar segments. The most common localization in the upper lobes is the boundary between the upper division and the lingular segment in the upper left lobe.

Mediastinal systematic lymph node sampling should be performed with all sublobar resections. For right-sided lesions, stations 4R-7 and 9 should be sampled, and for left-sided lesions, stations 5-6-7 and 9 should be sampled. In wedge resections, only station 10 is sampled as the N1 lymph node.

If wedge resection is to be performed as a sublobar resection, the surgical margins should be intraoperatively checked by frozen section or margin cytology examination.

Width of the Resection

For a sublobar resection, the analysis of the near parenchymal area is more important than the analysis of the bronchial surgical margin. This is due to the fact that the local recurrence rate is found to be increased for resections with a clear margin below 1.5 cm (15, 16). While the extent of the resection is a controversial issue, there is a consensus that a wider resection is better. There are reports recommending the intra-operative cytologic study of negative margins (17). Lobectomy should be considered if segment margins are exceeded or positive margins exist.

The local recurrence rate is the lowest with a tumor size below 3 cm, consolidation/tumor ratio below 0.5, solid tumor size of 1.2cm or below, carcinoembryogenic antigen level of 5.0ng/mL and the presence of a histological type of adenocarcinoma (18).

In wedge resections, a clear surgical margin of less than 1.5 cm in tumors smaller than 2 cm obviously reduces the local recurrence rate, whereas segmentectomy should be preferred for lower recurrence rates in tumors larger than 2 cm (16, 19). If sublobar resection is planned in stage I patients diagnosed with squamous cell NSCLC, wedge resection is not recommended, but segmentectomy should be preferred. Local recurrence and lymph node positivity rates in squamous cell carcinomas are higher than in adenocarcinomas (20).

According to the recommendations of the National Comprehensive Cancer Network (NCCN, Version 1.2016) guidelines, the distance between the tumor and the surgical margin at sublobar resections should be greater than 2 cm or at least the size of the tumor.

The rate of local recurrence is lower because the malignancy rate is lower compared to solid tumors in NSCLC cases with ground-glass opacification. It has been reported that the length of the clean surgical margin may be lower in these tumors (21).

Pulmonary Functions after Sublobar Resections

The reports of the lung cancer study group in 1995 showed that limited resection has an advantage in terms of loss of pulmonary function in the early postoperative period, but this advantage disappeared after 12 months or longer (1). However, it should not be forgotten that the patient follow-up period was indicated as a limiting factor. Takizawa et al. (22) showed that postoperative FEV_1 values were higher in patients undergoing segmentectomy compared with lobectomy, but proposed segmentectomy only for patients with limited pulmonary reserve.

Survival Rate after Sublobar Resection

In a study by Khullar et al. (23) featuring 13,606 patients, it was reported that lobectomy was still the gold standard treatment in T1A-N0 NSCLC cases, but sublobar resections may be an alternative to lobectomy in patients with limited pulmonary reserves only if surgical margin and lymph node negativity are present. Another report evaluated 2,090 patients with a tumor size of less than 1cm, and showed that sublobar resections were more commonly performed in elderly patients, female patients, and patients with adenocarcinoma and lower lobe tumors and that disease-free survival and overall survival rates were equal to that of lobectomy (24).

Sublobar Resection and Brachytherapy

As local recurrence rates are higher, sublobar resections are usually performed alternatively to lobectomy in patients with limited pulmonary function. Adjuvant RT reduces local recurrence rates, but respiratory movements and the difficulties of determining the stapler line can limit and complicate RT to be applied from outside the body. Adjuvant intraoperative RT has been successfully used in many centers through the application of iodine-125 on the stapler line (25). The direct application of radiation emitting systems on the surgical field has many advantages; it provides more specific targeting, minimizes the effect of RT on normal lung tissue, reduces the time and dose of treatment, patient tolerance is excellent, and treatment

begins immediately during surgery. In 1998, D'Amato et al. (26) covered stapler lines with I-121 Vicryl meshes during VATS sublobar resections performed in stage I tumors and demonstrated success in terms of the control of local recurrence in the postoperative period. No implant displacement, radiation pneumonia or loss of pulmonary function were observed in these studies. Although its effect on the current long-term survival rate is not entirely clear, intraoperative brachytherapy seems promising for the future. Studies have shown that local recurrence rates in sublobar stage-I NSCLC cases corroborated by intraoperative brachytherapy are reduced, even at lobectomy levels (27).

As a general safety guideline, it is recommended that children under 18 years of age and pregnant women should not get closer than 1m away from patients who have received intraoperative brachytherapy treatment for a period of three months.

CONCLUSION

Sublobar resections are considered superior to RT in terms of the application of lymph node dissection and the absence of damage to residual lung tissue after treatment. Intraoperative microscopic border analyzes are performed to reduce recurrences, which are the most important local failure of sublobar resection therapy. Intraoperative brachytherapy removes the difficulties and limitations of RT applied from outside the body. The data of patients with sublobar resection corroborated by intraoperative brachytherapy is promising in terms of presenting an alternative to lobectomy.

RECOMMENDATIONS

1. In stage-I NSCLC patients who are medically eligible, if the tumor is confined within a segment, extended segmentectomy or the addition of lymph node dissection in lobectomy is recommended, and these techniques have similar five-year survival rates.
2. In the high-risk stage I NSCLC patient group, sublobar resections in which a clear surgical margin is achieved and hilar/mediastinal lymph node sampling is added is an alternative surgical procedure to lobectomy.
3. Sublobar resection is an effective and potentially useful treatment, especially in patients over 75 years of age with NSCLC.
4. A clean surgical margin of more than 1cm is recommended for sublobar resections in stage I NSCLC cases.
5. Patients undergoing sublobar resection should be closely monitored due to high local recurrence rates, which includes follow-ups every three months for the first year, followed by follow-up every six months.
6. If sublobar resection is performed, anatomic segmentectomy should be preferred to wedge resection.
7. The distance between the tumor and the surgical margin appears to be an ineffective factor for local recurrence rates in patients undergoing R0 sublobar resection and with N0 ground-glass opacities and tumors smaller than 3 cm.

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The Ability of Surgery in T4 Lung Cancer

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ABSTRACT
According to the staging system, T4 cases have been identified as tumors larger than 7cm or invasive tumors on tissues, such as the diaphragm, mediastinum, heart, large vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or separate tumor nodule(s) on a different lobe on the same side. In this manuscript, the srugical treatment of T4 N0-1 lung cancer that made tracheal, carina, vertebra, thoracic inlet, vena cava superior, mediastinal structures and diyafragmatic invasion. Medical literature in the thoracic surgery and oncology network was reviewed, and studies, cases, and meta-analysis studies that included surgical treatment practices in oligometastatic small cell lung cancer treatment and their results were examined. A discussion was made by also analyzing the survival data in light of the literature studies and available guidelines. In recent years, indications of lung cancer surgery have also been expanded in parallel with the advancements in multidisciplinary surgery and in multidisciplinary oncological treatment protocols, and thus surgery has become applicable for more patients. T4 N 0-1 cases are approximately 30 % of all lung cancer cases and despite 5 year survival is about 10 %, there are survival advantages in patients who have complete resection. T4 tumor surgery should be applied in experienced centers and by multidisciplinary surgery teams. Treatment decisions should be individualized, and complete surgery should be considered for NO-1 cases whose activity rate could be high.
Keywords: T4, lung cancer, extended surgery.

INTRODUCTION

In recent years, indications of lung cancer surgery have also been expanded in parallel with the advancements in multidisciplinary surgery and in multidisciplinary oncological treatment protocols, and thus surgery has become applicable for more patients. The eighth revision of the tumor, node and metastasis (TNM) classification was analyzed by the Lung Cancer Society with the participation of more than 100,000 cases, 19 different countries and 46 centers. In this analysis, staging has been changed after careful consideration of the relationship between T, N, M factors and survival rates. The eighth TNM Classification entered into force on January 2017 with the participation of the Union for International Cancer Control and the American Joint Committee on Cancer.

According to the staging system, T4 cases have been identified as tumors larger than 7cm or invasive tumors on tissues, such as the diaphragm, mediastinum, heart, large vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or separate tumor nodule(s) on a different lobe on the same side. It should be noted that superior sulcus tumors turning into Pancoast tumors due to brachial plexus, subclavian artery vein invasions, and artery involvement intracardial intervention should be considered as T4 (1).

Stage III B cases correspond to approximately 30% of all cases. In this group, the 5-year survival rate was reported to be 10%, while there are apparent survival advantages in T4 - N 0-1 cases after complete resection (1).

The term extended resection was first defined by Chamberlain in 1959. This procedure consists of the resection of the tumor creating a local invasion together with the lung. The surgery should be conducted if complete resection is possible, and optimal conditions should be provided for this surgical procedure. Mediastinal lymph node involvement is very important in these cases undergoing major surgery. Even at the slightest doubt, invasive staging must be carried out. Surgery is contraindicated in the presence of N2. However, upper paratracheal lymph nodes for Pancoast tumors and sub-carinal lymph nodes for carinal tumors can be considered as local invasions and can be operated on.

Patients undergoing surgery should have the appropriate cardio-pulmonary reserve; advanced age is a relative contraindication. In order to speed up post-operative recovery in these patients undergoing major surgery, preoperative serum albumin level should be kept above 3 gr/dL, and if necessary, preoperative and postoperative enteral support therapy should be administered.

T4 NSCLC Cases and Surgical Treatment Forms

Trachea-carina invasion

Resection of lung tumor invasion on the lower end of the trachea, trachea bronchial angle, carina and main bronchus, and reconstruction of these areas using bronchoplastic methods (Figure 1-3). Isolated carina resection or carinal sleeve lobectomy can be administered as a tracheal sleeve pneumonectomy (TSP). Although this

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Figure 1. Carinal resection and reconstruction

Locus of the tumor (a); First the trachea, then the left main bronchus and right intermediary bronchus are cut (b); -/3 of back side of end to end anastomosis between the trachea and left bronchus are completed with individual suturing (c); Oval hole where the right bronchus can be anastomosed by removing one cartilage from "^" of the remaining sections is created (d); Finally, the right bronchus is anastomosed to this oval hole with end to end anastomosis, using the continuous suturing technique (e)

Figure 2. Barclay surgery: After carinal resection of the left tracheobronchial tumor, end to end anastomosis of the right main bronchus to the trachea and end to side anastomosis of the left main bronchus to intermediary bronchus

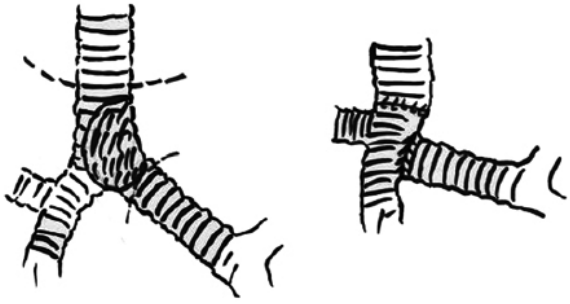
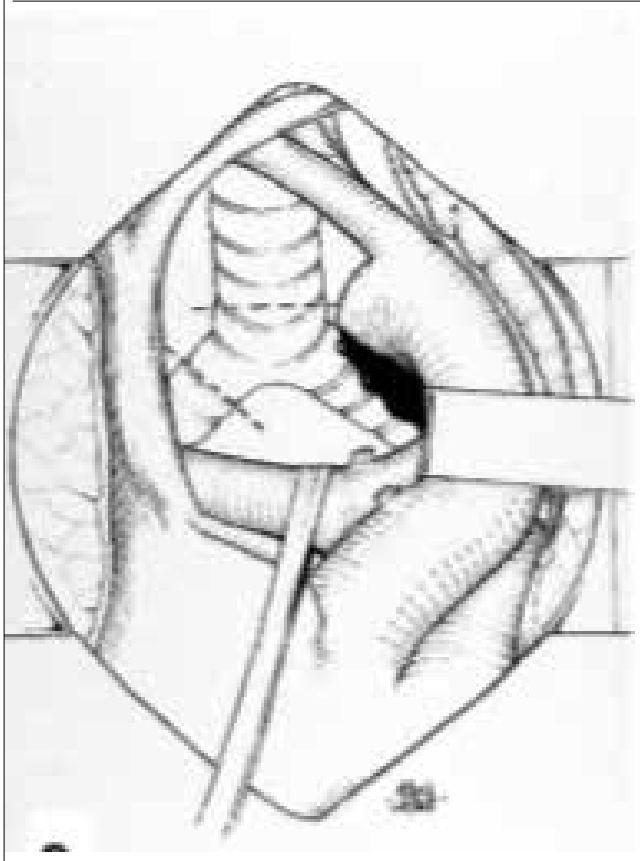


Figure 3. Transsternal approach for left TSP



method is used for NSCLC cases more frequently; it is also used for carcinoid tumor and adenoid cystic carcinoma. Positive surgical margin after standard pneumonectomy is another indication.

Through endotracheal tubes and jet ventilation application, this operation can now be applied without cardio-pulmonary bypass. Planning and staging should be extremely carefully before TSP application, which has a high morbidity rate.

As anastomosis of the trachea and main bronchus can increase the blood pressure, the length of the distal trachea must be limited to 3-4 rings or 2-3 cm, while the left main bronchus invasion must be limited to 1-1.5 cm. Pre-operative bronchoscopic examination, therefore, is highly important. The invasion margin should be measured with care, areas which can be surgical margins should be identified, and a biopsy should be carried out. Even if sleeve lobectomy is planned, it should be noted that TSP can be preferred (2-3).

