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Research Article

# Utilization of Advanced Molecular Analyses in Clinical Practice in Lung Cancer: A Country Perspective

**Haci Ibrahim Petekkaya,[1] Veysel Atilla Ayyildiz[2]**

[1]Department of Internal Diseases (Medical Oncology), Izmir Tinaztepe University, Faculty of Medicine, Izmir, Turkey
[2]Department of Radiology, Suleyman Demirel University, Faculty of Medicine, Isparta, Turkey

## Abstract

**Objectives:** This study evaluated the clinical practices of medical oncologists in Turkey for utilization of molecular and genetic analyses in lung cancer.

**Methods:** All medical oncologists registered to the Turkish Medical Oncology Society participated in an online survey about their practices of molecular and genetic analyses for management of lung cancer patients.

**Results:** Participants were 189 medical oncologists. Results showed that 88.4% checked mutations in adenocancer, 75.7% checked EGFR, EML-ALK, and ROS-1 in NSCLC, 75.1% checked markers only for locally advanced/metastatic diseases; 45% obtained results in 8–14 days and 31.2% in 15–21 days. A positive EGFR/ALK report after initiating chemo led 68.3% to re-evaluate patient after 2/3 cycles, 20.6% to stop chemo and shift to targeted therapy and 12.2% to continue full-regimen. Of the participants, 46% requested secondary biopsy in progressions under treatment, 22.2% in young patients, 34.9% in never-smokers, 46.6% in patients testing negative but presumed to be clinically positive.

**Conclusion:** Most medical oncologists in Turkey use molecular/genetic analyses in their clinical practice. However, the limited availability and delays in results lead oncologists to initiate treatment primarily based on clinical findings. Once these methods become widespread, targeted therapies and consequent favorable outcomes will increase in the practice of oncology.

**Keywords:** Molecular analyses, precision oncology, medical oncologist, perspective, Turkey

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Cancer is a disease that basically originates from genomic disorders, which play a role in both progression of the disease and also in escape from treatment.[1-3] In this complex environment of genetic interactions, molecular profiling analyses have emerged as a standard of care in many cancer types.[4, 5] The widespread utilization of molecular profiling analyses has brought the concept of precision oncology into today's oncology practice.

One of the most important application fields of molecular studies in oncology is lung cancer. Today, lung cancer ranks first for men and fourth for women for mortalities due to cancer in Turkey.[6] The ongoing research for identifying molecular pathogenesis of lung cancer reveals novel molecular targets for treatment. Currently, targeted therapies for patients with epidermal growth factor receptor (EGFR) tyrosine kinase mutations and anaplastic lymphoma kinase (ALK) gene translocations provide improved outcomes in both survival and health-related quality of life.[7-10] Some of the other targets for molecular profiling are KRAS mutations, MET overexpression, and ROS1 translocations.[11-13] As

**Address for correspondence:** Haci Ibrahim Petekkaya, MD. Ic Hastaliklari Anabilim Dali (Medikal Onkoloji), Izmir Tinaztepe Universitesi Tip Fakultesi, Izmir, Turkey
**Phone:** +90 232 454 14 14 **E-mail:** drpetekkaya@gmail.com

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research continues, novel biomolecules and potential targets for contemporary treatments will emerge for management of lung cancer.

The advances in the field of biotechnology cannot be separated from the practice patterns of medical oncologists for management of lung cancers. The availability of laboratories in healthcare facilities, wait times for obtaining the results of molecular analyses, patient factors and the physician choices for management of the disease are major factors that affect the demand for and application of molecular analyses. Currently, there is no baseline data regarding utilization of molecular analyses in the clinical practice of lung cancer management in Turkey. This study aimed to evaluate the daily clinical practices of medical oncologists regarding utilization of these methods in lung cancer patients in the context of a country.

## Methods

This study was conducted as a cross-sectional study to evaluate the current practice patterns of medical oncologists in Turkey for utilizing molecular analyses as a part of patient management in lung cancer. For this aim, a nineteen-item questionnaire was designed to evaluate the demographic characteristics and work environment of the participants, their knowledge about molecular and genetic analysis methods and barriers to utilization of these methods in clinical practice. The questionnaire is presented in Table 1.

The target population of this study included all medical oncologists registered in the database of the Turkish Medical Oncology Society who were called to participate to an online survey. A total of 189 medical oncologists completed the survey and were included in the analyses.

### Statistical Analysis

Descriptive statistics are presented as frequencies and percentages for the categorical variables and means and standard deviations for the numerical variables. Analyses were performed with SPSS 21 (IBM Inc., Armonk, NY, USA).

