Lung Cancer in Brazil

Clarissa Mathias, MD, PhD, Gustavo Faibischew Prado, MD, PhD, Eldsamira Mascarenhas, MD, Paula Antonia Ugalde, MD, Ana Carolina Zimmer Gelatti, MD, Elizangela Santos Carvalho, MD, Lilian Dantonino Faroni, MD, MSc, Ricardo Oliveira, MD, Vladmir Claudio Cordeiro de Lima, MD, PhD, Gilberto de Castro Jr., MD, PhD, on behalf of the Grupo Brasileiro de Oncologia Torácica

Lung cancer is one of the most common incident cancers and a leading cause of cancer mortality in Brazil. Here, we aim to describe some aspects related to its prevention, diagnosis, and treatment in our country.

Lung Cancer Epidemiology

In Brazil, lung cancer is the second most common cancer in men and the fourth most common cancer in women, with 18,740 and 12,530 new cases, respectively, estimated for 2018 (Fig. 1). It is the leading cause of death due to cancer in men and the second such leading cause in women. These numbers are largely underestimated, though, on account of a high rate of under-diagnosis and underreporting. The incidence of adenocarcinoma has been progressively increasing in comparison with that of squamous cell carcinoma in Brazil; in fact, it has become the predominant histologic type. In addition, the prevalence of NSCLC has been decreasing among men, whereas it has increased in the female population, mainly among never-smokers.

Lung Cancer Screening

Several studies have evaluated strategies for the screening of lung cancer during the past few decades. In Brazil, because of the high prevalence of infectious granulomatous diseases, especially tuberculosis, the benefits of lung cancer screening need to be better evaluated. An uncontrolled Brazilian study called the Brazilian Lung Cancer Screening Trial evaluated 790 volunteers with eligibility criteria similar to those of the National Lung Screening Trial (NLST). In all, 39.4% of the Brazilian Lung Cancer Screening Trial participants had positive scans, which is significantly different from the results of the NLST; nevertheless, the prevalence of NSCLC was similar to that observed in the NLST (1.3%). Local constraints related to the public health system, presenting with low per capita investments, are major barriers to the recommendation and implementation of lung cancer screening locally; in addition, feasibility, cost-effectiveness, and access remain to be determined in Brazil.

Public health policies have led to notable reductions in tobacco consumption in Brazil, from 35% of the population older than 15 years in 1989 to 10.1% of the population older than 18 years in 2017, according to the Ministry of Health. Therefore, the country serves as an example for other countries to follow. Considering that synergy exists between smoking cessation and lung screening, further efforts should be made to promote both in Brazil.

Address for correspondence: Gilberto de Castro, Jr., MD, PhD, Department of Clinical Oncology, Instituto do Câncer do Estado de São Paulo, Av. Dr. Arnaldo 251, 5th Floor, São Paulo, SP 01246-000, Brazil. E-mail: gilberto.castro@usp.br

© 2019 International Association for the Study of Lung Cancer. Published by Elsevier Inc. All rights reserved.

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2019.07.028
cancer screening in terms of reducing lung cancer mortality, further discussions on the implementation of lung cancer screening remain essential.

**Diagnosis and Staging**

In Brazil, 70% of lung cancer cases are diagnosed as locally advanced or metastatic, whereas only 8% are diagnosed in stage I. Access to invasive techniques for obtaining tissue samples for diagnosis differs between private and public institutions. In the public system, nonsurgical diagnostic procedures, such as percutaneous needle biopsy or bronchoscopy, are scarce, leading to major delays in the timeline of the care of patients with lung cancer. In fact, lung nodules detected by means of computed tomography scans are often managed in the operating room for diagnostic purposes (e.g., by performing wedge resections) followed by a definitive treatment if malignancy is proved. Surgeons usually rely on intraoperative diagnosis by using the frozen section procedure, but a critical limitation is the deficient number of lung cancer–dedicated pathologists.