It should be noted that the tumors localized here can be invasive to the superior vena cava, main pulmonary artery, left atrium and esophagus due to the anatomy of this area; therefore, these areas should be examined preoperatively, using angiography and transesophageal ultrasound.

The most important matter to be considered in the staging process is the presence of N2 disease. Therefore, mediastinoscopy is recommended in the beginning of the operation due to the possible negative effect of preoperative mediastinoscopy-induced inflammation on carinal resection. Furthermore, mediastinoscopy should provide insight for the evaluation of the external pressure on the trachea.

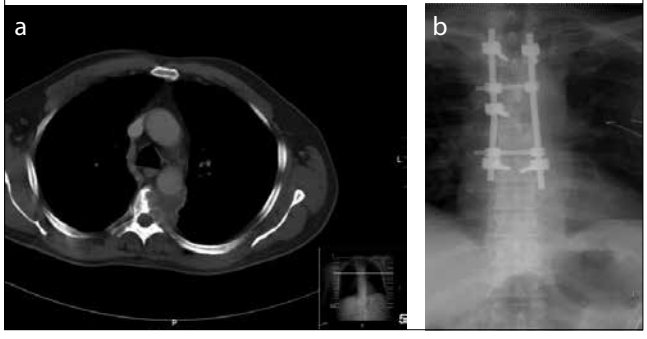
As SVC involvement and sub-carinal lymph node involvement can be totally resected, the first being technically, and the latter locally considered an invasion, they can be operable (2, 3, 4). Carinal sleeve resections can be applied in the right-side lesions more easily than the left ones. Besides this, left-side lesions are the tumors which are more likely to be inoperable because they are invasive to the aortopulmonary window; therefore, left TSP is applied less frequently. In the left-side tumors, first vascular structures are dissected at once trans pericardially with median sternotomy, then the operation is completed with left side thoracotomy. In the two-stage method, first, the carina and the main bronchus are dissected by right thoracotomy during the same session, the left main bronchus is cut, and the operation proceeds in the same way as right TSP. Left pneumonectomy is completed by left thoracotomy conducted in same session (2-4).

In order to prevent impairment in local feeding, excessive use of cautery should be avoided. After the trachea is cut, putting fixation sutures on the main bronchus through the cartilage makes the surgeon's work easier. The anastomosis technique and the materials to be used can change depending on the surgeon's

experience but supporting the anastomosis line with live tissues is important. To relieve the tension that can emerge on the anastomosis line, the inferior pulmonary ligament should be cut, the hilus should be dissected and a U-shaped incision should be made on the pericardium to relieve the tension on the area. In cases with increased tension, jaw wiring should be applied for one week.

It was reported in 1982 that the preoperative complication rate was 29.5% and survival rate was 15%. Dartevelle et al. (5), in his 138 patient series, reported that during the first 30 days, mortality was 9.4% and the average survival rate was 27 months, while 5-year and 10-year average survival rates were 41.3% and 27.7%, respectively. It was determined that the 5-year survival rate for N 0-1 cases and N2-3 cases were 47% and 24% respectively. Also induction treatment increased the intraoperative mortality rate from 6.7% to 13% in Turkey. Yaran et al. (4) applied 11 right and 2 left TSPs to 13 patients, and they reported that the average survival duration was 87 months and 5-year survival rate was 77% (4, 5).

Figure 4. a, b. Preoperative and postoperative images of our case on which total corpectomy with posterior instrumentation were applied



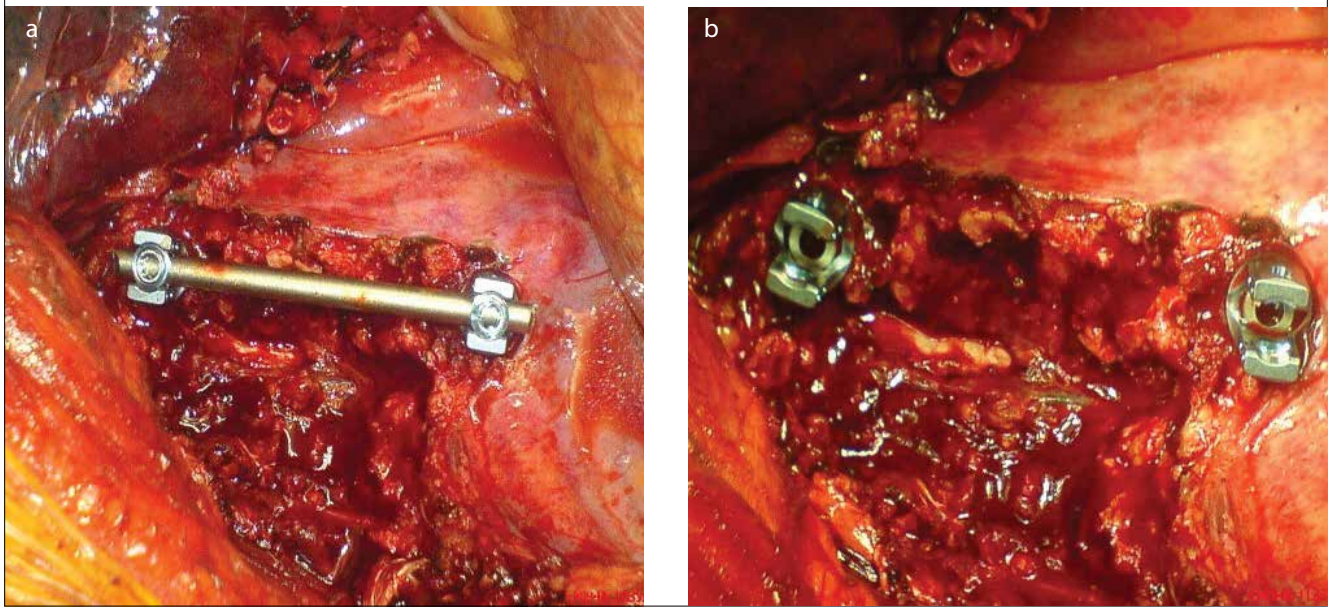
It was reported that the total complication rates in the post-operative period are approximately 30-50%, and the most important complications are anastomosis- induced fistula and empyema at a rate of 8-10%. Due to denervation related to the cutting of tracheobronchial system, mucociliary activity is lost and secretion stasis and pneumonia risk are increased (2-7).

Vertebra invasion

Although vertebra transverse spurs are identified as a T3 tumor, the vertebra bridge is a T4 tumor. Extended lung cancer resections have long been rarely reported for the following reasons: the bone structure of the vertebra is prone to complications that can result in paraplegia due to medulla spinalis, it is difficult to identify complete resection intraoperatively, and spinal surgery is a very different discipline from thoracic surgery. The first serious publications were made first by De Meester in 1989 and then by Ginsberg, and it was emphasized that complete resection is a required to ensure survival (4, 8, 9).

In cases with vertebra invasions, the spread of the tumor, dural sac invasion and compression are evaluated with the thorax and spinal MRI and this evaluation is sufficient most of the time. Spinal cord arteriography, on the other hand, is applied to evaluate anterior spinal artery in tumors with high vascularity. Its involvement is the criterion of inoperability. Thoracic CT determines the spread over the parietal pleura, muscle tissue and chest wall. The degree of vertebra involvement is important for the form of the resection. According to spinal surgeons, while partial or hemi corpectomy are conducted for involvements between 30-50%, total corpectomy and instrumentation to maintain spinal stability are applied for involvements above 50%. For involvements below 30%, the decision to apply instrumentation depends on whether the posterior structures are healthy or not. The issue of which protocols will be applied–a supplementary surgery containing induction

Figure 5. a, b. Instrumentation stages of our case on which anterior hemi corpectomy was applied



chemoradiotherapy treatment or a postoperative adjuvant chemoradiotherapy protocol–is another controversial subject. Medical oncologist and radiation oncologists would rather recommend treatment protocol involving induction treatment, while operating surgeons prefer adjuvant treatment protocols as the stabilization of the used metal instrument in the area receiving radiotherapy is not strong.

Survival analyses change depending on clinics due to the absence of randomized studies. It has been reported that invasion depth does not affect survival in cases where complete resection is applied while incomplete resections do not contribute to survival (10). Koizumi and Haraguchi (10) reported that 1, 3, and 5-year survival rates are 68.6%, 22.9% and 22.9% respectively. At our clinic, we are working with orthopedist spinal surgeons. (Figure 4, 5)

The medulla spinalis damage that can emerge due to the application of intraoperative routine neuromonitorization is predetermined and the patient is protected from paraplegia. An effort is made to conduct the operation in the most unblocked condition possible. For this purpose, the cancerous area is separated from the lung with a stapler and en-bloc resection is performed. Adjuvant treatment is preferred to neoadjuvant treatment. In our series consisting of 12 cases, which is in the publication phase, the first 30-day mortality is not available, while the 1-year survival rate is 87.5 and the 5-year survival is 19.1%.

Thoracic inlet invasion

Thoracic inlet tumors can be investigated under two groups. These are the tumors invasive to subclavian vessels other than anterior type brachial plexus. Posterior type are tumors invasive to the brachial plexus, subclavian vessels, vertebral artery, sympathetic chain, paravertebral muscles and vertebra. Cervical trachea, esophagus, brachial plexus above C8 and vertebra constitute common involvement contraindications. Limited vertebral involvements that can be resected with subclavian vessels and vertebrectomy do not constitute contraindications. Although in the preoperative diagnosis, MRI provide sufficient insight, angiography may still be required to check the condition of the vertebral artery inside the subclavian artery. If the vertebral artery is not well-developed, the patient may have brain infraction (5, 11). Although there are publications suggesting induction radiotherapy, post-operative adjuvant treatments are frequently preferred in the appropriate cases (5).

Even if there is a tendency to apply trans-clavicular cervico-thoracic (Dartevelle incision) thoracotomy to anterior tumors and extended posterior thoracotomy to posterior tumors (Poulson-Shaw incision), Dartevelle et al. (5) as an author on this subject reported that he applied his incisions as trans-clavicular cervico-thoracic applications (Figure 6). This incision is an L-shaped incision extended from the anterior of the sternocleidomastoid muscle to the intercostal area, and clavicle and manubrium resection are required. Through this incision, all anatomic structures can be accessed and checked more easily. It is resected depending on the subclavian artery involvement; end to end graft is anastomosed and the internal jugular subclavian vein can be bonded. T1 is frequently cut from the intervertebral foramen; rib resections, sympathetic ganglions and all invasive tissues are resected in unblocked condition through upper lobectomy. In vertebra involvement, posterior hemi vertebrectomy is added by switching to the prone position; in this case, all the tissue is extracted from the posterior proximity and vertebra instrumentation is carried out.

Dartevelle et al. (5) reported that the complete resection rate is 90.5%, 30-day operative mortality is 0.8%, 5 and 10-year survival rates in N0-1 cases are 41.5% and 29.7%, and 5-year survival rate in N2-3 cases is 9.4%. Subclavian vessels and limited vertebral involvements that can be resected by hemi vertebrectomy are negative prognostic factors, although they do not constitute a contraindication (5).

Figure 6. a, b. Dartevelle (trans-clavicular cervico thoracic) and Poulson Shaw (posterior extended) incisions

