Lung Cancer in Turkey

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Introduction

Turkey stretches from the Balkans to the Middle East and is among the larger countries in terms of land area and population (Fig. 1). Turkey's population of approximately 85 million people encompasses a diverse genomic, ethnic, and cultural heritage with roots from several empires and civilizations dating back to the Paleolithic age. According to the GLOBOCAN 2020[1] registry, lung cancer (LC) comprises 17.6% of all cancer types. It ranks highest in Turkey, with 41,000 new cases in 2020 and an age-adjusted incidence rate of 41.7 and 8.7 per 100,000 for men and women, respectively.[1] The non-small cell histologic type is the most frequent subtype, comprising almost 80% of all thoracic cancers, half of which are adenocarcinomas, and small cell histology comprises 16.5%.[2] These ratios have remained constant in the last 5 years, with most cases attributed to cigarette smoking. Turkey has a high prevalence of smoking but, since 2004, it has adopted bold and courageous steps to reduce tobacco consumption. In 2019, Turkey ranked among the top ten countries with the highest number[1]of tobacco smokers, alongside People's Republic of China, The United States of America, Russia, and several Asian countries, despite strict measures and awareness programs warning against tobacco consumption. Together, these countries comprise almost two-thirds of the global smoking population.[3–5]

Health Care System

Health services in Turkey are provided by state hospitals, hospitals affiliated with medical schools, and private hospitals. Turkey has 112 hospitals affiliated with medical schools, 81 of which are state owned and 31 are private universities belonging to nonprofit foundations.[6] Although most state-owned medical school hospitals are independent institutions, the Ministry of Health (MoH) affiliated all the state-owned "Training and Research Hospitals" to the University of Health Sciences. The MoH has 944 state hospitals with 160 thousand

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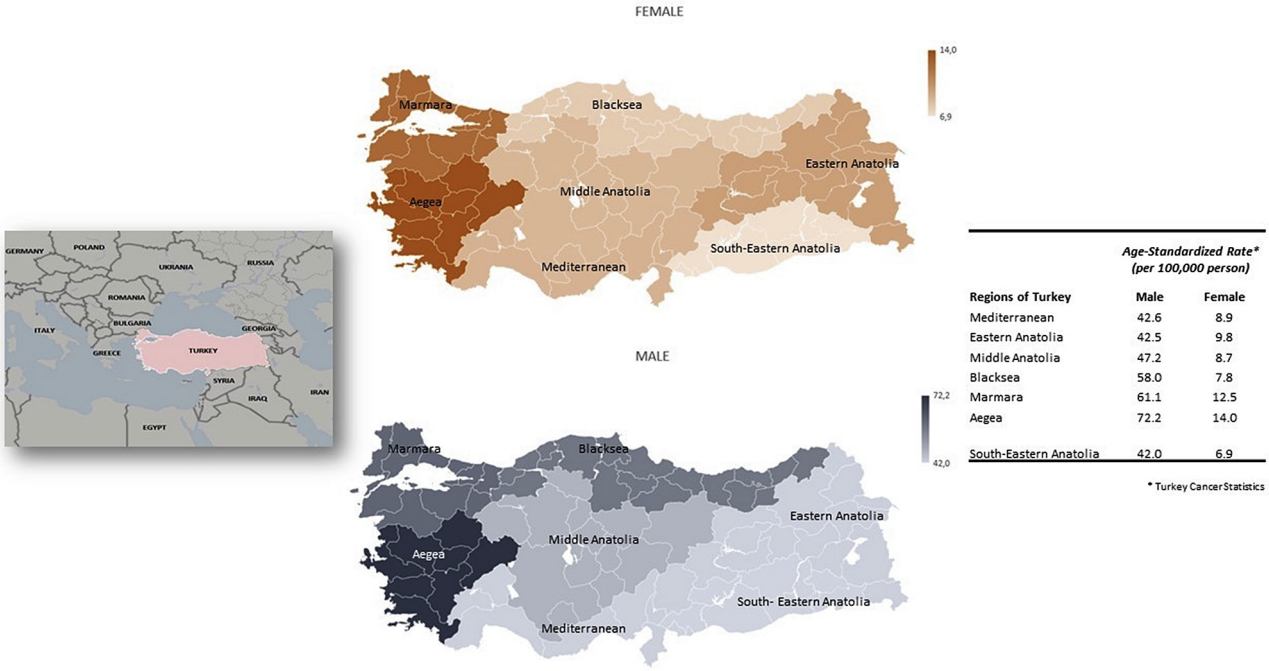
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Regions of Turkey	Age-Standardized Rate* (per 100,000 person) Male	Female
Mediterranean	42.6	8.9
Eastern Anatolia	42.5	9.8
Middle Anatolia	47.2	8.7
Blacksea	58.0	7.8
Marmara	61.1	12.5
Aegea	72.2	14.0
South-Eastern Anatolia	42.0	6.9

* Turkey Cancer Statistics

Figure 1. Regions of Turkey and age-standardized rate of LC (per 100,000 person). LC, lung cancer.

inpatient beds and employs more than 1,240,000 health care workers.[7]

In the Turkish health care system, 86% of the population is reimbursed by the Social Security Institution (SSI) of the Turkish Government.[8] In 2019, private insurance companies supported 2.9% of the "Health Expenditure Budget of Turkey."[9] The medical expenses of all eligible patients treated in the MoH state hospitals and state university hospitals are covered by the SSI. The SSI partially covers treatment costs in most private hospitals and private university hospitals, and the additional fees are covered by private insurance or the patient. This is also the case for patients with cancer treated in oncology centers, usually located in secondary and tertiary health care facilities. Patients can apply directly to any university, state, private, or foundation hospital without their primary care physicians' referral.

