Mexico: Demographics and the Health Care System

For more than 30 years, lung cancer (LC) has remained unchallenged as the most frequent neoplasm in the world. Accompanying the high incidence rates, LC also leads the list in terms of cancer-related mortality, and this epidemic is projected to continue both in developed and developing countries. Mexico, located in the Americas region, is populated by 123 million individuals, making it the third most populous country of the Americas, following the United States and Brazil. In terms of economy, Mexico falls in the classification of upper-middle-income economies according to the World Bank. The country is divided into 32 states. Population density averages 61 inhabitants/km²; however, this varies according to the geographic area, from 5967 inhabitants/km² in Mexico City, to 14 inhabitants/km² in the northern state of Chihuahua (Fig. 1).

The Mexican health care system is divided into a public and a private sector, with an overwhelming 93% of the population treated in the publically funded facilities. These include the Mexican Institute of Social Security (IMSS), which covers 50% of the population, the State Workers Institute for Social Security and Health (ISSSTE), or the most recent Popular Health Insurance (SPS). This last one, also known as “Seguro Popular,” is a voluntary health insurance scheme which was introduced in 2004 to provide coverage for the poor and uninsured. It grew so rapidly that by 2011 nearly 90% of the population was covered; however, it currently does not include LC treatment, which leaves this impoverished sector without treatment options. Only 7% of the population is estimated to hold private sector insurance. Although the system has been successful in providing universal health coverage for the country’s population, there are still many challenges which arise from this fragmented system, which ultimately derive in different standards of care within each institution.

LC Epidemiology in Mexico

According to data from GLOBOCAN, 190,667 incident cancer cases occur in Mexico every year, among which 7811 correspond to LC cases, with a standardized rate of 5.8. In terms of mortality, a total of 33,781 deaths due to LC occurred in Mexico from 2012 to 2016. In 2016 alone, 7044 deaths were attributable to LC, making this the highest-mortality neoplastic disease in Mexico; further, LC is a sub-diagnosed disease, and therefore this figure might be higher. LC deaths in Mexico are more frequent in men, in a 1.6:1 ratio, older age individuals, with 53% of all deaths presenting in patients older than 70 years of age, and more frequently affect the northern region of the country. Moreover, 80% of all deaths are reported in patients who resided in urban regions. As can be seen from these alarming numbers, LC remains a major public health problem in Mexico; nonetheless, encouraging data has emerged in the last 3 years which evidences the effort currently undertaken to fight this epidemic. The mortality rate has steadily declined from 6.4 in the year 2000 to 5.7 in 2016. Additionally, whereas LC represented 10.8% of all cancer-related deaths 20 years ago, this has decreased to 7.9% currently (Table 1). It is important to stress that caution must be taken when interpreting these results, particularly when considering the aging population.
within this country. In fact, absolute numbers of LC cases and deaths are expected to increase substantially in the next years as a result of these characteristics. Following the current world trend, women will lead this increment in mortality. Mexican women tend to have a disease presentation at an earlier age, with a median of 59 years of age at diagnosis.1

Screening and Early Detection

The LC burden in Mexico is evident. However, Mexican patients with LC still suffer from shortcomings when considering several aspects pertaining to their health care. For example, there is currently no active public screening program for high-risk populations despite the fact that these risks are well characterized within the national setting. Subjects with known risk factors have the option of paying for screening; however, severe cost-constraints limit the wide implementation of this strategy, along with a considerable demographic impairment due to the fact that in Mexico approximately 20% of the population resides in rural areas, with scarce-to-no access to medical equipment. This in turn restricts performing a timely diagnosis throughout the country. In Mexico, stage I-II lung cancer patients are almost anecdotic, and 98% to 99% of patients are diagnosed with late-stage disease.2 In August 2018, a government press release announced the launching of a national screening program for all subjects with tobacco or wood-smoke exposure; however, the economic package of 2019 for public health has left this much needed project in uncertainty.

Diagnosis and Staging

Aside from the challenge to perform a timely diagnosis, another important issue is assessing disease stage. Most patients live in areas which lack the medical equipment and field specialists required to correctly assess the disease; therefore, many patients must travel within their state or the country to be properly staged. For example, the availability to perform endobronchial ultrasound-transbronchial needle aspiration is limited throughout the country, which negatively affects the adequate assessment of newly diagnosed patients. The urgent need for medical oncologists in Mexico is well recognized, with approximately 1700 specialists registered, among which 40% reside in three large urban areas (Mexico City, Monterrey, and Guadalajara).