a

b

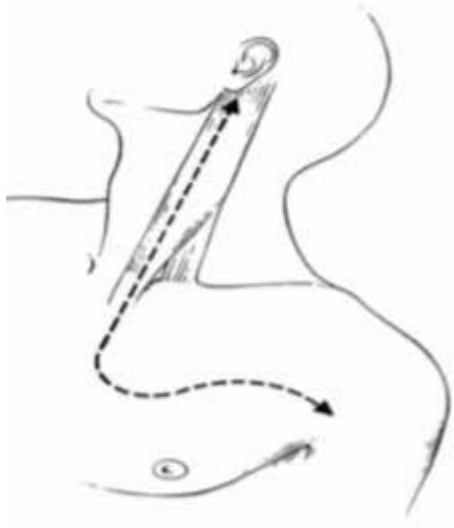


Figure 7. a, b. Tangential primary suture and pericardial patch application

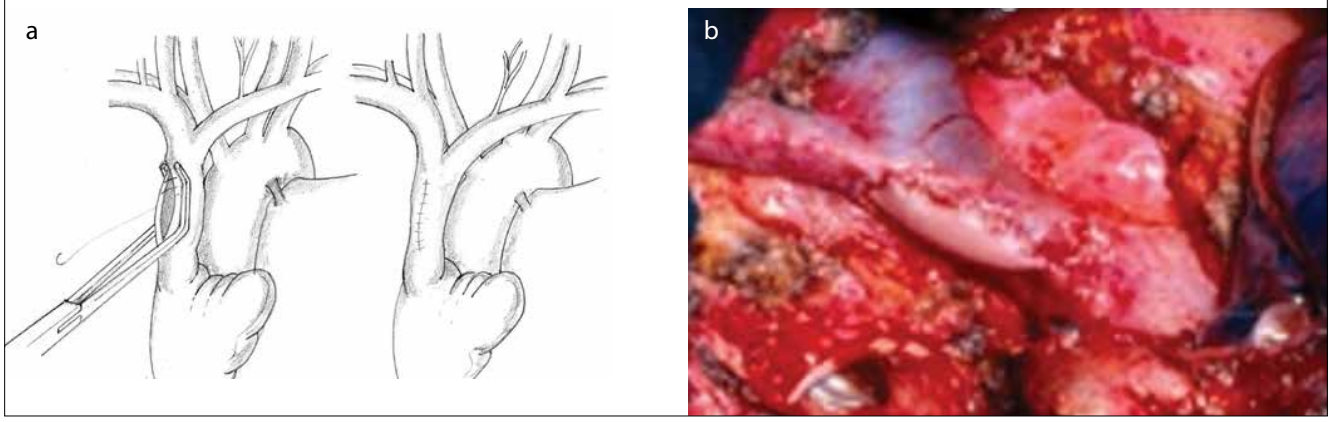
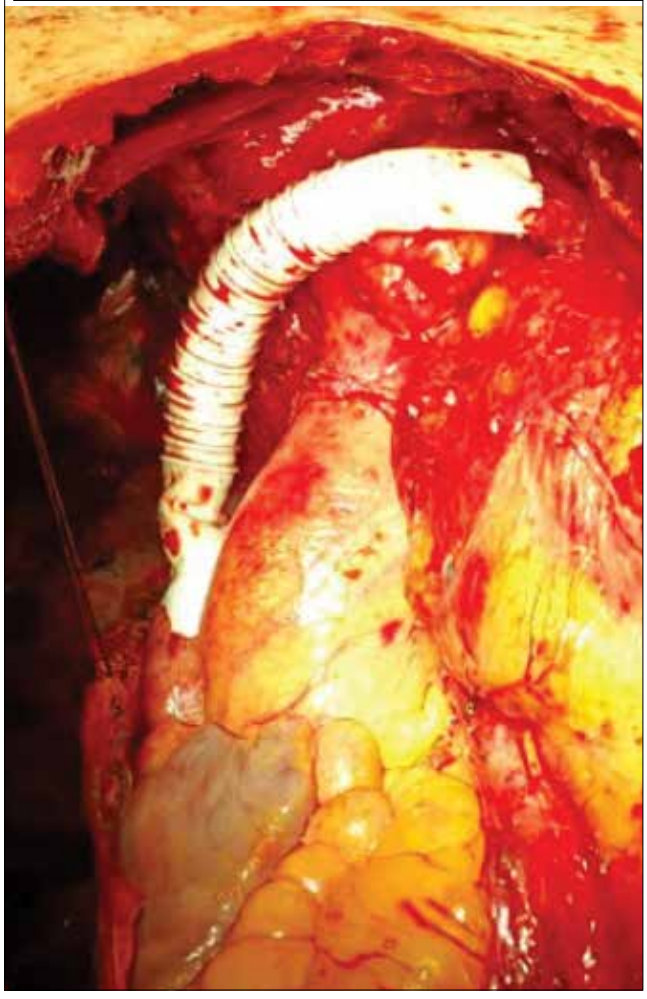


Figure 8. Our clinic's SVC graft application. Right innominate vein totally occluded, left innominate vein-right atrium PTFE graft application with median sternotomy



On the other hand, in tumors which are not completely invasive to the thoracic inlet, the Poulson -Shaw approach is applied and sometimes, both approaches should be used.

Superior vena cava (SVC) invasion

Tumor with invasion into the SVC can happen directly or via the lymphatic gland. The lymphatic gland is surgically contraindicated in invasive cases. In cases where the SVC is fully occluded, the tumor, even if it is resectable, is surgically contraindicated due to both impaired hemodynamics and mediastinal invasion. MRI in preoperative diagnosis, echocardiography for atrial thrombus, and if needed, superior venocavography for the control of innominate vein patency, should be carried out.

In limited invasive cases where the SVC diameter is less than 50%, tangential primary suture or pericardial patch can be applied (Figure 7, 8). When these applications are impossible, clamping, resection and graft replacement must be applied. Posterolateral thoracotomy is usually sufficient; but in case of a difficulty in proximal anastomosis, cervical sternotomy can be added to thoracotomy. Graft replacement is a simple procedure as a vascular surgery in SVC involvement. Graft thrombosis is the main problem due to its structure containing high-rate blood flow at low pressure and since although the native vessel can provide the same response to the atrium pressure by becoming negative, the graft has no such characteristic. Therefore, long-term anticoagulation therapy is required.

The right ventricular preload is decreased as a result of SVC clamping and while systemic hypotension emerges, cerebral venous pressure increases. Therefore, vasoconstrictor agents, 50 IU/kg heparin and intravenous liquid are administered; if not, cerebral perfusion pressure will decrease, and fatal ischemia, intracranial thrombosis and edema will occur. For this purpose, keeping the systemic tension at 100 mmHg is sufficient.

Although internal shunting is recommended, clamping and graft replacement are the ideal methods. It was shown that clamping applied for 30 minutes does not cause any neurological damage. The graft is surrounded by the local tissues after the operation.

Dartevelle et al. (5) reported that the most suitable graft is polytetrafluoroethylene (PTFE), and that administering warfarin certainly provides a graft patency on the condition that the lifetime INR 2-3 level is kept after 2mg/kg/day intravenous hepa-

rin applied for 6 months post-operatively (5). Dartavelle et al.(5) reported the following: 30-day mortality is 8%, 6 months graft patency rate is 88%, average survival time is 23 months, and 5 and 10-year average survival rates are 36.7% and 32.1%. The 5 and 10-year survival rates were identified to be 46.6% and 37.7% respectively in the N0-1 group, and 21% in the N2-3 group (5).

Invasion of mediastinal structures

In tumors displaying central localization, intrapericardial pneumonectomy (IPP) is applied in the case of dissection difficulty and left atrium invasion due to invasion of the pulmonary artery and veins, lymphatic gland and retractions. For anatomic reasons, right central tumors can be invasive to the left atrium because of the right superior pulmonary vein being short. Left hilar tumors are more frequently invasive to the left atrium aorta and esophagus because of the aorta pulmonary window stratum. Therefore, left IPP is used less frequently. As invasion of the mediastinal structures leads to N2 disease, a detailed investigation should be carried out in these cases for neoadjuvant treatment response, persistent N2 presence, and cardiopulmonary capacity secondary to chemoradiotherapy.

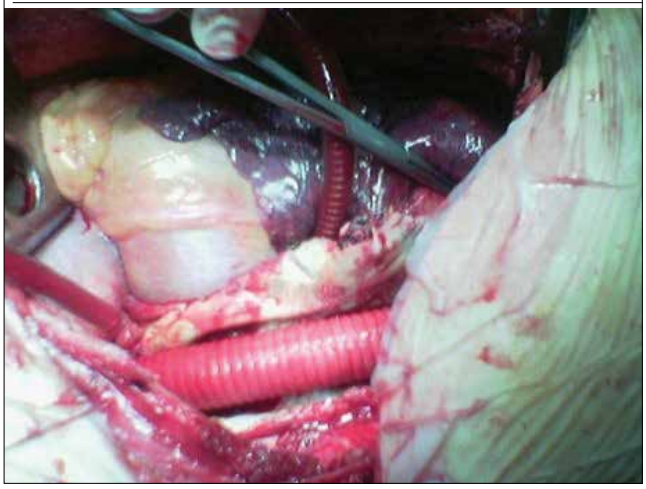
Up to this day, Mitsos et al. (12) have reviewed 14 substantial studies with high evidential value to investigate the application of pneumonectomy in the presence of persistent N2. As a result of this collected work, they reported that surgery can be applied safely and with acceptable mortality rates in cases diagnosed with Stage III-B persistent N2 and who have received neoadjuvant treatment (12). Atrium invasion, intrapericardial pulmonary artery vein invasion, and aorta invasion should be assessed from the viewpoint of cardiovascular surgery. Cardiopulmonary bypass technique can be used together with major aorta and pulmonary truncus surgeries for lung resections.

Atrium resection is the extraction of the tumor involved atrium part together with the pulmonary veins. It is important for the remaining atrium to have the sufficient volume to be tolerated hemodynamically. Therefore, it should be clamped and held for a while before being resected. According to our experience, this takes 5 minutes. In the presence of invasion where a clamp cannot be placed, the atrium is constricted by contour sutures, then resected with scissors. 14 cases have had atrium resection at our clinic between 2002-2010. It was found that the first 30-day mortality is 2.4%, 1-year survival rate is 90.5% and 5-year survival rate is 27%.

The most frequently seen complication of intrapericardial pneumonectomy is arrhythmia and cardiac herniation. Hypotension, tachycardia and venous congestion can develop as a result of the VCI and pulmonary artery being bent in the presence of the right-side defect. Therefore, the pericardium should be closed every time. Strong contraction in the left side prevents herniation. Primarily closing the defects is sufficient. Although some cardiac surgeons recommend that a pericardial drain be placed constantly, we make a small puncture on the right pericardium and place stitches at intervals.

Eleven cases have had surgery due to lung cancer and aorta invasion in the joint study of İstanbul University Cerrahpaşa School of Medicine and Dokuz Eylül University Thoracic Surgery Clinics. Four cases underwent patch plasty and 7 cases underwent graft application. Three cases who underwent patch plasty were operated with a partial clamp, and other cases were operated through cardiopulmonary bypass. The average survival time is 16 months (Figure 9).

Figure 9. Intraoperative image of the patient on whom thoracic aorta partial resection, graft interposition and lower left lobectomy were applied following partial cardiopulmonary bypass on the heart functioning through venous cannulation to the left atrium and artery cannulation to the femoral artery in the case with lower left lobe tumor invasive to the aorta



Diaphragm invasion

Although the diaphragm is an easily resectable organ, the reason why it is classified as a T4 tumor is that it has a lymphatic network and drains directly to the mediastinum and the ductus thoracicus.

Complete resections including the lung and diaphragm are applied. Generally, it can be primarily closed. A reconstruction is applied with PTFE graft, if necessary.

CONCLUSION

It is debatable as to whether induction therapy is a requirement for T4 patients. The fact that published works and studies have been designed to support chemoradiotherapy, and the errors made when choosing patients, provide results favoring induction treatment. According to the results from the most extensive meta-analyses conducted on these publications, it was found that 151 publications were made between 1950-2010, and that all these publications are retrospective cohort studies, with no randomized phase III study and with 2-3 (medium) levels of evidence. Only 15 studies were found to be sufficient in terms of their levels of evidence. These studies recommended surgery as a first line treatment. Similarly, in a study conducted at MD Anderson Cancer Center, 143 cases were examined, and it was found that pre-operative and post-operative radiotherapy influences the survival rate at the same degree if the tumor can be resected at the beginning (14).

When reviewing the valuable studies regarding T4 NSCLC surgery, an average 5-year survival rate between 19.1-57% (6 studies) was determined in T4N0-N2 tumors. Pulmonary artery invasion has the best 5-year survival rate with 52.8%. It was also found that left atrium N0, N1 and N2 had 5-year survival rates of 28.94%, 27.92% and 17.95%, respectively. Meanwhile, the 3-year survival rate was detected to be 100%, 37.1% and 0% for aorta N0, N1 and N2, respectively, 11-29.4% for SVC (4 studies), 28-42.5% for carina (two studies), 16% for vertebral body, and 12% esophagus (13).

T4 tumor surgery should be applied in experienced centers and by multidisciplinary surgery teams. Treatment decisions should be individualized, and complete surgery should be considered for NO-1 cases whose activity rate could be high. For multidisciplinary surgery therapy of T4 NSCLC cases to be conducted with optimal accuracy, prospective randomized studies are needed. However, it is hard to reach a sufficient number of cases eligible for the surgery to be randomized.

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Surgical Treatment in Oligometastatic Lung Cancer

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ABSTRACT
Lung cancer is the primary cause of cancer-related deaths across the world. About four fifths of lung cancer patients are diagnosed with non-small cell lung cancer (NSCLC), and diagnosis can be established only at the advanced stage of disease in 70% of these patients. Among NSCLC patients, who have a maximum of five metastatic lesions which are suitable for radical therapy with local treatment (surgical resection, radiotherapy or both) to achieve long-term survival are considered to be at the oligometastatic disease stage. In this study, we examined the surgical treatment practices and their results in oligometastatic NSCLC patients. Medical literature in the thoracic surgery and oncology network was reviewed, and studies, cases, and meta-analysis studies that included surgical treatment practices in oligometastatic small cell lung cancer treatment and their results were examined. A discussion was made by also analyzing the survival data in light of the literature studies and available guidelines. The most common treatment option in oligometastatic NSCLC patients is surgical metastasectomy. The use of this method especially in patients with metastasis isolated in the contralateral lung, brain and adrenal glands has been widely accepted. For patients that are classified as M1b stage in the international guidelines, aggressive local treatment is recommended on metastatic and primary areas. If patients with multiple metastatic regions have between two to five independent metastases, then systemic chemotherapy must be applied. Long-term disease control and even improvement is possible in these patients with ablative treatment of the primary tumor and metastases.
Keywords: Lung cancer, oligometastasis, surgery

INTRODUCTION

Lung cancer is the primary cause of cancer-related deaths across the world. According to EUCAN (European Countries), 409,911 new lung cancer cases were diagnosed in Europe in 2012, with almost 80% being non-small cell lung cancer (NSCLC) cases (1). In about 70% of the patients with NSCLC, the disease is at the advanced stage when diagnosed, and these patients are not considered eligible for curative treatment. Traditionally, all metastatic NSCLC patients have been grouped under a single category (Stage IV) using TNM classification under the M identifier.

Electronic and printed literature was used when planning this review. In Internet searches performed by using the key words "non-small cell lung cancer", "oligometastasis" and "surgical treatment", studies were found on various databases. Among these studies, the research studies, collected works and meta-analyses including patients at a stage where surgical treatment can be applied were selected.