Although health care is provided by the MoH, the Ministry of Labor and Social Security is responsible for covering all health care services and treatment costs through the SSI. The MoH is also responsible for licensing drugs in Turkey. Physicians must personally apply for off-label use of any unapproved drugs within their specialty scope. When the MoH approves the application, the SSI re-evaluates this application and, if deemed appropriate, it is included in the scope of reimbursement. If the SSI does not reimburse the drug, the patient must pay for this off-label agent.

"E-nabız" is a web-based registry implemented by the MoH of the Republic of Turkey in 2015. It is a national medical record system providing access to personal health information by desktop and mobile devices, regardless of where the examinations and treatments are conducted. Physicians can access their patients' previous medical histories within limits set by the patient. This health record system has improved the diagnosis and treatment process of many diseases, including LC.

Epidemiology

In Turkey, the cancer registry started in 1982 as a passive system. As this method made it impossible to collect high-quality data, active system entry began in 1992, with Izmir as the first and index city. Currently, there are population-based cancer registry centers in 14 Turkish cities, covering 50.2% of the population.[2] The data are transferred to the MoH Cancer Department database, where they are checked for duplicate entries and errors. Reports are sent to the provincial cancer registry centers for corrections in the local database, and a new "Turkey Cancer Data Pool" is created.

The last Turkish cancer registry report was published in December 2021 and includes 2017 data.[10] The report reveals that LC is the most common type in men with a frequency of 56.7 per 100,000 people, whereas it ranks fourth among women (11.1 per 100,000 people). Mean age of NSCLC diagnosis was 63.3 plus or minus 12.5 years in a study which reviewed the data of 703 patients (77.7% male) from 25 different centers.[11]

Table 1 lists the numbers of newly diagnosed LCs in Turkey by total and sex and their age-standardized frequency in the five-year period between 2013 and 2017.

Table 1. Number of New Cases and Change in Turkey's Age-Standardized Lung Cancer Incidence Rate Between 2013 and 2017

	Total		Male		Female	
Years	New cases	ASR	New cases	ASR	New cases	ASR
2013	26,361	33.2	22,007	59.3	4354	10
2014	24,065	29.3	20,194	52.5	3871	8.7
2015	25,297	29.4	21,099	52.5	4198	9
2016	28,679	32.4	23,946	57.7	4733	9.8
2017	29,839	32.5	24,321	56.7	5518	11.1

ASR, age-standardized incidence rate (per 100,000 population).

Although the age-standardized rate (ASR) decreased in 2014 and 2015, it has remained reasonably stable in the whole 5-year period. Nevertheless, the ASR in women peaked in 2017. Figure 2 reveals the LC ASR trend by sex in a 5-year period.

From 2013 to 2017, more than 50% of Turkish patients with LC were diagnosed at an advanced stage, and approximately 30% presented with locally advanced disease. Figure 3 reveals the distribution of LC cases in Turkey by stages.

The frequency of LC by histologic type in the five-year period is presented in Table 2. Adenocarcinoma histology is the most common subtype of all the LCs, the incidence of which increased to 47.7% in 2017, whereas the incidence of not otherwise specified decreased, indicating improved pathologic diagnosis accuracy. The incidence of SCLC was approximately 16% of all thoracic tumors and has remained stable.

The most common histologic cancer type in men and women is adenocarcinoma. The frequency of adenocarcinoma in men is 43.2% and 68.9% in women. The frequency of SCLC is similar in both sexes (16.5% in men; 16.7% in women). The frequency of squamous cell LC is 40.5% in men and 18.8% in women.

Screening

Prevention with smoking cessation and screening are the most effective strategies to reduce the burden of LC.

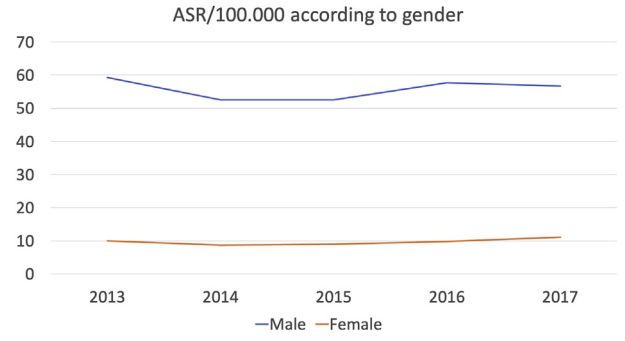


Figure 2. ASR of lung cancer according to gender in Turkey between 2013 and 2017. ASR, age-standardized rate.

After initial reports from the National Lung Cancer Screening Trial revealing a 20% decrease in LC mortality, screening for LC is broadly recommended by many experts.[12] In 2016, Turkey staged an LC screening workshop led by the MoH.[13] There was general agreement on the importance of community screening owing to the epidemiologic characteristics of LC in Turkey. Nevertheless, a nationwide screening program was not deemed feasible because of occupational and environmental exposure and the risk of false-positive results and overdiagnosis associated with endemic tuberculosis infection. Therefore, the final decision was to conduct a regional pilot study in the Aegean region.

No official LC screening program is currently implemented for high-risk smokers or ex-smokers in Turkey.

On the basis of previous favorable results reported in the NLCST trial and recent data from the NELSON study revealing that LC screening is associated with a mortality reduction of 26% in asymptomatic high-risk men,[14] further efforts must be made to establish a national LC screening program.[12–14]

Tobacco Control in Turkey

Turkey currently has approximately 65,000 patients with LC, and the total expected number of cancer cases attributed to smoking is expected to be approximately 31,000.[2,15] A study in 2017 revealed that 4786 deaths could be prevented or delayed in Turkey if a 30% reduction target in tobacco use was met.[16]

Turkey has had a history of ambitious tobacco control laws and regulations since 1986. For example, it passed the following landmark legal provisions: Law No. 4207 on the Prevention of Hazards of Tobacco Products in 1996 that ratified the WHO Framework Convention on Tobacco Control in 2004; Law No. 5727 of 2008 which substantially amended Law No. 4207 that defined prohibitions on public smoking, tobacco advertising, promotion and sponsorship, packaging and labeling of tobacco products, and penalties for violations, all of which were major landmarks in tobacco control legislation. In 2019, the regulations were expanded to

