EDITORIAL: LUNG CANCER WORLDWIDE

Lung Cancer in Colombia

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Epidemiology and Health Care System

Colombia is a country on the northwest of South America, and it is divided into 32 departments, a capital district, 1121 municipalities, and indigenous territories. Population growth in the period 1990 to 2016 was 42.0%, during which time population structure became regressive and older, with most living in urban areas (82%) (Fig. 1*A–C*). The Colombian health system is made up of a social security sector and a private sector. The system's backbone is the General Social Security Health System, with a coverage near to 100%.[1]

According to data from GLOBOCAN, 6876 incident cases of lung cancer (LC) occur every year in Colombia. LC represents the sixth place among the malignant neoplasms documented annually in the country, with an estimated age-standardized incidence rate of 10.5 per 100,000 inhabitants.[2] LC ranked second in overall cancer mortality in both sexes, accounting for 11.8% of deaths. It was the third cause of death in men (7.1% of the total) and the fourth in women (4.7%). The country's age-adjusted rate for mortality from this cancer was 11.5 per 100,000 in men and 6.4 per 100,000 in women, with a gradual decrease in the

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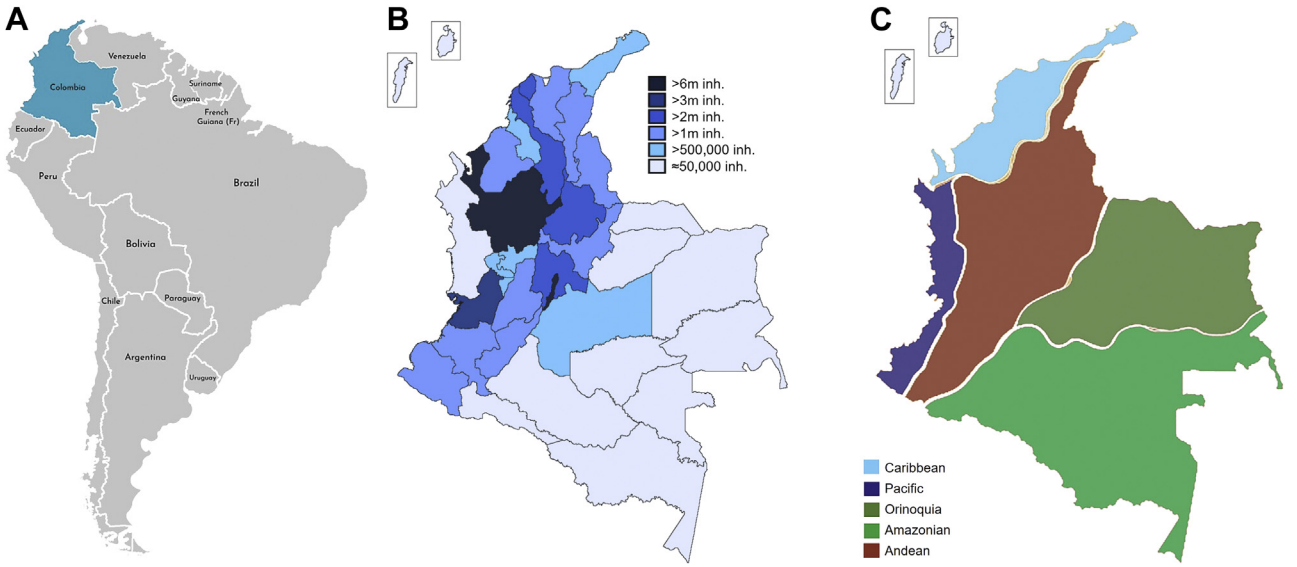