CLINICAL AND RESEARCH CONSEQUENCES

Non-small cell lung cancer and the Oligometastatic Disease Stage
In the eighth version of the lung cancer TNM classification, the M category of the International Association for the Study of Lung Cancer (IASLC)'s staging was revised. It was recommended to continue to group the patients with pleural/pericardial effusion, contralateral/bilateral lung nodules, contralateral/bilateral pleural nodules, or the combination of these parameters under the M1a category. However, single metastatic lesion in a single distant organ was advised to be assigned to the M1b category. It was stated that patients who had multiple lesions in an organ or multiple lesions in multiple organs must be re-classified as M1c category. Thus, the first step was taken towards the having a definition for a reasonable oligometastatic disease stage in NSCLC in the future (2).

The concept of oligometastatic condition was first used by Hellman and Weichselbaum (3) in 1995, and refers to the group consisting of patients with a limited number of metastases in number and location. This stage is an intermediate condition between local limited and disseminated metastatic cancers.

The number of metastases for it to be considered as an oligometastatic condition varies. Such variance might be from a single metastatic lesion in a single organ to multiple metastatic lesions in multiple organs (4). However, the most commonly accepted criterion for it to be considered oligometastatic is the presence of a maximum of five metastatic lesions, which are suitable for radical therapy with local treatment (surgical resection, radiotherapy or both) to achieve long-term survival.

The most important prognostic factor for oligometastatic disease is the condition of the primary tumor. Patients with uncontrollable primary tumor seem to have a worse prognosis compared to patients with primary tumors that are under control.

Oligometastases are seen relatively commonly. Single metastasis was reported in 7% of the metastatic lung cancer cases. In a study, Parikh et al. (4), performed an analysis on 725 patients with Stage IV NSCLC, and 186 (26%) patients were found to be at the oligometastatic disease stage (≤5 lesions) during the diagnosis. The disease was limited to a single lung in 81% of cases, and a single metastatic lesion was found in 51% of the patients. Compared with patients who had multiple lesions, patients with

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oligometastatic disease were found to have a longer median overall survival (OS) (17 months vs. 14 months).

The International Association for the Study of Lung Cancer (IASLC) found that 225 (22%) of 1025 metastatic patients with NSCLC had a single metastatic lesion. It also stated that there were prognostic differences between patients with multiple metastatic lesions in a single organ and those with multiple lesions in multiple organs (2). The most common location of the single lesion in NSCLC is the bone tissue, followed by the brain, adrenal glands and liver.

The most common option selected as treatment in oligometastatic condition is surgical metastasectomy (55%) (5). However, use of less invasive, ablative techniques such as stereotactic radiosurgery (SRC) has increased remarkably during recent years.

If there is metastasis isolated in contralateral lung, brain and adrenal glands in NSCLC patients, metastasectomy is performed. Sometimes, patients with metastasis isolated in other sites, such as bone, liver, etc. have also been treated with surgery, however the number reported in the literature is quite low (6). In a retrospective analysis of 99 NSCLC patients with synchronized single metastasis treated with curative surgery (primary tumor surgery and metastasectomy), 5-year OS was found to be 38% (7). Good prognostic factors for OS are a lack of mediastinal node involvement (the median OS in patients with and without involvement was 40 and 10 months, respectively, p = 0.015), limitation of metastases only to lungs, and the absence of non-lung pulmonary metastases (5-year OS 48.5% vs. 23.6%, respectively) (7).

In a study by Ashworth et al. (8) performed in 2014, the metastasis rates in NSCLC patients were found to be as specified in the below Table 1.

Oligometastatic Lesions in the Brain and Surgery

Lung cancer is the main cause of brain metastasis in cancer patients, and constitutes the primary focus in 63% of all patients with brain metastasis (9, 10). Such metastases are seen in 30-50% of NSCLC patients and they are the phenomena that can emerge in the early period during the natural course (11). In the past, brain metastases were associated with weak prognosis. Among these patients, the treatment of both the primary tumor and brain metastases for aggressive purposes is recommended in patients with a good Karnofsky Performance Scale (KPS) score who can undergo resection or receive radiotherapy in both areas.

Table 1. Metastasis rates on organs in NSCLC patients Ashworth et al. (8)

Oligometastasis Site	N (%)
Brain	269 (36)
Lung	254 (34)
Adrenal Gland	98 (13)
Bone	64 (9)
Liver	18 (2)
Lymph Node	18 (2)
Other	59 (8)

In NSCLC patients with synchronous brain metastases who received radical therapy for metastases and primary tumors, the median OS was 5.2-64.9 months and 1-year OS was 22-95% (6). When radical therapy was not performed on the primary tumor, survival was observed to decrease. Arrieta et al. (11) examined the results of the treatment of primary tumor in the breast and metastasis in the brain with concurrent radiotherapy in 30 NSCLC patients who had brain metastasis during diagnosis and had no metastasis findings in other areas. All patients were in the RPA class II, and there was N2-3 node involvement in 47% of them. Median survival without progression and OS were 8.4 and 31.8 months, respectively. The 1 and 2-year OS rates were 71.1% and 60.2%, respectively. Three-year OS was found to be significantly superior in patients with N0-N1 stage of the disease, compared to those with N2-N3 stage of the disease (60% vs. 24%, respectively; p=0.038)

Sakamoto et al. (12) reported that metachronous brain metastasis developed in 3.2% of NSCLC patients after surgery for primary tumor. Post-relapse survival results were not very good.

In a recent study, median survival time after lung resection was found to be 25 months for these patients and the OS rate was 79.1%, 38.6% and 22% in 1 year, 3 years and 5 years, respectively. Survival duration was found to be only 11 months after the treatment of brain metastasis (13).

Oligometastatic Lesions in the Adrenal Glands and Surgery

The adrenal gland is one of the areas where metastasis is common in NSCLC. Even though adrenal gland metastases are generally seen in patients with metastasis in other distant regions, metastatic NSCLC has been reported to be solitary adrenal gland metastasis in 4-20% of cases. The effectiveness of computerized tomography (CT) in imaging the adrenal involvement is limited, because adrenal growth is a benign lesion in significant portion of cases. Magnetic resonance (MR) and positron emission tomography (PET) can be helpful in distinguishing incidental the benign adenoma from the adrenal metastases. However, as the treatment and prognosis of the patient depend on the benign or malignant nature of the lesion, histologic confirmation is recommended.

Traditionally, adrenalectomy (firstly open surgery, and laparoscopic in the later period) has been the type of therapy used in treatment of adrenal metastases; however, the use of stereotactic body radiotherapy (SBRT) for treatment purposes has increased remarkably during recent years.

Recently, in a study by Barone et al. (14) performed on 2298 patients with NSCLC, adrenal metastasis was reported in 1.6% "37" of the patients. 13.5% "5" of these patients were reported to have bilateral adrenal metastasis. When 37 patients with adrenal metastasis were examined in terms of OS, and cases with bilateral metastasis (11 months), ipsilateral (27 months) and contralateral metastasis (29 months) were compared, OS was shown to be significantly worse in patients with bilateral metastasis. In this study, adrenalectomy was performed on 18 of 37 patients with adrenal metastasis. The median overall life expectancy of these patients who underwent adrenalectomy was 31 months (3-year OS 48% and 5-year OS 29.3%) while the median OS was found to be 13 months in medical treatment areas only.

Oligometastatic Lesions in the Liver and Surgery

Aggressive treatment for the liver metastasis of colorectal cancer is a recognized method, and has been shown to increase OS (a 5-year OS rate of 30-60%) (15, 16). However, NSCLC-related liver metastases are more rare cases compared to other regions, and cases in which the single metastasis area is the liver are particularly rare. When metastases on the liver were compared to metastases of other areas such as the brain or bone, they were shown to be associated with worse survival (17, 18).

In most of the NSCLC patients with liver metastasis, surgery is contraindicated due to the number and distribution of extrahepatic diseases. Information about the effectiveness of liver resections for metastases in NSCLC is limited, with a low number of cases published, and therefore an apparent bias is likely to occur (6). However, long-term survival was found to be unexpectedly high in patients who underwent liver resection in these studies (>60 months in some cases) (19-22). An OS rate that was higher than expected in these patients probably arose from the failure to make the patient selection with care, and therefore it did not reflect the overall NSCLC population with liver metastasis.

Oligometastatic Lesions in the Lungs and Surgery

The median survival duration for patients with intrapulmonary metastatic disease (56 months, 95% CI, 37.2-74.8; p=0.001) was found to be better compared to the median survival duration expected for patients with extrapulmonary metastasis (18 months; 95 CI, 8.5-27.5) (7). Metastases are more often seen in the lungs on the same side (23). When synchronous single contralateral lesion is diagnosed, bilateral staged lobectomy is performed in most patients, and long-term survival is achieved (5-year survival duration: 45%). This therapeutic strategy is suggested as the likelihood of the presence of two independent primary tumors is high (23, 24).

In a study performed by Okubo et al. (25) in Japan in 2009 on 76 patients with NSCLC diagnosis and pulmonary metastasis that was resected, 5-year survival was 79.6% and 41.6% for patients with synchronous metastasis on the same or different lobe, respectively. In patients with relapsing pulmonary metastases, 5-year survival was found to be 34.8%. The presence of multiple pulmonary metastasis and mediastinal node metastasis in patients were reported to be other important factors affecting survival. No significant difference was observed between ipsilateral and contralateral metastases in terms of OS.

Similarly, in a study where surgical resection was performed for multiple lung cancer with synchronous ipsilateral (n=27) or contralateral (n=28) metastasis, no significant difference was found between the two groups in terms of 5-year survival (27% vs. 43%). Mediastinal node involvement was reported to be a negative prognostic factor for survival. Five-year survival was found to be 57% and 0% for patients without lymph node metastasis (n=25) and with lymph node metastasis (n=18), respectively (26).

In another retrospective analysis, including 66 patients for whom full resection was performed on synchronous pulmonary malignant lesions, median OS was 25.4 months and five-year survival rate was 38% (27).

Based on these findings, as survival was shown to be lower in patients that were thought to have Stage IV disease and treated with palliative systemic treatment, consideration of surgical resection was recommended even in patients with contralateral lung oligometastasis who did not have lymph node involvement or distant metastasis findings, as suggested by a pre-operative comprehensive study (28). Similarly, 2-year OS was 33-84%, and local control was 51-96% in patients with lung metastasis that were treated with SBRT (6).

Oligometastatic Lesions in the Parietal Pleura and Surgery

Pleural involvement is seen at a rate of 8-15% in lung cancer (29). If there is pleural effusion in patients with suspected lung cancer, firstly thoracentesis and malignant effusion must be distinguished. Such distinction is important in terms of staging of the disease, and might change the treatment pursued in some patients (30).

There are varying views in the literature about the role of surgery in these patients, especially the effects of extrapleural pneumonectomy (EPP), on the local disease control and survival of patients. Some studies on EPP for NSCLC patients have claimed that surgery is not beneficial for survival in patients who have malignant pleural effusion and/or pleural nodules (31, 32).

However, in the study performed by Isik et al. (33) between January 2009 and December 2011 on 19 patients with metastatic malignant pleural effusion (MPE), patients were treated with localized hyperthermic perfusion chemotherapy (HIPEC) after surgical interventions, such as pleurectomy/decortication and/or lung resection (Group 1). The control group of this study consisted of patients who underwent talc pleurodesis (Group 2), video-assisted thoracoscopic surgery (VATS) in the treatment of metastatic MPE, and pleurectomy/decortication (Group 3) between June 2007 and June 2008. Patients in the control group received systemic chemotherapy for the treatment of metastatic MPEs following these treatments. The median survival lengths in Group 1, 2 and 3 were 15.4, 6, and 8 months, respectively. One-year survival was found to be at a rate of 54.7%, 0.6% and 0.8% in group 1, 2 and 3, respectively. Operative mortality was not observed in this study. As a result, it was reported that HIPEC treatment combined with cytoreductive surgery appeared to be a promising treatment option for patients with metastatic MPE.

CONCLUSION

Patients with oligometastatic status having a limited number of lesions (generally between 1-5) have a better prognosis compared to those with polimetastatic disease, despite the heterogeneity in its definition, and the retrospective methodology used in many studies. Long-term disease control and even improvement can be achieved in these patients with ablative treatment of the primary tumor and metastases. In many lung cancer guidelines, there are treatment recommendations for this patient sub-group. The guidelines of the European Society for Medical Oncology recommend systemic therapy and radical local therapy (high dose radiotherapy or surgery) for Stage IV patients with one to three metastases in the diagnosis. Additionally, the NCCN Guidelines 3.2017 suggest that aggressive local therapies on metastatic and primary areas for patients classified as M1b Stage (a single metastatic area only) under the 8th version of the lung cancer staging system recommended by IASLC. If patients with multiple metastatic regions have between 2-5 independent metastases, then systemic therapy must be applied.

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Synchronous, Metachronous or Metastases?

