Lung Cancer in Chile

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Introduction

Chile is a long and narrow country located in South America; its population as of 2017 was 18,419,192. Life expectancy is 83 years for women and 77 years for men.[1] Cancer is currently the second leading cause of death in Chile, causing 25.6% of total annual deaths, and recent estimations report that cancer will be the leading cause of death by 2030. It is also the main cause of disease burden measured in terms of disability-adjusted life-years.[1] The increasing incidence of cancer can be explained by aging of the Chilean population and known risk factors such as obesity, cigarette smoking, sedentary lifestyle, and other environmental factors. The Chilean health system has universal coverage; it is based on a two-tier system with both private and public health providers. This has led to significant health inequalities, which have been the focus of several health reforms. Current public health spending is 8.1% of the gross domestic product. The new National Cancer Plan is still being debated in Congress, and it is hoped that this plan will improve prevention, diagnosis, and treatment for Chilean patients.

Epidemiology

Lung cancer in Chile, as in many countries in the world, is one of the most common cancers in the country. According to Globocan statistics, 53,365 new cases of cancer and 28,443 deaths were projected for Chile in 2018. The reported annual incidence of new cases of lung cancer in 2018 in both sexes was 3873, with lung cancer being the first cause of cancer death and accounting for approximately 3581 deaths.[2] The incidence of lung cancer in two different regions of Chile that are Antofagasta and De Los Rios are shown in Figure 1.[3] Torres-Avilés et al. analyzed the m (e.ortality rate in Chile for lung cancer between 1990 and 2009 and observed that there was a 19.9% reduction in the lung cancer mortality rate in male patients but an increase of 28.4% in female patients.[4]

Considering traditional risk factors, smoking is an important problem in Chile. According to data from the national health survey, 32.5% of the population are active smokers. Subgroup analysis shows that the prevalence of active smokers between the ages of 25 and 44 years has remained stable, although in the group of those 15 to 24 years old the prevalence of smoking has declined in recent years.[5] This could be due to the restrictive legislation and tax rate increase that were implemented in Chile in 2010. Exposure to secondhand smoke remains a big problem in Chile. Nicotine concentrations in the indoor air of public places and workplaces in Santiago were among the highest in Latin America, particularly in restaurants and bars. Erazo et al. measured air nicotine concentrations, which were 3.2, 35.5, and 56.2 times higher in nonsmoking areas in mixed venues, smoking areas in mixed venues, and smoking venues, respectively, than in smoke-free venues in 30 bars in Santiago, Chile.[6]

A special consideration is arsenic exposure in the Chilean population. Marshall et al. compared two different regions of Chile according to exposure to water contamination with arsenic between the years 1950 and 2000. The lung and bladder cancer mortality rate ratios for the region Antofagasta (region II), which was exposed to water contamination, compared with those for the region Valparaiso (region V) started to increase about 10 years after high levels of arsenic exposure commenced and continued to rise until peaking in 1986–1997.[7] Despite installation of treatment plants in 1970 and 1978, which reduced concentrations to less than 10 μg/L, combined

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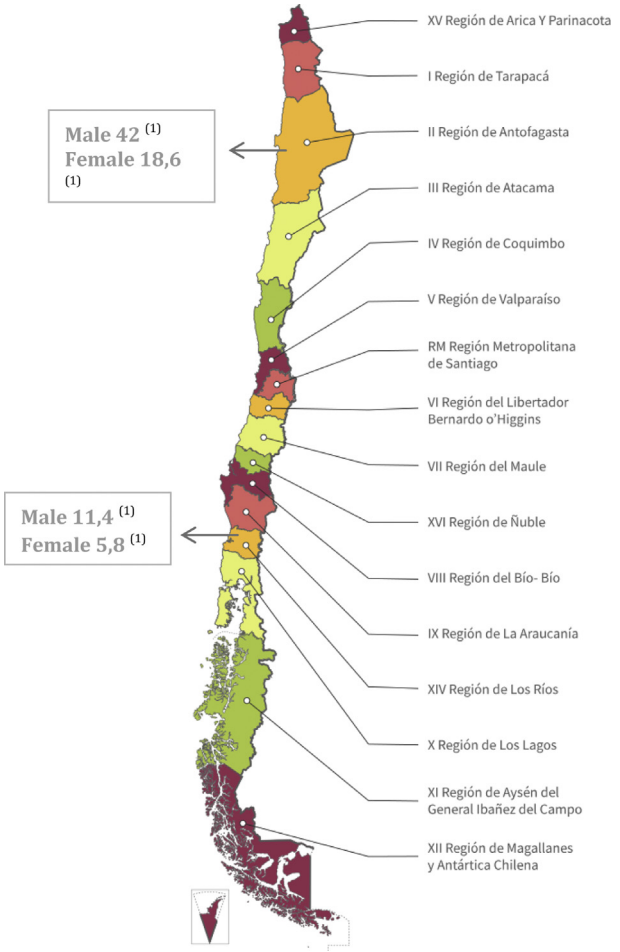