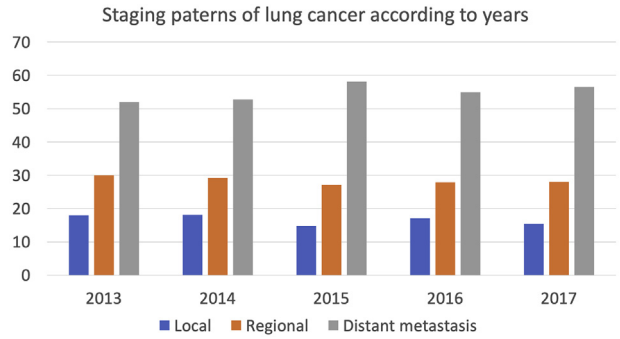


Figure 3. Stage distributions of lung cancer according to years in Turkey between 2013 and 2017.

implement emissions and reporting requirements, plain packaging, and updated health warnings on tobacco products. By 2021, amendments were made to require health warnings covering 85% of the front and 100% of the back of the packaging.[17] Smoking was prohibited in 2008 in most indoor workplaces and public places in Turkey, and prohibitions were expanded to include restaurants and bars in 2009.

Because the relevant departments and institutions have had to adhere to law number 4207 between 2008 and 2011, Turkey has had remarkable success, with a 12% decrease in total tobacco consumption and a 15% decrease in the overall smoking rate.[18,19] According to the Global Adult Tobacco Survey (GATS) results, the prevalence of tobacco smoking decreased from 47.9 to 41.5% in males, from 15.2 to 13.1% in females, and from 31.2 to 27.1% in the overall population from 2008 to 2012.[20] The GATS results in Turkey for 2012 revealed a decrease in tobacco use of 13.7% in women and 13.5% in men compared with those for 2008.[18] There was also a marked decrease in exposure to secondhand smoke from 56.3% to 38.3% in homes, 37.3% to 15.6% in workplaces, and 55.9% to 12.9% in restaurants from 2008 to 2012.[20] Nevertheless, the 2016 GATS results indicated that the rate of tobacco use in Turkey increased to 44.1% in men, 19.2% in women, and 31.6% in the overall population. The results revealed that 10.6%, 26.7%, and 28.0% of adults were exposed to tobacco smoke in the workplace, at home, and in cafes, respectively.[21] The overall population who noticed cigarette advertising, promotion, or sponsorship was 13.3%, 15.7%, and 16.2% in the GATS 2008, 2012, and 2016 results, respectively.[20,21] The main reasons for the increase in overall tobacco consumption and smoking incidence are noncompliance with the smoke-free law policy, advertising and promotion violations, and applications that conflict with the Framework Convention on Tobacco Control Article No. 5.3.[22,23]

Because of cultural influences, waterpipe tobacco smoking is an emerging public health problem, particularly in the Middle East region. In 2012, 0.8% of the adult population enrolled in the GATS reported waterpipe smoking.[18] In the 2017 GATS, the rate of ever use for waterpipe smoking was 27.6% among 13- to 15-year-olds.[21] More recent findings reveal remarkably high waterpipe smoking use for both genders; 41.7% and 24.1% for male and female university students, respectively.[18,20,21] A new generation of tobacco products, such as electronic cigarettes and heat-not-burn tobacco products, represents further public health threats. Despite the banned sale and import of electronic cigarettes, they are widely marketed illegally, and their use is expanding rapidly in Turkey.[22,23]

Smoking among young people is consistently increasing in Turkey. In 2018, a global survey revealed that approximately a third of adults aged more than 15 years and 18% of teenagers were active smokers.[17,18] Recent data reveal that 90% of patients with LC are smokers, and three-quarters of deaths from thoracic and upper airway cancers are attributable to tobacco use.[19] Furthermore, recent financial reports have revealed that overall imports of tobacco and products reached 1.2 billion U.S. dollars in 2020, creating a budget deficit of approximately 300 million U.S. dollars and highlighting the overwhelming toll of tobacco use and the devastating financial burden in Turkey. A broad spectrum of national policies is required to reduce smoking among teenagers

Table 2. Change in the Frequency of Histology of Thorax Malignancies in Turkey Between 2013 and 2017

Years Histology	2013 (%)	2014 (%)	2015 (%)	2016 (%)	2017 (%)
Squamous cell carcinoma	39	37.5	38.2	37.7	36.8
Adenocarcinoma	40.2	43.8	47.1	47.1	47.7
Large cell carcinoma	2	1.8	1.9	1.6	1.9
NOS	18.8	16.8	12.7	13.6	13.7
Others	3.5	4.2	3.4	4.3	3.9
Small cell carcinoma	16.2	16.6	16.1	16.3	16.5
Mesothelioma	3	2.8	2.1	2.5	2.2

NOS, not otherwise specified.

effectively and improve smoking cessation rates among adults to achieve a healthier population and a more prosperous society.

Diagnosis and Staging

In Turkey, diagnosis and staging of LC are carried out in pulmonary disease and thoracic surgery (TS) clinics that comply with current international guidelines. Pulmonary lesions are evaluated by functional imaging studies, including contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT). Diagnosis and staging of LC are by an integrated approach using various invasive and noninvasive modalities, including CT, PET-CT, MRI, and transthoracic or transbronchial tissue biopsies. The most important technique used to diagnose LC is that of high-resolution CT. Contrast CT is recommended for most central LCs, cancers with enlarged mediastinal lymph nodes, and three-dimensional reconstructions. The diagnostic and staging processes are generally optimized through the widespread availability of radio diagnostic and nuclear medicine centers with adequate CT, MRI, and PET-CT scanners available in almost all cities.