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ABSTRACT
Multiple primer lung cancer (MPAK) satellite tumors (accessory tumor of the same type with the same tumor in the same lobe) synchronous tumors (at the time of diagnosis, or at the same site within 3 months or with other tumors in the opposite lung) and metachronous tumors (a newly developed tumor in a patient with a definitively treated tumor). Satellite tumors are synchronous tumors also. It may be difficult to understand whether MPAC is primer tumors originating from different areas of the lung, or whether they are metastases from each other. If the histopathological types of the tumors are different from each other, it can be said that they are generally MPAK. However, if histopathological types are the same, histopathological, molecular, genetic and clinical data are needed. It is useful to demonstrate histopathologically that the detailed analysis of tumors (subtype, dominant type, especially in adenocarcinomas) and carcioma insitu background. Genetic and molecular tests are still a matter of debate. It is both very expensive and can be performed in a small number of centers, and not at the expected activity. Because the cancer cells are very complex and constantly undergoing mutation and change. The clinical criteria, especially the Martini-Melamed criteria have been used for a long time. It is still valid. If the histopathological types are different for metachronous tumors, there is no problem, but if they are the same, the second tumor is defined according to the development time. However, it may be more accurate to evaluate these patients independently from time to time. The best survival data is obtained with surgery even if it is second cancer or local recurrence or metachronous cancer Therefore, if patients with synchronous or metachronous cancer are considered to have no distant metastasis or mediastinal involvement, surgical treatment should be the priority.
Keywords: Multiple primary lung cancer, non-small cell lung cancer, metachronous lung cancers, satellits tumors

INTRODUCTION

Multiple primary lung cancer (MPLC) is a tumor that develops in the lungs and originates from the bronchial epithelium. It can be classified into three main types:

- Satellite tumors
- Synchronous lung cancer
- Metachronous lung cancer

Multiple primary lung cancer (MPLC) is being seen frequency increasingly in parallel with the developments in diagnosis-treatment methods.

Satellite Tumors

This refers to the presence of one or more tumor nodules with the same histopathological type within the same lobe. Although there are descriptions based on clinicopathological data to distinguish between satellite tumors and especially synchronous lung cancer (SLC), there is still no clear definition. The American College of Chest Physicians (ACCP) considers tumors that have the same histopathological type found in the same lobe as satellite tumors regardless of their T and N status and the segment in which they are located, without taking into account whether these tumors were detected by surgeons, radiologists or pathologists (1). This type of tumor was first described by Deslauriers in 1989 and defined as a criterion of poor prognosis (2). The prevalence of satellite lesions has been reported to be 5.9-16%, and they are expected to become more familiar due to the developments in imaging modalities (3-5).

Due to the uncertainties concerning the definition of satellite tumors in most of the studies in the literature, some cases have been assessed as SLC and some as metastasis and it is seen that the patients in these studies were not homogeneous (3, 6, 7). Despite this, almost all studies conducted after Deslauriers et al. (2) work showed that ST has a satisfactory survival time and its position in the staging system was thus changed from M1 to T3 in time (2, 8).

In practice, it is not necessary to diagnose additional nodules if the diagnosis of the main tumor is known. If the tumors have the same histopathology, then the diagnosis is satellite tumor with a good prognosis. If the tumors have different histopathological types, the diagnosis is synchronous tumor and resection is recommended as these tumors also have good survival times (1, 4, 9).

Many surgeons use the Martini and Melamed (10) and Antaklı et al. (11) criteria for diagnosis. However, these criteria exhibit uncertainties regarding satellite tumors. According to these criteria tumors with the same cell type located in different segments are considered as SLC (if other criteria match). On the other hand, Detterbeck et al. (9) stated that the possibility of such tumors being SLC is low and the possibility of them being satellite tumors is very high as their survival time is generally good (Table 1). At

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Table 1 Martini and Melamed (10) and Antakli et al. (11) criteria were explained.

Regarding the oncologic treatment in the postoperative period, NCCN guidelines recommend cisplatin-based chemotherapy after surgery for N0 or N1 patients with satellite tumors (12). According to our study conducted in 2010 involving patients with satellite tumors, 5-year survival rate was found to be 52%, the main tumor and satellite tumor characteristics and the distance between tumors did not affect survival, while postoperative adjuvant treatment affected survival positively (p=0.0043) (13).

Today, there are still unanswered questions regarding satellite tumors; is a satellite nodule intraparenchymal metastasis? Is the distance between two tumors important? Does it matter if tumors are in the same segment/different segments? How should patients that have a satellite tumor with N1 and/or N2 involvement evaluated?

Synchronous Lung Cancer

Synchronous lung cancer (SLC) is the presence of second primary lung cancer in a lung cancer case at the time of diagnosis (1, 9). In 1924, two different cancer foci were incidentally detected in a tuberculosis case by Beyreuther et al. (14). The prevalence of SLC was reported as 2-14.5%. However, the population of SLC patients is gradually expanding due to the developments in diagnosis methods (15-17).

Although the definition states "second tumor at the time of diagnosis", there are publications that report second tumors diagnosed within 2 months, 6 months and even 2 years after the diagnosis of the first tumor that can be accepted as synchronous lung cancer (18-22).

Table 1. Martini and Melamed (10) and Antakli et al. (11) criteria

Martini and Melamed Criteria
I. Tumors' being distant from each other and separated
II. Histological types
a. Different histology
b. Same histology Located in different segments, lobes or lungs and;
i. Originates from carcinoma in situ
ii. No carcinoma is detected in common lymphatic drainage pathways
iii. There is no extrapulmonary metastasis at the time of detection
Antakli Criteria
I. Different histology
II. Same histology
a. Located in different anatomical areas
b. Associated with premalignant lesion
c. There is no systemic metastasis
d. There is no mediastinal lymph node involvement
e. Possesses different DNA ploidy
At least 2 of these 5 criteria should be satisfied

The literature regarding the approach to synchronous lung cancer patients is not sufficiently extensive and there are variable results in terms of survival (1). The possible causes of this variability could be the challenges in diagnosing SLC, the inclusion of bronchoalveolar carcinoma cases, N2 tumor cases, carcinoid tumor cases and satellite nodule cases in some studies, the shortcomings in evaluation due to the limited number of cases, or the fact that the second cancer is actually metastasis in some patients (23-26).

Synchronous lung cancer can be seen in the same lung (same lobe; satellite tumor?) in a different lobe or in the other lung. It is easy to make a diagnosis when they are different histopathological types. On the other hand, it is nearly impossible to make a definitive diagnosis when they are the same histopathological types.

Tumors with the same histopathology are more likely to be considered as metastasis. However, the development of tumors with the same histopathological type is possible in an individual who has the same genetic structure and is exposed to the same etiologic factors. Until recently, it was thought that immunity and genetic studies could be guiding in the differentiation of tumors with the same histopathological type. However, recent studies have shown otherwise. Various methods can be used in order to determine the genetic characteristics of tumors. However, none of these methods have worked completely as of yet. Tumors are much more complicated structures than predicted. Tumor mutations are very commonly and frequently seen. In other words, the first tumor cell is not the same as the 100,000th or the 1,000,000th tumor cell. Therefore, there may even be differences between the main tumor and its metastasis in terms of histopathological type. Cancer cells continuously undergo mutations and modifications. This is more frequently seen in patients who receive chemotherapy. Hence, it is not possible to make a definitive diagnosis with genetic or molecular studies. In addition, these studies are quite expensive and are conducted in few centers (27).

Detailed histopathological evaluation of the tumor is easier than mutation and molecular analyses and it can be guiding (28). Showing that tumors originate from carcinoma in situ, conducting immunohistochemistry workup, and determining the subtype and predominant pattern in adenocarcinomas in particular may be helpful for differential diagnosis.

The study conducted by Girard et al. (29) also supports this notion. The survival results, molecular studies, and detailed histopathological evaluations of patients who were differentiated in terms of synchronous/metastasis using clinical criteria [Martini and Melamed (10)] were shown to have no significant differences.

Each case of suspected synchronous lung cancer should be evaluated by a multidisciplinary team and a decision should be made using clinical data. The most commonly used criteria today are Martini and Melamed (10) criteria. Although it has been

more than 30 years since these criteria were first defined, they are still valid. In 1991, Ichinose showed the difference of tumors with the same cell type in DNA ploidy studies conducted using flow cytometry (28). Antakli et al. (11) modified the Martini and Melamed (10) criteria in 1995. These criteria are based on showing that distant metastasis and involvement of common lymphatic pathways are not present. Although not very widely known, Warren and Gates successfully defined synchronous tumors a long time ago in 1932 (30).

In the 8th edition of the staging system, SLC has not been studied under a separate title and there have been no amendments. However, it has been reported that the predominant pattern and subtype can be guiding in tumors that are classified as adenocarcinomas in terms of histopathological type (31). In the 8th edition of the staging system (as in the 6th and 7th editions), an evaluation has been made by considering one tumor as the metastasis of another (8, 32). Tumors in the same lung but in different lobes have been accepted as T4. However, this evaluation was made considering 180 cases, some of whom were bronchoalveolar cancer patients. Nodules in the other lung were classed as M1a. The evaluation was made considering 369 bilateral SLC cases and only 7 patients among those received surgical treatment on both sides [8]. Therefore, the place of SLC cases in the staging system is debatable.

There are significantly different results regarding survival in synchronous tumors[11,15]. The possible cause of this variability is the heterogenicity of patient populations and treatment methods. However, almost all of the studies conducted in recent years have satisfactory survival results and the patients concerned benefit from surgical treatment (33, 34). At the Table 2. A comparison of publications in the literature on MPLC.

The second lesion is incidentally detected during surgery in nearly one-third of synchronous lung tumors. Resection can be performed in patients that do not have mediastinal and distant metastases postoperatively using aggressive methods if both tumors are resectable, and also if the patient is already faced with thoracotomy morbidity. The absence of mediastinal involvement and distant metastasis should be proven before surgical treatment. Patient's respiratory reserve determines the extent of the surgical procedure (1). Patients should undergo PET-CT and cranial MRI and mediastinoscopy should be performed before surgery. It has been reported that patients with mediastinal lymph node involvement should be treated using nonsurgical methods (1). However, Detterbeck et al. (8) estimated that one-third of patients with mediastinal lymph node involvement may have no metastasis (according to tumor stage, time of tumor occurrence, metastasis properties, and survival rates). In other words, a NSCLC with N2 involvement and another concomitant NSCLC can be present. Still, the general opinion is in favor of accepting patients with mediastinal involvement and the same histopathological type as metastasis instead of SLC and not performing resection on these patients (1).

Table 2. Publications in the literature related to Multiple Primary Lung Cancer

Author	Year	n	Survival (5 years)
Roberts et al. (35)	2003	14	64
Mun et al. (25)	2007	18	75.8
Chang et al. (36)	2007	92	35.3
Trousse et al. (22)	2007	125	34
Riquet et al. (37)	2008	118	26
Rostad et al. (26)	2008	94	27.6
Voltolini et al. (38)	2010	43	34
Fabian et al. (39)	2011	67	69
Kocaturk et al. (40)	2011	26	49.7
Shimada et al. (36)	2015	67	53.6

In cases with bilateral synchronous lesions, surgery should be performed on the side that has the more advanced stage (14). In cases with bilateral synchronous lesions with the lesion on one side definitively diagnosed with cancer and one on the other side not diagnosed, priority should be given to the undiagnosed side. If one side requires pneumonectomy, the order of priority may be changed to be able to perform segmentectomy on the side with the smaller tumor, as resection on the other side can only be limited if the side that requires pneumonectomy is operated on first. Similarly, both sides requiring sleeve resection might change the order of priority. Briefly, it would be appropriate to evaluate each patient individually instead of obeying the rules at this point (24).

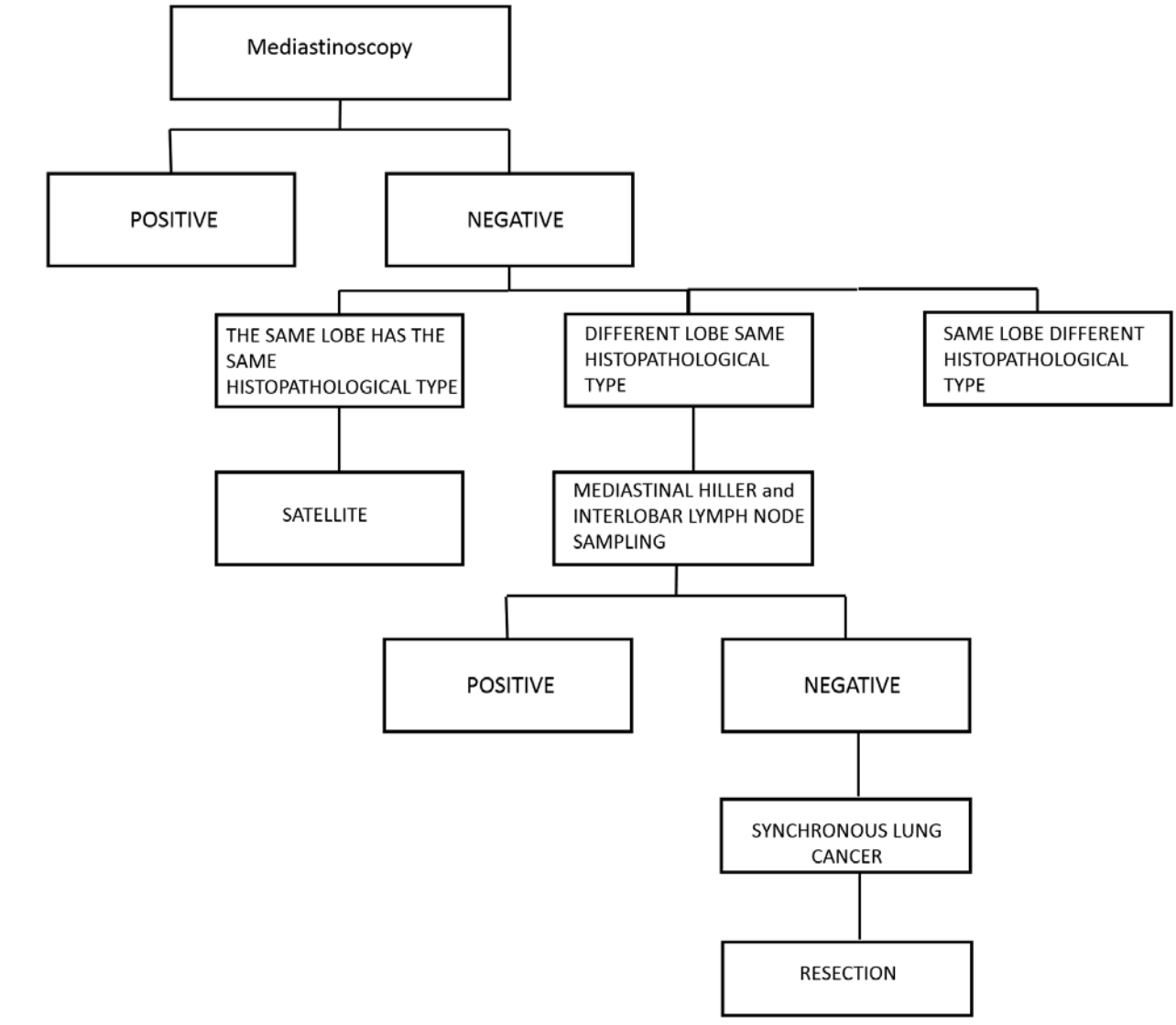
Successive thoracotomy is the generally preferred surgical approach. Recently, VATS has also frequently been used. As palpation is not possible during VATS, cases with suspected additional nodules should be approached carefully. The recommended time period between two surgeries is 4-6 weeks. However, a patient's performance, the morbidities developing after the first surgery, and the surgeon's opinion might change this time period (24, 25, 41).

