

Lung Cancer in Peru



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A Perspective From Peru

Peru is a South American nation with a growing and aging population of 31 million people with a life expectancy at birth of 76.7 years. The country is divided into 25 regions, 79% of the population is urban, and Lima, the capital, concentrates more than a third of the population.¹ Although Peru is an upper-middle-income country, health expenditure represents only 5.1% of the gross domestic product, which is lower than the average of Latin America and the Caribbean (LATAM) (8.56%).² Out-of-pocket health expenditure is 30.9%.³ Peru has a comprehensive National Cancer Plan and two population-based cancer registries in Lima and Arequipa.

The Peruvian health care system is fragmented into public and private sectors, leading to considerable disparities. The public sector is further divided into a subsidized regimen and a contributory regimen. Within the subsidized regimen, the provision of health services is covered by Seguro Integral de Salud (SIS) in the network of establishments, hospitals, and institutes of the Ministry of Health (MOH), including the Peruvian National Cancer Institute (INEN) and the two regional cancer institutes. The contributory regimen corresponds to the social security system (EsSalud) that provides services in its own establishments for the salaried population and their families. The private sector is composed of multiple private insurers, private clinics, and medical centers and offers services for the population with capacity to pay. Overall, SIS and the social security cover 44% and 25% of the population, respectively, whereas only 5% of the population has a private insurance.¹ However, this general overview covers marked national variation. The rural population is affiliated to SIS and the social security in 76% and 6%, respectively. In contrast, whereas 10% of Lima's population has a private insurance, those affiliated to this type of insurance do not reach 5% in 21

of 25 regions.⁴ Recently, the government made a great step toward universal health insurance, as it authorized the affiliation of all persons without any health insurance who reside in Peruvian territories to SIS, regardless of their socioeconomic status.⁵

Epidemiology

Lung cancer is the sixth most common cancer and the second cause of cancer deaths in Peru. According to Globocan statistics, 3210 new cases and 2844 deaths were projected in 2018, with standardized incidence and mortality rates of 9.5 and 8.9, respectively, and a mortality-incidence ratio of 0.93. Lung cancer incidence in Peru is lower than the LATAM average.⁶

A nationwide health information system (REUNIS-MINSA) now provides visual data on several diseases,

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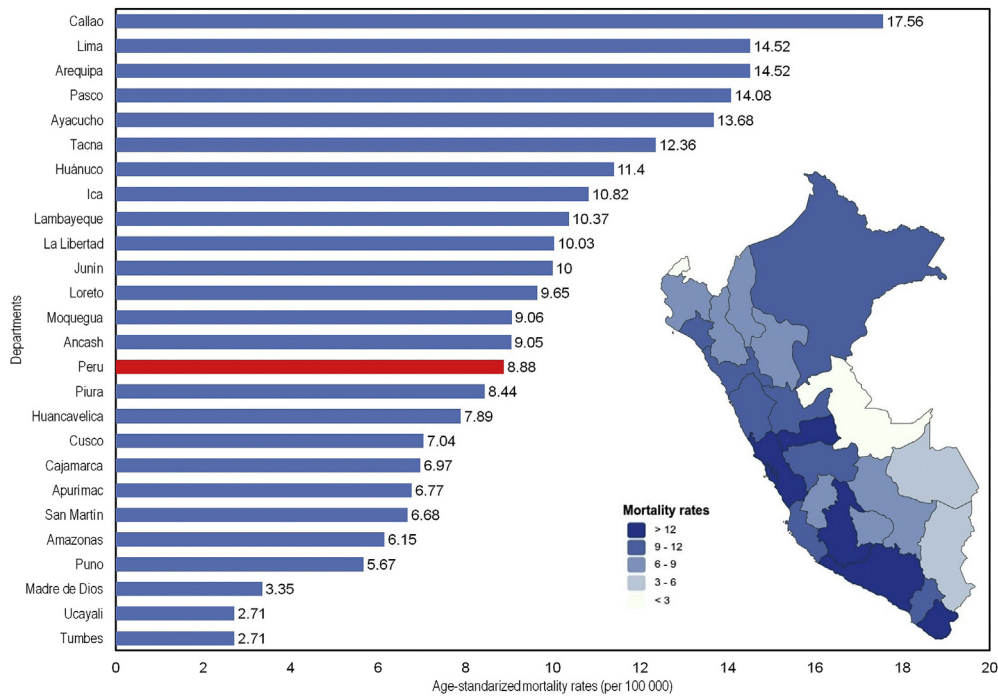