Depending on the location(s) of the suspicious lesions, tissue is obtained by bronchoscopy, endobronchial ultrasound (EBUS), endoscopic ultrasound, ultrasound, or CT-guided biopsies. Bronchoscopy, a basic LC diagnostic method, can be performed by interventional pulmonologists or thoracic surgeons in almost every province of Turkey. Transthoracic needle aspiration biopsy or transthoracic fine-needle aspiration biopsy is a routine procedure performed by interventional radiologists in university hospitals or tertiary centers. In the past decade, new EBUS systems (linear and radial EBUS) and ultrathin bronchoscopes to diagnose lesions adjacent to airways and peripheral pulmonary lesions have been increasingly introduced in clinical practice. In university hospitals or tertiary centers, EBUS system-transbronchial needle aspiration (EBUS-TBNA), needed to stage LC, and especially mediastinal lymph node, is routinely performed by interventional pulmonologists or thoracic surgeons. Centrally located tumors are usually diagnosed by flexible bronchoscopy or EBUS-transbronchial needle aspiration, and samples are collected for molecular analyses. Mediastinoscopy or video mediastinoscopy is also used for LC diagnosis and staging in university hospitals or tertiary centers. Most universities and tertiary centers are equipped with bronchoscopes, EBUS, multidetector CT, magnetic resonance imaging, and PET-CT scanners. Because most of the cost of these diagnostic modalities is covered by national health insurance, a universal state-of-the-art diagnostic workup is readily accessible.

Patients newly diagnosed with having LC are often evaluated in multidisciplinary tumor boards comprising thoracic surgeons, chest physicians, medical oncologists, radiation oncologists, pathologists, and radiologists, where further recommendations are made regarding staging interventions and personalized treatments.

Pathology, Molecular Testing, and Access

In 2022, Turkey had 1666 pathologists (according to MoH, Health Services General Directorate, Health Manpower Planning Department) (Table 3). Most of them do not specialize in any particular field and cover all or many body systems. Nevertheless, approximately 90 pathologists specialize in lung pathology in large or dedicated hospitals. Routine histopathologic, immunohistochemical (IHC), and cytopathologic examinations are available in all major hospitals. Nevertheless, in some smaller and peripheral hospitals, pathology services are outsourced to larger hospitals in the same region. Rapid on-site evaluation for fine-needle aspiration biopsies is performed in a few centers. In Turkey, molecular testing facilities are restricted to major academic centers, tertiary hospitals, and large private laboratories.

Current WHO classifications are used to diagnose and classify LC and all other cancer types in Turkey. When a new edition is published, widespread use of the new classification is encouraged in scientific meetings organized by the local pathology associations and the Federation of Turkish Pathology Societies, the umbrella organization of Turkish pathologists.

According to 2017 data, 79.6% of pleuropulmonary malignant tumors are nonsmall cell cancer histology, 36.8% are squamous cell carcinoma, and 47.7% are adenocarcinoma. Small cell carcinoma and mesothelioma constitute 16.5% and 2.2% of all malignancies in this localization, respectively.

Because the disease is usually diagnosed in advanced stages, small biopsy and cytology specimens are important portions of the diagnostic material in lung carcinomas. Although preparation of cell blocks from cytology specimens is recommended and encouraged in national and regional pathology meetings, it is not yet applied in

Table 3. Current Manpower Resources According to MoH Database

Manpower	Total
Pulmonologists	2167
Thoracic surgeons	670
Pathologists	1666
Radiation oncologists	593
Medical oncologists	632

all centers. The sample tissue should be conserved, and only one squamous, one glandular (usually P40 and TTF1), and neuroendocrine markers are used when necessary for the initial histologic classification of pulmonary carcinoma using small biopsies and cell blocks. Nevertheless, the precious tumor tissue is sometimes used up before it arrives at the molecular pathology laboratory, probably owing to the country's widespread availability of automated immunohistochemistry facilities. Hence, *EGFR* mutation analysis could not be performed in 4.5% and 16% of cases owing to insufficient residual tumor or poor DNA quality, respectively.[24,25]

After pathologic diagnosis, many large centers routinely perform investigations of targetable mutations in advanced-stage adenocarcinomas and other nonsquamous NSCLC cases. The Federation of Turkish Pathology Societies prepares, publishes, and updates guidelines regarding molecular examinations.[26] Although commercial real-time polymerase chain reaction assays and Sanger sequencing were used to evaluate *EGFR* mutations in the past, in the last 5 to 10 years, next-generation sequencing has replaced other methods to a large extent. Although the interinstitutional approach varies regarding the panel content, all panels contain druggable and *KRAS* mutations. *EGFR* mutations are the most common targetable mutations, whereas the *KRAS* mutation rate was 26% among 1081 NSCLC cases.[27] More extensive data series from Turkey revealed an *EGFR* mutation rate of 12.1% to 16.7%.[11,24,25,28–30] There was no difference in the *EGFR* mutation rate across the geographic regions of Turkey.[26] Nevertheless, a study evaluating asbestos exposure and changes in LC driver genes found more frequent *EGFR* mutations and *ALK* rearrangements in asbestos-exposed nonsmokers in Turkey, where environmental asbestos exposure is common.[30] The most common *EGFR* mutations are exon 19 deletions and the L858R mutation.[24,25,28,31]

In most centers, *ALK* and *ROS1* rearrangements are evaluated simultaneously with *EGFR* mutations. Many pathology laboratories use *ALK* IHC examination as the screening test and confirm positive cases with fluorescence in situ hybridization (FISH) because the SSI mandates FISH positivity for reimbursement purposes. IHC is also used to screen for *ROS1* rearrangement in many laboratories and confirmation by FISH. In Turkey, the rate of *ALK* rearrangements in NSCLC is 3.4% to 8.3%, and the rate of *ROS1* rearrangements is 0.4% to 1.9%.[29,30,32,33] Different combinations of next-generation sequencing panels, IHC, and FISH tests are used for other less common mutations (such as *BRAF* and *NTRK*). The SSI also covers programmed death-ligand 1 (PD-L1) IHC testing. Although not routine, liquid biopsy assays have been performed in some laboratories. The application of plasma testing to evaluate resistance mutations is gradually increasing, especially in patients developing resistance under *EGFR* tyrosine kinase inhibitor (TKI) treatment.[34,35]

The SSI and some private insurance plans cover the costs of tests to determine treatment targets in advanced lung carcinoma (Table 4). Although reimbursement for an emerging test by the SSI depends on the approval of the related treatment agent, sometimes reimbursements are partial and require out-of-pocket payments. In addition, although there is a consensus in Europe that tests should be performed primarily in pathology laboratories and under the supervision of pathologists in cooperation with clinicians,[36] this is not fully understood by all parties in Turkey. As a result, some laboratories struggle to perform molecular tests because local health administrations impose restrictions on the purchase of consumables by pathology laboratories.

