Real-World Evidence of Diagnostic Testing for Driver Oncogene Mutations in Lung Cancer in Japan

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ABSTRACT

Introduction: Diagnostic testing is important in determining appropriate treatment for individuals with lung cancer. In 2018, testing of five biomarkers (EGFR, ALK, ROS1, BRAF, programmed cell death-ligand 1 [PD-L1]) was approved in Japan. Information is lacking regarding real-world testing patterns.

Methods: This descriptive, retrospective observational study used the Japan Medical Data Vision Co., Ltd. (MDV), database (June 2017–November 2018) and covered data for EGFR, ALK, ROS1, and PD-L1; records on BRAF testing were not yet available. Adults diagnosed with having lung cancer (International Classification of Diseases-10 C34) with record of any biomarker test ordered were included.

Results: Of 8323 patients with any biomarker test, 83.2% were tested for EGFR, 55.3% for ALK, 32.2% ROS1, and 77.2% PD-L1. Combinations of EGFR with other biomarkers accounted for approximately 80% of the testing patterns; 1427 patients (17.1%) had combination testing ordered for EGFR/ALK/ROS1/PD-L1, but some biomarker combinations were tested in less than 1% of the cases. Median time from first testing order to treatment order was 22 (range: 2–525) days overall and increased with number of testing instances: 21 (2–509) days for patients with one, 28 (3–525) days for patients with two, and 30 (9–502) days for patients with three. A 7-day pattern of peaks was observed in the test order date and time to treatment.

Conclusions: This real-world evidence revealed variations in diagnostic testing patterns, which could affect time to treatment in Japan. Variations are likely influenced by individual biomarker prioritization considering limited tissue samples in clinical practice.

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Introduction

In recent years, a number of anticancer therapies targeting various driver oncogene mutations have been approved along with a corresponding companion biomarker diagnostic test.\textsuperscript{1} Companion diagnostic testing is required to determine the most appropriate treatment option for individual patients with lung cancer to help achieve the best possible outcome.\textsuperscript{1-3}

The Japanese Society for Medical Oncology guidelines for routine diagnostic testing recommendations for patients with advanced NSCLC include routine molecular biomarker testing for mutations or alterations in \textit{EGFR, ALK, ROS1, BRAF, and programmed cell death-ligand 1 (PD-L1)}.\textsuperscript{4} International guidelines (including the American Society of Clinical Oncology, College of American Pathologists, International Association for the Study of Lung Cancer, Association for Molecular Pathology Clinical Practice, and European Society for Medical Oncology) also recommend a rapid turnaround time for results, which is critical to achieve the best possible efficacy with targeted treatment.\textsuperscript{1} Simultaneous testing of several biomarkers is therefore encouraged to reduce the time between diagnostic testing and treatment.\textsuperscript{5}

Despite these recommendations, there are differences in the diagnostic and therapeutic approaches used by various medical institutions in Japan owing to limited availability of tissue samples along with individual hospital circumstances that affect the priority order and comprehensiveness of diagnostic testing. Experience with individual biomarkers may also vary owing to the differing length of time each test has been approved and available for use. \textit{EGFR} was the first biomarker to be approved in Japan (in June 2007), followed by \textit{ALK} (in May 2012), PD-L1 (in February 2017), \textit{ROS1} (in June 2017), and \textit{BRAF} (in November 2018). The recent introduction of next-generation sequencing (NGS) (approved in Japan in 2018) now allows simultaneous testing of multiple biomarkers and may improve future testing rates by removing the difficulty of sequentially testing individual biomarkers with small amounts of tissue available.\textsuperscript{6}

Nationwide information regarding the proportion of patients who receive biomarker testing, \textit{ROS1} testing in particular, is limited for Japan. Understanding the real-world diagnostic landscape relating to individual driver genes in current clinical practice may help to identify if there are any particular considerations related to testing individual biomarkers and highlight areas where improvements are needed to ensure the appropriate use of individual therapies. The primary objective of this study was to investigate the real-world patterns of single biomarker testing and subsequent treatment in patients diagnosed with having lung cancer in Japan before the introduction of NGS. Patient demographic and clinical characteristics at baseline (the time of lung cancer diagnosis) were also evaluated.