According to our study conducted in 2010 regarding synchronous lung cancer, the 5-year survival rate was found to be 49.7%; 40.6% in unilateral cases and 62.8% in bilateral cases. It was found that pneumonectomy was a factor of poor prognosis and receiving adjuvant chemotherapy was a factor of good prognosis in terms of survival (40). The recommended treatment approach for cases with suspected unilateral and bilateral synchronous lung cancer is shown in Figure 1, 2 (40).

In the literature, it has been reported that female gender, bilateral localization, no lymph node involvement, complete resection, and postoperative adjuvant therapy were factors of good prognosis, whereas N1-2 involvement, advanced age and performing pneumonectomy were factors of poor prognosis (33, 38, 39, 42, 43). The most important prognostic factor in many studies is the N status (4).

The average morbidity of surgeries has been reported as 10.5-37% (38-40, 45). The average mortality rate is around 5%.

Figure 1. Approach to suspected unilateral SLC cases



In a pooled analysis (467 patients) conducted with a group of authors studying MPLC in 2012, we found the median survival to be 52 months. Male gender, advanced age, unilateral tumor localization and nodal status were found to be factors of poor prognosis (46).

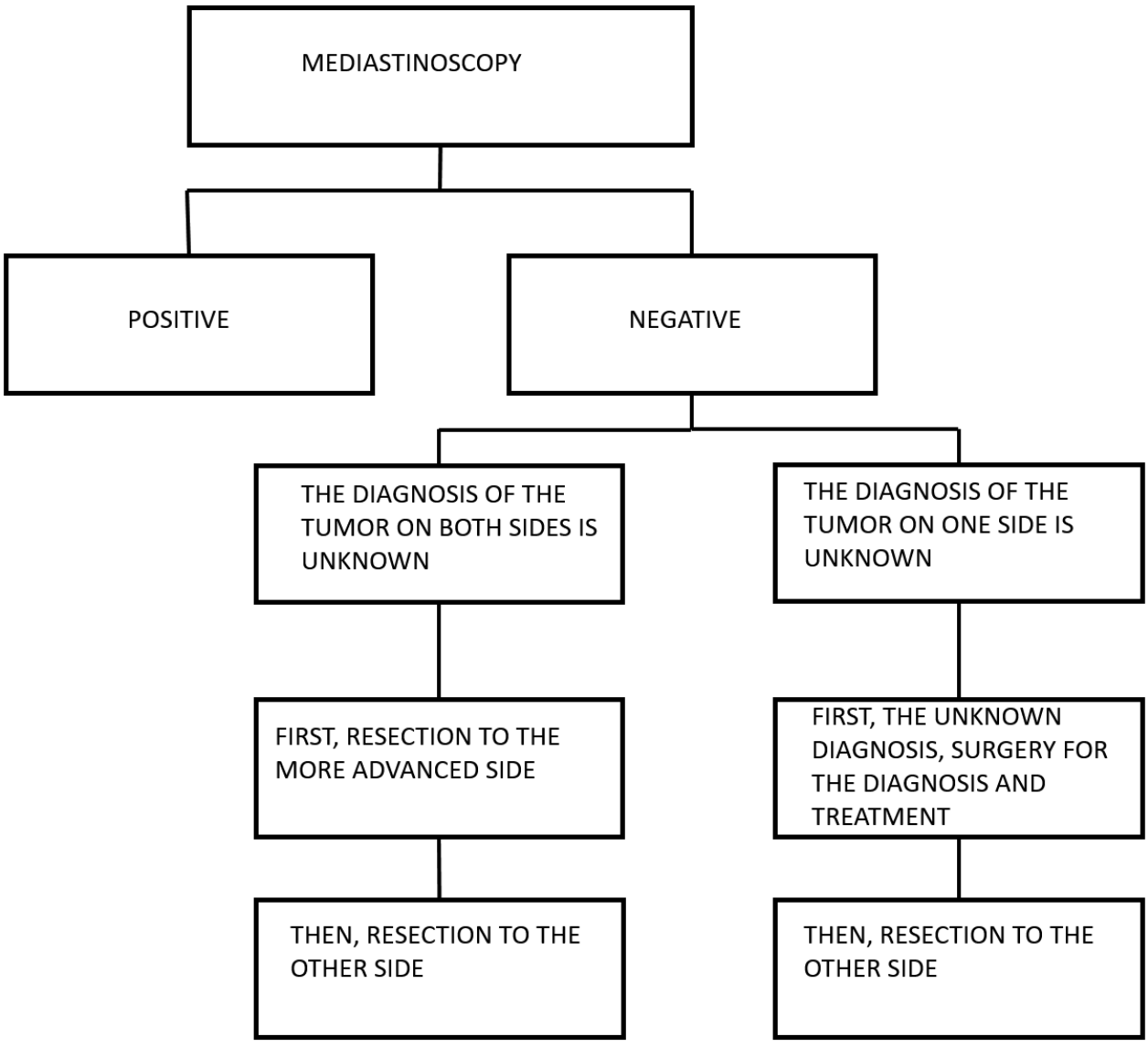
In another study conducted with the same group in 2015, we found that the best survival was observed in the adenocarcinoma patient group without N involvement and we tried to predict survival with a nomogram which we developed (21).

Metachronous Lung Cancer

Detection of a new lung cancer during the period following curative treatment for primary lung cancer implies metachronous lung cancer (MLC) (47). In every patient receiving curative treatment for primary lung cancer, recurrence may be seen as well as metachronous lung cancer. Therefore, patients receiving treatment for lung cancer should be followed up regularly. Metachronous lung cancers constitute 55-65% of multiple primary lung cancers (18). Many of them are detected during routine PA and 75% of these are in Stage 1 (48).

It is easy to make a metachronous cancer diagnosis when the histopathological type of the newly developed cancer is different. However, the newly developed lung cancer is usually on the same side and has the same cell type in nearly two-thirds of cases (generally squamous cell carcinoma). Some clinical parameters can be used in evaluating such patients (10). According to the ACCP guidelines, in a patient with a detected second tumor which is the same histopathological type as the previous one and without systemic metastasis, the second tumor is accepted as MLC if the time period between the occurrence of the two tumors is more than 4 years, and as the metastasis of the first cancer if the same is less than 2 years. The time period between two-four years is called the "gray zone" and it is very hard to make a differential diagnosis precisely (47, 48). According to Martini and Melamed (10), MLC diagnosis can be made if the disease-free pe-

Figure 2. Approach to suspected bilateral SLC cases



riod after the first tumor is more than 2 years, the second tumor originates from carcinoma in situ, the second tumor has developed in a different lobe or in the other lung, there is no carcinoma in the common lymphatic drainage pathways, and there is no extra-thoracic metastasis (10).

As shown above, these criteria are based on showing that distant metastasis and involvement of common lymphatic pathways are not present. In patients with suspected metachronous lung cancer, invasive mediastinal staging and extra-thoracic imaging (whole body PET-CT or abdominal CT and bone scintigraphy, as well as cranial CT/MRI) are recommended (47, 48). Resection is contraindicated in the presence of mediastinal lymph node involvement or metastatic disease (2).

Curative surgical resection is recommended for metachronous lung cancer patients. Surgical treatment of metachronous lung cancer depends on the side of the newly developed tumor, the extent thereof, the surgical procedure performed for the first tumor, and the patient's pulmonary function capacity (5). Resection can be performed in 65% of the cases, wherein one-third of the patients that undergo resection receive sub-lobar resection (49). The 5-year survival rate is 20% in all patients who have metachronous lung cancer, whereas the average 5-year survival rate in patients who undergo resection is 36% (20-50) (2, 5). The indication of adjuvant therapy after surgical resection is the same as with other patients (12). Operative mortality has been reported as 2-7% in metachronous tumors (50). However, in patients with tumor development on the same side and who need complementary pneumonectomy, this rate can be as high as 20%. The risk is higher in patients who have received adjuvant treatment (especially RT) after the first surgery (50).

Although the second tumor with the same histopathological type developing within less than 2 years is accepted as metasta-

sis, the possibility of the newly detected tumor being metachronous lung cancer should be remembered.

Recurrence after the primary lung cancer is most frequently seen within the first 1-2 years. Recurrence can be local, locoregional and in the form of distant metastasis. Recurrence in patients who have received surgical treatment and have negative surgical margins and no mediastinal lymphatic involvement is generally in the form of distant metastasis. In these patients, the possibility of metachronous tumor is higher, although the second tumor in the lungs is the same histopathological type as the first tumor.

In a patient who has previously received treatment for lung cancer, the recurrence of cancer in resection margins (bronchi, vascular structures, chest wall, pericardium, etc.) is called "local recurrence", the recurrence of cancer in the lymph nodes within the same-sided hemithorax is called "regional recurrence", and the recurrence of cancer in other areas of the body is called "systemic recurrence" (21).

In patients with resected Stage-1 NSCLC, the rate of local or regional recurrence is around 7% and the rate of systemic recurrence is around 20% (51, 52). The prevalence of recurrence increases with advanced stage[49]. When all cases who have undergone resection are considered, local, regional or systemic recurrence is seen almost in half of patients (49). Recurrence most commonly occurs in the same hemithorax (50% of cases) and second most commonly in the other hemithorax (49). The risk of recurrence is the highest in the first year after surgery and decreases in the following years (51). The survival rates of patients with recurrence is low (nearly 50% one-year survival and 20% two-year survival). The worsening of survival is more remarkable in patients who develop systemic recurrence (49, 51-53).

The ratio of reoperation in the treatment of patients who develop recurrence is very low (54, 55). Therefore, there is limited information concerning the results of reoperation in patients with local recurrence. It has been reported that the 2-year survival rate after reoperation for local recurrence is approximately 20%, whereas patients who have local recurrence detected in the early stage had nearly 50% five-year survival rate after complementary pneumonectomy (51, 56). Therefore, it is recommended to follow-up all patients who have been operated on for primary lung cancer closely so as to detect a potential local recurrence in the early stage. For the treatment of local recurrence in these patients, surgical resection should be preferred if the tumor is resectable (57).

Surgical treatment of local recurrence was found to be more effective especially in the Stage-1 NSCLC patients who underwent resection in comparison to the patients treated with CT and/or RT 8 (53). As a matter of fact, the contribution of CT to survival could not be demonstrated in patients who developed local recurrence[58]. RT should be preferred in patients who have not undergone surgery in the treatment of local recurrence (12). Although information regarding the treatment of regional recurrence is lacking, it is recommended to administer concomitant chemoradiotherapy instead of surgical treatment (12).

If there is isolated metastasis (brain or adrenal metastasis), satisfactory survival may be achieved by surgical treatment in patients with systemic recurrence (12, 49, 59). RT can be applied in patients who have isolated metastasis (brain or adrenal metastasis) and who cannot be operated on. Systemic CT should be added to the local treatment (surgical or RT) of patients with isolated metastasis. In patients with generalized metastasis or patients who have multiple metastases in one organ, RT and systemic CT should be administered based on local symptoms (12).

The prevailing debate on metachronous lung cancers regards tumors that develop within the first 2 years and between 2-4 years and that have the same histopathological type. We would like to share one of our analyses that is awaiting publication. We conducted a study on patients on which complementary pneumonectomy was performed due to a newly developed tumor on the same side and we found that the survival of patients with the same histopathology was good regardless of the time when the second tumor developed. In this study, we evaluated 32 NSCLC patients who underwent complementary pneumonectomy between January 2000 and December 2015. The five-year survival rate of the patients operated on with the same histopathology was found to be as follows: surgery time <2 years 62.5%, 2-4 years 63%, >4 years 75% (p=0.54).