The turnaround times for molecular tests are longer than ideal in many centers. Furthermore, additional tests must be requested by the clinician, causing treatment delays. The SSI or public hospitals do not fund participation in quality assurance (QA) programs. Therefore, participation in external QA programs is low.

Organization of Decision Making in Oncology

Decision making regarding the diagnostic workup or treatment of patients with LC is orchestrated by multidisciplinary boards instituted at most private or state hospitals providing oncologic care. At hospitals where a thoracic surgeon is part of the treatment team, dedicated thoracic oncology multidisciplinary team meetings are usually held weekly. Thoracic oncology multidisciplinary team meetings are typically attended by medical oncologists, thoracic surgeons, radiation oncologists, chest physicians, radiologists, interventional radiologists, nuclear medicine specialists, and pathologists. The issues discussed most frequently concern the best approach for a specific solitary pulmonary nodule, the optimal

Table 4. List of Tests for Therapy Targets for Pulmonary Carcinoma That Are Reimbursed by SSI

List of Therapy Targets	Test
EGFR mutations	NGS, single-gene sequencing
BRAF mutations	NGS, single-gene sequencing
KRAS mutations	NGS, single-gene sequencing
ALK rearrangements	Immunohistochemistry, FISH
ROS1 rearrangements	Immunohistochemistry, FISH
NTRK rearrangements	Immunohistochemistry, FISH
PD-L1	Immunohistochemistry

Note that other genes can be included in the test panels, as relevant NGS panels are reimbursed.
FISH, fluorescence in situ hybridization; NGS, next-generation sequencing; PD-L1, programmed death-ligand 1.

diagnostic workup, assessment of relapse or response to a specific treatment, sequences and combinations of therapeutic modalities, the preferred treatment algorithm for a particular patient, and the use of certain molecular and biological markers. Not all new LC cases are discussed in these meetings, as cases that pose a diagnostic or treatment challenge are often selected for discussion.

Although multidisciplinary tumor boards play a pivotal role in patient-centered clinical management and decision making, they are generally located in large academic centers. Therefore, patients residing in limited-resource areas or diagnosed at small-scale community hospitals may not have the advantage of a multidisciplinary evaluation, resulting in undertreatment. In such circumstances, consultations are sought to finalize the management plan. In addition, the Turkish Cancer Control Program is a nationwide initiative on cancer registry, prevention, and screening programs and is supported by the Turkish MoH.[7]

Treatment Modalities in Turkey

Thoracic Surgery

In Turkey, thoracic surgeons perform LC surgery; they play a major role in LC diagnosis, staging, and treatment. TS certification training can be started after completing six years of medical school. After that, trainees must undergo 5 years of specialized TS training. TS has been a differentiated surgery specialty since 1983. In 2022, Turkey had 670 thoracic surgeons (0.79 per 100,000 inhabitants) performing LC surgery across 126 hospitals (Table 3).[37] There were 24 high-volume centers that perform more than 100 anatomical lung resections yearly.[37] Standard procedures such as diagnostic biopsies or anatomical lung resections by video thoracoscopy (video-assisted thoracoscopic surgery [VATS]) or open thoracotomy can be performed in all TS hospitals. Extended resections of tumors with N2 involvement or extension to the chest wall or great vessels, and resections requiring extracorporeal support, are usually performed in specialized university clinics.

According to the MoH database, approximately 9500 lung resections are performed annually for primary LC.[7] Resection for LC includes wedge resection, segmentectomy, lobectomy, sleeve lobectomy, and, rarely, pneumonectomy. In recent years, pneumonectomies have been replaced by sleeve resections to a great extent. As there is no specific nationwide database for TS, reliable information on the proportion of open VATS and robotic procedures performed for LC is currently unavailable. Thoracotomy is generally required for complex resections, such as large or centrally located tumors, and surgeries after induction treatment. Minimally invasive techniques (with VATS) for anatomical lung resections have become very common in the last 10 years. In Turkey, most lung resections are done thoracoscopically using either a uniportal or a two-hole approach. Robotic procedures are increasingly used by experienced centers equipped with the latest developments in modern technology. Currently, 37 Da Vinci systems are in use, which perform approximately 300 LC resections annually (3%).[37] Nevertheless, robot-assisted TS operations are not widely adopted for routine use in Turkey owing to high costs and lack of evidence of superiority compared with VATS.

The accepted standard for LC resection is lobectomy with lymph node dissection. Sublobar resections (wedge and segmentectomy with lymph node dissection) are usually performed in cases of early stage LC, usually with ground-glass opacification nodules of less than 1 to 2 cm, or in patients with inadequate respiratory reserves or those with significant comorbidities. The general consensus is that patients with stage I NSCLC are advised to undergo resection only, whereas those with stage II are recommended adjuvant chemotherapy after resection. Patients with stage IIIA disease are evaluated for neoadjuvant treatment followed by restaging and resection. In rare circumstances, patients with stage IIIB or stage IV oligometastatic NSCLC undergo lung resection after induction of systemic therapy and radiotherapy (RT). Encouraging results obtained with modern systemic treatments consisting of biological agents and immunotherapy have expanded the indications for surgical intervention in advanced stages.