Figure 1. Age-standardized mortality rates (per 1,000,000) from lung cancer by regions in Peru from 2011 to 2015.

including lung cancer mortality rates by regions, showing significant differences across the board and ranging from 2.7 to 17.5 per 100,000 inhabitants (Fig. 1). The regions with the highest mortality are Callao, Lima, and Arequipa,⁷ and this distribution has been maintained since 2005.⁸

According to the Metropolitan Lima Cancer Registry (2010–2012),⁹ lung cancer has a standardized incidence rate of 11.2 (13.3 in males and 9.6 in females) and a standardized mortality rate of 9.2 (11.0 in males and 7.8 in females). Most cases (75%) occurred in people older than 60 years. Lung cancer in patients younger than 40 years represents 4.3% of all cases as presented in a recent series.¹⁰

Data from Metropolitan Lima Cancer Registry indicate as well that from 1968 to 2012, lung cancer incidence has decreased in men and increased in women (Fig. 2),⁹ although the absolute number of cases is increasing because of population growth and aging. Data on mortality, corresponding to a shorter period (1990–2012), indicate a nonsteady decrease for men and an increase for women. In Lima, standardized lung cancer incidence varies greatly among districts, ranging from 6.34 to 35.97 in the male population and from 5.47 to 21.66 in the female population. When comparing two periods, 2004 to 2005¹¹ versus 2010 to 2012,⁹ it was found that incidence has increased, especially in women;

four and eight of 49 districts entered the highest tier of incidence in men and women, respectively (Fig. 3).

Tobacco Control and Other Risk Factors

The prevalence of tobacco use in adults in Peru has more than halved from 27% in 2000¹² to 13.3% in 2010—19.7% in men and 7.8% in women.¹³ This is lower than the current prevalence of smokers in the LATAM region, which has also decreased from 28% in 2000 to 17.4% in 2015.¹⁴ Likewise, current cigarette and tobacco smoking among youth (aged 13–15 y) has decreased from 19.4% in 2007 to 9.7% in 2014.¹⁵ These results suggest that tobacco control policies as outlined in the following are having a progressive impact.

Peru ratified the WHO Framework Convention on Tobacco Control (WHO FCTC) in November 2004,^{16,17} and enforced it in 2005. Significant progress has been made in adhering to the framework through the endorsement of laws guaranteeing a 100% smoke-free public environment and regulating tobacco advertising, packaging, and labeling.^{18–20} In Peru, tobacco advertising within 500 m from a health or education establishment is banned. The amount of nicotine, tar, and monoxide must be disclosed in the cigarette packages, and 50% of both sides of the packages must include graphic and text warnings, which are rotated every 12 months. In addition, the use of the terms “light” or “soft” is prohibited. Importantly, retail sale or sale in packages less