Surgical Approaches

In terms of therapeutic strategies, patients in Mexico have access to surgery; however, most patients who are candidates for surgery will be treated by a cardiothoracic surgeon, rather than by a thoracic oncology specialist. Currently only two centers in the country offer high-specialty training in thoracic oncology (medical and surgical), demographically limiting the training options in order to reap highly specialized, critical physicians in this field. As a consequence, nationwide oncology teams usually lack thoracic oncology field specialists in terms of surgical training, or other disciplines, particularly in decentralized regions. The recently published national guidelines for LC treatment recommend that patients with early-stage LC be offered a lobectomy as a surgical approach, preferably through a minimally invasive procedure. It is important to mention that the technology

| Table 1. Comparison of Different Lung Cancer Parameters in Mexico |
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| Parameter             | 2000                  | 2016                  |
| Mortality rate          | 6.4 per 100,000 individuals | 5.75 per 100,000 individuals |
| Percentage of cancer-related deaths | 10.8%                | 7.9%                 |
| Lung cancer deaths in women | 31.7%               | 38%                  |
| Minimum daily wage (USD) | $ 2.11              | $ 5.37               |
| Estimated cost of lung cancer treatment (USD)/ Mexican minimum wage days required to pay for treatment (2019) |
| Stage II               | $ 9,441.6/1758 d     | $ 7,025/1308 d       |
| Stage III              |                       |                      |
| Stage IV with Targeted therapy (1st generation) |                       |                      |

Figure 1. Population density in the 32 states of Mexico.
to perform video-assisted thoracic surgery is available nationwide; however, surgeons who meet the strict learning curve to offer a high-quality procedure are scarce, limiting the widespread availability of this technique. Segmentectomy or wedge resections are also available for patients with low pulmonary capacity. Further, all patients who undergo surgery also undergo mediastinum staging, either by mediastinal lymph node sampling or by systematic mediastinal lymph node dissection. Last, for patients with stage IA disease who are not candidates for surgery, radiosurgery is preferred to radiofrequency ablation.

**Radiation Therapy**

Radiotherapy has been a cornerstone for LC treatment for several decades. For the small proportion of patients who are diagnosed with inoperable stage I disease, guidelines recommend that they be referred to a specialized center with access to stereotactic body radiotherapy, although there are only two cities which currently offer this modality (Mexico City and Monterrey). For the majority of patients who have stage IV disease, radiotherapy might be administered to the primary tumor to improve survival outcomes. As discussed below, patients in Mexico almost never have access to third-generation targeted therapies, due to severe cost-constraints. Therefore, in this population, the role of prophylactic cranial irradiation to delay the development of brain metastases should be adequately appraised, particularly for well-characterized high-risk patient subgroups.

An important limitation in terms of radiotherapy in Mexico is, once again, access. For example, IMSS offers health care to 74 million Mexicans, yet as of 2018 there were only 35 linear accelerators in the country, and they were all concentrated in nine states, leaving the other 23 states without equipment for this treatment modality.

**Systemic Therapy**

Choice of systemic therapy is dictated by the molecular profile of the tumor and access to therapy according to the insuring institution. In terms of the tumor molecular profile, patients in Mexico treated at one of the reference institutions (such as the National Cancer Institute [INCan]) all undergo molecular profiling which includes EGFR, ALK receptor tyrosine kinase (ALK), and programmed death ligand 1 (PD-L1) testing. This number varies in other institutions; for example, approximately 40% of patients treated at ISSSTE compared with none of the patients treated at IMSS have a molecular profile. As previously mentioned, because of the fragmented health care system in Mexico, patients will have access to the therapies approved by the institution which insures them. In 2016, an inter-institution board released a master catalogue of medications available throughout these institutions. Among the 114 systemic drugs available for cancer treatment, only 14 were approved for LC. Further, 4 of these drugs are obsolete in this indication (cyclophosphamide, doxorubicin, ifosphamide, and mitomycin), leaving 10 therapeutic options for patients throughout the country. Only 3 targeted agents are present in this list, all first-generation drugs (crizotinib, erlotinib, and gefitinib), leaving 93% of the Mexican population unable to gain access to the highly efficacious, low toxicity drugs from the second and third generation of tyrosine kinase inhibitors (TKIs). Immu-no-oncology drugs were not included in this catalogue at all. Despite this limitation, the newer targeted agents are approved by the drug administration agency in Mexico (COFEPRIS); therefore, these are available for patients with private insurance or enough funds to acquire them. The standard-of-care for patients with stage IV lung cancer includes a molecular profile which includes EGFR, ALK, ROS1, BRAF, and PD-L1 testing. Patients with adenocarcinomas without actionable mutations should be offered immune checkpoint inhibitors (ICls). In first-line therapy, patients with greater than or equal to 50% PD-L1 expression can be treated with pembrolizumab alone or in combination with platinum-based chemotherapy. For patients with less than 50% PD-L1 expression, ICI options include pembrolizumab combined with platinum-based chemotherapy, and COFEPRIS approval is pending for the combination of atezolizumab/carboplatin/paclitaxel/bevacizumab in the first-line setting. Second-line options include platinum-based chemotherapy or nivolumab, pembrolizumab, or atezolizumab for patients who did not receive ICls in the first-line setting. Chemotherapy monotherapy is reserved for third- and beyond-line therapy (Figs. 2 and 3). ICI use is very limited due to cost constraints. Prices for these agents vary; however, treatment using these agents exceeds 100,000 Mexican pesos. Considering that the minimum wage in the country is 3080 pesos monthly, it is clear that most patients in Mexico will not benefit from these agents.

