

Lung cancer in Brazil: epidemiology and treatment challenges

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Abstract: Lung cancer persists throughout the world as a major cause of death. In 2014, data from the Brazilian National Cancer Institute (INCA) estimated 16,400 new cases of lung cancer among men (second most common) and 10,930 new cases among women (fourth most common). These data are consistent for all Brazilian regions and reflect the trends of cancer in the country over the last decade. Brazil is a continental country, the largest in Latin America and fifth in the world, with an estimated population of >200 million. Although the discrepancy in the national income between rich and poor has diminished in the last 2 decades, it is still huge. More than 75% of the Brazilian population do not have private health insurance and rely on the national health care system, where differences in standard of cancer care are evident. It is possible to point out differences from the recommendations of international guidelines in every step of the lung cancer care, from the diagnosis to the treatment of advanced disease. This review aims to describe and recognize these differences as a way to offer a real discussion for future modifications and action points toward delivery of better oncology care in our country.

Keywords: NSCLC, screening, drivers mutations, diagnosis, Brazilian scenario

Epidemiology

Cancer is a major public health problem worldwide and is currently the second leading cause of death, after cardiovascular diseases, which it is expected to surpass in the next years. The overall estimate for 2015 is ~1.5 million new cases in the US and >500,000 in Brazil.^{1,2} Lung cancer is the second leading cancer in men and women, but it is by far the most common cause of death in both sexes. In 2014, data from the Brazilian National Cancer Institute (INCA) estimated 16,400 new cases of lung cancer among men (second most common) and 10,930 new cases among women (fourth most common). These data are consistent for all Brazilian regions and reflect the trends of cancer in the country over the last decade.²

In contrast with developed countries, where lung cancer rates in men increased until the 1990s and decreased thereafter, in Brazil, they are still rising. Trends in the age-adjusted mortality rate revealed an increase from 10.6/100,000 to 13.1/100,000 among men and from 3.0/100,000 to 5.4/100,000 among women from 1979 to 2004. Although lung cancer mortality is significantly higher among men, data are pointing to a greater increment in the relative variation in mortality among women. The increase in mortality from lung cancer is detected in all age strata in both sexes, except for men aged 30–69 years. Since lung cancer has a long latency period from exposure to tobacco to the development of the disease, the real impact of the anti-tobacco campaign

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takes years to be reflected in the population data. The lung cancer mortality essentially reflects the tobacco habits of the Brazilian population in the last decades and not the real consumption nowadays.³

Since lung cancer is mostly tobacco related, the trends in incidence mortality are highly influenced by the prevalence of smokers in the population over the years. Smoking behavior drastically increased after World War II and achieved its peak in the 1970s. As a direct effect of tobacco control measures implemented by the Brazilian government, active smoking rates are strongly declining. The first large population-based study evaluating the prevalence of smokers in Brazil after the implementation of the tobacco control program estimated a decline of 35% between 1989 and 2003, albeit >20% of the population are still actively smoking.⁴ More recently, in 2008, another population-based study confirmed the trend of decreasing rate of smokers, still with ~17% of active smokers.⁵

The success in the campaign for tobacco control is unequivocal, and the authorities are projecting a further annual reduction in smoking population, expecting a prevalence of 11% by 2020.⁴ Both the decline in prevalence and the reduction in the intensity of smoking tended to be stronger among males, younger age groups and higher socioeconomic strata. There is high concern regarding the women, because although the active smokers are declining, in some Brazilian cities, girls smoke more than boys do.^{3,4,6}

Lung cancer screening

The National Lung Cancer Screening Trial (NLST) recently demonstrated that low-dose computed tomography (LDCT) screening could effectively reduce lung cancer mortality among current and former heavy smokers.⁷ The NLST findings together with extrapolations of the trial to the US population led the US Preventative Services Task Force (USPSTF) to recently revise their assessment and recommendation for lung cancer screening for at-risk populations.^{8,9} The USPSTF now recommends, with a grade B recommendation, annual screening for lung cancer with LDCT in adults aged 55–80 years who have a 30-pack-year smoking history and are current smokers or have quit within the past 15 years. Consequently, it is expected that lung cancer screening will become prevalent across the US in the next decade. Although screening is anticipated to have a positive impact on reduction in lung cancer mortality in common with other cancer screening modalities, it will also likely to lead to overdiagnosis.^{10,11}