Although positron emission tomography–computed tomography (PET-CT) is the most important imaging technique for evaluating the mediastinum and distant sites, almost 50% of the population covered by the public health system does not have access to this technology. In addition, because of the high incidence of tuberculosis in Brazil, the yield of PET-CT for mediastinal staging has been questioned. In an area endemic for tuberculosis in Brazil, the specificity and positive predictive value of PET-CT in the context of mediastinal staging in NSCLC were estimated at 52% and 38%, respectively, highlighting the recommendation of histologic confirmation of suspected N2 disease.

Mediastinoscopy is the most popular method of invasive mediastinal staging, and the use of endobronchial ultrasound techniques is increasing. Unfortunately, the percentage of patients who still undergo preoperative mediastinal lymph node sampling is unknown.

**Lung Cancer Surgery**

In the past 10 years, general thoracic surgery has been revolutionized by the rapid development and assimilation of minimally invasive techniques for lung cancer surgery. According to the Brazilian Thoracic Surgery database, between August 2015 and December 2016, 52% of patients with lung cancer underwent minimally invasive anatomical lung resection. This number is superior to those reported by the Society of Thoracic Surgery and the European Society of Thoracic Surgeons. Recently, robotic-assisted thoracic surgery was also adopted. However, access to this technology is still very restricted, and of the 41 robotic platforms available in the country, 75% are located in Rio de Janeiro and São Paulo. Lobectomy is the surgical procedure performed most frequently.
Radiation Therapy for Lung Cancer

Radiation treatment represents an important approach for the treatment of lung cancer, as 60% to 70% of all patients will be irradiated during the course of their disease. Access to a radiotherapy facility is a social problem in Brazil, with about 100,000 patients per year dying without receiving adequate radiation therapy. There are 30 radioactive cobalt-60 teletherapy machines and around 3600 linear accelerators in use in Brazil, and only 30% of radiotherapy facilities have access to image-guided radiation therapy, which is extremely important for more sophisticated treatments, such as intensity-modulated radiotherapy/volumetric modulated arc therapy and stereotactic body radiation treatment (SBRT). Treatment delays are common on account of difficult access to radiation therapy facilities, with long waiting lists to start treatment (mean waiting time 113 days), mainly in public health care centers, which can have a negative impact on patient outcomes. Some recent initiatives by the federal government may help to ameliorate this serious problem.

SBRT can offer disease control rates similar to that of surgery in stage I NSCLC and has become the criterion standard for inoperable patients. Indeed, recent data suggest that patients with oligometastatic disease have global survival benefit with SBRT. Unfortunately, access to image-guided radiation therapy, intensity-modulated radiotherapy/volumetric modulated arc therapy, and SBRT is limited to few patients in Brazil, with most treated in the private sectors.

Systemic Therapy for Lung Cancer

There is an almost complete lack of reliable structured and centralized data regarding lung cancer treatment in Brazil, with very high rates of misdiagnosis and underreporting all over the country.

In a retrospective study, Younes et al. collected data from 2673 patients with metastatic NSCLC treated in two cancer centers between 1990 and 2008. Notably, only 10.2% of patients had a Karnofsky performance score (KPS) of 90% to 100%, and 49% of the patients had a KPS of 70% or less, reflecting the late access of the patients to specialized cancer centers. More recently, the PIVOTAL study collected real-life data from 1256 patients from seven countries, including 175 patients from Brazil. All patients in the Brazilian cohort received first-line therapy. EGFR mutation testing was performed in 58% of patients (17% of patients harbored such mutation), and ALK receptor tyrosine kinase gene (ALK) rearrangement testing was performed in 11% (none tested positive). Most patients were treated with a platinum-containing doublet, and carboplatin was