Figure 1. The incidence of lung cancer in two regions of Chile. Lung cancer incidence rates are per 100,000. Adapted with permission from Primer informe de registros poblacionales de cáncer de Chile, Quinquenio 2003-2007.[3]

lung and bladder cancer mortality rates in region II were highest in the period 1992–1994, with mortality rates of 153 and 50 per 100,000 men and women, respectively, compared with 54 and 19 per 100,000 in region V. An update published in 2017 by Smith et al. demonstrated that the population exposed to arsenic-contaminated water had increased risks of bladder and lung cancer, even 40 years after reduction of the exposure.[8]

Screening

As of this moment, there is no national screening program for lung cancer in Chile. Considering the recently published positive results of the NELSON trial, in which computed tomography (CT) screening was shown to be effective in assessing lung nodules in people at high risk for lung cancer, major efforts are needed to implement effective strategies for the near future.[9] Saldias et al. studied 160 high-risk patients who underwent screening for 3 years with CT scans and follow-up for 5 years. Lung cancer was diagnosed in 5.6% of those patients. In most patients, the diagnosis was made in early stages of the disease, and 92% of patients had false-positive results.[10] In countries such as Chile, funding efforts in screening have to be balanced with the eventual different findings of CT and the resolution capacity of our health system. In most of the public hospitals in Chile, lack of radiologists specialized in lung pathology and thoracic surgeons make it unreasonable to pursue a screening program at this moment.

Lung Cancer Management in Chile

Chile has universal health coverage for its population; coverage is based on a two-tier system: a publicly funded system (called Fonasa), which provides health to approximately 80% of citizens, and a privately funded system, in which several companies cover the remaining 20%. These companies are called Isapres. The public sector has an oncology network with 25 centers capable of providing surgery and chemotherapy.[11] The private system budget is almost three times higher per capita than the public system,[12] which is reflected in the different availability and reimbursement for some therapies, as we will discuss later. This problem of health inequality is well documented,[13,14] and there have been efforts to correct it through health reforms and public health spending: measured as percentage of the Chilean gross domestic product, public health spending has grown from to 6.6% in 2005 to 8.1% in 2017.[15,16]

In very general terms, NSCLC management in Chile follows international guidelines, and can be outlined by stage as follows: stage I, surgery alone; stage II, surgery followed by adjuvant chemotherapy; stage III, definitive concurrent chemoradiation (which is the most frequent approach) and induction chemotherapy followed by surgery in select patients; and stage IV, chemotherapy and palliative care.

As for SCLC, a similar broad approach can be summarized as follows: stages I and II, surgery followed by adjuvant chemotherapy; stage III, definitive concurrent chemoradiation; and stage IV, chemotherapy and palliative care.

Surgical Approaches

As already mentioned, in NSCLC stage I and stage II disease is always managed with surgery if pulmonary function allows it. As for stage III disease, if no nodal disease is evident on staging studies, surgery is also the preferred approach. If suspicious nodes are detected, one of several methods can be used for nodal staging, depending on which stations are to be studied; they are endobronchial ultrasound, endoscopic ultrasound, or mediastinoscopy. A significant gap exists in available staging methods in Chile, as most public centers do not yet have endobronchial ultrasound or endoscopic

Table 1. Novel Drugs Approved in Chile for Advanced/Metastatic NSCLC

Drug	Approved in First Line	Approved in Second Line	Reimbursement (Public System)	Reimbursement (Private System)
Erlotinib	✓		No	Yes
Afatinib	✓		No	Partial[a]
Gefitinib	✓		No	Yes
Osimertinib		✓	No	Partial
Crizotinib	✓		No	Partial
Ceritinib		✓	No	Partial
Alectinib	✓		No	Partial
Dabrafenib + trametinib (If *BRAF* V600F mutation is present)	✓		No	Partial
Pembrolizumab	✓		No	Partial
Nivolumab		✓	No	Partial
Atezolizumab		✓	No	Partial

[a]The term *Partial* indicates that is up to each specific private insurance company to decide whether they reimburse the drug, usually on a case-by-case analysis. Indicated approvals are based on publicly available information[16] from the local drug regulatory authority (National Institute of Public Health) as of January, 2019.

ultrasound available. If nodal disease is confirmed, the usual approach is concurrent chemotherapy and radiotherapy regimens, although chemotherapy induction followed by surgery remains as an alternative for specific patients.