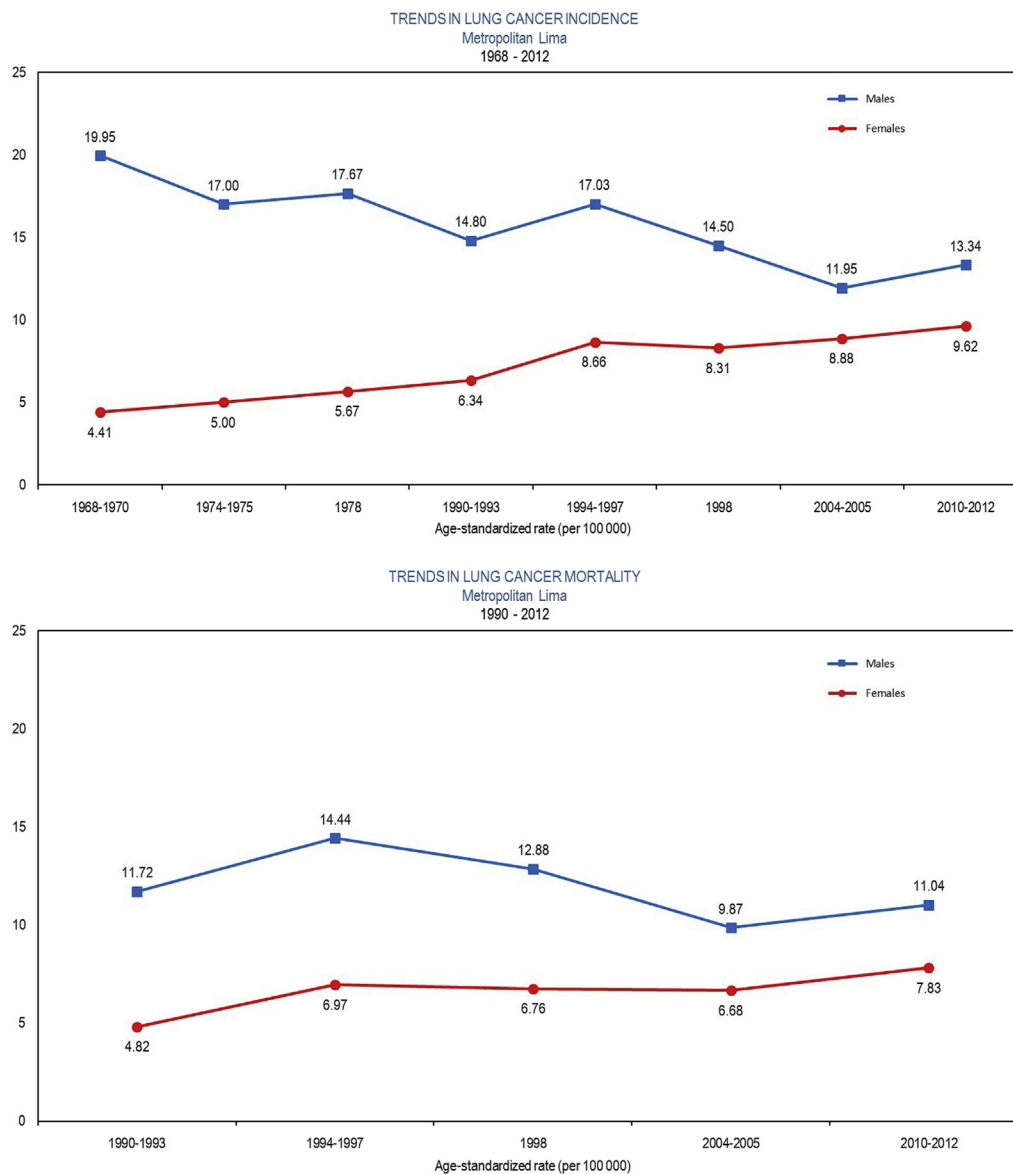


Figure 2. Trends in incidence and mortality. Reprinted with permission from Departamento de Epidemiología y Estadística del Cáncer. Instituto Nacional de Enfermedades Neoplásicas.⁹

than five cigarettes and selling to people under 18 years old is illegal. Nevertheless, there are pending commitments to fully implement the WHO FCTC, to integrate smoking control programs and strategies into a National Tobacco Control Plan, which is still nonexistent, to develop a tobacco cessation program, to take action to avoid interference from the tobacco industry, and to increase taxation further to reduce tobacco demand. In 2018, the tax per pack of cigarettes was increased to 61%, which is the highest recorded in the country.^{21,22} However, the recommendation of the WHO FCTC is 75%.

Under the leadership of the MOH, a multisectoral approach has been used to formulate and implement

tobacco control actions. For its part, the Ministry of Education has established prevention programs in the school curriculum to prevent the start of tobacco consumption. Local governments carry out marketing inspections and ensure smoke-free environments. It is worth emphasizing the role of the civil society through Comisión Nacional Permanente de Lucha Antitabáquica, an institution with international support that since 1988 has been promoting and advocating for public policies regarding tobacco control, educating human resources, and verifying compliance with the law.