Thoracic surgeons perform invasive procedures, such as talc pleurodesis (thoracoscopic or bedside), pleural catheter placement, or pericardial drainage, in patients with symptomatic malignant pleural or pericardial effusion.

RT Approaches

In Turkey, radiation oncology is indispensable as part of the multidisciplinary treatment plan. As of December 2021, there are 593 active radiation oncologists (including 68 associate professors and 125 full professors) at 145 facilities, who are almost equally distributed between private and public institutions (Table 3). There are also 198 residents in training. Medical physics has a firm foundation, with approximately 600 active RT physicists. Turkish centers have 256 largely modern linear accelerators, three MR-guided linear accelerators (two are in the installation process), 58 dedicated units (12 cyberknife, 24 TomoTherapy, 14 gamma-knife units, and eight intraoperative RT devices), and 64 high-dose rate after-loading brachytherapy systems.[38] Intensity-modulated RT and stereotactic body RT

(SBRT) have become the preferred treatment modalities for locally advanced and early stage LCs after efforts in the last 10 years to improve the image-guided RT, intensity-modulated RT, and volumetric modulated arc therapy capabilities of Turkish RT centers, including targeted advanced technology training courses run by the Turkish Society for Radiation Oncology and MoH initiatives (Fig. 4).[39]

SBRT is used in patients with early stage NSCLC who are medically inoperable or fragile with comorbidities.[40,41] Depending on the institutional policy, patients with stage IIIB to C NSCLC are generally treated with chemoradiotherapy, whereas patients with stage IIIA are treated with upfront surgery, neoadjuvant chemoradiotherapy with surgery, or chemotherapy with or without immunotherapy.[42–45] There is consensus for recommending adjuvant RT based mainly on positive surgical resection margins and pathologic N2 status. Nevertheless, in selected cases, a multidisciplinary treatment discussion for tailored adjuvant RT may include the surgeon's operative findings, the presence of close surgical margins, multiple N1 nodes with major extracapsular invasion, lymphovascular invasion, and parietal/visceral pleural invasion.[46] In frail or older patients with stage III disease, either exclusive RT or sequential RT and systemic treatment may be advocated.[46] Concomitant chemoradiotherapy with accelerated or conventional fractionation is advised for patients with limited-stage SCLC, with RT commencing at cycles 2 or 3, and prophylactic whole-brain irradiation is included in standard treatment protocols for young patients.[47–49] Consolidation lung irradiation is most often used for individuals with extensive-stage SCLC who respond to chemotherapy. SBRT is increasingly prescribed for patients with oligometastases and bone metastases. In contrast, single or fractionated cranial stereotactic radiosurgery is frequently the first therapeutic option for brain metastases in patients with good performance status.[50,51]

Systemic Treatment

As in many countries globally, the diagnosis and treatment of LC in Turkey have advanced. The management of patients who need systemic therapies (such as chemotherapy, targeted therapy, and immunotherapy) is carried out by medical oncology specialists and chest physicians with experience in LC in tertiary care centers. In Turkey, medical oncology training requires a fellowship for three years after completing four years of internal medicine residency; Turkey has 233 fellows in training and 632 medical oncologists (Table 3). Systemic treatment applications are carried out in line with the indications approved by the MoH of the Republic of Turkey, considering the Food and Drug Administration, National Comprehensive Cancer Network, and the European Medicines Agency guidelines. Oncologists can prescribe drugs that have not been approved for use in their designated indication only after obtaining an off-label application from the MoH. Patients are also evaluated for enrollment in several ongoing phase 2 and 3 clinical trials, which provide access to modern investigational agents. Centers for phase 1 clinical trials also exist, and one houses the first national drug trial currently enrolling patients with NSCLC. Furthermore, to a lesser extent, new treatments are delivered to patients through expanded access programs. The health expenses of patients with LC in Turkey are covered mainly by the SSI and, to a lesser extent, by private health insurance. Depending on personal plans, most private insurance companies cover the costs of Food and Drug Administration and Europe, the Middle East, and Africa–approved cancer therapies.

Systemic treatments are administered by medical oncology specialists and chest physicians with experience in LC. Chemotherapy remains the standard adjuvant treatment for patients with resected stages II to III NSCLC and selected patients with stage IB NSCLC as per international guidelines. Targeted therapy and immunotherapies are not reimbursed in the adjuvant setting, though most targeted agents are approved for use in patients with driver mutations. Patients without activating mutations are recommended platinum-based dual combination regimens, including gemcitabine, taxane, and vinorelbine as adjuvants. Although pemetrexed has been used as second-line therapy for more than 10 years in patients with nonsquamous histology, its use as a first-line therapy still requires off-label approval.

Patients with SCLC are also treated following multidisciplinary approach principles. In limited-stage disease, treatment starts with a platinum or etoposide combination as the standard of care, with concurrent RT initiated as early as possible, usually with the first chemotherapy cycle. Prophylactic cranial irradiation is given after the completion of systemic therapy. In extensive-disease SCLC, systemic treatment is started with a platinum/etoposide combination, followed by thoracic irradiation and prophylactic cranial irradiation in patients with a complete or near-complete response. Cisplatin is the preferred agent in young and fit patients, whereas carboplatin is used in older adults or patients with comorbidities. Immunotherapy is added to first-line chemotherapy in patients with private insurance coverage.