Materials and Methods

\textbf{Study Design}

In this descriptive, retrospective, observational study, data from the Japan Medical Data Vision Co., Ltd. (MDV), database from June 1, 2017 to November 30, 2018 were collected and evaluated. This time frame includes real-world data for molecular diagnostic testing of \textit{EGFR, ALK, ROS1, and PD-L1}, but not \textit{BRAF} (as it was not yet available), as single companion diagnostics in Japan. This was also before the use of NGS testing in Japan, a confounding factor that we did not include in our analysis.

The MDV database is a real-world database in Japan that has previously been used to assess treatment patterns in patients with NSCLC.\textsuperscript{7-9} The database contains health claims, administrative, and Diagnosis Procedure Combination data from more than 350 acute hospitals and more than 23 million patients in Japan.\textsuperscript{8} Available information includes diagnoses coded according to the International Classification of Diseases 10th revision coding scheme produced by the WHO, disease names coded using Japanese Disease Name Codes, procedures coded using Japanese Procedure Codes, and generic drug names on prescriptions submitted for health insurance claims. The MDV database includes not only hospitalization data but also outpatient and prescription data collected subsequent to a hospital visit, unless the patient had transferred to another hospital.\textsuperscript{8} It should be noted that, although baseline data for patient demographics and clinical characteristics are available, results of biomarker tests are not captured.

\textbf{Study Population}

\textbf{Inclusion Criteria.} Eligible patients were aged greater than or equal to 18 years at the time of lung cancer diagnosis (International Classification of Diseases 10th revision C34) (the diagnosis date was the index date), had visited healthcare facilities represented in the MDV database, and had records of biomarker tests ordered at any time.

\textbf{Exclusion Criteria.} Patients were excluded if they had received antineoplastic therapies previously (the full list is provided in Supplementary Table 1) on or before the first order date of a biomarker test (i.e., between June 1, 2017, and the first biomarker test date) or if they had received molecular-targeted therapies that were not supported by a molecular diagnosis (e.g., prescription of an \textit{EGFR} tyrosine kinase inhibitor without an \textit{EGFR} test).

As this was a retrospective review of an anonymized claims database, informed consent was not required.
Analyses

Patterns of diagnostic testing (e.g., on the basis of one or several biomarkers) were analyzed using descriptive statistics. Three main analyses of the time between biomarker testing and treatment were performed. Time-to-treatment (TTT) analysis 1 was defined as the time from the first test to the initiation of treatment with a molecular-targeted therapy or immune-checkpoint inhibitors (ICIs). TTT analysis 2 was defined as the time from the first test to the initiation of treatment with chemotherapy. TTT analysis 3 was defined as the time from the first test to the initiation of treatment with any antineoplastic therapy. Subanalyses were performed for TTT according to the number of diagnostic biomarker testing instances and testing patterns.

Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Study Population and Patient Characteristics

A total of 13,087,453 patients were identified with available data in the MDV database during the data collection time frame; 560,451 were diagnosed with lung cancer. Of 23,747 patients whose physicians ordered at least one biomarker test, 12,877 (54.2%) received antineoplastic therapy; 8323 patients met the inclusion criteria (Supplementary Table 2). The median age was 71.0 years. Most patients (68.6%) were of male sex. Among 5770 patients with available data, 3821 (66.2%) had a history of smoking (Table 1).

Pattern of Diagnostic Testing

Of patients with at least one biomarker test, 6925 (83.2%) had one ordered for EGFR, 4602 (55.3%) for ALK, 2680 (32.2%) for ROS1, and 6429 (77.2%) for PD-L1 (Table 1). Among all patients, 6806 (81.8%) had only one instance of diagnostic testing (Supplementary Table 3): 1087 (13.1%) for EGFR, 75 (0.9%) for ALK, 33 (0.4%) for ROS1, and 1037 (12.5%) for PD-L1; other patients with one instance of diagnostic testing had simultaneous tests ordered for several different biomarkers.

A total of 221 testing order patterns were observed; EGFR testing was the most frequent biomarker ordered and was often ordered at the same time as the other biomarker tests, being included in approximately 80% of all testing patterns (Table 2). Notably, 1427 patients (17.1%) were ordered combination testing of all four
diagnostic biomarkers (EGFR, ALK, ROS1, and PD-L1) simultaneously.

