review article

Challenges in Lung Cancer Screening in Latin America

abstract

Lung cancer is the deadliest cancer worldwide and is of particular concern for Latin America. Its rising incidence in this area of the world poses myriad challenges for the region's economies, which are already struggling with limited resources to meet the health care needs of low- and middle-income populations. In this environment, we are concerned that regional governments are relatively unaware of the pressing need to implement effective strategies for the near future. Low-dose chest computed tomography (LDCT) for screening, and routine use of minimally invasive techniques for diagnosis and staging remain uncommon. According to results of the National Lung Screening Trial, LDCT lung cancer screening provided a 20% relative reduction in mortality rates among at-risk individuals. Nevertheless, this issue is still a matter of debate, particularly in developing countries, and it is not fully embraced in developing countries. The aim of this article is to provide an overview of what the standard of care is for lung cancer computed tomography screening around the world and to aid understanding of the challenges and potential solutions that can help with the implementation of LDCT in Latin America.

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INTRODUCTION

Most countries in Latin America (LATAM) are experiencing an epidemiologic transition in the primary burden of disease from infectious diseases to chronic noncommunicable conditions. The rising incidence of cancer is an important contributor to this epidemiologic change and, because > 70% of cancers are diagnosed at later stages, when the disease is incurable, this change creates a growing challenge. Cervical cancer is a major threat in less-developed countries of the region and in pockets of greater poverty within more advanced countries, and rates of prostate cancer and breast cancer are increasing. Most importantly, the specter of tobacco looms ominously. It is anticipated that if smoking rates do not decrease, lung cancer will emerge as the main killer in the next few decades.[1] Fragmented and underfinanced public health systems across the region are not prepared to address this imminent challenge and, for most of them, lung cancer does not yet constitute a public health problem. Evidence is increasing that supports the importance of a well-structured screening approach and its effect on lung cancer mortality, which cannot be ignored. To decrease lung cancer mortality, early detection is very important.[2]

According to results of the National Lung Screening Trial (NLST), low-dose computed tomography (LDCT) lung cancer screening provided a 20% relative reduction in mortality rates among at-risk individuals. Other study findings suggest it is possible to detect early-stage disease in 80% of cases. Nevertheless, this issue is still a matter of debate, particularly in developing countries,[2] and it is frustrating that these results have not been embraced, even in developed countries like the United States. This may be one factor we have to consider when we discuss these issues in developing countries, which tend to follow the model of the most developed ones. Our aim in this review is to reflect on what is the standard of care of lung cancer screening around the world and to understand the challenges and potential solutions that can help with the implementation of LDCT in LATAM in daily practice.

ESTABLISHMENT OF LUNG CANCER SCREENING BY LDCT SCAN OF THE CHEST AS STANDARD OF CARE:

Computed tomography (CT) scans of the chest in high-risk populations are standard of care; implementation of their use in LATAM is a challenge we will have to confront sooner rather than later. Few people are aware of data regarding LDCT scans of the chest. In the 1970s, the US National

Cancer Institute sponsored three prospective randomized trials, each enrolling approximately 10,000 men who were active smokers. Participants were randomly assigned to either annual chest radiograph (CXR) or annual CXR plus sputum cytology.[3,4] These studies demonstrated that sputum cytology had no benefit, but researchers were unable to draw conclusions about the value of CXR as a screening tool. The Mayo Lung Project[5] randomly assigned participants to either CXR or sputum cytology every 4 months, or a recommendation for an annual CXR; no difference in lung cancer mortality was found. Nevertheless, after 20 years of follow-up, the number of cancers in the screened group remained higher than in the control group.[6] Similar results were found in the subsequent and much larger Prostate, Lung, Colorectal, and Ovarian (PLCO) trial.[7] From 1993 to 2001, almost 155,000 smokers were randomly assigned to either annual CXR or usual care. As in the Mayo Lung Project, more cancers were diagnosed in the screened group, but there was no stage shift and there was no difference in lung cancer mortality.[7]

In the 1990s, development and widespread availability of CT imaging reinvigorated the quest for an effective screening tool. The Early Lung Cancer Action Project (ELCAP)[8] demonstrated that CT scan of the chest was superior to CXR for detection of early-stage lung cancers and spawned the much larger International Early Lung Cancer Action Program (I-ELCAP).[9] I-ELCAP enrolled 31,567 participants between 1993 and 2005 and detected 484 lung cancers, of which 412 (85%) were early stage and surgically resectable. Survival among the 302 patients who ultimately underwent lung resection was 92%, which was superior to that of historical control subjects. Without a control group for comparison, however, the potential for overdiagnosis and lead-time bias meant this study was unable to prove any benefit for screening with CT.