Figure 1. Colombia is a country of significant geographical differences, profound variations in economic and social development of its regions (and within its territories), and regional markets dependent on the so-called intermediate cities. (*A*) Location of Colombia in South America. (*B*) The population is concentrated mainly along the Caribbean coast and the Andean highlands. The eastern lowland areas, which account for 54% of the country's size, have less than 3%. Despite being one of the top 30 most populous countries, Colombia is sparsely populated with just 41 people per square kilometer (106/square mile), which ranks 173 in the world. Colombia is the third most populous country in all of Latin America, and it is home to the third largest number of Spanish-speaking people in the world after Mexico and the United States. The population growth rate of Colombia is currently 1.08%, which has decreased consistently every year. (*C*) The geography of Colombia consists of six main natural regions, and each region represents its own different and unique characteristics. On of the main features of Colombia that highlight its geography are the Andes Mountain range that is shared with Ecuador and Venezuela, the Pacific coastal area that joins with Panama and Ecuador, the Llanos plains that are shared with Venezuela, the Caribbean coastal region with Venezuela and Panama, and the Amazon rainforest area that connects with Venezuela, Brazil, Peru, and Ecuador. The largest city and capital is Bogotá, which has a population of 7.9 million. The greater metropolitan area has a population of 12 million. Other major cities include Medellin (1.9 million), Cali (2.4 million), and Barranquilla (1.2 million). inh., inhabitant; m, million.

last two decades (Fig. 2*A* and *B*).[3] The highest rates were observed in men in all departments. The regions with a higher concentration of risk for LC, by standardized mortality ratio, were Antioquia and departments of the Coffee Region (Risaralda, Quindío, and Caldas). On the contrary, the areas with the lowest risk for both sexes were found in the southern departments of Nariño and Cauca. From 1994 to 2013, the mortality trend for LC in men slightly decreased in the average annual percentage change (−0.02%), but in women, it increased (0.5%).[3,4]

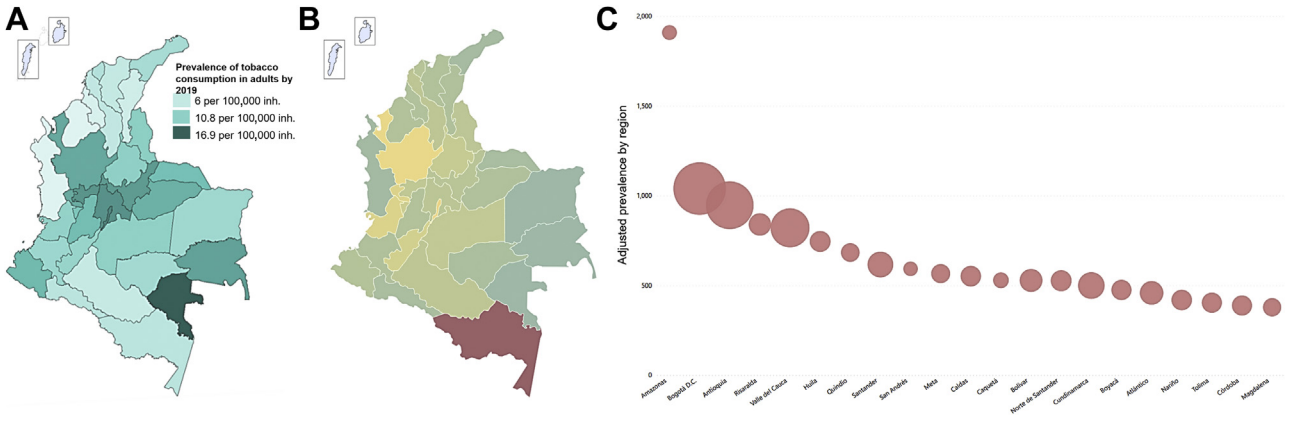

Figure 2. (*A*) Prevalence of LC considering political division by departments of Colombia. (*B*) Most cases are concentrated within the 10 departments with the highest population concentration, including Antioquia, Bogotá, Risaralda, Valle del Cauca, Huila, Quindío, and Santander (CAC, 2020). (*C*) Distribution of the prevalence of tobacco use (by departments) in adults for 2019 (National Survey on the Use of Psychoactive Substances, 2019). Only eight regions of the country are in the highest quartile of prevalence, being above 11%, specifically Risaralda, Antioquia, Guainía, Boyacá, Caldas, Cundinamarca, Bogotá, and Vaupés (figure modified with permission from the CAC, Bogotá, Colombia). CAC, Cuenta de Alto Costo; inh., inhabitant.