## Results

A total of 189 medical oncologists (M/F: 117/71; mean age: 39.3±6.7 years) participated the study. The distribution of the participants' institutions was as 48.7% university hospital (n=92), 32.8% research and training hospital (n=62), 18% private practice (n=34) and 0.5% foundation university hospital (n=1).

About 88.4% of the participants declared that they referred patients to molecular or genetic mutation analyses for adenocancers in their clinical practice. The proportion of the participants' institutions that were able to analyze molecular tests was 61.4%, and 52.9% of the participants reported that they referred patients to another center for these analyses.

About 75.7% of the participants declared that they checked for all among EGFR mutation, EML-ALK fusion and ROS-1 mutation in patients with NSCLC, and 58.2% stated that they had no priority for choosing these markers. The proportion of the participants who checked for these markers at diagnosis in locally advanced or metastatic disease was 75.1%.

Of medical oncologists that participated in the survey, 88.4% reported that these analyses were requested by themselves. Almost half of them could obtain the results in between 8 and 14 days (45%), and some in 15 to 21 days (31.2%).

In cases where chemotherapy was initiated at diagnosis but were then reported to be EGFR or ALK-positive, 68.3% of the participants reported that they should decide after 2 or 3 cycles of chemotherapy, 20.6% reported that they should cease the chemo and shift to targeted therapy, and 12.2% reported that they should continue with chemotherapy. The rate of providing maintenance regardless of mutation status in patients that responded to chemotherapy was 36%. The cytotoxic chemotherapy regimen of choice at first line in metastatic adenocancers that took targeted therapy regardless of mutation status was reported to be cisplatin+pemetrexed by 50.2% of the participants.

The mutation analyses were reported to be performed from the primary tumor mass by 95.8% of the participants, and 91.5% of them reported that they request a re-biopsy in case of inadequate material for molecular studies. The rate of re-biopsy in case of an EGFR/ALK discordance was 38.1%. The distribution of re-biopsy preference was as 46.6% for patients that tested negative but clinically positive based on the oncologist's consideration, 46% for every patient that progressed during treatment, 34.9% for patients who had not smoked before and 22.2% for young patients.

The detailed distribution of responses to the questionnaire is presented in Table 2.

## Discussion

Incorporation of molecular and genetic testing in treatment of lung cancer along with other clinical data from laboratory and imaging studies significantly affect patient outcomes and provide more favorable survival rates and quality of life in these patients. Additionally, these tests guide medical oncologists towards better patient management

**Table 1.** Utilization of molecular and genetical advances in clinical practice for patients with lung cancer (Questionnaire)

1. Age: _____; ☐ Male ☐ Female
2. Your institution: ☐ University ☐ Education and research hospital
☐ Foundation university ☐ Private practice
3. For which subtypes of lung cancer do you check molecular or genetic mutations in your clinical practice?
☐ Adenocancer ☐ Squamous
☐ Unknown subtype ☐ All NSCLC
☐ Other: _____
4. Does your institution have the capability to analyze molecular markers?
☐ Yes ☐ No
If "No": ☐ I refer to another center
☐ I do not check molecular tests
5. Which molecular markers do you check in a patient with a newly diagnosed NSCLC?
☐ Only EGFR mutation (according to the clinical data)
☐ Only EML-ALK fusion (according to the clinical data)
☐ Only ROS-1 mutation (according to the clinical data)
☐ All of the above
☐ Other: _____
6. Do you check molecular markers based on a priority ranking?
☐ Yes ☐ No
If "Yes": ☐ Based on reimbursement
☐ Based on a readily available kit
☐ Based on the clinical status of the patient
7. Which method is used for ALK mutation?
☐ FISH
☐ Immunohistochemistry
☐ Immunohistochemistry and subsequent FISH
8. When do you check for molecular markers?
☐ In all NSCLCs even non-metastatic
☐ At diagnosis of locally advanced or metastatic patients
☐ At second line in metastatic patients
☐ After metastasis in metastatic patients
9. Who makes requests for checking molecular or genetic mutations?
☐ Myself
☐ My colleague (medical oncologist)
☐ Another colleague from other specialties: _____
10. When do you receive the results of molecular marker tests?
☐ 1-7 days
☐ 8-14 days
☐ 15-21 days
☐ More than 21 days
11. If more than 21 days, what is the reason for this long period?_____
12. What is your approach to a patient who took chemotherapy at diagnosis and reported to be EGFR or ALK-positive after initiation of chemotherapy?
☐ I continue with chemotherapy
☐ I cease chemotherapy and shift to targeted therapy
☐ I decide according to assessment after 2 or 3 cycles of chemo
13. Do you give maintenance to patients that responded to chemotherapy regardless of mutation status?
☐ Yes ☐ No
If "Yes": ☐ After which cycle? _____
14. If you consider initiating targeted therapy without checking for mutation status, what is the choice of cytotoxic chemotherapy regimen at first line in metastatic lung adenocancers? _____