There are now results from several prospective, randomized trials of LDCT screening of the chest. The largest and most influential is the National Lung Screening Trial (NLST),[10] which randomly assigned participants (who had at least a 30 pack-year smoking history and were 55 to 74 years of age) to either annual LDCT or annual CXR. Between August 2002 and April 2004, a total of 53,454 smokers and former smokers were enrolled at 33 different sites across the United States. Interim analysis found a reduction in lung cancer mortality of 20% (247 *v* 309 per 100,000 person-years) and, therefore, the study was stopped early. The effect of screening was so significant that all-cause mortality was 6.7% lower. More cancers were diagnosed in the LDCT arm (n = 1,060 *v* 941) and, in contrast to the earlier studies of CXR, screening produced a clear stage shift, with a reduction in the number of stage III/IV cancers in the screened group (n = 447 *v* 566). A key finding of this study was that 96% of all positive findings leading to further investigation by LDCT were not cancer.

In contrast to the results of the NLST, two smaller randomized trials from Europe found no benefit to LDCT screening. The Randomized Study of Lung Cancer Screening with Spiral Computed Tomography (DANTE)[11] compared LDCT to CXR plus sputum cytology, and enrolled 2,472 participants. The Danish Lung Cancer Screening Trial (DLCST)[12] compared annual LDCT with usual care and enrolled 4,104 participants; there was no difference in lung cancer mortality. Based primarily on convincing results from the NLST, many organizations now recommend LDCT screening for smokers and former smokers. These include the National Comprehensive Cancer Network, the American College of Chest Physicians, ASCO, the American Thoracic Society, the American Association for Thoracic Surgery, the Society of Thoracic Surgeons, the American College of Surgeons, and the American Lung Association. In December 2013, the US Preventive Services Task Force recommended LDCT screening for lung cancer.[13,14] However, in January 2014, the American Academy of Family Physicians recommended against routine screening.[15] They based their dissention on concern about too heavy a reliance on positive results from only one study (the NLST) and on the potential for harm from unnecessary testing and invasive procedures in the majority of patients whose nodules are benign. In the following section, we use Brazil as an example of the implementation of a screening program in LATAM.

Experience in LATAM With CT Screening Implementation: CT Lung Screening in Brazil

There are > 20 countries in LATAM, but we are using the example of Brazil because of the large number of people that live there and because

it is the first country in LATAM to be more in favor of LDCT. After the publication of the results from the NLST,[16] the First Brazilian Lung Cancer Screening Trial (BRELT1)[17] was established—the first program for lung cancer screening in Brazil. The program became active in 2013, with the goal of recruiting 1,000 individuals at high risk for lung cancer for LDCT screening and a comprehensive smoking cessation program. A multidisciplinary approach was discussed with the research staff, in particular to follow positive results and determine criteria for negative results.[18-20] The inclusion and exclusion criteria were based on the NLST.[16] The management of CT findings was based on the National Comprehensive Cancer Network lung cancer screening guidelines[19] and the Fleischner Society pulmonary nodule recommendations.[20] The data collection was based on the I-ELCAP database.[8] Some analytic tools for quality of life, anxiety and depression, and nicotine dependence, previously validated in the Portuguese language, were also included.[21-23] As part of this initial planning, the definition of the work team was established (Fig 1). The program comprised different stages:

Stage 1. Community outreach: Marketing and informational materials are created and specifically tailored for the media and for distribution to hospital staff through institutional Web sites, the placement of posters in specific locations, and mailed flyers.