Exposure to occupational carcinogens and specific circumstances are factors associated with LC. Nowadays, 28 substances, work situations, and associated occupations (group I—International Agency for Research on Cancer) have been described as risk factors for LC. Furthermore, air pollution, socioeconomic status, and diet could be additional risk factors for LC.[5]

Cancer is a high-cost disease, and considering the need for real-world information with a national scope, the National Cancer Information System, managed by the High-Cost Diseases Fund (CAC), was created to improve the decision-making process through the evaluation of access to cancer diagnosis and follow-up into the National Health System (NHS).[6] According to the CAC, for 2020, LC was the seventh cause of cancer-related deaths, and it had an adjusted incidence and mortality rate of 2.89 and 3.00 per 100,000 inhabitants, respectively (Fig. 3*A and B*).[7]

Tobacco Use

According to the National Study of Consumption of Psychoactive Substances in Colombia, carried out in 2019,[8] 12.1% of people surveyed declared having smoked tobacco in the last year (16.9% men and 7.6% women) (Fig. 2*C*) and approximately 10% reported having smoked in the previous month (13.8% men and 6% women). In addition, 5.7% of the population declared smoking daily, mainly men (8.1%), between 45 and 64 years (7.3%), and among those with less socioeconomic development (6.4%). The most frequent age of onset of tobacco use was 18 years, and 25% of people who have smoked did so for the first time at age less than 15 years. A significant percentage of the people (85%) consider smoking cigarettes as a health risk; however, teenagers see it as a minor problem.

Law 1335 of 2009 sought to guarantee compliance with environments 100% free of tobacco smoke in the nation. In addition to that, it increased 100% in taxes indexed to the Consumer Price Index and the Gross Domestic Product for tobacco products and its derivatives before 2021. Besides that, the sizes of health warnings in tobacco packing have been increased.[9]

Screening and Early Detection

Some clinical trials revealed the importance of early detection of LC with low-dose radiation chest tomography (LDCT) and reduction in specific mortality from LC, resulting in the mandatory use of LDCT in high-risk populations in many countries.[10] Since 2012, the Colombian Ministry of Health has established priorities for the care of the most common cancers, LC included. In 2014, the first National Guideline for the Management of LC was published. The Guideline defined the recommendations for early detection in high-risk populations (aged 50–74 y, cigarette consumption with a pack-year index $>$ 30, and cessation in the past 15 y).[11]

Besides the existence of standardized guidelines for screening and detecting LC in Colombia, its implementation is challenging. The main difficulties for this have been realted to a fragmented NHS, access to