![Figure 2. General treatment decision tree for metastatic nonsquamous NSCLC in the private and public sectors in Brazil. The preferred treatment options in each situation are highlighted in bold. Dashed lines depict treatment options that have been adopted by some public institutions but are not largely available for patients treated in the public health system. ALK, ALK receptor tyrosine kinase gene; NTRK, neurotrophic receptor tyrosine kinase; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor.](image-url)
prescribed more frequently than cisplatin. Around 50% and 17% of patients received second- and third-line chemotherapy, respectively. The median overall survival in this cohort was 9.7 months.9

These poor results might reflect the fact that most Brazilian patients with a diagnosis of advanced/metastatic NSCLC and a good KPS are being treated with a platinum-based chemotherapy doublet, containing either a taxane, gemcitabine, or vinorelbine, which are affordable because of the public health system. The combination of pemetrexed and bevacizumab, which has been shown to improve outcomes for patients with metastatic lung adenocarcinoma, is not usually available outside the private health sector (Figs. 2 and 3).

In the private health care system, treatment is driven by histologic type, molecular findings, and programmed death ligand 1 expression, following the current recommendations. In Brazil, it is necessary to optimize strategies to identify the appropriate driver mutations to match the respective approved molecular-targeted therapies or immunotherapy. Regarding EGFR activating mutations, as an example, there is a huge access gap between the public and private sectors. A retrospective study showed that 38% of patients with NSCLC in Brazil were tested for EGFR mutations (76% in the private sector and 24% in the public health system).10 Osimertinib, a third-generation EGFR-tyrosine kinase inhibitor that has been approved here for the first-line treatment of metastatic NSCLC harboring exon 19 deletions or exon 21 L858R mutation in EGFR, is not uniformly adopted as a first-line choice. National financial constraints and barriers by third-party payers are among the reasons that can explain why most of our patients are receiving first-generation EGFR tyrosine kinase inhibitors (Table 1).

The first ALK receptor tyrosine kinase inhibitor approved for clinical use in Brazil was crizotinib, in February 2016. The delay in the approval of crizotinib has been estimated to have resulted in premature deaths of more than 700 patients on account of the lack of access to this drug. Recently, alectinib, a second-generation ALK receptor tyrosine kinase inhibitor, was also approved in Brazil, and in 2018, crizotinib was approved for the treatment of advanced NSCLC with ROS1 gene rearrangement, as was the combination of dabrafenib and trametinib for patients whose tumors harbor BRAF V600E mutation.

The diagnosis of tumor-driven mutations is essential for selecting the better-matched treatment. Broader access to tumor genomic profiling and the respective matched molecular-targeted therapy is a high-level priority in Brazil.

Regarding the use of immune checkpoint inhibitors, nivolumab, pembrolizumab, and atezolizumab are approved for patients with NSCLC after platinum failure, with pembrolizumab also being approved as first-line treatment as a monotherapy in patients whose tumors have a tumor proportion score of at least 50%, or in combination with chemotherapy. Again, national financial constraints and barriers by third-party payers are among the possible reasons that explain the clinical use of immune checkpoint inhibitors in few patients treated in the private health system.

Figure 3. General treatment decision tree for metastatic squamous NSCLC in the private and public sectors in Brazil. The preferred treatment options in each situation are highlighted in bold. PD-L1, programmed death ligand 1.
Conclusions

To apply the state-of-the-art recommendations in terms of diagnosis, staging, and treatment to all Brazilian patients with NSCLC, not only to the privately insured ones, and establishing both basic and academic clinical research groups to fulfill the specific needs of training, care excellence, and development in different areas are the major challenges in the lung cancer care in Brazil. The lack of local data in many sectors highlights the need for regional studies to help policymakers develop effective prevention programs, as well as screening, diagnosis, and treatment algorithms and guidelines in Brazil.