In general, lobectomy is preferred over limited resections, and video-assisted thoracoscopic surgery is preferred over open surgery if technically feasible; most centers performing lung surgery have the technical capabilities for video-assisted thoracoscopic surgery, but the final decision on the surgical approach will depend on a case-by-case analysis by the surgical team. Three centers in Chile have robotic-assisted surgery capabilities, but the use of this technique is very low in lung cancer locally.

Radiation Approaches

Radiation therapy is an essential component in lung cancer management, and as such, it is available on a national level. There are a total of 21 radiotherapy

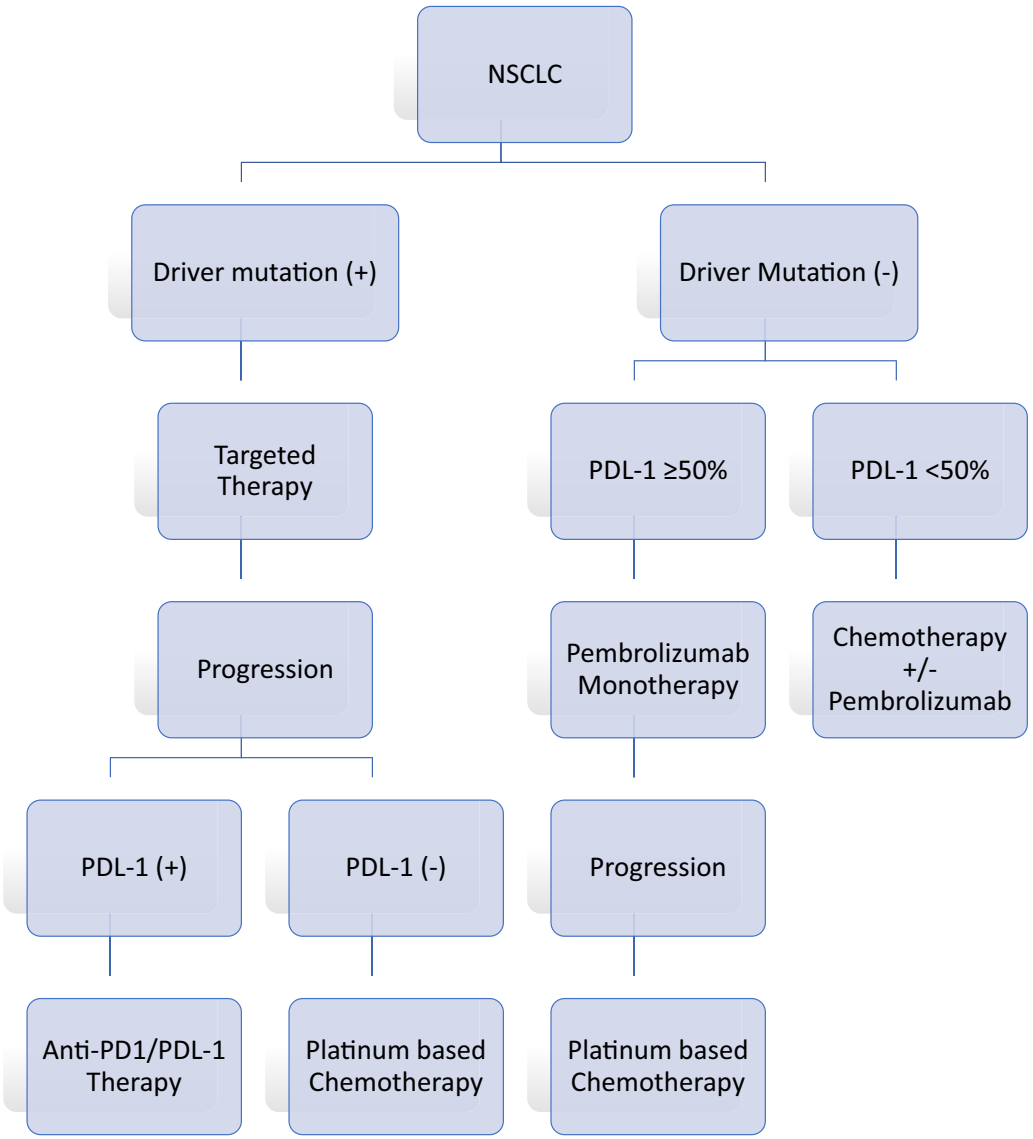

Figure 2. Metastatic NSCLC treatment algorithm. PD-1, programmed cell death 1; PD-L1, programmed death ligand 1.

centers counting both private and public institutions.[17] The public sector has seven centers with three-dimensional conformal radiation therapy capabilities, and five of them also have intensity-modulated radiation therapy capabilities; this figure is expected to grow significantly according to the new National Cancer Plan[10] that was recently presented by the government. As for stereotactic body radiation therapy, it is still in the very early stages, with only one public center and two private centers using this technique in lung cancer.