In Brazil, screening is not recommended in the daily practice and the data are very limited. A major concern in

the applicability and effectiveness of LDCT is the high rates of granulomatous disease in the country, where many pulmonary nodules can be secondary to an inflammatory cause. To address this question, dos Santos et al recently launched the First Brazilian Lung Cancer Screening (BREL1), using the same inclusion criterion as that for the NLST: a pulmonary nodule >4 mm was considered positive and required evaluation by a multidisciplinary team. Indeterminate nodules should be evaluated with fluorodeoxyglucose positron emission tomography (PET)/computed tomography (CT) or biopsy when indicated.¹²

In 2015, the results of the prevalence phase were published, and now the study is in the follow-up phase. From January 2013 to July 2014, 790 participants were enrolled. Positive LDCT scans were reported in 312 (39.4%) participants, with a total of 552 nodules >4 mm. The comparison between positive findings in the NLST (7,191 of 26,722 cases) and those in the BREL1 (312 of 790 cases) showed a significant difference ($P<0.001$). The positive predictive value was lower in the BREL1 than in the NLST (3.2% versus 3.8%, respectively). Follow-up imaging was indicated in 278 of 312 (89.1%) participants; 35 procedures were performed in 25 participants. In 15 cases, benign lesions were diagnosed. Non-small-cell lung cancer (NSCLC) was diagnosed in 10 patients (prevalence of 1.3%). In 8 patients (stage IA/IB disease), treatment was by resection only; in 1 patient, neoadjuvant chemotherapy was used (stage IIIA) and in 1 patient, advanced disease was diagnosed (stage IV). It was concluded that using NLST criteria, a larger number of patients had positive scans (nodules), compared with previous lung cancer screening studies. However, the number of participants requiring surgical biopsy procedures and who were ultimately identified as having cancer was similar to other reports. This supports the role of screening in patient populations with a high incidence of granulomatous disease, as in Brazil.¹²

Although the data from the BREL1 support lung cancer screening in a high-risk population, the implementation of this strategy as a public health practice is not simple. In Brazil, most of the population are not instructed about disease prevention and usually arrive in the health system with high grade and symptomatic disease. Another concern is the difficulty to get good quality scans, sometimes with a longer waiting list (>3 months). PET/CT or thoracic nodule biopsy is limited to tertiary hospitals, not available in many Brazilian regions. For all these issues, the government and medical societies have directed efforts to tobacco control campaign instead of lung cancer screening.

Treatment

A comprehensive clinical and pathological investigation is essential to determine the correct staging and to define optimal treatment approach. All the cases should be discussed in a multidisciplinary cancer care board. Limited data from Brazilian patients about treatment outcomes are available in the literature. Most of these are retrospective reports from single institutions, and only 1 multicenter phase III clinical trial has been published.

Early stage disease

Surgical resection is the treatment of choice in all patients with stage I or II and good performance status.¹³

Despite complete resection, some patients may experience recurrence, and the survival depends heavily on the grade and stage of tumors at the time of the initial diagnosis.¹⁴ Adjuvant chemotherapy or radiotherapy may play a role for stage IB and II patients in the postoperative period.

Several prospective randomized trials confirm the survival advantage of adjuvant cisplatin-based chemotherapy with an absolute increment of 5% for stage II or III patients. For stage I disease with tumors >4 cm, adjuvant therapy can also be beneficial.^{15–17} Postoperative radiation therapy should only be used for patients with positive surgical margins or N2 disease. Despite a better local control with the radiation treatment, its impact on survival is unclear.¹⁸ There is no benefit of radiotherapy for complete resected stage I patients.