**Time to Treatment**

Time to treatment was less than 100 days for approximately 95% of patients who were ordered a test. A weekly pattern emerged with respect to the number of patients tested and the TTT, with the number of patients initiating treatment peaking on days 8, 15, 22, 29, and 36 after the test order date (Fig. 1A). The overall median TTT (regardless of subsequent treatment) was 22 days (mean ± SD, 35.69 ± 51.71 d, range: 2–525 d) (Fig. 1A and Supplementary Table 4). Similar weekly peak patterns were observed on the basis of the numbers of patients tested on one or two instances (Fig. 1B and C), but this weekly pattern was not observed for those tested on three instances (Fig. 1D). Subanalyses of TTT by the number of diagnostic testing instances indicated that the duration of TTT from the first diagnosis tended to increase with the number of testing instances (Fig. 1B–D and Supplementary Table 4). A pattern of weekly peaks was also observed in the subanalyses according to the six most frequent testing patterns (Fig. 2A–F). Subanalyses by testing pattern revealed similar median durations (medians: 20–22 d) for all patterns analyzed (Fig. 2A–F and Supplementary Table 5). The treatments that patients were prescribed are found in Supplementary Figure 1.

Analyses of the median TTT according to the number of testing instances suggested that a higher number of testing instances may be associated with a longer TTT, regardless of the prescribed therapy (Fig. 3A and Supplementary Table 5).

TTT was shorter in patients prescribed molecular-targeted therapies or ICIs versus those prescribed chemotherapy regardless of testing pattern, except for PD-L1 alone (Fig. 3B and Supplementary Table 5). In patients prescribed molecular-targeted therapies or ICIs, TTT was shortest for those who received simultaneous testing for EGFR, ALK, and ROS1 (n = 59), with a median of 16 days (mean ± SD, 20.22 ± 12.01 d, range: 6–70 d), followed by testing for EGFR alone (n = 472), with a median of 16.5 days (mean ± SD, 33.57 ± 69.95 d, range: 2–509 d; Fig. 3B). Conversely, these diagnostic testing patterns were associated with the longest TTT for patients prescribed chemotherapy.

**Discussion**

In this study, we used the MDV database to evaluate the real-world companion diagnostic biomarker testing and treatment patterns of patients diagnosed with having advanced lung cancer in Japan. Most patients were of male sex, reflecting national statistics which projected that 67.5% of the patients in Japan diagnosed with lung cancer in 2018 would be male individuals. 

EGFR and PD-L1 were the most often tested biomarkers, with fewer patients tested for ALK or ROS1. Identification of EGFR as the most often tested biomarker and ROS1 as the least often tested biomarker may be partly explained by the timing of the approvals of their diagnostic tests in Japan (EGFR testing was approved in June 2007, ROS1 in June 2017); however, PD-L1 testing was approved only a few months before ROS1 (in February 2017). Physician and patient awareness may also influence testing patterns; the higher prevalence of mutations and alterations in EGFR and PD-L1 compared with the less common alterations in ALK or ROS1 may be associated with greater awareness and testing of EGFR and PD-L1. Data from the observational BRAVE study in Japan also revealed that the testing rate for first-line treatment decisions for NSCLC in 2017 was highest for EGFR (97.5%) and lowest for ROS1 (67.3%), although the testing rates were similar for ALK (88.1%) and PD-L1 (87.1%). Low testing rates for ROS1 may be due to some centers only testing for ROS1 if results for EGFR and ALK are negative, as these biomarkers are mutually exclusive. However, the BRAVE study focused on clinical records from a relatively small number of patients (N = 202) from 11 medical centers in Japan, whereas ours is a larger study using nationwide claims data over a longer time period (June 2017 to November 2018, compared with January 2018 to May 2018 in the BRAVE study), and is therefore more likely to provide a broader view reflecting real-world practice throughout Japan.