CONCLUSION

In light of this information, in patients who previously received curative treatment and developed a new lung cancer within 2-4 years, if the new tumor is the same histopathological type as the first one, a decision that it is inoperable should not be made immediately, and the tumors that develop within the first 2 years should be considered after the first operation with the same histopathological type as the metastasis. One may act more boldly and administer surgical treatment especially in the treatment of tumors that develop in the same hemithorax. For lung cancers that develop in the other hemithorax, it may be appropriate to act on a case-by-case basis and choose limited resection.

Briefly, the following question needs an answer: is it necessary to make a definitive diagnosis in suspected synchronous and metachronous tumor cases?

If the patient has sufficient cardiopulmonary capacity, no mediastinal and distant metastasis, no multiple tumor nodules (more than 2), and is suitable for complete resection, the preferred treatment method in these patients should be surgical. If the patient has synchronous tumors or metastasis, then there is no problem. It is possible to evaluate this metastasis as oligometastasis. These patients also benefit more from surgical treatment in comparison to other treatment options.

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Surgical Treatment in Small Cell Lung Cancer: Delayed Evaluation?

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ABSTRACT
Lung cancers are the most common solid organ cancers and are responsible for a major part of cancer deaths. They account for 1/3 or 1/4 of all deaths from cancer. Small cell lung cancers (SCLC) are known for having very poor outcomes in survival analyses, despite multiple treatment applications. Even though the traditional literature claims that treatment of this disease is essentially medical, surgical experiences do not confirm such claim. In this study, we examined whether small cell lung cancer is a non-surgical disease as it is believed to be. The medical literature in the thoracic and cardiovascular surgery and oncology network was reviewed, and studies, cases, and meta-analysis articles that provided small cell lung cancer treatment outcomes were examined. A discussion was made by also analyzing the survival data in the light of the available guidelines. It is seen that treatment of small cell lung cancer is not mainly medical and that the surgical option can be administered similarly to non-small cell lung cancer (NSCLC). Unfortunately, even the targeted treatment options do not provide recovery at a satisfactory level in the current state of cancer treatment. Surgery option keeps it validity as the most important weapon against all stages and cell types in lung cancer.
Keywords: Lung carcinoma, small cell, surgery

INTRODUCTION

Lung cancer is not only the most common organ cancer in men, but also the cancer type that leads to the most deaths (1/3 to 1/4 of all deaths from cancer). According to various study results, its incidence varies between 80-300/100,000. The American Cancer Society reported that 222,500 new lung cancer cases were seen in 2010 in the United States (1). Patients diagnosed with small cell lung cancer (SCLC) account for 10-15% of these new cases. Since 1926, the year when it was named and diagnosed, SCLC has been a type of cancer that is difficult to treat due to its aggressive nature and very high level of relapse (50-80%) (2, 3). However, the place of surgery among treatment options is unfortunately still contradictive. According to the National Comprehensive Cancer Network (NCCN) 2017-2 Guidelines, there are four main hypotheses. These are as follows: Treatment of small cell lung cancer is chemotherapy; tumors that exceed T1-2 do not benefit from surgery; surgical treatment must be lobectomy, then additional therapy must be given; and if nodal metastasis is observed, additional therapy must be performed with chemotherapy (4). Validity of such hypotheses are the subject matter of a study alone. Therefore, in this article, we will discuss the place of the surgical treatment option in small cell lung cancer whose treatment is very difficult and restricted.

Both electronic and printed literature were used while planning this review. In internet searches performed using the key words of "small cell lung cancer", a large amount of studies was found on various pages. For instance, in the scan performed on CTSNet, we found between 1,700-32,000 articles depending on the different journals included in the review. Therefore, as the material of this article, we mainly tried to use the studies that include surgical series and can historically draw a direction for us. Most of these studies were research studies, while some were collected works, and a smaller part consisted of meta-analyses.

History

Small cell lung cancer (SCLC) entered the medical literature in the 1920s (5). The first written statement was made by Bernard in 1926 after attempts to understand it and the emergence of its definitions. This was followed by staging studies made between 1960 and 1980, and a period of recession started in the 1990s, which we attribute to the lack of options in treatment. In the past 25 years, the inclusion of some new medication within treatment, and the increase in the studies on these medications has supported non-preference of surgery as the primary option. However, the hypothesis that treatment of SCLC is mainly medical relies on the decision made by British Medical Council in the 1970s based on three studies (6). All these studies were published on Lancet, and when examined in detail, the methodology of these articles was problematic (7-9). Among these, in the article published by Miller et al. (8), full resection could be performed in only 48% of the patients that were included in the surgical treatment group, while survival analysis was performed on all 71 patients. Besides this, even though the number of patients that underwent exploration alone in the surgical patient group was 24, these patients were also included in the survival anal-

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ysis. Still, 24-month survival, 48-month survival and 60-month survival rates were found to be 4% and 10%, 3% and 7%, and 1% and 4%, respectively, in 71 surgical patients and 73 radiotherapy cases: As we can see, the radiotherapy group had no superiority compared to the surgery group.

In studies where the contribution of surgical treatment to survival was evaluated, we see that the 5-year survival data is not as bad as claimed. Even though they include a low number of patients, we see that in Stage 1-3A patients, the 5-year survival rate was between 15% and 60% (10-15).

Treatment Options

The most important reason behind the fact that small cell lung cancer is philosophically examined independently from other lung cancers is that there is no consistency between the tumor size and the spread rate of metastasis. In other words, even very small sized tumors can lead to lymphatic gland and distant organ metastasis. This is probably the reason why the majority of patients already have metastasis when they are diagnosed (16). However, today, the reversibility of this situation is increased due to the high accessibility to healthcare services, physicians' sensitivity towards cancer, and the possibility of performing advanced level radiologic examinations at a lower cost and more easily. In Quoix et al. (17) study published in 1990, they found a pulmonary nodule in 25 of 408 SCLC patients during a 5-year period. Additionally, a total of 2301 patients with T1 and T2 N0 small cell lung cancer in the national cancer database between the years of 2003-2011 were reviewed in Yang et al. (18) latest article published in 2017. Surgical treatment and chemotherapy were used together in 681 of these patients who had a solitary pulmonary nodule.

According to the National Comprehensive Cancer Network 2017-2 Guidelines, the publication used most in the surgical treatment section of the SCLC guidelines has been the study performed by Lad et al. (19) in 1994. This study seems to have gained importance due to its prospective randomized design. However, considering the fact that only 11 of the 235 articles found in the guidelines included surgical series, the realistic extent of the obtained analyses is open to questioning. Lad et al. (19) divided their series consisting of 328 patients with SCLC, who received systemic chemotherapy, into surgical and non-surgical groups through randomization. As a result, we can see that 146 of the patients who received chemotherapy were included in the study. The responses of patients to chemotherapy were also stated, among which 90 were identified to have responded fully. The number of patients with no response was 111. The meaning of how the patients responded to chemotherapy is shown in Table 1. Looking at the data presented in the article, the randomization method seems to be insufficient in selecting a treatment that is suitable for the patient and there are suspicions as to whether these are the right methods. This is because it is not known how many of the cases were suitable for surgery before randomization. Besides this, to the extent that is understood from the article, full response rate was 19% in the surgical group, while it was 40% in the non-surgical one. Number of patients that could receive full resection in the surgical group was 54. Therefore, no surgical treatment was performed on 16 cases. However, all these cases were included in the total survival analysis.

In a meta-analysis performed for radiotherapy, a total of 2573 cases were included in 13 randomized studies, and 2013 of these cases that were discovered to have limited disease were able to receive chemotherapy or chemotherapy and concurrent radiotherapy (20). Five-year survival was 4.8% in chemotherapy patients, and 7.2% in the cases that also received radiotherapy. It is seen that contribution of non-surgical treatment modalities to survival is limited. However, 5-year survival rates exceed 60% especially in small tumors in some series with surgery and additional practices (chemotherapy and/or radiotherapy) (21, 22).

In Badzio et al. (23) study performed in 2004, they compared adjuvant chemotherapy and surgery combination with definitive chemotherapy treatment in limited stage patients. The mean survival rate was found to be 22.3 months and 11.2 months, respectively, in operative and non-operative groups. Five-year survival was 27% for the surgical group, and 4% for the non-surgical group. Relapse occurred within an average of 20.9 months in 53% of the surgical patients, whereas this figure decreased to an average of 7 months in 86% of the non-surgical patients. However, such superiorities of surgery could not be observed in patients with N2 disease. Even though the small number of patients was a disadvantage, it is clear that the results of the treatment options were akin to those in the NSCLC group. A similar study was performed by Schreiber (24). The 5-year survival data of the surgical and non-surgical groups was 34.6% and 9.9%, respectively.

Takenaka et al. (25) compared the results of patients who underwent resection (consisting of patients who received and did not receive adjuvant chemotherapy and radiation treatment) and did not undergo resection. In this study, the 5-year survival of these groups was compared for each stage. A statistically significant difference was seen in 5-year survival only in Stage I patients (62% in the operative and 25% in non-operative group), while the difference was not statistically significant in Stage II patients, but an apparent five-year survival advantage seemed in favor of the operative group (33% vs. 24%). For Stage III disease, there was no survival advantage in the surgical resection group, and 5-year survival was found to be 18% in both groups.

Type of Surgical Treatment

The type of resection can play a key role in patient outcomes. In a study by Schreiber et al. (24) where they evaluated the operative and non-operative treatment of patients with limited stage CSLC,

Table 1. Classification of the response given to chemotherapy

Term	Definition
Full Response	Disappearance of all targeted lesions during or after treatment
Partial Response	A minimum of 30% reduction in the largest diameters of the targeted lesions
Stable Disease	Lack of change in the targeted lesions
Progressive Disease	A minimum of 20% increase or enlargement in the targeted lesions or new lesion(s)

Table 2. Summary of the retrospective surgery studies that evaluated 5-year survival by resection type in limited stage small cell lung cancer

			5 year survival rates by resection type	
Study team	**Year**	**Number of patients**	**Sublobar (%)**	**Lobectomy (%)**
Brock et al. (22)	2005	82	20	50
Schreiber et al. (24)	2010	863	—	52.6
Varlotto et al. (30)	2011	584	28.5	47.4
Weksler et al. (27)	2012	895	18.70	30.10
Takei et al. (29)	2014	243	30.6	58.3
Stish et al. (26)	2015	54	15	48
Combs et al. (28)	2015	2476	40	21

Table 3. Role of surgery in small cell lung cancer

Study	**Protocol/Patient (Surgical/total patients)**	**Local Relapse**	**Survival**
Fujimori et al. (21)	CT + Surgery (21/22)	5%	Median survival 61.9 months Stage 1–2: 73% (3 years) 3A: 42.9% (p=0.018)
Eberhardt et al. (36)	CT + Surgery (30/46)	0%	Overall Survival (46 patients): 5 year survival: 39% 10 year survival: 35% Stage 2B–3A (22 patients) 5 year survival: 44% 10 year survival: 41%
Rostad et al. (37)	Surgery + CT (38)		5 year survival for Stage 1: 44.9%
Brock et al. (22)	Surgery + CT (82)		5 year survival for Stage 1: 58% Stage 2, 3 and 4 survival, respectively: 18%; 23%; 0%
Tsuchiya et al. (38)	Surgery + CT (62)	10%	Stage 1–3A 5 year survival, respectively: 73%; 38%; 39%
Bischof (39)	Surgery + CT +/ RT+PCR (39)		Median 47 months 1.3 and 5 year survival, respectively: 97%; 58%; 49%
Lim et al. (40)	Surgery or Surgery + CT		5 year survival: 52%

PCR: Prophylactic cranial radiotherapy, CT: Chemotherapy, RT: Radiotherapy

it was found that the resection type affected the survival rates in the surgical group. The median survival rate was 40 months, 20 months and 23 months for lobectomy, pneumonectomy, and sublobar resection, respectively. However, they emphasized that the median survival rate was 65 months in the patients that had lobectomy for localized disease. Lobectomy achieves a 25-month median survival rate in the regional disease. Five-year survival was observed in 52.6% of those that underwent lobectomy in both groups.

Stish et al. (26) evaluated the type of resection in terms of intrathoracic relapse, and they found that the incidence of intrathoracic relapse was higher in patients that underwent sublobar resection. Therefore, they stated that resection type can affect not only the 5-year survival, but also the relapse risk. Findings of Schreiber and Stish have been supported by many studies as lobectomy has a better survival and carried lower local relapse risk compared to sublobar resection (22, 27-30) (Table 2). Additionally, NCCN has been recommending lobectomy treatment for Stage I SCLC since 2017 (19).

Stage I Small Cell Lung Cancer

Many studies conducted on Stage I SCLC patients have shown that survival was better in patients who received chemotherapy together with surgical resection, compared to those who underwent surgery alone (22, 28, 31). Combs et al. (28) examined 2476 patients who underwent surgery for SCLC, and divided the patients into two groups; surgery, and chemotherapy with surgery,

depending on their treatment type. They found that mortality was lower in patients who were operated on after chemotherapy. In Stage 1 SCLC patients, 5-year survival was found to be higher in the group that received chemotherapy with surgery, compared to those who underwent operation only (51% vs. 38%). The effects of surgery and chemotherapy treatment on the life expectancy of patients found in various studies have been summarized in Table 3.