There are 3 historical cohort reports^{19–21} on adjuvant treatment in Brazil in the literature. A retrospective cohort study performed in the National Cancer Institute – INCA included 51 stage I–III NSCLC patients treated with surgery and adjuvant chemotherapy from 2004 to 2008. The mean age of the patients was 61 years, 53% were female, mainly had adenocarcinoma (57%) and all had a good performance status (0 or 1). Lobectomy was performed in 80% of the patients. Adjuvant chemotherapy regimen used was cisplatin + etoposide for up to 4 cycles. Stage 3 patients (27%) received radiotherapy after the chemotherapy treatment. After a median follow-up period of 31 months, the median overall survival was 57 months and only 31% were alive after 5 years. Also, there was a trend, but without statistical significance, toward lower median survival in stage III patients when compared to those with stage I or II disease, with an overall survival of 34 months and 57 months, respectively.²² There are no data about the recurrence or the treatment used for advanced disease.

The other 2 studies included sequential patients (stages I–IV) evaluated in different private institutions. In the first one, a total of 566 patients were followed after surgery for

a median follow-up time of 12.8 months. Surgery with curative intent was performed in 155 (28.1%) patients. Of these patients, 67 received adjuvant therapy, and the median overall survival was 99.7 months for patients with stage I and 32.5 months for patients with stage II.²³ The second study included 737 patients evaluated between 1990 and 2000. Complete resection was performed in 149 stage I–IIB patients. The median 5-year survival was 95 months for stage IB, 78 months for stage IIA and 73 months for stage IIB.²⁴ Neither study provided information regarding epidemiological data, adjuvant therapy or recurrence in these patients.

Locally advanced disease

NSCLC stage III patients have several therapeutic options. Mediastinal pathological assessing is mandatory to determine the presence of lymph node metastasis. Some cases of stage IIIA with limited mediastinal disease could be managed with neoadjuvant therapy, while patients with bulky mediastinal disease or unresectable lesions should be treated with definitive chemoradiation. In the neoadjuvant setting, induction therapy with chemotherapy alone is preferred over chemoradiation, although the more intense treatment can be an option for the patient with an outstanding performance status. Clinical data are restricted, and most of the Brazilian trials have important limitations.^{19,20}

In Brazil, the information about neoadjuvant treatment in lung cancer is very poor and prospective studies are not available at this time. However, a phase II trial included 30 patients with stages IB–IIIA NSCLC from January 2001 to August 2002. All patients received 3 cycles of induction chemotherapy and reassessment for mediastinal lymph nodes. Those with negative mediastinal nodes were taken to surgery, and the positive ones were treated with definitive radiotherapy. Twenty-three patients had clinical response, including 8 out of 12 N2 patients. In 22 patients, surgery was performed, and 21 patients could have a complete resection.²¹ No data about survival were provided.

Patients with locally advanced or bulky mediastinal positive lymph nodes are better managed with a multimodality approach, including both chemotherapy and irradiation, and surgery is not recommended. Concurrent chemoradiotherapy is better than sequential treatment or radiotherapy alone.^{25,26} Although the combination of cisplatin and etoposide is widely used in this context, weekly carboplatin and paclitaxel, among others, is also popular.^{27,28} Both chemotherapy doublet agents are widely used in Brazil without any limitations.

Regarding the chemoradiation treatment in Brazil, in a retrospective study presented in the world conference of

lung cancer in 2015, Coelho et al reported the outcome of chemoradiotherapy in a university hospital in the south of Brazil. Seventy-three patients with stage IIIA or IIIB NSCLC were treated with cisplatin–etoposide regimen concurrent to radiotherapy. Most patients were male (63%), had a good performance status (89%), and the most common histological type was adenocarcinoma (52%). All patients were treated with etoposide–cisplatin concurrent with radiation, and 14 (19.2%) received 2 consolidation cycles of chemotherapy. During a follow-up period of 15.7 months, 64 patients (88%) had died, with a progression-free survival of 10.1 months and overall survival of 15.9 months. Clinical stage and performance status were independently associated with survival.²⁹ The PARSIMONY study, a larger, multicenter, observational study, addressing this subject in the Brazilian population is expected to be present during the 2016 World Conference of Lung Cancer.