Although EGFR was the most often tested biomarker in ours and other studies, testing of several different EGFR mutations as part of overall EGFR testing may have contributed to the higher rates observed. The nationwide diversity of medical institutions in Japan also may

| Table 2. Diagnostic Testing Patterns (Patterns for ≥1% of Patients) |
|---------------------------------------------------------------|
| **Testing Pattern**                                      | **No. (%) of Patients (N = 8323)** |
|---------------------------------------------------------------|
| (EGFR, ALK, PD-L1)                                         | 1466 (17.6)                     |
| (EGFR, ALK, ROS1, PD-L1)                                   | 1427 (17.1)                     |
| EGFR                                                        | 1087 (13.1)                     |
| PD-L1                                                       | 1037 (12.5)                     |
| (EGFR, PD-L1)                                              | 737 (8.9)                       |
| (EGFR, ALK)                                                 | 293 (3.5)                       |
| (EGFR, ROS1, PD-L1)                                        | 222 (2.7)                       |
| EGFR → PD-L1                                               | 171 (2.1)                       |
| (EGFR, ALK, ROS1)                                          | 130 (1.6)                       |
| (EGFR, ROS1)                                                | 105 (1.3)                       |
| (EGFR, PD-L1) → ALK                                        | 93 (1.1)                        |

Note: Biomarkers in parentheses refer to those tested at the same time; → indicates the subsequent test ordered.

PD-L1, programmed cell death-ligand 1.
explain differences between studies; in the BRAVE study, “physician/hospital policies” was a relatively common reason for a lack of ROS1 and ALK testing. The earlier PIvoTAL (Global treatment Patterns, resource utilisation and biomarker Testing of Advanced non-small cell Lung cancer) observational study revealed a lower rate of ALK testing (19%), although this study took place between 2011 and 2013 and ALK inhibitors were first approved in Japan in 2012. Another study (MDV records from 2010 to 2017) also found that only 4.6% of all patients with lung cancer were ordered an ALK biomarker test, although it has been suggested that EGFR and ALK testing may not be well captured by the MDV database (on the basis of MDV records from 2008 to 2015).

Our study found that 17.1% of the tested patients were ordered combination testing of four diagnostic biomarkers (EGFR, ALK, ROS1, and PD-L1); however, some combinations of two biomarkers were tested in less than 1% of the cases. This is concerning given that the Japan Lung Cancer Society recommends
Figure 2. TTT, regardless of subsequent treatment, in patients with one biomarker testing instance of the following six most common testing patterns: (A) EGFR, ALK, and PD-L1; (B) EGFR, ALK, ROS1, and PD-L1; (C) EGFR; (D) PD-L1; (E) EGFR and PD-L1; and (F) EGFR and ALK. Black bars indicate peaks in the number of patients experiencing a particular TTT. Vertical dashed lines represent 7-day interval between peaks found in the overall population (Fig. 1A). PD-L1, programmed cell death-ligand 1; TTT, time to treatment.
The higher frequency of simultaneous testing in the BRAVE study (31.7% for EGFR/ALK/ROS1/PD-L1)\textsuperscript{11} may suggest that simultaneous testing is more common in larger, specialized centers than in the smaller hospitals included from a nationwide perspective. The use of single biomarker versus simultaneous testing may be an important testing barrier in which different individual biomarkers are prioritized in a situation influenced by limited tissue sample availability.

The overall median TTT of 22 days observed in our study may reflect typical procedures in Japan. In the BRAVE study, the median time from confirmed diagnosis to initiation of first-line treatment was 19 days (range: 0–232 d) and the median time from the first biomarker test order to obtaining the last test result was 11 days (2–67 d).\textsuperscript{11} A median time of 23 days from diagnosis to result was reported elsewhere for patients tested for EGFR and ALK between 2013 and 2015 in the United States.\textsuperscript{13} A slightly longer time of 28 days was reported on the basis of testing all seven of the biomarkers recommended by the National Comprehensive Cancer Network,\textsuperscript{13} which may reflect variations in the testing methods for individual biomarkers and time taken to confirm results. Other studies also report a range of turnaround times and times from test to treatment.\textsuperscript{14–16}
The patterns revealing weekly peaks in the numbers of patients for different TTT durations observed in our study are likely due to many clinics operating on a weekly basis (including a first outpatient visit, bronchoscopy, and return outpatient visit), with other variations in timing owing to differences in factors such as hospital size, geographic region, institutional equipment and framework, and irregular requests by institutions and pathologists. The clinically acceptable turnaround time (in alignment with U.S. guidelines) for receipt of biomarker testing results is 14 days; however, in Japan, this time is subject to the working procedures of individual hospitals and diagnostic vendors, which may lead to variation in turnaround time. TTT initiation may be longer than the time to receipt of results depending on the time taken to review results and to discuss with the patient before determining the appropriate therapy.