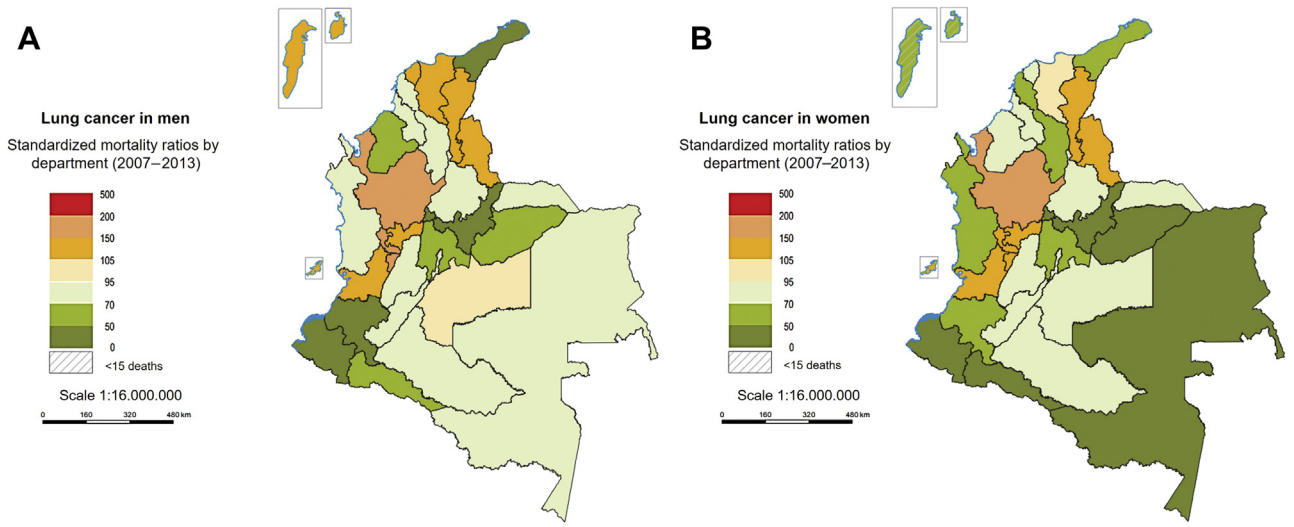

Figure 3. LC mortality for men (*A*) and women (*B*) in Colombia, 2007 to 2013 (atlas of cancer mortality in Colombia, 2017). Color gradients and areas of concentration of risk for LC whose areas of greatest concentration correspond to the area of Caldas and the departments of Antioquia and Valle del Cauca. Departmental risk maps were prepared with two colors (green and red) in seven ranges with fixed values. It was sought to easily identify departments with a risk higher than the national average, those with lower risk, and those at the same level of risk as the country (figure modified from the Atlas of Cancer Mortality in Colombia 2017, National Cancer Institute—INC, Bogotá, Colombia). INC, Colombian National Cancer Institute; inh., inhabitant; LC, lung cancer.

established programs, LDCT or specialists with knowledge of early detection, few institutions with the necessary infrastructure, and care focused on other types of cancer.

Four years ago, a structured program for the early detection of LC was established in a respiratory care-focused institution at Bogotá. This is a hybrid, private program where the patient finances the costs of tests and clinical follow-up (near 300 U.S. per y). The program was implemented considering the recommendations of the American Thoracic Society and the U.S. Preventive Task Force.[12,13] In addition to LDCT, pulmonary function tests and advice for tobacco cessation are applied. Structured reporting of LDCT is performed using the Lung-RADS,[14] and abnormal test results suggestive of LC are discussed in a multidisciplinary tumor board. Nowadays, the center has reached a high adherence to the program, with the main difficulties being the referral and follow-up of candidates and lung-RADS-based reading.

Ancestry Contribution to Molecular Epidemiology

Disease phenotypes are diverse among different latitudes. Variation in *EGFR*-sensitizing mutation frequencies has been widely described especially when comparing Asian with Western cohorts. In the case of Colombia, it is a nation with ancestral contributions from southeast Asia, native America, western Europe, Mediterranean, and Africa.[15] A recent study analyzed samples from Latin American patients, including 552 nonsmoker Colombian patients. It revealed that with increased representation of native American haplotypes (southeast Asian), *EGFR* mutation frequency increases proportionately. Furthermore, *KRAS* mutation frequency was inversely associated with native American marker allelic frequency.[16]

Interestingly, ancestral distribution is heterogeneous across Colombia, with some regions enriching one or more of the populations mentioned previously.[15] By evaluating the prevalence of the *KRAS*-G12C mutation across the LC samples, we were able to identify regional differences in terms of local prevalence. We constructed a model based on genomic identification markers using short tandem repeats to reveal that the population composition played a role in determining these variations. The model considered the different allelic frequencies of each marker across sampled regions and the corresponding local *KRAS*-G12C frequency. With an adjusted R^2 of 0.946, the model revealed that differences in ancestral composition are highly associated with this type of mutation.[17] We also conducted a similar study using the same short tandem repeat methodology evaluating population composition and its impact on *EGFR* mutations, programmed death-ligand 1 (PD-L1) expression, and *ALK* translocations. By analyzing more LC markers and grouping administrative regions in clusters, we also determined that the geographic distribution of tumor markers is highly associated with population composition (data in print).