The National Comprehensive Cancer Network and European Society for Medical Oncology guidelines recommend immunotherapy (as monotherapy) as the current standard of care in the first and later lines of

treatment for advanced NSCLC lacking a driver mutation. Immunotherapy can be administered as monotherapy, in combination with chemotherapy, or as dual immunotherapy in combination with/without chemotherapy. In Turkey, pembrolizumab and atezolizumab are approved as monotherapies to treat advanced NSCLC with a PD-L1 level of at least 50% expression and without *EGFR*, *ALK*, and *ROS1* alterations. Only pembrolizumab is licensed to be given in combination with chemotherapy regardless of histology and PD-L1 level. In addition, atezolizumab and nivolumab are approved in patients treated with at least one previous line of chemotherapy for *EGFR*-, *ALK*-, and *ROS1*-negative advanced or metastatic NSCLC regardless of the PD-L1 status. Nevertheless, since 2022, only nivolumab has been reimbursed in this setting. Durvalumab is approved as monotherapy for patients with unresectable locally advanced NSCLC without progression after platinum-based chemoradiotherapy and a PD-L1 level of at least 1%. For extensive-stage SCLC, one year of atezolizumab is approved in combination with carboplatin and etoposide regimens as the first-line treatment. Nevertheless, despite label approval by the MoH, none of the above-mentioned immunotherapy agents are reimbursed in Turkey. Furthermore, Turkey has not approved the ipilimumab-nivolumab combination alone or with two cycles of chemotherapy in the first-line advanced setting or immunotherapy agents as adjuvant or neoadjuvant treatments. Therefore, access to immunotherapy is limited to patients enrolled in clinical trials, patients in early access programs, and patients with private insurance.

Recently, new drugs with efficacy in NSCLC have undergone development, and new targeted therapies have been approved. Until recently, the first-generation *EGFR* TKIs, erlotinib and gefitinib, and the second-generation TKI, afatinib, were approved and reimbursed as the standard of care for first-line treatment of advanced NSCLC with *EGFR* exon 19 deletion and 21 mutations. Nevertheless, osimertinib, a third-generation *EGFR* inhibitor, was recently approved for first-line treatment of advanced NSCLC with *EGFR* exon 19 deletion and 21 mutations but was not reimbursed by the social security system. Osimertinib is approved and reimbursed in Turkey for patients with T790M-mutant advanced NSCLC who progressed after the first- or second-generation *EGFR* inhibitors.

Crizotinib was the first drug approved and reimbursed universally for those with *ALK*-translocated tumors. As ceritinib is more effective than chemotherapy and alectinib and brigatinib significantly improve patient outcomes compared with crizotinib, these drugs were approved and reimbursed for treatment of naive *ALK*-positive NSCLC and patients with progressive disease on crizotinib. Recently, a third-generation lorlatinib was

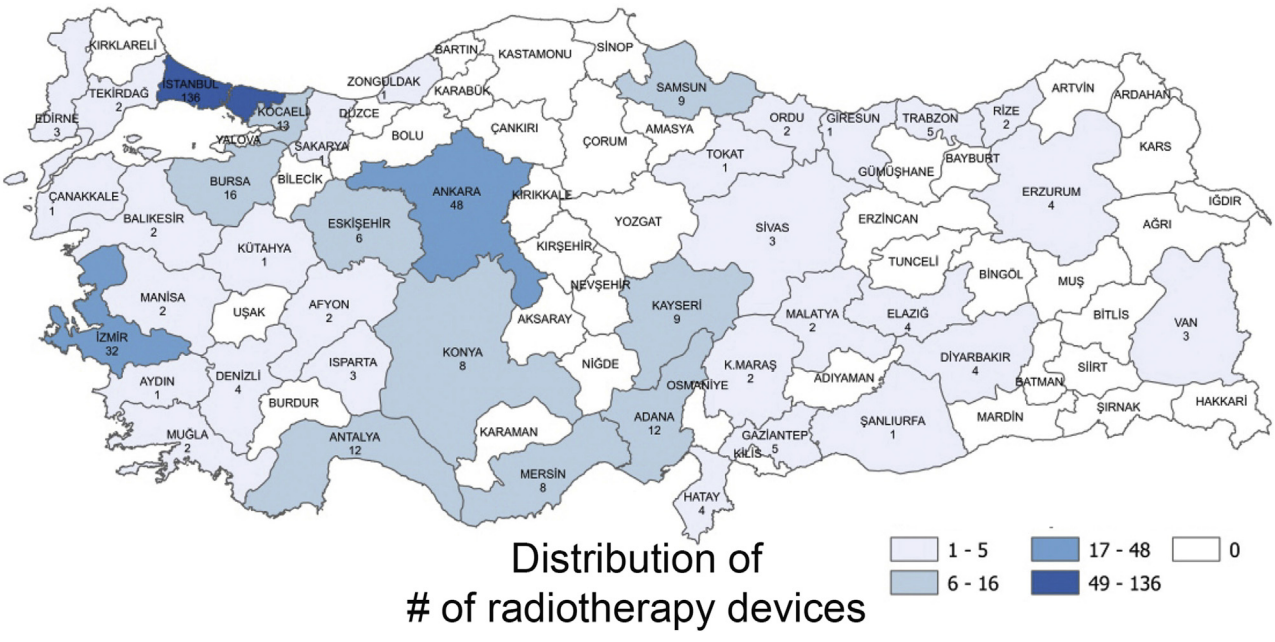
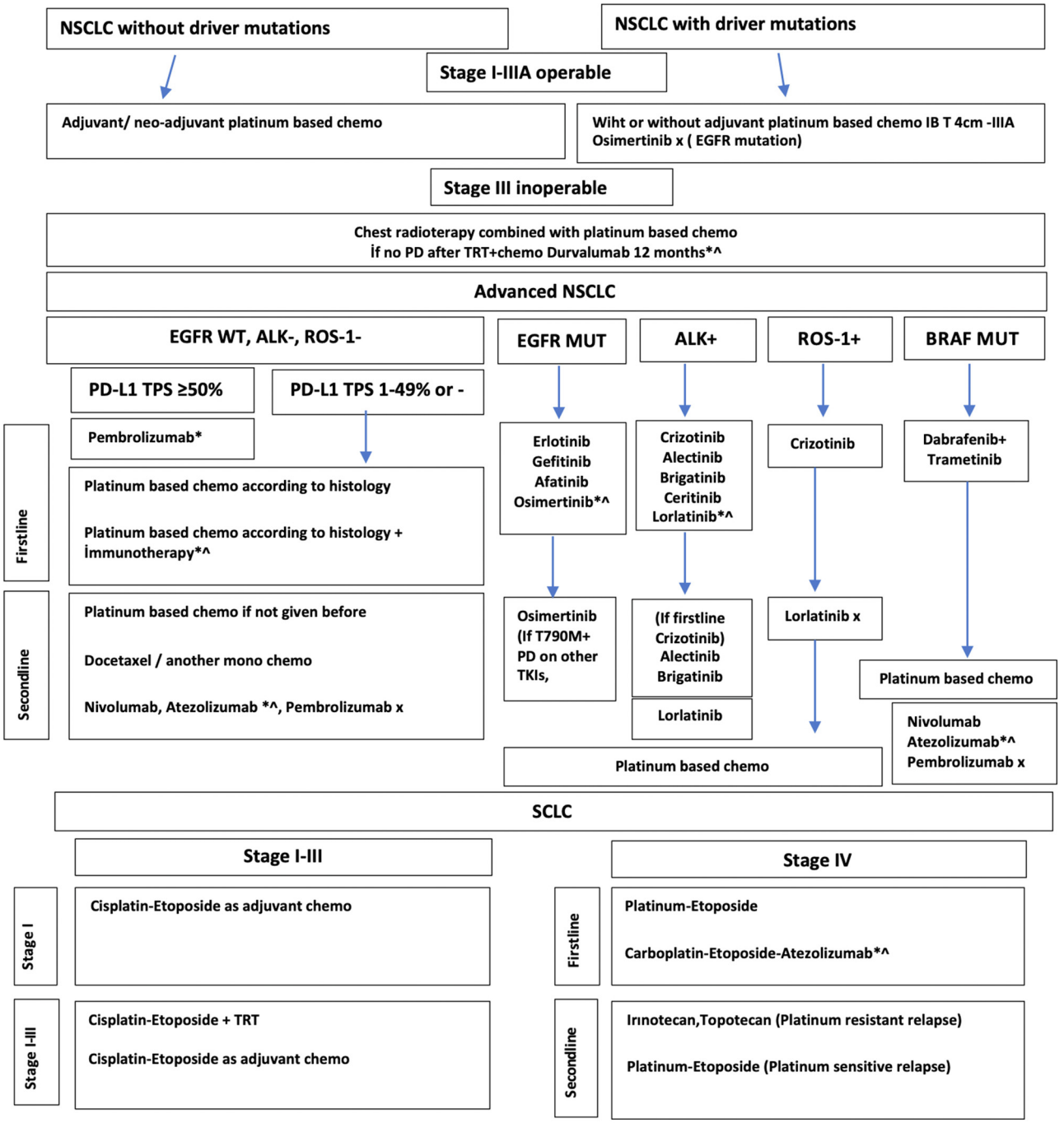