Advanced disease

The management of metastatic disease has changed drastically in the last years. Although rare patients with limited metastasis could be treated by an aggressive multimodality to try to achieve cure, in general, systemic palliative therapy is recommended. Initial complete evaluation with tissue diagnosis is mandatory, because the management will be individualized according to the histologic subtype. Patients with metastatic non-squamous lung carcinoma should have the tumor tested for driver mutations, such as EGFR, ALK fusion and ROS1.¹³

Metastatic patients without driver mutation in the tumor or when this information is unknown are candidates for cytotoxic chemotherapy with a platinum doublet for 4–6 cycles. This therapeutic approach not only increases the overall survival but also improves the quality of life regarding the cancer symptoms. Systemic chemotherapy should be offered even to asymptomatic patients.^{13,30}

Brazilian data on stage IV NSCLC are also limited and based on individual center experience. There is a great heterogeneity of patients and drug regimens used in the treatment. In general, the overall survival was better than in those who received chemotherapy in comparison to best support of care, but considerably lower than in those reported in the literature.^{23,24,31–33} There are no data regarding maintenance therapy in the Brazilian population.

A retrospective observational study analyzed the data of 564 metastatic NSCLC patients treated between 1990 and 2003 in 3 different cancer centers in São Paulo. The majority of the patients were males (71%) and older than 50 years

(83.7%) with adenocarcinoma (52.8%). Chemotherapy was the treatment for 335 (59.4%) patients, and 47 different chemotherapy regimens were used. The median overall survival was 8.3 months, and 37% of the patients were alive after 1 year.²³ Another observational study included 227 stage IV lung cancer patients. No epidemiological data or treatment regimen was available. The median overall survival for this group of patients was 10 months.²⁴

There is 1 randomized, phase III trial conducted in 8 Brazilian cancer centers for frail patients with stage IV disease. A total of 205 patients with a performance status of 2 were randomized from April 2008 to July 2011 to receive pemetrexed–carboplatin or pemetrexed alone as the first line chemotherapy. The mean age was 65 years, 60% were males and the most common histology was adenocarcinoma (80%). After a median follow-up of 27.5 months, better progression-free survival and overall survival were achieved in the pemetrexed–carboplatin arm, 5.3 months compared to 2.8 months with a single agent. The 1-year PFS and OS, respectively, were 2% and 21.9% in the single drug arm and 17% and 40.1% in the combination arm. Grade 3 or 4 toxicities were low, but 4 deaths occurred in the more intense regimen.³⁴

Brain is a common site for metastases and affects ~40% of NSCLC patients with a poor prognosis. Few data are available about this group of patients, and there is only one report about Brazilian population. Weis et al presented the data of 70 patients with brain metastases from a university hospital at the 2016 Latin American Lung Cancer Conference. Adenocarcinoma was the most common histology; 45% of patients had a Karnofsky performance status <70, 20% had the systemic disease under control, 66% had extra cranial metastases and 37% had >3 brain lesions. Surgery or stereotactic radiotherapy was performed in 29% of the patients; 51% received whole brain radiation and 20% best supportive care. The median overall survival after the diagnosis of brain disease was 5.0 months, but varied significantly according to the treatment. The overall survival for patients treated with radiosurgery was 13 months, while for patients who received whole brain radiotherapy was 5.9 months and for the best supportive care population was only 0.46 months.³⁵

Targeted therapy

Special populations with targetable specific driver molecular pathway should have an individualized treatment with target agents. The developments of these specific drugs have been a great progress in the treatment of lung cancer. Three driver mutations in NSCLC have specific treatment with a

great increase in the outcomes when compared to cytotoxic chemotherapy. The EGFR mutation is the most common, present in ~15% of lung adenocarcinoma in the USA and in up to 60% of Asians.³⁶ Patients with this target alteration should receive first-line treatment with an anti-EGFR TKI, such as erlotinib, gefitinib or afatinib, which leads to a better response rate, progression-free survival and quality of life when compared with cytotoxic chemotherapy.^{37–40}