Another contribution of germline composition found in patients in Colombia related to the *BIM* gene. This polymorphism leads to anti–*EGFR* tyrosine kinase inhibitor (TKI) resistance. With an estimated 15.7% prevalence among *EGFR*-positive sample patients, it becomes relevant when considering approximately 26% of *EGFR* positivity in Colombia.[18] These examples of germline contributions to LC phenotypes strengthen the hypothesis of disease modulation by individual genomic composition, especially in our country.

Diagnosis and Staging

In Colombia, few institutions can implement interventional pulmonology. The main indications for bronchoscopy are the suspicion of LC, mediastinal staging, and infections (tuberculosis). Seven centers have an endobronchial ultrasound for invasive diagnosis and staging. The main difficulties are the disposition of these centers in main cities and that the personnel trained for their realization and the support personnel (pathologists and cytotechnologists) are scarce. In institutions where minimally invasive endoscopic and surgical diagnostic techniques are available (conventional bronchoscopy, endobronchial ultrasound, mediastinoscopy), these would be preferred over traditional approaches.[19]

Thoracic Surgery

Thoracic surgery has been a differentiated surgery specialty in Colombia since the 1950s when some thoracic surgeons trained in the United States returned to the country. In 1990, the first and only training program in General Thoracic Surgery opened. It is a 2-year program for general surgeons, and since 2009 it has had a clear emphasis on oncologic thoracic surgery. There are 86 certified thoracic surgeons across the country. The relationship with the population is one thoracic surgeon per 586,000 inhabitants, distributed in 18 department capitals. Of the 33 regions in Colombia, 15 do not have thoracic surgeons in their hospitals. In addition, 12 (14%) general thoracic surgeons are not trained in advanced minimally invasive thoracic surgery. Still, approximately 74% of the thoracic surgeons have enough learning curve in video-assisted thoracic surgery (VATS) to offer a high-quality lobectomy with a systematic or lobe-specific lymphadenectomy. Recent efforts to implement LC screening strengthen the need to

advance in the performance of anatomical segmentectomies in tumors diagnosed earlier, but it is still a developing practice (Table 1).[2,20-22]

VATS technology is available nationwide, but robotic-assisted thoracic surgery (RATS) is performed only in Bogotá. Colombia pioneered RATS in Latin America in 2012, when a trained surgeon performed the first lobectomies several years in other neighboring nations. Nevertheless, RATS lobectomy is an expensive procedure, and it is available only in three hospitals in Bogotá. The National Guidelines for LC recommend lobectomy for early stage NSCLC and induction therapy in locally advanced disease.[11] Nevertheless, the number of surgeries with curative intent is low. Still, following these procedures, the rate of minimally invasive thoracic surgery lobectomies in Colombia is approximately 75%, most of them performed by VATS. Nowadays, more thoracic surgeons evaluate patients for possible resection of residual disease after treatment of initially unresectable disease.

Radiation

The general landscape of Radiation Oncology in Colombia has been changing rapidly in the last decades. In 2005, a study by the Colombian National Cancer Institute reported the availability of 14 megavoltages, 26 cobalt, and 25 brachytherapy machines to deliver radiotherapy in Colombia.[21] In 2018, these numbers doubled and the cobalt machines were replaced with new estimates of 67 megavoltage machines and 28 brachytherapies authorized.

Despite the many significant advances, there are several challenges to providing radiotherapy care for patients with LC in Colombia. For once, the amount of treatment units is insufficient to meet the country's demands, with an estimated deficit of approximately 47 megavoltage machines.[21] Moreover, there is a high concentration of radiotherapy units in capital cities, while 11 of the 33 districts in the country do not have radiotherapy services.[23] Furthermore, the number of radiation oncologists is significantly below the local requirements. Finally, and importantly for the treatment of LC requiring stereotactic body radiation therapy (SBRT), few of the available treatment units are dedicated radiosurgery and stereotactic machines; hence, many patients end up receiving inferior quality treatments.