TTT in our study was generally longer for patients who were prescribed chemotherapy than for those prescribed targeted therapies or ICIs, which may be due to a longer pretreatment phase between receiving test results and starting chemotherapy versus targeted therapies. Treatment with pemetrexed is associated with a pretreatment period of approximately seven days. PD-L1 was the only marker associated with a slightly longer TTT for patients prescribed targeted therapies versus chemotherapy, which may reflect the time required for testing and reporting from a commercial laboratory rather than in the hospital pathology department. TTT was longer in patients tested on two or three instances than in those with one testing instance; many patients who were tested only once may have been simultaneously tested for multiple biomarkers, thereby avoiding delays associated with sequential testing.

Our study focused only on patients who had at least one biomarker test ordered. A U.S.-based study by Gutierrez et al., which included both tested and untested patients, found that 41% of the patients with advanced NSCLC were not tested for both EGFR and ALK, and 92% were not tested for all seven of the biomarkers recommended for testing by the National Comprehensive Cancer Network. In that study, among patients who were not tested for EGFR and ALK, 52% received chemotherapy with no documented reasons stating why testing was not performed. The finding that patients receiving chemotherapy without previous biomarker testing is concerning given that median overall survival in that study was shorter for patients treated with chemotherapy (12.7 mo) compared with those treated with a targeted therapy (31.8 mo); overall survival was 15.5 months in the 17 patients with EGFR or ALK mutations who received chemotherapy rather than targeted therapy. A recent review also reported increasing evidence for superior outcomes with targeted therapies versus chemotherapy.

Although the reasons for selecting individual treatment approaches were not available for our study, improving access to appropriate targeted therapies through comprehensive testing may ultimately lead to improvements in overall survival and other outcomes for patients with advanced lung cancer.

Our study provides important data regarding the nationwide diagnostic testing and treatment patterns for these four biomarkers of NSCLC (EGFR, ALK, ROS1, and PD-L1), which are covered by Japan’s National Health Insurance in patients with lung cancer in Japan. However, this may be different to the biomarker testing that is approved, and often performed, in other countries. In addition, the following limitations should be noted. The data are based on hospital records from the MDV database (health claims, administrative, or Diagnosis Procedure Combination) and may not be representative of hospitals not included in the MDV database. The turnaround time for testing is based on the time between testing and treatment, and factors that may have altered this interval (e.g., appointment backlog, patient choice) cannot be accounted for. Barriers to testing may vary depending on hospital settings and between countries and include logistical and cost considerations. The data are based on test order, and respective data for test results were not available, and the rationale for testing patterns was not provided by physicians. Therefore, it is assumed that patients who had a biomarker test and were subsequently treated with a targeted therapy or ICI were biomarker-positive, and those who received chemotherapy were biomarker-negative, but this cannot be confirmed. Data regarding the patient journey were not available; therefore, it was not possible to assess any effects of patients transferring between hospitals. Finally, histologic subtypes (small cell, nonsmall cell, squamous cell, etc.) were not specified in the MDV database. A recent U.S. study found that testing rates for ALK were lower in patients with squamous versus nonsquamous NSCLC. This and other patient/clinical characteristics may affect the likelihood of being tested for ALK or other diagnostic biomarkers.

Our real-world data and other studies highlight variations between biomarker testing patterns and TTT in patients with lung cancer. Diagnostic testing and treatment patterns in Japan are subject to differences between hospitals in working practices and procedures and are likely influenced by priorities given to testing a specific biomarker when considering limited tissue samples in clinical practice. Improved compliance with Japanese guidelines is needed to increase the proportion of patients tested and to reach a consensus on testing patterns that will provide the most appropriate treatment approach for individuals. The use of new technologies such as NGS that allow simultaneous testing of...
multiple biomarkers is expected to reduce the TTT. Simultaneous testing of biomarkers in lung cancer, along with ensuring testing is performed as early as possible, will aid in the selection of appropriate and timely treatment and ultimately improve outcomes for patients in the future.