The prevalence of EGFR mutation in Brazil is 25.5%–30.4% and in Latin America is 26%, but these data may not reflect the real situation of our population because of the restricted access to the test in various regions.^{41,42} Pontes et al reported the largest experience in screening for EGFR mutation in NSCLC, performed in an industry-sponsored access program in Brazil. Between 2011 and 2013, 3,364 samples were analyzed and 857 (25.5%) were positive for EGFR mutation. Deletions in exon 19 were detected in 463 (54%) of the positive samples, point mutations in exon 21 in 240 (28%), mutations in exon 20 in 83 (9.7%) and mutations in exon 18 in 71 (8.3%). There are no data about the treatment outcome in these patients.⁴³

The 2 other driver abnormalities are ALK fusion oncogene and ROS1 mutations. Usually, the population is young, with a weak history of smoking.^{44,45} Both alterations should be treated with crizotinib with a huge impact in progression-free survival, overall survival and quality of life.^{44,45} The drug is recently available in Brazil, and there are no data about this treatment in this population.

Although the knowledge of target mutation on lung cancer brings important changes in the treatment of advanced cancer, a new paradigm in the management of the disease is arriving with immunotherapy. Using the immune system to act against the tumor, new therapies, with much less toxicity and promising results, are being tested in the different clinical settings. Nivolumab and pembrolizumab, 2 anti-PD1 monoclonal antibodies, have already been approved to be used in pretreated advanced NSCLC. While all patients can be treated with nivolumab, pembrolizumab was approved to be used only in those who express PD-L1.^{46–48} Nivolumab has just been approved to be used in Brazil, and no data are available about the expression of PD-L1 and treatment outcome.

An important issue is that the Brazilian population is generally not represented in the clinical trials because of limited access and few research centers in the country. Probably, there are differences regarding survival and quality of life of patients treated in the community oncology center compared to those treated in the scope of clinical trials. Barrios et al evaluated the difference in the survival

of stage IV lung cancer patients comparing the public health system of a Brazilian university cancer center with a research center of the same institution. Forty-one patients were treated in the public health system and 66 patients in the research center with an impressive difference. The median overall survival was 5 months and 10 months, respectively, favoring the research center treatment, with the hazard ratio of 0.6.⁴⁹

Discussion

Important disparities in lung cancer care exist, not only between developing countries and high-growth economics nations, but also especially between poor and rich inhabitants of developing countries.⁵⁰ Brazil has a public health system that provides treatment to the whole population. Although it provides the access to medical care for an important part of the Brazilian population, discussions regarding the quality of the service, especially to cancer patients, exist. There are evident differences between a recognizable standard of cancer care and the treatment available in the public system for the population. It is possible to point out differences from the recommendations of international guidelines in every step of the cancer care, from the diagnosis to the treatment of advanced disease. Because of the differences between the treatment within guidelines and the public services, almost 25% of the Brazilian inhabitants pay for a private health insurance.⁵¹

The Brazilian Ministry of Health published in 2014 a national guideline for cancer treatment that was developed to be the cornerstone on cancer care within the public health system.⁵² This document does not acknowledge the most recent developments in cancer care; thus, it is not supported or recognized by any medical society in the country, and the international guidelines from the American Society of Clinical Oncology and European Society for Medical Oncology are still the references. The gap between the international guidelines for cancer care and the resources available in the public health system does not allow the clinicians to follow important recommendations. The current existent national guideline and the standard of care practiced in the insured patients are so different and show huge treatment differences in the practice of lung cancer treatment.³²

Another important fact is that the public oncology cancer centers in Brazil are not uniform regarding the technology for staging methods and images, pathologic and molecular diagnoses, drugs available for treatment and facilities for clinical support. Contrasting with this diverse and suboptimal scenario, there are great private institutions and university hospitals with massive technology and new-generation

treatment options. Thus, it is clear that major discrepancy with the state-of-the-art patient care happens in Brazil.

The lung cancer patients under the guard of the public health system do not have as many resources and options as those under the private ones. The difficulties start in the diagnostic setting, the staging process and continue in the treatment options. An important issue is the delay in the time from the onset of symptoms until the diagnosis of lung cancer. Although the Standing Medical Advisory Committee recommends that it should take no longer than 6–8 weeks from the onset of symptoms to treatment, Knorst et al⁵³ reported in a historical cohort a period of time superior to 140 days from the development of the first symptoms to the diagnosis of lung cancer in a university hospital in south of Brazil.