Figure 4. Distribution of the number of radiotherapy devices in Turkey.

approved and reimbursed for patients who progressed with first- and/or second-generation *ALK* inhibitors, and it was approved but not reimbursed as first-line treatment. For ROS-1 translocations, the only approved and reimbursed TKI is crizotinib. Dabrafenib plus trametinib is approved for patients with advanced NSCLC, only with the *BRAF* V600E mutation, regardless of the treatment line, but still awaits reimbursement.



Abbreviations; Chemo; chemotherapy, PD; progressive disease, TRT; Thoracic radiotherapy,
* Drugs that are approved by MoH but not reimbursed by MoLSS
x Drugs that aren't approved by MoH and reimbursed by MoLSS
^ Drugs that are only reimbursed by private Insurance system or Drugs that are self paid

Figure 5. LC current treatment algorithm in Turkey. LC, lung cancer.

Except for the *EGFR*, *ALK*, *ROS1*, and BRAF mutations, the approval process for drugs targeting NTRK fusion (larotrectinib and entrectinib) is ongoing. In addition, selpercatinib for RET fusions, capmatinib or tepotinib for MET14 skipping mutations, amivantanab for exon 20 insertions, sotorasib for *KRAS* G12C mutations, and anti-HER treatments for HER2 mutations are not approved nor reimbursed in Turkey. Figure 5 summarizes the current LC treatment algorithm in Turkey.

Future Challenges and Perspectives

Considering the high incidence of lung carcinoma in Turkey, future targets include initiating LC screening programs alongside smoking cessation programs that are structured according to the needs and resources of the country. Alongside the recent increase in detecting ground-glass lesions, the number of operations performed in the early stages has also increased. The increased number of cases requires more standard use of minimally invasive surgical methods in TS. The number of experienced physicians, equipment, and hospital beds needed to diagnose and treat LC in Turkey have been increasing annually; they are currently sufficient and of high quality. Nevertheless, diagnostic and therapeutic facilities are not equally accessible in all parts of the country, and providing easier access to sophisticated diagnostic and therapeutic facilities in rural areas is critical.

We plan to create a multidisciplinary platform that combines all specialties, updated treatments, and clinical trials, where patients across Turkey can be discussed and treated individually.

CRediT Authorship Contribution Statement

Ayten Kayı Cangır, Perran Fulden Yumuk, Serpil Dizbay Sak, Serap Akyürek, Ahmet Demirkazık: Conceptualization, Methodology, Data curation, Original draft preparation, Visualization, Supervision, Writing-reviewing and editing.

Yeşim Eralp, Atilla Eroğlu, Ali Murat Tatlı: Data curation, Writing- reviewing and editing.

Ülkü Yılmaz, Uğur Selek, Saadettin Kılıçkap: Data curation, Visualization, Writing- reviewing and editing.

Fazilet Öner Dinçbaş, Mehmet Ali Nahit Şendur, Asli Görek Dilektaşlı, Hakan Şat Bozcuk, Serdar Özkök, İlhan Öztop, Erkan Topkan, Şükrü Dilege, Akın Kaya: Writing- reviewing and editing.

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