However, the debate as to whether adjuvant treatment is superior to neoadjuvant chemotherapy is still ongoing (31). Furthermore, no study has shown that the use of post-operative radiation provides an important advantage for Stage I disease (24, 30). The current recommendation of the American Society of Clinic Oncology (ASCO), American College of Clinical Pharmacy (ACCP) and NCCN is the performance of platin based adjuvant chemotherapy on all Stage I SCLC patients who have undergone curative surgery resection (4, 32, 33). The current ASCO, NCCN and ACCP guidelines indicate that surgical resection might be considered in Stage I SCLC patients. Besides this, some new studies give rise to the thought that surgery might also have a role in patients with N1 and N2 involvement. Yang et al. (34) compared patients who had N1 disease and received adjuvant chemotherapy with surgical resection with patients who received concurrent chemoradiotherapy only (34). The use of chemotherapy in addition to the operation was determined to be associated with improvement in the overall survival level and 5-year survival (31.4% vs. 26.3%); however, such difference was not statistically significant.

Granetzny et al. (35). evaluated the N0 patients who underwent surgical resection and N2 patients who underwent surgical resection after neo-adjuvant chemotherapy treatment,-they showed that patients with N2 involvement whose tumor load in the lymph nodes totally regressed histologically (patients downstaging pN0) had a median survival that was comparable to the N0 patient group (N0: 31.3 months vs. N2: 31.7 months). However, it was found that patients with permanent N2 disease had a worse survival rate (12.4 months).

CONCLUSION

Speculations on the treatment of small cell lung cancer must be illuminated. This is because patients must be given the chance to undergo a surgery and benefit from such opportunity. Today, pre-surgery diagnosis and surgical treatment technology has developed, and it would be suitable to plan the treatment for SCLC just as it is planned for NSCLC. Regardless of whether they were retrospective or prospective, the studies performed show that 5-year survival chance can be achieved with a multimodal treatment approach which includes surgery.

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Are Lung Cancer Publications Up-to-Date in terms of Advances in Statistics and Bioinformatics?

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ABSTRACT
This study was performed to evaluate whether literature of lung cancer follow advances in statistics and bioinformatics. Four medical journals with high impact factors were reviewed between January 2013 and December 2017. Among 1649 published manuscript, 514 of them were about lung cancer. Also, Medline was searched with key words combinations of e-learning AND education AND cancer AND patient for last 5 years. New statistical methods weren't applied in the cancer researches performed by clinicians. Furthermore, unlike increasing number of successful studies using internet and computer technologies, number of the study is limited. Working with professional statisticians or collaboration to Biostatisticians will increase the quality of lung cancer papers.
Keywords: Regression analysis, statistical methods, e-learning

INTRODUCTION

Statistics is an essential component of medical research from design to reporting, data collection to analysis and interpretation of data (1). Editors of medical journals want to ensure the quality and accuracy of the statistical methods of the papers. Standards of a manuscript were determined by international committee of medical journal editors and several checklist such as strobe for STROBE checklist for observational cohort, case control and cross sectional studies and CONSORT checklist for randomized controlled trials are available to identify basic requirements of a report (2, 3). All of the checklists have a special section for standards of the statistical methods used in the report. Because of the trend of improving quality of papers, researchers pay more attention to statistical analysis part. Some studies were performed to investigate how accurate statistical analysis are (4-6). But there is no study to show how up-to-date statistical analysis used in medical literature. Parallel to medical research, medical statistics is also improving (7). This study was performed to evaluate whether literature of lung cancer follow advances in statistics and bioinformatics.

CLINICAL AND RESEARCH CONSEQUENCES

First, Medical journals with high impact factors namely; The Lancet Oncology, The Annals of Thoracic Surgery, The Journal of Thoracic and Cardiovascular Surgery and European Journal of Cardio-Thoracic Surgery were reviewed between January 2013 and December 2017. Among 1649 published manuscript, 514 of them were about lung cancer. All of the published lung cancer manuscripts were classified in terms of statistical method used. Second, lung cancer word was searched in one of the most popular biostatistics journal, Statistics in Medicine, to review recent statistical methods were introduced for lung cancer research questions and applied to real lung cancer data. The last Medline was searched with key words combinations of e-learning AND education AND cancer AND patient for last 5 years.

Frequency of the statistical method used in the same year and overall for 5 years were given in Table 1 and Figure 1. Kaplan-Meier method was the most commonly used method to estimate survival analysis with 28.71%. Frequencies of using the method were relatively similar across the years. Chi-square test was the second most frequently used method to show relationship between categorical variables. Student t/ Mann Whitney u test and one way ANOVA/Kruskal Wallis tests relatively lost their popularity in 2017.

Regression methods including hazard, logistic and linear regression were still not frequently used methods. Area under the roc curve and ROC curve were rarely used statistical methods. Furthermore power analysis was only reported by 5% of the published study.

Starting from the design issue, determining the minimum sample size for a study convinces an adequate power to detect statistical significance and consequently, it is a critical step in the design of a lung cancer research (8). Among the published studies, only approximately 5% of the studies reported their power analysis which is very low. Additionally, majority of statistical method applied in the published studies was univariate analysis (87.47%). Considering applied statistical methods, it can be concluded that in lung cancer studies complex rela-

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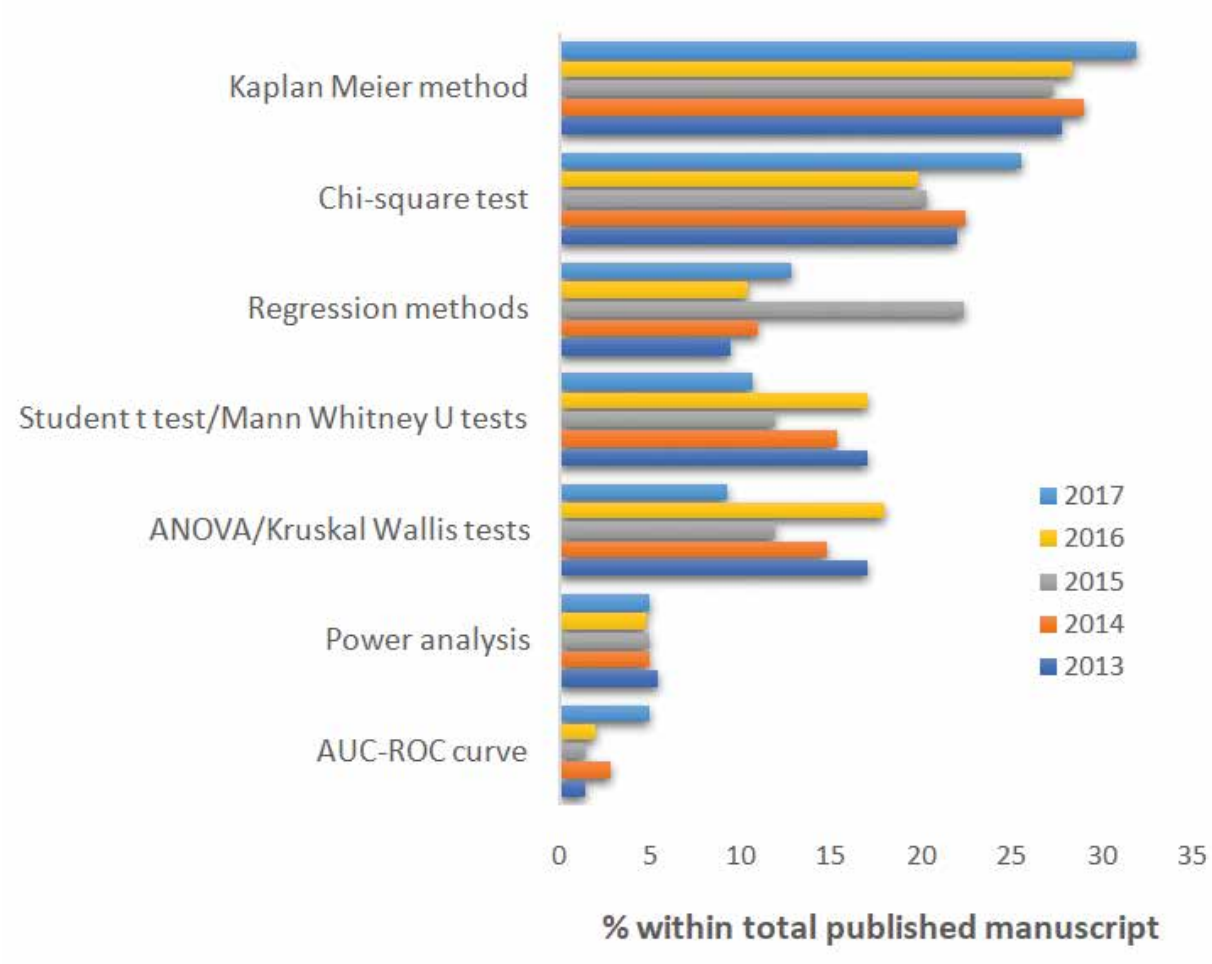
Table 1. Frequency (%) of the statistical method used in the same year and overall for 5 years

	Year of the publication					
Statistical Methods	**2013**	**2014**	**2015**	**2016**	**2017**	**Overall (%)**
Kaplan Meier method	27.80	28.96	27.27	28.30	31.91	28.71
Chi–square test	21.97	22.40	20.28	19.81	25.53	21.84
Student t test/Mann Whitney U tests	17.04	15.30	11.89	16.98	10.64	14.86
One way ANOVA/Kruskal Wallis tests	17.04	14.75	11.89	17.92	9.22	14.75
Regression methods	9.42	10.93	22.38	10.38	12.77	12.53
AUC–ROC curve	1.35	2.73	1.40	1.89	4.96	2.32
Power analysis	5.38	4.92	4.90	4.72	4.96	4.99

Figure 1. Frequency (%) of the statistical method used in the same year



tionships were not investigated enough. Main target of most of the publication was to estimate mean or median overall survival and risk factors affecting survival time. Kaplan Meier method is the most popular method for estimating mean or median time from censored and non-censored data (9). A competing risk is an event whose occurrence stops the occurrence of the primary event of interest (10). But Kaplan Meier method doesn't take into consideration of confounders and competing risks which is a very common situation for cancer studies. Several practical methods for competing risks analysis were mentioned in the study of Bakoyannis and Touloumi (11). It is known that especially in the observational and retrospective studies, confounding factors should be eliminated from studies (12). In other words, results of causal relationships should

be adjusted by possible confounding variables to eliminate the bias (13). Besides, e-learning practices or use of mobile technologies become very popular in medical research to support health professionals and patients (14-17). We believe, another problem about the lung cancer studies is rarely using this recent bioinformatics technologies in lung cancer research. In the following part we will review recent improvements in biostatistics and bioinformatics.

Recent Advances in Biostatistics

There are several statistical research journals publish papers about new statistical methods with real data applications. For this study we reviewed Statistics in medicine, which is one of well-known biostatistics journal, with key word of lung cancer for last 5 years. Several papers introduced novel and advance statistical methods with application of real data. To identify genetic markers associated with the prognosis of lung cancer Wu et al. (18) advised a penalized robust semiparametric approach for gene-environment interactions. Furthermore, Wu et al. (19) also showed effectiveness of penalized robust approach to estimate the association between lung cancer prognosis with gene expression measurements and clinical covariates). Schipper et al. (20) used a dataset of lung cancer patients treated with radiation therapy and applied a special statistical model for toxicity and efficacy with dose and biomarkers as covariates. Receiver operating characteristic (ROC) curve analysis is used to determine the optimal cut off values for a numerical variable and to investigate diagnostic value of a continuous medical test (21). But this method is usually used for classification of two categories. Wang et al. (22) proposed methods for classification of 3 or more categories and in the applications a microarray data set for lung cancer was used. Branscum et al. (23) developed flexible regression model for evaluating the accuracy of a continuous medical test or biomarker with or without a gold standard. Gasparini et al. (24) modelled the relationship between occupational exposure to radon with distributed lag non-linear models and lung cancer mortality by using the data from the Colorado Plateau miner's cohort.

Recent Advances in Bioinformatics

Milne et al. (25) conducted a cross sectional study to determinate level of eHealth Literacy in primary lung cancer survivors. They showed 78% of the survivor had access to eResources via computer, Internet, or smartphone. Because of the increasing number of smartphone users and internet users, E-learning and mobile technologies have become recent issue to inform and support patients, update doctors and health professions knowledge, (15, 16, 26-28). In Medline, several bioinformatic studies with successful results were available. For example; in some studies web based support and decision-making systems were used for clinical decision. Masood et al. (29) proposed a Computer-Assisted Decision Support System in Pulmonary Cancer detection by using the learning based. Murgu et al. (30) designed interactive a program (GAIN 3.0) to enhance interdisciplinary collaboration for effective Non-small Cell Lung Cancer diagnosis, assessment, and treatment. And the program improved participants' knowledge, competence, and likely the clinical care provided to patients. In the study performed by Basch et al. (31) tablet computers in clinic waiting areas were given to patients and reporting of adverse events at 6 time points was asked. DuBenske et al. (32) introduced a Web-based lung cancer information, communication, and coaching system for caregivers (family members of patients). Lower burden and negative mood were observed among caregivers who joined the eHealth intervention.

CONCLUSION

New statistical methods weren't applied in the cancer researches performed by clinicians. Working with professional statisticians or collaboration to Biostatisticians will increase the quality of papers. Furthermore, unlike increasing number of successful studies using internet and computer technologies, number of the study is limited.

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