Stage 2. Triage: A screening interview is conducted over the telephone to review all the inclusion and exclusion criteria. Once the potential participant is deemed eligible, they are invited to complete a full questionnaire for lung cancer risk assessment, quality of life, nicotine dependence, and anxiety/depression.

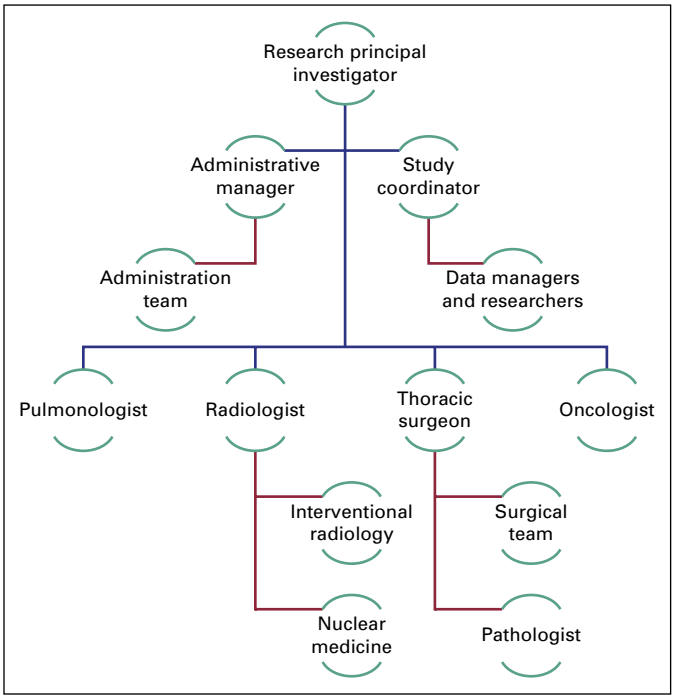
Stage 3. Multidisciplinary approach: After the radiology assessment, all positive findings are discussed by the multidisciplinary team in a formal conference to define the optimal workup strategy. Minimally invasive techniques such as CT-guided transthoracic needle biopsy, bronchoscopy, and video-assisted thoracic surgery are preferred options.[23]

To sustain these program activities, it was imperative that hospital administration support them. Patients at high risk for lung cancer were called to discuss further options, including recommendations for positron emission tomography (PET)-CT or biopsy. Another critically important administrative function was budget control. BRELT1 was a free access program funded by a federal grant to determine the utility and main cost involved in the lung CT screening process.

Although there have been studies of the use of LDCT screening for lung cancer, most of them were of populations with a low incidence of granulomatous disease. The main concern is that in this population, the large number of benign nodules could lead to unnecessary diagnostic testing and surgical procedures.[2]

Initial results from BRELT1[17] indicated 39.4% of 790 participants had positive CT scans, significantly different from results of the NLST, and a non–small-cell lung cancer prevalence of 1.3%, similar to that of NLST and other studies. These results support the role of lung cancer screening in countries with a high incidence of granulomatous inflammation. In this study, most patients (80%) were diagnosed with early-stage IA or IB non–small-cell lung cancer.

Fig 1. Organizational structure of a computed tomography screening program working team.



Challenges of LDCT Implementation in Other LATAM Countries

In others LATAM countries, teams are building and taking the first steps toward implementation

of lung cancer screening. This process must begin with resource optimization and implementation of accessible screening methods pertinent to the Latin population.

In Buenos Aires, Ulla et al[24] reflected on lung cancer screening with LDCT and considered also its possible negative consequences, such as false-positive results, use of invasive procedures, patient's psychological stress, overdiagnosis, and radiation damage. They concluded it was important to discuss with the patient the benefits and potential damage of screening, including expectations about possible curable treatment, or the clinical importance of the findings.[24]

In Mexico, in 2016, Arrieta et al,[25] proposed reaching out to individuals at risk at local and regional levels and then referring them to main centers for LDCT screening and subsequent follow-up. This would lead to a control of the number of patients at risk and the effects of early diagnosis and treatment.[25] This is an interesting proposal coming from the national cancer institute in Mexico that can have a broader implementation if adopted by the government in several areas of the country, maximizing the available technology.