The current treatment guidelines in Mexico are highlighted in Figures 2 and 3; however, although these guidelines are based on the best scientific evidence available, it is true that most patients in the country do not have access to the newer-generation therapies, although these are approved by COFEPRIS. Unfortunately, knowing the exact treatment patients in Mexico receive is very challenging due to the fact that the National Cancer Registry has only just launched in Mexico this year. Therefore, treatment variation as per region cannot be precisely defined. This is particularly the case due to the fact that Mexico’s public health care system, which covers
Figure 2. Treatment recommendations for advanced stage NSCLC according to Mexico's national treatment guidelines in 2019.

Figure 3. Treatment recommendations for advanced stage NSCLC as per programmed death ligand 1 (PD-L1) expression, according to Mexico's national treatment guidelines in 2019.
93% of the country’s population, is highly fragmented, including six different institutions, each of which manages patients according to their available resources. However, estimates have been made which show that approximately 70% to 75% of the patients who have advanced-stage LC in Mexico receive treatment with platinum-based chemotherapy. Patients who have actionable mutations have access to certain TKIs within the public health system (free of copayments). For example, patients with EGFR-mutations may receive first- or second-generation TKIs (gefitinib, afatinib, or erlotinib), whereas patients with ALK-rearrangements have access to crizotinib in the first-line setting. Approximately 50% of the patients with EGFR-mutations receive TKIs, whereas this number is reduced to 30% in ALK-rearranged patients. Upon disease progression, patients treated in the public health sector will receive platinum-based chemotherapy. Third-generation TKIs including osimertinib and alectinib are not included in the public health sector; therefore, less than 3% of patients can receive treatment with these agents due to cost constraints (this percentage includes patients with private health insurance or who are enrolled in active clinical trials). In terms of ICIs, only patients with private health insurance or those enrolled in active clinical trials will receive this therapy. Figure 4 highlights the real-world treatment that patients treated at the public health sector in Mexico usually receive.

**Patient Characteristics and Etiologic Factors in Mexico**

The unfortunate feature in terms of access to therapy is even more relevant in Mexico, due to the specific characteristics of the patients from this country. In Mexico 1.6 million people continue to use biomass (particularly wood) as an energy source for cooking and heating purposes. Previously, two meta-analyses evaluated the association between wood-smoke exposure and LC development (odds ratio [OR]: 1.50, 95% confidence interval [CI]: 1.17–1.94) and (OR: 1.17, 95% CI: 1.01–1.37). In Mexico, two case control studies also found this association in specific populations, with an OR of 1.9 (95% CI: 1.1–3.5) and 2.0 (95% CI: 1.6–2.6),

**Figure 4.** Real-world treatment management in Mexican patients treated within the public health sector. CT, computed tomography; PD-L1, programmed death ligand 1.
respectively. As a result, many of the patients with LC in Mexico have a history of wood-smoke, rather than tobacco-smoke, exposure, which derives in different disease characteristics, including a higher EGFR-mutation frequency (34%) and lower KRAS-mutation frequency (15.9%) compared to other North American and European countries. Consequentially, a high proportion of patients with LC in Mexico are candidates to receive targeted therapy; however, mortality records show that among all patients who died from LC in 2016, less than 15% had access to targeted therapy within their health insurer. Moreover, one-third (33%) of all patients who died from LC either received no medical attention (12.5%) or were insured by a policy which did not cover lung cancer treatment (20.5%). Another important factor to consider in Mexico is air pollution (AP), a group 1 carcinogen in humans. AP has been consistently associated with LC risk, and at least 38,000 people in Mexico died between 2001 and 2005 due to exposure to considerable (>70 μg/m³) AP levels. In this regard, several cities are already recognized for having a severely low air quality, including Monterrey (370 μg/m³), Mexicali (281 μg/m³), Salamanca (233 μg/m³), Guadalajara (222 μg/m³), and Toluca (216 μg/m³) (Fig. 5).

It is an unfortunate truth that patients with LC in Mexico will generally not benefit from the great advances in the field of thoracic oncology which have arisen in the last 10 years. These conditions highlight the need to pressure authorities to secure availability and access to therapies which have become the standard of care in developed nations. Many of these therapies have been proven cost-effective, and interestingly, in the specific case of LC, survival has been strongly associated with access to greater financial funds; therefore, failure to act upon this urgent matter will relegate LC deaths to poorer states, widening the gap in terms of global health inequalities.

References

Figure 5. Recommended concentration limits for PM_{10}, PM_{2.5}, particulate matter 10 micrometers or less in diameter; NAAQS-USEPA, National Ambient Air Quality Standards-United States Environmental Protection Agency; UE, European Union; WHO, World Health Organization; CARB-US, California Air Resources Board-United States.