The PET/CT imaging is an important tool for staging lung cancer, but only a small fraction of patients has access to this technology. Because of its high cost and limited availability in the hospitals of public health system, it is rarely used. Furthermore, its use is only approved in the public setting for those with early disease who are potential candidates for curative surgery. Until now, there are no data about PET performed for lung cancer in Brazil. The clinical staging is mostly done with CT imaging.

Despite the existence of several biomarkers in lung cancer, limited reimbursement exists for its use.⁵⁴ The EGFR mutation and the ALK fusion test are done in private laboratories, and usually, the pharmaceutical companies sponsor the test. There are no available data about these tests in the public health system, but it is estimated that <30% of the lung adenocarcinomas are tested for EGFR and only ~1% are tested for ALK fusion. Some reasons for the low rates of testing are the difficulty to have access and the cost of the test, small tissue samples of the biopsies and issues regarding limited access to the drugs needed in these scenarios. Patients diagnosed with EGFR mutation have access to anti-EGFR drugs, such as erlotinib and gefitinib, but the government reimbursement to the cancer center is only ~25% of its cost. Anti-ALK fusion drug is not provided by the public health system.

Regarding the classic chemotherapy drugs, most of them can be used and guidelines can be followed. Cisplatin–vinorelbine regime is the standard of care in the adjuvant setting.^{16,17} Locally advanced tumors are treated with combined modality, and cisplatin–etoposide is still the most common chemotherapy regime used with radiation therapy, although the use of paclitaxel–carboplatin is increasing.^{27,28} Three-dimensional conformal radiation therapy is available in many of the institutions, and 60 Gy in 6 weeks regimen established by the RTOG 7301 is the standard of care.⁵⁵

Intensity-modulated radiation therapy is rarely available, and proton therapy does not exist in Brazil.

Stage IV lung cancer patients are usually treated with a platinum-doublet regime. For frail patients, single-agent docetaxel is an option. Maintenance therapy for patients with adenocarcinoma is not recommended or provided in the public system. For second line and beyond therapies, drugs commonly used include docetaxel, gemcitabine or vinorelbine.³²

The oncology daily practice in the private sector is much similar to the practice in the developed countries. Patients have access to as close as possible the standard of care of international guidelines. PET/CT and brain magnetic resonance imaging are easily done for clinical staging; minimal invasive and robotic assistant procedures are available in biopsy and tissue diagnosis. In the pathology field, guidelines for molecular test are available, and an accurate histopathological diagnosis is possible to select the population to target therapy.

Despite this golden scenario in the diagnosis setting for insured patients, the same does not happen in the treatment area. Brazil is well known for delaying the approval of new therapeutics options. The last-generation chemotherapeutic agents are available, but target therapy and immunotherapy are limited. The EGFR mutation and ALK fusion test are widely available, but only first-generation anti-EGFR drugs can be easily prescribed. Although crizotinib, a first-generation anti-ALK fusion, is currently in clinical practice for >5 years, it was approved in Brazil only in February 2016, and the new-generation anti-ALK is not yet available in the country. Immunotherapy, such as anti-PD1 drugs, should be available in the near future for treatment of lung cancer and melanoma. Approved in early April, nivolumab and soon pembrolizumab will be available only to insured patients.

Inappropriate delay in the approval and registration of new medications in Brazil has an important impact and serious consequence on the Brazilian population. As an example, Barrios et al estimated the impact of crizotinib refusal in the registration process by the Brazilian Regulatory Agency. In a period of 3 years, the estimated 1.367 years of life would have been lost, 846 years of deterioration of life symptoms with human suffering could have happened and 772 additional patients could have remained alive if the drug was approved.⁵⁶

Conclusion

The socioeconomic disparities reflected by the existence of 2 different health care systems with a restricted access to diagnosis and therapeutic methods by the largest part of the

population pose a special and difficult task on clinical care of lung cancer patients and an enormous challenge to Brazilian health administrators. Although a high standard of care is offered to the insured patients, the majority of the population are still waiting for adequate coverage of basic products for diagnosis, evaluation and treatment of lung cancer.

Disclosure

The authors report no conflicts of interest in this work.

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