It is curious that in the Hispanic population living in the United States, the incidence of and mortality associated with cancer is generally lower than that of the white non-Hispanic population, but the former have a lower chance of an early-stage diagnosis. The late diagnosis and the difficulty accessing medical care and treatment could help explain the differences between survival outcomes. Others factors such as socioeconomic situation, access to medical insurance and preventive medical care, education level, and cultural aspects can also affect outcomes. Some states are investigating the Latin/Hispanic population to get a more adequate cancer registry for this subpopulation.[26]

LATAM and the Caribbean lack reliable cancer registries, have a low level of investment in cancer development and research compared with developed countries, and as much as 40% of the LATAM population lives in rural areas with restricted access to health care support. Investment in this area is fundamental and would contribute to the definition of a public cancer policy that includes screening programs.[27] This is key because establishing cancer registries across all countries is one of the first necessary steps to start the fight against cancer.

Another important point to consider is the simple lack of access to up-to-date information. In partnership with ASCO, we currently operate several educational initiatives with ASCO's International Committee and the International Mentorship programs for cancer, and it is our experience that there are challenges in the knowledge and information about studies like NLST. Maybe because the prevalence of and mortality associated with lung cancers in LATAM are different than in the United States and Europe, doctors in LATAM do not place enough attention on these topics. For example, cervical cancer and gastric cancer are among the most popular cancer topics in LATAM due to the large number of patients that are treated.

As in Brazil, in the Andean countries (eg, Peru, Bolivia, Ecuador) where pulmonary tuberculosis is prevalent, there are many patients with granulomas in the lungs that will lead to unnecessary workup and increase mortality and costs for the health care systems, although we know that only a fraction of them will be diagnosed as lung cancer. We did not want to do a review of the cost effectiveness of LDCT, but it is obvious that countries that are just moving from infectious diseases as their main public health problems to chronic diseases will need more time before they consider and absorb the costs of LDCT. For example, in countries in the Caribbean (eg, Haiti, Nicaragua, Honduras) and in the Andean region, the governments have limited resources and still need to prioritize the fight against communicable diseases. When they prioritize chronic conditions, like cancer, they focus only on the most prevalent ones. Certainly, lung cancer is not yet one of them, so it is not easy for them to consider an uncommon condition like lung cancer, where the screening is going to generate unnecessary workups.

EUROPEAN PERSPECTIVE ON LUNG CANCER SCREENING

To be more open minded, instead of just following the American approach, we can review the European approach and see what our LATAM countries can learn with regard to LDCT. In Europe, most national health authorities are awaiting results from the Netherlands-Belgian

Table 1. Overview of Low-Dose Computed Tomography Screening Trials

Study	Patients With Cancer, No. (%)	Biopsy Procedures, No. (%)	Lung Cancer Diagnosed, No. (%)
NLST	7,191 (27.0)	758 (2.8)	270 (1.0)
ELCAP	233 (23.0)	28 (2.8)	27 (2.7)
PluSS	1,477 (41.0)	90 (2.5)	36 (1.0)
DLCST	594 (29.0)	25 (1.2)	17 (0.8)
LUSI	540 (27.0)	31 (1.5)	22 (1.1)
DANTE	199 (15.0)	52 (4.1)	28 (2.2)
ITALUNG	426 (30.0)	22 (1.6)	21 (1.5)
LSS	325 (21.0)	57 (3.6)	30 (1.9)
Depiscan	152 (45.2)	NA	8 (2.4)
NELSON	493 (6.5)	NA	200 (2.6)
BRELT1	312 (39.5)	25 (3.1)	10 (1.3)

NOTE. Adapted from dos Santos et al.[2]

Abbreviations: BRELT1, First Brazilian Lung Cancer Screening Trial; DANTE, Randomized Study of Lung Cancer Screening with Spiral Computed Tomography; Depiscan, French randomized pilot trial of lung cancer screening comparing low-dose computed tomography scan and chest radiography; DLCST, Danish Lung Cancer Screening Trial; ELCAP, Early Lung Cancer Action Project; ITALUNG, Italian Lung Cancer Screening Trial; LSS, Lung Screening Study; LUSI, German Lung Cancer Screening Intervention Trial; NA, not available; NELSON, Netherlands-Belgian Lung Cancer Screening trial; NLST, National Lung Screening Trial; PluSS, The Pittsburgh Lung Screening Study.