Nevertheless, there are plenty of reasons to believe that radiation oncology in Colombia will continue improving. First, the availability of megavoltage machines is expected to increase, some of them with the creation of a new major national cancer center. Second, thanks to the use of technologies such as surface-guided radiotherapy, it is now possible to provide LINAC-based SBRT, and it has been successfully done for the treatment of early stage LC or oligometastatic disease.[23] Remarkably, this strategy has been increasingly adopted to upgrade the installed capacity to provide SBRT.

Systemic Therapy

According to the Colombian cancer situation report in 2020, most new LC cases were in advanced stages; 67.7% of LC cases were in stage IV and 15.6% in stage III.[4] Systemic therapy was administrated in 42.2% of the population, and almost 40% did not receive any active treatment (radiation, surgery, chemotherapy [CT]). The mean time between diagnosis and first treatment was 49 days, and it was longer in poor or rural populations. The distribution by histopathology subtypes was led by adenocarcinoma (80% of patients).[24]

The selection of systemic therapy depends on the molecular characteristics of the tumor (Fig. 4). In this

Table 1. Total Number of Specialists Related With Diagnosis or Treatment of LC in Colombia According to the National Statistics

Medical Specialty	Number of Specialists	Relation With Population (Specialist/Number of Habitants)	Number of Specialists Over Incident LC Cases (Specialist/New LC Cases Over Year)
Pulmonologists	300	1/153,800	1/22
Interventional pulmonologists	21	1/2.197,000	1/325
Medical oncologists and hemato-oncologists	218	1/211,600	1/560
Radiation oncologists	101	1/473,670	1/68
Thoracic surgeons	86	1/586,000	1/84
Radiologists	1280	1/37,350	1/6

Data obtained from national organizations record and Ministry of Health projections about the number of registered specialists in the country. The relation of specialist over population was obtained with the number of medical specialists over 100,000 habitants over 18 years of age and the number of specialist over incident cases was obtained with the relation of medical specialist over new LC cases in Colombia according to GLOBOCAN data.[2] Some of the date can underestimate the actual numbers because affiliation to associations such as the Colombian Society of Pulmonology and Thoracic Surgery, Colombian Association of Hematology and Oncology, and Colombian Association of Radiologists is not mandatory for clinical practice in the country.[20,21,22]
LC, lung cancer.