The prevalence of smokers among Peruvian patients with lung cancer in recent series has been reported to

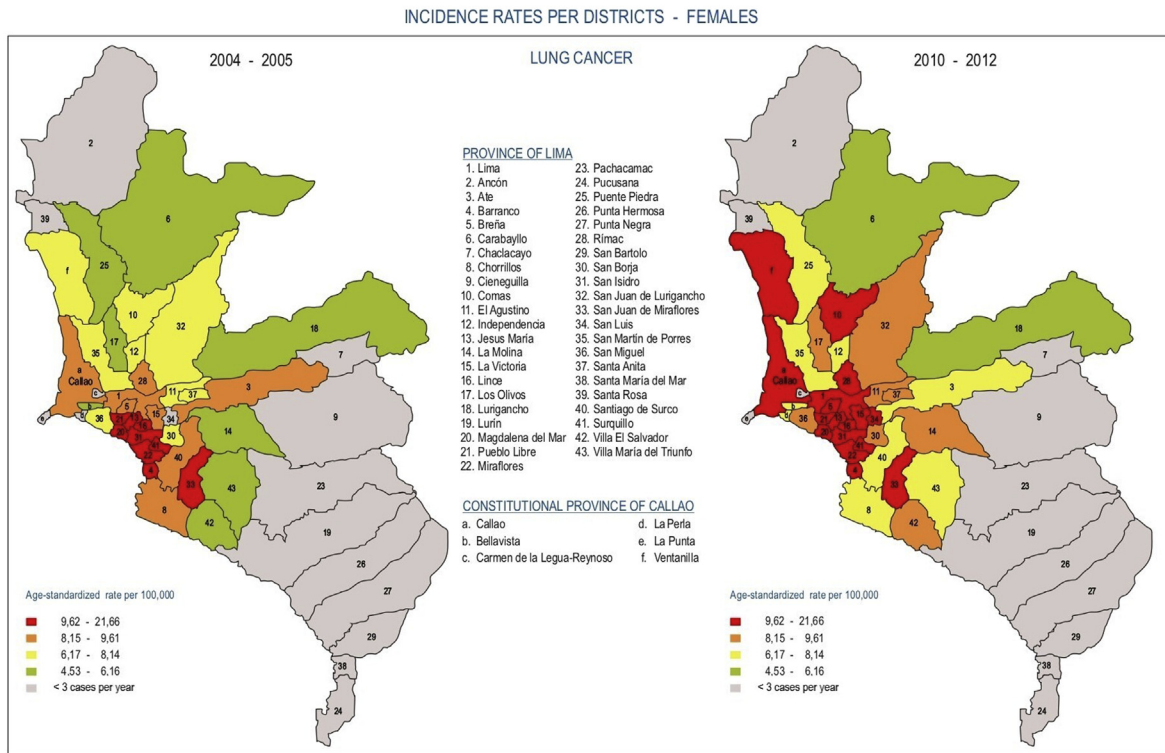
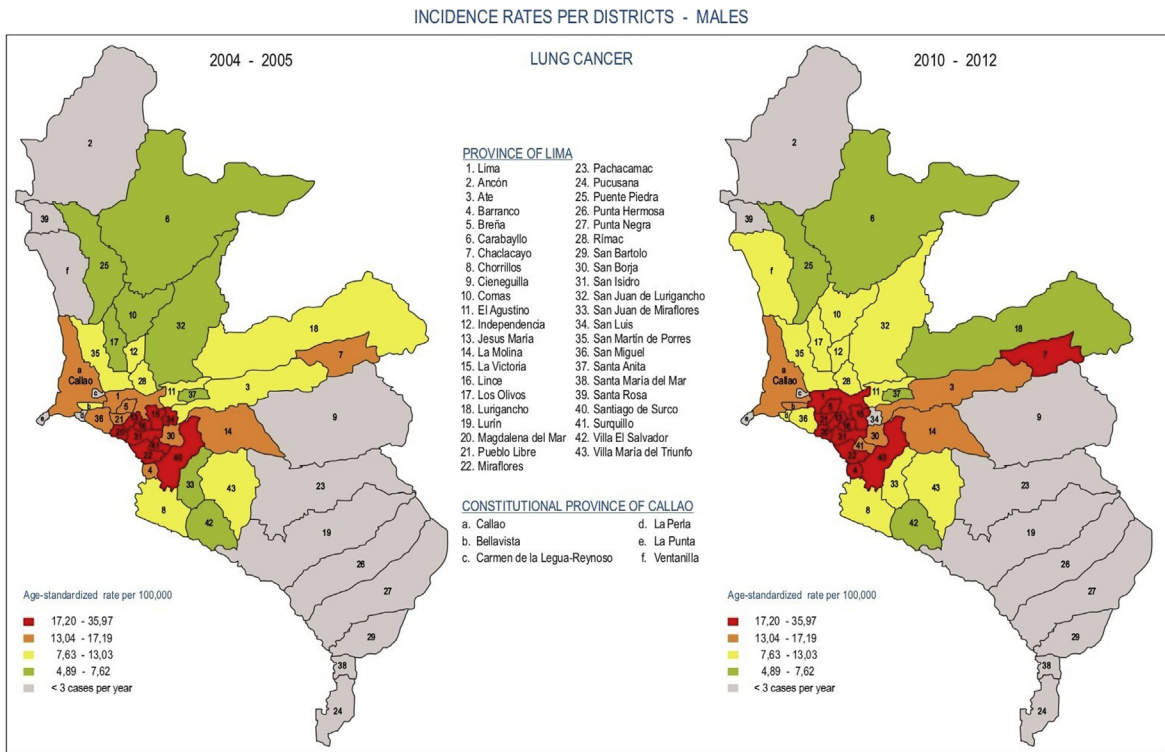