Lung Cancer Screening trial (NELSON) before making decisions regarding LDCT implementation.[28] Some questions about the screening approach remain unanswered, such as which patients to include in the high-risk group, the time between LDCT screenings, and which patterns of nodules and nodule size should be considered suggestive of malignancy.

The NELSON trial[29] investigated the growth rate of lung nodules, taking in to account different nodules' characteristics. Researchers concluded that a large volume in new solid nodules was the strongest independent predictor of lung cancer. Another interesting point is that the suggestion of malignancy increases as the solid component of tumors increase, which leads us to think that other radiologic parameters should be taken into account in screening evaluations. Also, the endobronchial lesions and tumor presentation in lymph nodes represent another challenge.[29]

To date, CT screening in Europe is only recommended in a white paper by the European Society of Radiology and European Respiratory Society[30] and in a statement from the Swiss University Hospitals.[31] No European national funding bodies have yet decided to support implementation of CT screening; the general consensus in Europe is to await the final results of the NELSON trial before making decisions regarding implementation of lung cancer screening.[28] However, there is considerable variability between European countries. In the United Kingdom, plans will probably follow the methodology applied in the UK Lung Screening Trial, with risk stratification of participants selecting a high-risk cohort with a minimum 5% risk of getting lung cancer within the next 5 years. This is to increase the cost effectiveness of the screening program, which is expected to be more of a focus of the program compared with the United States.[32] In Germany, extrapolation of the NLST results, assuming a 50% recruitment rate, indicates that 1.3 million persons would have to undergo annual CT screening.[33] In many countries, it seems probable that there will be a shortage of public radiology services, and it is expected that some countries may have to integrate private operators and perhaps financing for this process.[31]

Most European countries are considered developed countries, owing to their economic status, but they are not yet fully embracing the concept of LDCT. Therefore, it is hard to believe that without their lead that LATAM countries will move forward with LDCT implementation. We already mentioned that the same problem exists in United States, where, despite the long time since the publication of the NLST results, implementation at the community level (where most of the lung cancers are treated and detected) is minimal. Table 1 provides an overview of LDCT screening trials.

HOW SHOULD A STRUCTURED SCREENING PROGRAM BE ESTABLISHED?

Pedersen and Ashraf[28] have published a paper about the implementation process, the hurdles, guidelines, and requirements for the structure and components of high-quality CT screening programs. These are essential points covering how to achieve a successful program with the least possible harm and a best possible mortality benefit, like the one documented in NLST.

We agree and are concerned that the way a lung cancer screening program is organized and structured will have a profound influence on the results and costs generated by the program, and that mismanagement of the screening process

may jeopardize the mortality benefit, which is the overall goal of screening.[28]

The main elements of a screening program, as mentioned by these authors, include the following:

Eligibility: Specify inclusion and exclusion criteria, such as age, smoking history, time since smoking cessation, and family history. Previous studies usually considered only smoking status to refer patients to screening. In one study by Global Initiative For Chronic Obstructive Lung Disease (GOLD), which had the benefit of screening within a population with chronic obstructive pulmonary disease (COPD), in the population being investigated with mild to moderate COPD (GOLD 1 and 2), lung cancer occurred more frequently, particularly in individuals with alterations of the diffusing capacity of the lungs for carbon monoxide. This study's findings support the incorporation of patients with mild to moderate COPD in lung cancer screening programs.[33]

Education: A smoking cessation program should be an integrated part of the screening program, then participants and staff should be educated about benefits and harms of screening, and informative material should explain benefits and possible harms before informed consent is requested.

Imaging acquisition: LDCT is the standard method, according to technical specifications in protocols (eg, American College of Radiology[34] and NLST).[35,36] There is always the risk of harm due to radiation: It is calculated that approximately one cancer death may have been caused by radiation from CT per 2,500 persons screened.[37] However, the benefit in preventing lung cancer death using the NLST was greater than the radiation risk. We expect that technical improvements in CT scanners will lead to lower radiation doses.