When definitive chemoradiation is used for stage III NSCLC, the standard approach is external beam radiotherapy, 60 to 70 Gy in 2-Gy fractions with concurrent platinum-based chemotherapy. Radiation is also an alternative for earlier stages when patients are not surgical candidates; in this case, stereotactic body radiation therapy is the preferred approach, but as we have already mentioned, access to this technique is still very limited, and some centers will use intensity-modulated radiation therapy in this setting.

Another indication for radiotherapy is prophylactic brain irradiation in SCLC if there is response to initial treatment. Radiation therapy also plays an important role in the palliative care setting, as painful bone lesions have good response to external beam radiotherapy, and this is widely available for Chilean patients as part of palliative care programs.

Systemic Therapy

Chemotherapy agents utilized in the management of NSCLC and SCLC, including cisplatin, carboplatin,

etoposide, gemcitabine, and docetaxel, are available and covered by the health systems, both public and private. Novel agents such as EGFR tyrosine kinase inhibitors (TKIs), ALK receptor tyrosine kinase inhibitors, and BRAF inhibitors pose a significant problem given their high cost. In general, these drugs are not reimbursed by the public health sector, so they must be paid for by patients who can afford them. In the private health sector reimbursement is possible, although limited, and will ultimately depend on the insuring company (Isapre) to determine this.

A similar situation applies to immunotherapy: pembrolizumab is approved by local regulatory authorities for metastatic NSCLC in the first-line setting for programmed death ligand-1–positive patients, whereas both atezolizumab and nivolumab are approved in second-line treatment after progression to EGFR TKIs, ALK receptor tyrosine kinase inhibitors, or platinum-based therapy. A recent analysis by the Chilean Health Ministry deemed these agents not cost-effective in the local setting.[18] They are not covered by the public health system, and although some Isapre programs do reimburse these treatments, the reimbursement is available for only a very small segment of the population. A summary of drugs available in Chile and their reimbursement is presented in Table 1.[18] The treatment algorithm shown in Figure 2 reflects current drug approvals and clinical standard of care; however, availability of the full array of treatment options will depend on the patients health insurance, as we have previously mentioned.

Discussion

Lung cancer is the deadliest cancer in Chile, with increasing mortality in the female population. This grim outlook underscores the need to improve prevention, detection, and treatment in an urgent manner.

Tobacco control is one of the areas that has received attention in the past few years, with new laws restricting smoking spaces, increasing taxation, and requiring better labeling of cancer risk on cigarette boxes. The impact of these measures has been significant, as the percentage of active smokers has decreased from 43% in 2003 to 33% in 2017.[5] An area that clearly needs improvement is local data on lung cancer; there is no lung cancer registry, and the only existing data are mortality data obtained through death certificates of the Chilean national registry service. There are no established early detection programs, and we should consider implementing low-dose CT screening for high-risk patients.

As established in the report of the Economist Intelligence Unit, in which economic modeling to estimate the direct and indirect costs of lung cancer in 12 countries in the region was performed, the estimated direct health care cost for lung cancer in Chile is $118,494,725, and the estimated per-patient direct cost for lung cancer is $30,679, which is one of the highest costs in Latin America.[19]

This, in association with a well-documented health inequality problem in Chile that is reflected in a significant gap in access to effective therapies (because of which more than 80% of the population does not have access to EGFR TKIs and other costly drugs that are considered standard of care), makes lung cancer one of the important priorities in the near future. An additional effort is needed from authorities to increase coverage and access for the population.

In this setting, clinical trial involvement is a good alternative for patients to access newer and more effective therapies. The new National Cancer Plan project will be a significant milestone for the country, and it is undergoing discussion in Congress right now. This is a great opportunity to change the landscape of cancer in our country, and it is hoped that the plan will implement some of the needed improvements discussed in this article.

Finally, we have to understand lung cancer and tobacco control as a global challenge, with regional and international partnerships playing a crucial role in improving the future of our patients.

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