**Table 1.** CONT.

15. How are the mutation analyses reimbursed?
- ☐ SGK (social security institution)
- ☐ Patient self-sponsored
- ☐ SGK and patient share
- ☐ Being included in compassionate use
- ☐ Other: _____

16. What is the primary site for mutation analyses?
- ☐ Primary lung tumor mass
- ☐ Mediastinal LAP
- ☐ Metastasis site

17. If there is no adequate biopsy material for molecular study, do you recommend re-biopsy?
- ☐ Yes ☐ No

18. Do you request a second biopsy in cases of EGFR/ALK discordance?
- ☐ Yes ☐ No

19. For which cases do you request a second biopsy?
- ☐ For every patient that progressed during treatment
- ☐ For patients that test negative but clinically positive based on my consideration
- ☐ For young patients
- ☐ For patients who have not smoked

and for better choice of medications that are available. The current literature data suggest that even patients with poor performance may respond well to targeted therapies, which should inform physicians about the importance of these molecular and genetic evaluations.[14, 15] Under the light of these general considerations about these methods, identification of the preferences of medical oncologists for utilizing these assessments during their clinical practice gains importance. Since there is no baseline data on this topic in Turkey, this study aimed to constitute a basic foundation of comprehension regarding the current status of preferences for molecular and genetic testing in medical oncology society in Turkey.

As an overall interpretation of our findings, the majority of our sample were familiar with molecular and genetic testing methods and used these analyses for patient management in their clinical practice. The main barriers against using these methods were the limited availability at some centers and delays in obtaining the results of these analyses. In these cases, the medical oncologists tended to initiate treatment, based on primarily clinical findings and routine laboratory and imaging studies.

Currently, the available literature data suggest several barriers for adoption of molecular and genetic testing in the practice of oncology. One of these barriers is skepticism about the clinical value of these methods in the practice.[16, 17] This skepticism is particularly about next-generation sequencing techniques that incorporate multiple gene mutation analyses rather than single gene and molecular marker analyses. A recent survey study about the beliefs of clinicians about the clinical value and utility of these tests in clinical practice revealed that only half of the participating physicians believed that these tests will be widely available in clinical practice over several years of utilization.[16] Some factors might underlie this skepticism, like inadequate knowledge about genomics, unavailability of resources or patient-related factors. Particularly, wait time to obtain the results of molecular studies is known as a major factor that affects incorporation of these tests into clinical practice.[16] The results of our study also confirmed this finding in the literature, and almost half of our participants stated that they obtained the results of molecular analyses after 15 days or more, which is a significant barrier against widespread adoption of these methods in routine practice.

Another unfavorable issue that emerges as a barrier is the possible need for re-biopsies in molecular studies. After an initial invasive procedure, both patients and physicians become more reluctant for an additional invasive procedure to obtain more tissue samples for analyses.[18] Nevertheless, the literature data are partly in conflict with our results. Accordingly, more than 90% of our participants declared that they requested a re-biopsy in case of an inadequate tissue sample. However, if an EGFR/ALK discordance were determined, only less than 40% of them would request a re-biopsy, which indicated a reluctance against re-biopsies in molecular testing.

The participants of our study emphasized the importance of reimbursement for molecular testing as a priority-deter-