Another major driving force and need of lung cancer care in Brazil is the development of proper advocacy for the disease. Empowering the advocacy groups with the help of long-standing organizations such as the

Table 1. Availability, Approvals, and Reimbursement in Brazil of Drugs Usually Used in the Treatment of NSCLC

| Drug                      | Availability | Approved for NSCLC | Indication                                                                 | Reimbursed Private Health Care | Reimbursed Public Health Care |
|---------------------------|--------------|-------------------|---------------------------------------------------------------------------|-------------------------------|-------------------------------|
| Chemotherapy              |              |                   |                                                                           |                               |                               |
| Cisplatin                 | Yes          | Yes               | Neoadjuvant and adjuvant for early-stage disease; combined with chemotherapy for locally advanced disease and used as first- or second-line palliative systemic treatment | Yes                           | Yes                           |
| Carboplatin               | Yes          | Yes               |                                                                           | Yes                           | Yes                           |
| Paclitaxel                | Yes          | Yes               |                                                                           | Yes                           | Yes                           |
| nab-Paclitaxel            | Yes          | No                |                                                                           | No                            | No                            |
| Docetaxel                 | Yes          | Yes               |                                                                           | Yes                           | Yes                           |
| Gemcitabine               | Yes          | Yes               |                                                                           | Yes                           | Yes                           |
| Pemetrexed                | Yes          | Yes               |                                                                           | Yes                           | No                            |
| Vinorelbine               | Yes          | Yes               |                                                                           | Yes                           | Yes                           |
| Antiangiogenics           |              |                   |                                                                           |                               |                               |
| Bevacizumab               | Yes          | Yes               | Metastatic NSCLC, used as first-line, second-line, and maintenance treatment combined with or without chemotherapy | Yes                           | No                            |
| Ramucirumib               | Yes          | Yes               | Metastatic NSCLC, as second-line treatment combined with docetaxel         | Yes                           | No                            |
| Nintedanib                | Yes          | Yes               |                                                                           | No                            | No                            |
| Targeted therapy          |              |                   |                                                                           |                               |                               |
| Gefitinib                 | Yes          | Yes               | Metastatic EGFR-mutant NSCLC                                              | Yes                           | No                            |
| Erlotinib                 | Yes          | Yes               |                                                                           | Yes                           | No                            |
| Afatinib                  | Yes          | Yes               |                                                                           | Yes                           | No                            |
| Dacomitinib               | No           | No                |                                                                           | No                            | No                            |
| Osimertinib               | Yes          | Yes               |                                                                           | No                            | No                            |
| Crizotinib                | Yes          | Yes               | Metastatic ALK-rearranged and ROS1-rearranged (crizotinib only) NSCLC      | Yes                           | No                            |
| Alectinib                 | Yes          | Yes               |                                                                           | No                            | No                            |
| Ceritinib                 | No           | No                |                                                                           | No                            | No                            |
| Brigatinib                | No           | No                |                                                                           | No                            | No                            |
| Lorlatinib                | No           | No                |                                                                           | No                            | No                            |
| Dabrafenib                | Yes          | Yes               | Metastatic BRAF-mutant NSCLC                                              | No                            | No                            |
| Trametinib                | Yes          | Yes               |                                                                           | No                            | No                            |
| Larotrectinib             | Yes          | Yes               | Metastatic NTRK1-, NTRK 2-, or -NTRK3-rearranged NSCLC                     | No                            | No                            |
| Immune checkpoint inhibitors |            |                   |                                                                           |                               |                               |
| Nivolumab                 | Yes          | Yes               | Metastatic NSCLC, used as second-line treatment                           | Yes                           | No                            |
| Pembrolizumab             | Yes          | Yes               | Metastatic NSCLC, used as first-line treatment (alone for PD-L1 expression ≥50% or combined with chemotherapy) and second-line treatment (for PD-L1 expression ≥1%) | Yes                           | No                            |
| Atezolizumab              | Yes          | Yes               | Metastatic NSCLC, used as second-line treatment                           | Yes                           | No                            |
| Durvalumab                | Yes          | Yes               | Consolidation therapy after concurrent chemoradiotherapy for locally advanced disease | Yes                           | No                            |

*aSome drugs, although not included in the Agência Nacional de Saúde list, are reimbursed by some private health insurance companies.