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Supplementary Data
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References
1. Kim ES, Roy UB, Ersek JL, et al. Updates regarding biomarker testing for non-small cell lung cancer: considerations from the National Lung Cancer roundtable. J Thorac Oncol. 2019;14:338-342.
2. Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice guideline update. J Clin Oncol. 2018;36:991-919.
3. Hofman P, Barlesi F. Companion diagnostic tests for treatment of lung cancer patients: what are the current and future challenges? Expert Rev Mol Diagn. 2019;19:429-438.
4. Wu YL, Planchar D, Lu S, et al. Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS. Ann Oncol. 2019;30:171-210.
5. Japan Lung Cancer Society. Lung cancer practice guideline 2019 edition. https://www.haigan.gr.jp/guideline/2019/1/1/190101040100.html#cq13. Accessed June 25, 2020.
6. Yu TM, Morrison C, Gold EJ, Tradonsky A, Layton AJ. Multiple biomarker testing tissue consumption and completion rates with single-gene tests and investigational use of Oncomine Dx target test for advanced non-small-cell lung cancer: a single-center analysis. Clin Lung Cancer. 2019;20:20-29.e8.
7. Wang F, Mishina S, Takai S, et al. Systematic treatment patterns with advanced or recurrent non-small cell lung cancer in Japan: a Retrospective Hospital Administrative Database study. Clin Ther. 2017;39:1146-1160.
8. MDV medical data vision. Introducing MDV database. https://www.mdv.co.jp/mdv_database/english. Accessed April 30, 2020.
9. Goto Y, Yamamoto N, Masters ET, et al. Treatment sequencing in patients with anaplastic lymphoma kinase-positive non-small cell lung cancer in Japan: a real-world observational study. Adv Ther. 2020;37:3311-3323.
10. Cancer Information Service. Projected cancer statistics, 2018: projected cancer incidence 2018. https://ganjoh.jp/en/public/statistics/short_pred.html. Accessed April 30, 2020.
11. Shimizu J, Masago K, Saito H, et al. Biomarker testing for personalized, first-line therapy in advanced nonsquamous non-small cell lung cancer patients in the real world setting in Japan: a retrospective, multicenter, observational study (the BRAVE study). Ther Adv Med Oncol. 2020;12:175835920904522.
12. Lee DH, Tsao MS, Kambertel KO, et al. Molecular testing and treatment patterns for patients with advanced non-small cell lung cancer: PIvOTAL observational study. PLoS One. 2018;13:e0202865.
13. Gutierrez ME, Choi K, Lanman RB, et al. Genomic profiling of advanced non-small cell lung cancer in community settings: gaps and opportunities. Clin Lung Cancer. 2017;18:651-659.
14. Illei PB, Wong W, Wu N, et al. ALK testing trends and patterns among community practices in the United States. JCO Precis Oncol. 2018;2:1-11.
15. DiStasio M, Chen Y, Rangachari D, Costa DB, Heher YK, VanderLaan PA. Molecular testing turnaround time for non-small cell lung cancer in routine clinical practice confirms feasibility of CAP/IASLC/AMP guideline recommendations: a single-center analysis. Clin Lung Cancer. 2017;18:e349-e356.
16. Gregg JP, Li T, Yoneda KY. Molecular testing strategies in non-small cell lung cancer: optimizing the diagnostic journey. Transl Lung Cancer Res. 2019;8:286-301.
17. Pennell NA, Arcila ME, Gandara DR, West H. Biomarker testing for patients with advanced non-small cell lung cancer: real-world issues and tough choices. Am Soc Clin Oncol Educ Book. 2019;39:531-542.
18. Thunnissen E, Kerr KM, Herth FJ, et al. The challenge of NSCLC diagnosis and predictive analysis on small samples. Practical approach of a working group. Lung Cancer. 2012;76:1-18.