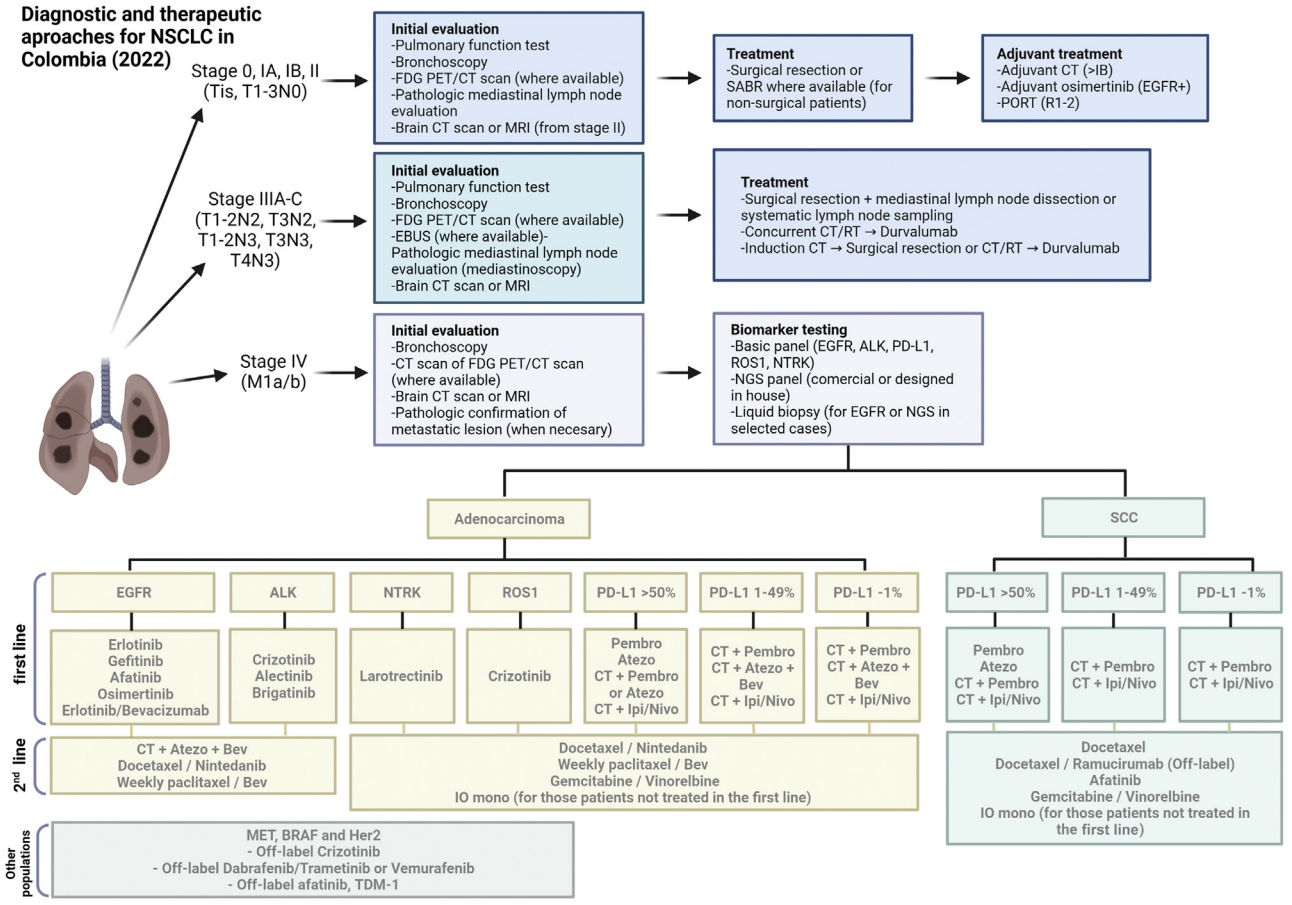

Figure 4. Diagnostic and therapeutic approaches for NSCLC in Colombia (2022). This is a flowchart for diagnostic and therapeutic options according to the stage of NSCLC based on the recommendations of the Colombian Guidelines for LC published by the Ministry of Health. We reveal the initial evaluation and treatment for early stages (0, IA, IB, II, IIIA-IIIC). For stage IV, we also include molecular profiling and the determination of the two main histologic subtypes of NSCLC, adenocarcinoma and squamous cell carcinoma; in those cases, according to the molecular profile, clinicians choose the treatment.[11] Access to many of the technologies depends on their availability according to insurance type, and the use of off-label drugs depends in most cases on the use of a legal procedure locally known as "Tutela." Atezo, atezolizumab; Bev, bevacizumab; CT, chemotherapy; FDG, fluorodeoxyglucose; Ipi, ipilimumab; LC, lung cancer; MRI, magnetic resonance imaging; NGS, next-generation sequencing; Nivo, nivolumab; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; PET/CT, positron emission tomography/computed tomography; PORT, postoperative radiotherapy; RT, radiotherapy; SABR, stereotactic ablative radiotherapy; SCC, squamous cell carcinoma.

regard, approximately 50% to 60% of Colombian patients with LC have access to molecular profiling, usually patients who received treatment in institutions located in main Colombian cities. The molecular characterization in Colombia is focused on *EGFR*, *ALK*, and PD-L1. In the last year, reactive oxygen species (ROS) evaluation was added considering the recent local approval of Crizotinib. Data in the local cohort revealed that patients with *ALK* rearrangement, *EGFR* mutation, or PD-L1 expression greater than or equal to 50% have better overall survival than patients without these features.[24]