*bThese drugs have been approved by the Agência Nacional de Vigilância Sanitária and can be sold in Brazil; nevertheless, their reimbursement by private health insurance companies is not obligatory because they are not included in the list created by the Agência Nacional de Saúde.

*cSome public cancer centers manage to offer gefitinib or afatinib to their patients thanks to individual negotiations with the pharmaceutical company.

ALK, ALK receptor tyrosine kinase gene; NTRK1, neurotrophic receptor tyrosine kinase 1 gene; NTRK2, neurotrophic receptor tyrosine kinase 2 gene; NTRK3, neurotrophic receptor tyrosine kinase 3 gene; PD-L1, programmed death ligand 1.
International Association for Lung Cancer Study can promote social impulse that may help persuade the government, society, and industry to act on proper solutions.

In the past decade, we have seen new drugs and health care technology innovations coming up at a high rate to allow cancer treatment customization; however increases in their affordability have not followed owing to the prohibitive costs. Frequently, prices have been set in the context of the appeal of satisfying an unmet need for a treatment for a given condition rather than the truly health benefits. It is a common practice to use the external reference prices to align prices in the international market. But if the first price is launched in countries (frequently in the United States) that do not use metrics based on evidence or clinical benefits, the price plateau could be replicated even without this price necessarily being deserved. Dr. L Bonan, in the last 2018 World Congress of Lung Cancer, showed that the United States has the highest drug prices followed by Brazil, especially for recently launched drugs. To evaluate and price drugs on the basis of value in order to benefit the largest number of patients is another major challenge.

Finally, collaboration among academia, different societies, and the government involved in lung cancer care and engagement of their members can lead to major steps toward better patient care.

References
1. Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA). Estimativa 2018: Incidência de câncer no Brasil. http://www.inca.gov.br. Accessed April 25, 2019.

2. dos Santos RS, Franceschini JP, Chate RC, et al. Do current lung cancer screening guidelines apply for populations with high prevalence of granulomatous disease? Results from the First Brazilian Lung Cancer Screening Trial (BRELTI). Ann Thorac Surg. 2016;101:481-486.

3. Araujo LH, Baldotto C, Castro G Jr, et al. Lung cancer in Brazil. J Bras Pneumol. 2018;44:55-64.

4. Werutsky G, Hochhegger B, Lopes de Figueiredo Pinto JA, et al. PET-CT has low specificity for mediastinal staging of non-small-cell lung cancer in an endemic area for tuberculosis: a diagnostic test study (LACOG 0114). BMC Cancer. 2019;19:5.

5. Tsukazan MTR, Terra RM, Vigo Á, et al. Video-assisted thoracoscopic surgery yields better outcomes than thoracotomy for anatomical lung resection in Brazil: a propensity score-matching analysis using the Brazilian Society of Thoracic Surgery database. Eur J Cardiothorac Surg. 2018;53:993-998.

6. Terra RM, Gouvêa FM, Araújo PH, Haddad R, Pêgo-Fernandes PM. Robotic-assisted thoracic surgery in Brazil, a review of the literature and our current experience. J Vis Surg. 2019;5:15.

7. de Moraes FY, Marta GN, Hanna SA, et al. Brazil’s challenges and opportunities. In Reply to Leung. Int J Radiat Oncol Biol Phys. 2015;93:721-722.

8. Younes RN, Pereira JR, Fares AL, Gross J. Chemotherapy beyond first-line in stage IV metastatic non-small cell lung cancer. Rev Assoc Med Bras (1992). 2011;57:686-691.

9. de Castro J, Tagliaferri P, de Lima VCC, et al. Systemic therapy treatment patterns in patients with advanced non-small cell lung cancer (NSCLC): PivOTAL study. Eur J Cancer Care (Engl). 2017;26.

10. Palacio S, Pontes L, Prado E, et al. egfr mutation testing: changing patterns of molecular testing in Brazil. Oncologist. 2019;24:e137-e141.