Figure 3. Incidence rate per districts in Lima. Reprinted with permission from Departamento de Epidemiología y Estadística del Cáncer. Instituto Nacional de Enfermedades Neoplásicas.⁹

range between 20%²³ and 42%,²⁴ which is very low when compared with what is reported by international series (75%–95%),²⁵ indicating that risk factors beyond tobacco must be considered. In rural areas in Peru, crop residues (1.4%), dung (1.8%), and particularly wood (17.3%) are the most used fuels for cooking.¹ In-house exposure to these fumes increases the risk of respiratory diseases in children (risk ratio [RR] = 2.3, 95% confidence interval [CI], 1.04–5.18) and adult women (RR = 3.2, 95% CI, 1.00–5.59) and of lung cancer also in women (RR = 1.9, 95% CI, 1.1–3.5).^{26,27} In the country, in 2017, 1,757,409 families (21.3%) cooked by burning biomass as fuel.¹ To address this issue, the government has developed the National Program of Improved Kitchens²⁸ that enhances the cleanliness of the interior environments through efficient combustion and appropriate dimensions of the holes and the chimney. In addition, pollution by particles in environmental air, which reaches a value of 50 $\mu\text{g}/\text{m}^3$ in Lima²⁹ (far greater than the WHO recommendation of 10 $\mu\text{g}/\text{m}^3$), has been estimated to cause more than 600 cases of lung cancer in Peru yearly.³⁰

Screening

In Peru, there is no population screening test for lung cancer; however, the National Cancer Plan includes the diagnosis and staging of patients with presumptive diagnosis of lung cancer. On a private level, there is an isolated effort using low-dose tomography for high-risk individuals. The implementation of a national low-dose tomography screening program is unfeasible at the moment owing to limitations in funding, infrastructure, expertise, and health system response.