In the nonmutant driver population (*EGFR* wild type, *ALK*, ROS1 negative), CT combined with immunotherapy (IO) was the most frequent systemic therapy administered.[4] The most common cytotoxic agents used were carboplatin, pemetrexed, paclitaxel, and cisplatin. Pembrolizumab was the most frequent IO used, alone or combined with CT. IO was introduced in Colombia in 2016 as second-line therapy. Furthermore, in 2017, it was approved for patients with PD-L1 greater than or equal to 50%; in 2018, in combination with CT for nonsquamous NSCLC regardless of PD-L1; and in 2019 for squamous NSCLC. The local regulatory agency (Instituto Nacional de Vigilancia de Medicamentos y Alimentos) approved other combinations of IO-CT (atezolizumab-bevacizumab-CT) in 2020 and IO-IO-CT (Checkmate 9LA regimen) more recently.

For patients with *EGFR* mutations (nearly 22% of the population), osimertinib (most frequently used),

erlotinib, gefitinib, and afatinib are approved.[7,24] Some combinations such as erlotinib plus bevacizumab, erlotinib, or gefitinib plus CT are also approved but less frequently used. It caused a concern about budget impact in NHS, considering significant differences in prices between third- and first- or second-generation agents, which could reduce their access. For patients with *ALK* rearrangement (10% of the population),[25] crizotinib and alectinib are approved. Third-generation agents are not available, and in case of failure to crizotinib or alectinib, CT is still an option. Less frequent molecular alterations such as BRAF mutations or RET rearrangements do not have approved treatments in Colombia.

There is a law figure to access medicines not available in the country, called not available-vital medicine, which consists in individual importation; however, its success is rare. The limitation to access to targeted therapies besides *EGFR* or *ALK* causes a low interest between oncologists to perform comprehensive molecular profiling in LC. In contrast, access to these therapies is unequally distributed, and it depends on the health insurance administrator company who can persuade or even deny access to treatment.

At the beginning of this year, the Colombian Ministry of Health included 11 pharmacologic therapies for treatment of NSCLC in the national health plan, previously approved by the Instituto Nacional de Vigilancia de Medicamentos y Alimentos. Nevertheless, these drugs have a different financial coverage mechanism from the national health plan, limiting their real access. Among the new inclusions are five TKIs, one antiangiogenic drug (bevacizumab), five immune checkpoint inhibitors, and one CT agent for SCLC (etoposide). A significant number of these new drugs correspond to checkpoint inhibitors (anti–programmed cell death protein-1 and anti–PD-L1), facilitating access to the group of patients with NSCLC without driver mutations. For patients with driver mutations in *EGFR*, *ALK*, and ROS1, Colombia has included the TKI treatment; however, other therapies for mutations in BRAF, NTRK, or HER2 are still pending for approval. Even in clinical scenarios of NSCLC with rearrangement in *ALK*, only crizotinib and alectinib are available, limiting the treatment for second- or third-line therapies. So, clinicians are forced to use CT and IO as the second line with higher clinical and financial toxicity odds. In addition, in patients with NSCLC and *EGFR* mutation, there are no available drugs for exon-20 insertions or combinations with antiangiogenics (ramucirumab) as first line.

As can be deduced, we have a heterogeneous situation in Colombia, with wide availability of options for the first line of NSCLC without oncogenic addiction, but with essential limitations for almost 40% of patients who have driver mutations, not only in terms of their treatment but also in the possibility of molecular profiling at the beginning of the therapeutic process.

CRediT Authorship Contribution Statement

Andrés F. Cardona: Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing—original draft, Supervision.

Sergio A. Mejía, **Lucia Viola, Leonardo Rojas Alejandro Ruíz-Patiño:** Conceptualization, Writing—original draft.

Diego F. Chamorro: Data curation, Resources, Writing—original draft, Writing—review and editing.

Adriana Serna, Stella Martínez: Formal analysis, Writing—original draft.

Álvaro Muñoz, July Rodríguez, Juan E. García-Robledo, Luis Eduardo Pino, Zyanya Lucia Zatarain-Barrón: Formal analysis, Data curation.

Oscar Arrieta: Conceptualization, Methodology, Writing—review and editing.

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