**Table 2.** Participants' responses to the questionnaire

| Items | n | % |
|---|---|---|
| For which subtypes of lung cancer do you check molecular or genetic mutations in your clinical practice? | | |
| Adenocancer | 167 | 88.4 |
| Squamous | 5 | 2.6 |
| Unknown subtype | 93 | 49.2 |
| All NSCLC | 28 | 14.8 |
| Does your institution have the capability to analyze molecular markers? | | |
| Yes | 116 | 61.4 |
| No | 73 | 38.6 |
| If "No": | | |
| I refer to another center | 100 | 52.9 |
| I do not check molecular tests | 1 | 0.5 |
| Which molecular markers do you check in a patient with a newly diagnosed NSCLC? | | |
| Only EGFR mutation (according to the clinical data) | 25 | 13.2 |
| Only EML-ALK fusion (according to the clinical data) | - | - |
| Only ROS-1 mutation (according to the clinical data) | - | - |
| All of the above | 143 | 75.7 |
| Other | 21 | 10.5 |
| Do you check molecular markers based on a priority ranking? | | |
| Yes | 76 | 40.2 |
| No | 110 | 58.2 |
| If "Yes": | | |
| Based on reimbursement | 50 | 26.5 |
| Based on readily available kit | 21 | 11.1 |
| Based on the clinical status of the patient | 33 | 17.4 |
| Which method is used for ALK mutation? | | |
| FISH | 141 | 74.6 |
| Immunohistochemistry | 11 | 5.8 |
| Immunohistochemistry and subsequent FISH | 30 | 15.9 |
| When do you check for molecular markers? | | |
| In all NSCLCs even non-metastatic | 17 | 9 |
| At diagnosis of locally advanced or metastatic patients | 142 | 75.1 |
| At second line in metastatic patients | 3 | 1.6 |
| After metastasis in metastatic patients | 38 | 20.1 |
| Who makes requests for checking molecular or genetic mutations? | | |
| Myself | 167 | 88.4 |
| My colleague (medical oncologist) | 43 | 22.8 |
| When do you receive the results of molecular marker tests? | | |
| 1-7 days | 18 | 9.5 |
| 8-14 days | 85 | 45 |
| 15-21 days | 59 | 31.2 |
| More than 21 days | 21 | 11.1 |
| What is your approach to a patient who took chemotherapy at diagnosis, and reported to be EGFR or ALK-positive after initiation of the chemotherapy? | | |
| I continue with chemotherapy | 23 | 12.2 |
| I cease chemotherapy and shift to targeted therapy | 39 | 20.6 |
| I decide according to assessment after 2 or 3 cycles of chemo | 129 | 68.3 |
| Do you give maintenance to patients that respond to chemotherapy regardless of the mutation status? | | |
| Yes | 68 | 36 |
| No | 117 | 61.9 |
| If you consider initiating targeted therapy without checking for mutation status, what is the choice of cytotoxic chemotherapy regimen at first line in metastatic lung adenocancers? | | |
| Cisplatin + Pemetrexed | 95 | 50.2 |

**Table 2.** CONT.

| | | |
|---|---|---|
| How are mutation analyses reimbursed? | | |
| SGK (social security institution) | 155 | 82 |
| Patient self-sponsored | 14 | 7.4 |
| SGK and patient share | 16 | 8.5 |
| Being included in compassionate use | 11 | 5.8 |
| What is the primary site for mutation analyses? | | |
| Primary lung tumor mass | 181 | 95.8 |
| Mediastinal LAP | 31 | 16.4 |
| Metastasis site | 19 | 10.1 |
| If there is no adequate biopsy material for molecular study, do you recommend re-biopsy? | | |
| Yes | 173 | 91.5 |
| No | 14 | 7.4 |
| Do you request a second biopsy in cases of EGFR/ALK discordance? | | |
| Yes | 72 | 38.1 |
| No | 112 | 59.3 |
| For which cases do you request a second biopsy? | | |
| For every patient that progressed during treatment | 87 | 46 |
| For patients that test negative but clinically positive based on my consideration | 88 | 46.6 |
| For young patients | 42 | 22.2 |
| For patients who have not smoked before | 47 | 34.9 |

mining factor for choosing analyses. This is also known as a significant factor on this topic in the literature. Several previous studies have reported that non-reimbursement of these methods, particularly next generation sequencing techniques, should be a major barrier for widespread application of these procedures in clinical practice.[19] A previous report also stated that, even if the costs of these tests decrease to an affordable level for patients themselves, there should still be avoidance for those self-sponsored analyses in an environment where many other costs are covered by social security institutions.[20] From this point of view, developing a national strategy and health policy for covering and promotion of application of genetic and molecular studies should be a proper approach to both increase the quality of patient management and improve the patient outcomes by means of both survival and quality of life. In this study, we found that the social security institution of Turkey reimbursed more than 80% of the molecular analyses requested. This is an important measure for promoting widespread adoption of these tests among medical oncologists in Turkey.

In this study, we found that molecular and genetic testing is widely adopted and used in most occasions by medical oncologists in Turkey. Nevertheless, the limited availability of these tests at every center and the wait times for the results cause oncologists to initiate treatment based on clinical findings. If these methods become more available, the society will embrace their utilization in clinical practice.

**Disclosures**

**Ethics Committee Approval:** This study was performed in line with the principles of the Declaration of Helsinki. Approval was obtained from the Clinical Research Ethics Committee of Suleyman Demirel University, Faculty of Medicine, for this study (Date: 12/21/2020 , Decision no: 395).

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