Diagnosis

Late lung cancer diagnosis is the most common presentation. According to a study from INEN, 9.2% and 85.5% of patients with lung cancer from 2010 to 2014 were diagnosed at stages III and IV, respectively.³¹ In contrast, in a recent publication from a private center, 20% of patients were diagnosed at stage III and 64% at stage IV during the same period of time.²⁴

Regarding pathologic diagnosis, adenocarcinoma is by far the most frequent subtype, accounting for 72% of all lung cancer cases.³¹ In Peru, there are few laboratories that perform molecular diagnosis, most of them in the private sector. Within the public sector, the detection of EGFR mutations by polymerase chain reaction, ALK rearrangements by fluorescence in situ hybridization, and the assessment of programmed death-ligand 1 by immunohistochemistry are covered through the subsidized and contributory regimens but available only at INEN and at the two higher

complexity hospitals of the social security. At INEN, 16% and 36% of the samples for EGFR and ALK assessment, respectively, are insufficient. Liquid biopsy and next-generation sequencing are available only in the private sector.

The predominant targetable alteration in Peruvian patients with lung cancer is the EGFR mutation representing between 32% and 39% of cases.^{24,32–34} These rates, which are the highest reported for the LATAM region, may be explained to some extent by the important Asian ancestry.³⁵ ALK rearrangements have been detected in around 10% of cases.^{24,36} A small targeted panel performed in 113 patients with lung cancer found mutations in KRAS and BRAF in 15.9% and 1.8% of patients, respectively (unpublished data).

Surgery

The Peruvian Society of Cardiothoracic and Vascular Surgery is composed of 120 active members as of today, with 10 of them being women. Approximately, a quarter of all these specialists are mainly advocated to the Thoracic Surgery subspecialty, and very few have training in Thoracic Surgical Oncology. These specialists are concentrated in Lima and in three regions of Peru (La Libertad, Arequipa, and Lambayeque). Only one center in the country provides specialized training in Thoracic Surgical Oncology. This shortage of specialists results in cardiothoracic surgeons also performing operations for the treatment of cancer and in prolonged waiting times for operation in the public sector.

Video-assisted thoracic operation for performing lobectomy is available in highly specialized centers, mostly in Lima, at which thoracic oncology surgeons are available. The equipment for performing video-assisted thoracic operation is available nationwide; however, the scarcity of specialists is the limiting factor for the widespread use of this procedure. Therefore, open thoracotomy is still the most common surgical approach, especially in public centers. Robot-assisted thoracic operation for thoracic malignancies is not available in Peru.

At INEN, stages I and II are eligible for primary operation. Patients with stage III receive multidisciplinary care, including chemoradiation and, very occasionally, operation. Thoracic operation for advanced cases with oligometastatic presentation is performed in selected cases, according to what is recommended by multidisciplinary tumor boards.

Radiotherapy

Radiotherapy (RT) is key in the management of early, locally advanced, and metastatic lung cancer. Currently, there are 104 radiation oncologists, 100 radiotherapists,

Table 1. Time to Drug Regulatory Approval and Access

Drug/Indication	FDA Approval	National Regulatory Approval	Access for the Subsidized Regimen	Use Authorization at INEN
Erlotinib	2004	2008	2017	2017
Afatinib	2013	2014	No	No
Osimertinib/T790M EGFR mutation	2015	2018	No	2019
Osimertinib/EGFR mutation first line	2018	2019	No	No
Crizotinib/ALK mutation	2011	2012	No	No
Alectinib	2015	2017	No	2019
Pembrolizumab	2015	2016	No	2019
Nivolumab	2015	2015	No	No
Atezolizumab	2016	2017	No	No

FDA, Food and Drug Administration; INEN, the Peruvian National Cancer Institute.

and 40 physicists in Peru. According to the National Institute on Nuclear Energy (IPEN),³⁷ 28 centers have RT services and are distributed over six of 25 regions in Peru (Lima, La Libertad, Lambayeque, Arequipa, Junín, and Cusco), with 15 of them located in Lima. Equipment available is limited to 32 high-energy linear accelerators and five cobalt machines; that is 1 U for every 1,031,250 inhabitants. In Lima, the ratio is 1 U for every 504,411 inhabitants, whereas in the rest of the country, there is one machine for every 1,628,333 inhabitants. In all cases, the availability of RT units falls short of the recommended International Atomic Energy Agency ratio of one machine for every 200,000 to 250,000 inhabitants. Approximately 100 more units are needed to close this gap. In the public sector, waiting times for treatment are prolonged.