Image review: A complete flowchart for management of nodules that follows established international guidelines, including criteria for when to initiate invasive diagnostic procedures, must be established. Management of screening-detected nodules should involve clinicians and radiologists with expertise in the management of lung nodules and treatment of lung cancer. Criteria for lung nodule identification, size, character, and growth of nodules to enable a definition of nodules as positive, indeterminate, or negative should be described. Data should be collected on location, number, size, and character of all lung nodules detected and registered.

Screening frequency: Criteria are needed regarding how often lesions should be screened or if annual screening is sufficient, because, more often, follow-up may be needed if, for example, lesions are ≥ 6 mm, or depending on other characteristics of the lesions, and clinical history of the patients.

PET scanning: Combination of PET and volumetric measurements increased the diagnostic accuracy and reduced the rate of false-positive test results in DLCST.[28]

Screening interval: The time interval between the CT scans has a great effect on the costs and the patient's cumulative radiation dose exposure. However, this is one of the most important points that must be addressed because, many times, the follow-up will confirm whether or not the suggestive lesion is malignant. An increase in the interval, however, may reduce the diagnostic sensitivity of the screening test. The recommended interval, on the basis of NLST data, is annual screening. In the NELSON trial, screening intervals of 1, 2, and 2.5 years are being evaluated. So far, results show that a 2-year interval after a baseline screening, and one annual repeated scan, did not impair the diagnostic sensitivity; however, during a 2.5-year interval, the frequency of interval cancer increased significantly. In the future, individually tailored screening intervals that are based on baseline CT scan characteristics and individual risk profile may be possible and will be done following established guidelines.

Communication: Results of the screening test should be communicated and explained to the participant in writing and by direct oral communication in case of a positive or indeterminate result. In case of a negative (normal) result, communication can be in writing.

Quality improvement and research: To ensure high-quality performance in the screening program, continuous research and audits are essential. Important areas of research include biomarkers, chemotherapy-prevention studies within screening programs, methods to recruit the hard-to-reach population, review of optimal screening intervals in CT screening, and development of minimal invasive treatment in early lung cancer.

According to guidelines for CT screening from major organizations (eg, Medicare, US Preventive Services Task Force, National Comprehensive Cancer Network, American Lung Association, American Association for Thoracic Surgery, American Cancer Society, International Association for the Study of Lung Cancer), screening should only be done in multidisciplinary centers.[30,32,34,38,39] A multidisciplinary team should include pulmonologists, pathologists, radiologists, thoracic surgeons, and oncologists. The center should also have CT-guided biopsy expertise or other minimally invasive procedures for small lung nodules biopsy , as well as all technical conditions to guarantee the best imaging approach.[28] Registration of all collected data at the national level is fundamental for the overall improvement of population screening.

In conclusion, we make the following four points:

1. Smoking cessation strategies and tobacco control policies should be stimulated and optimized—they are the most effective and important long-term initiatives to curb lung cancer incidence and mortality in the LATAM region.
2. The importance of early detection in high-risk populations such as smokers, passive smokers, and groups with environmental exposures should be recognized and advertised. Education, training, and active involvement of general practitioners and pulmonologists should be a priority. It is important in LATAM to provide education about LDCT screening.
3. We have to be conscious that we probably need to make LDCT more accurate in LATAM because we cannot afford to deal with so much granulomatous disease and false-positive results that the economic burden is not cost effective. We might learn from NELSON or other studies how to better select patients who might benefit from LDCT.
4. Screening programs aimed at early detection with the latest technologies (eg, LDCT) should be discussed and implemented with government involvement to allow access to most of the population, which is still underserved in most of the region. This probably has to be done in LATAM; in other countries, such as the United States, government-sponsored insurance like Medicare and Medicaid can provide patients of any population access to LDCT. However, that model likely will not be easy in LATAM, because the governments cannot afford to make LDCT available everywhere. The suggestion in Mexico to create dedicated centers that guarantee early and adequate referral of suspected cases to tertiary facilities with appropriate knowledge of how to treat early cases should be an integral part of the screening strategy.

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