Lima concentrates the six RT centers with capacity to perform special techniques such as intensity-modulated radiation therapy, volumetric modulated arc therapy, stereotactic body radiation therapy, and radiosurgery for the treatment of lung cancer; the two electronic intraoperative contact RT machines and the two CT simulators are able to perform 4-dimensional simulation. All of them but INEN are private. Regarding brachytherapy, there are 11 high dose rate brachytherapy machines³⁷, and only two centers, located in Lima, have experience in performing endobronchial brachytherapy. There is no access to Cyberknife units, tomotherapy, or proton therapy, but a Gammaknife equipment belonging to the private sector is available.

Systemic Treatment

In Peru, the regulatory approval of new therapies is given by the General Head of Medicines, Supplies and Drugs (DIGEMID) of the Peruvian MOH. Time from FDA approval to regulatory approval in Peru is becoming shorter (Table 1). However, the regulatory approval of new drugs does not imply access to the subsidized

regimen, which additionally depends on their incorporation to the Peruvian Essential Medicine List, on the basis of safety, efficacy, and cost-effectivity. For the previous years, this list has included mainly cytotoxic drugs and no biologicals or targeted therapy. It was not until 2017 that erlotinib was included in this list. To overcome this limitation, the MOH authorized its public institutions to acquire and use drugs not included in the Peruvian Essential Medicine List, on the condition that they undergo evaluation by institutional committees and health-technology assessment (HTA) by DIGEMID. However, the implementation of HTA continues to face significant challenges concerned with the fragmentation of the health care system and shortage of resources for a timely evaluation. For this reason, INEN and the MOH in a concerted effort have established the normative mechanisms to enable access to selected high-cost drugs, on the condition that they are present on institutional guidelines.³⁸ Currently, the scope of this directive is restricted to INEN but is projected to have national reach.

For its part, within the contributory regimen, HTA is performed by its own health-technology agency Instituto de Evaluación de Tecnologías Sanitarias e Investigación, allowing access to selected innovative drugs, most of which provide overall survival or quality of life benefit. Importantly, its methodological and evaluation documents are published online and are accessible to patients and other stakeholders.³⁹

The scenario is very different for private institutions, where only regulatory approval is needed for using a drug. However, increasingly, private insurers are also establishing HTA to regulate the use of high-cost medications. A summary of drugs available in Peru is shown in Table 1.

Regarding results of systemic therapies, a group of researchers from INEN recently presented real-world data on 55 patients with EGFR mutated lung cancer treated with erlotinib at any line of treatment from 2015

to 2018 and found an overall response rate (ORR) of 65.9% and an unexpectedly prolonged progression-free survival (PFS) of 18 months.³³ Results from another institution could not confirm these results; with follow-up time of 32.4 months, ORR was 73.6% and median PFS and median overall survival were 12 and 24 months, respectively (unpublished data). Results of immunotherapy use at any line have also been evaluated in a cohort of 68 patients. Although ORR was 38% and PFS was 5.5 m, duration of response was 18.6 months (unpublished data).

Conclusion

Lung cancer in Peru is a growing public health problem with characteristics that differ from what occurs in the LATAM region and the world. It is a disease that occurs predominantly in nonsmokers, with a high incidence of adenocarcinoma and EGFR and ALK mutations, the cause of which is not well elucidated yet.

Tobacco control policies have been successful and have resulted in a low prevalence of smokers in the country. Although strategies are being implemented to control other risk factors, research in this area is warranted to develop preventative targeted interventions. Likewise, further research is necessary to explain the geographic differences in incidence and mortality within the country. The lack of a screening program and the fragmentation of the health system could partially explain the high proportion of late diagnoses.

There is plenty of work pending concerning training and availability of human resources, access to modern surgery and radiotherapy techniques, and availability of molecular diagnosis. Regarding access to innovative drugs, significant efforts are being made in developing public policies that seek to improve access on the basis of HTA. However, the scope of these provisions is still limited.

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