The future of thoracic oncology

O futuro da oncologia torácica

Paulo M. Pêgo-Fernandes[1], Alberto J. M. Dela Vega[2]

[1]Full Professor of Thoracic Surgery. Director of the Division of Thoracic Surgery, Instituto do Coração (InCor), Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (HC-FMUSP), São Paulo, SP, Brazil
[2]Assistant Physician of Thoracic Surgery, Faculdade de Medicina, Universidade de São Paulo (FMUSP), Instituto do Câncer do Estado de São Paulo (ICESP), São Paulo, SP, Brazil

E-mail: ajmvega@yahoo.com.br

http://dx.doi.org/10.1590/1806-9282.62.01.1

A fight on several fronts is what characterizes the efforts to treat thoracic malignancies. It is a battle against a number of difficulties owing to the rarity of some diseases, such as thymic cancer and chest wall tumors, which hinders the conduction of strong evidence-based trials; the aggressiveness and high incidence of lung cancer, the deadliest cancer in the world; the high complexity of surgeries and chemotherapy; and more. Recent clinical research and development of new equipment in the last decade point to a horizon in rapid change.

The development of new diagnostic and therapeutic technologies has been sizable, but they will only consolidate if associated with constant organizing efforts to create guidelines and unify conducts. Initiatives, such as the International Thymic Malignancy Oncology Group, created in 2010 with the purpose of overcoming difficulties to establish guidelines for the treatment of thymoma, are examples of how to create opportunities to develop trials for relatively rare cancers whose conducts to date are based largely on retrospective studies.[1] There is no evidence supported by randomized clinical trials indicating a trimodality treatment for patients with thymoma. For example, the indication of radiotherapy and neoadjuvant or adjuvant chemotherapy in cases of completely resected thymoma is very controversial. Initiatives such as this would add to those of societies of thoracic surgery in the attempt of expanding international databases and promoting their integration. In Brazil, the São Paulo lung cancer registry implementation project thrives, and the Brazilian Society of Thoracic Surgery also shows progress toward this goal, with a plan to develop its own database.

In relation to lung malignancies, results from the National Lung Screening Trial published in 2011 have changed the perspectives on screening tests. Until its publication, there was no solid evidence regarding the benefit of this strategy. The study showed an increase in survival with the use of low-dose chest computed tomography as a screening method, compared to chest X-rays in patients aged 55 to 74 years with a smoking history greater than 30 pack-years.[2] The prospect of having a test for effective screening, comparable to those used for other cancers, naturally changes the way society intends to fight the disease. However, the actual implications of screening in terms of cost, effectiveness of treatment, and the need to choose an appropriate criterion for the selection of patients still require extensive analysis.[3] Much is expected of the results from Belgian-Dutch trial *Nederlands Leuvens Longkanker Screenings Onderzoek* (NELSON), which will soon be reaching the end of a follow-up phase, and aims to compare the result of chest CT screening *versus* no screening, in contrast with an American study that used X-ray in the control group.[4,5]

With the possibility of improved detection of early tumors, there will be concerns related to imaging test results, such as how to confirm the nature of lung nodules detected on screening tests. Advances in bronchoscopy and interventional radiology have provided quite varied alternatives to surgeons, oncologists and pulmonologists to intervene in these situations. Options include the improvement of technologies like endobronchial ultrasonography (EBUS), electromagnetic navigation bronchoscopy, and dissemination of CT-guided transthoracic needle biopsy. It is expected that the integration of these methods, the creation of hybrid rooms and the active participation of surgeons and pathologists may improve agility and make the investigation of nodules an increasingly safe activity, fully in line with the expectation of treatment, if lesion malignancy is confirmed.

Once lung cancer is detected at an early stage, treatment is surgery whenever possible, and in this area, advances have also been remarkable. Minimally invasive surgery is a reality not only for lung cancer but also for many mediastinal tumors, especially due to the widespread use of video-assisted surgery. More recently, robotic surgery has gained strength in various specialties, which is also true with thoracic surgery. The advancements in this technology are not limited to instruments with varied and wider motion or the tridimensional view enabled to the

surgeon. Since the robot has a very robust central processing unit capable of storing an exceptional amount of data, one can imagine that in the future this technology will exceed the current goal of long-distance surgery, and include other tools that enhance the safety of the procedure and facilitate the development and training of surgeons.

In the field of clinical oncology, we have advanced toward more comprehensive detailing of histological types and the genetic profile of tumors. For some time, the classification of lung cancer as non-small cell has been insufficient to plan appropriate treatment, and the use of more accurate tests such as immunohistochemistry for a clear definition of histological type is critical. This is because the therapeutic arsenal available today changes depending on tumor classification. In addition to the definition of a histological type, the current recommendation is that patients with lung cancer at an advanced stage, with tumors containing any adenocarcinoma component should be tested for changes in epidermal growth factor receptor (*EGFR*) gene and anaplastic lymphoma kinase (*ALK*) gene translocation.[6] Once these changes are detected, treatment should be guided and based on specific targeted therapies. Several other molecular targets have been studied such as mutations in the *KRAS* gene and changes in the *ROS1* gene, and there is much discussion about the possibility of developing tests to find several changes in small tissue samples. This leads to a possibility that in the future we will have at our disposal a long list of detailed characteristics of tumors, allowing us to create a fully personalized treatment, based on the exact genetic profile of the tumor that each patient has. Specific treatment would increase the efficiency and maybe minimize potential adverse effects that often hinder treatment with cytotoxic drugs.

There are also raised expectations for immunotherapy. Studies evaluating the use of anti-PD-1 (programmed death receptor 1) and anti-PDL-1 (programmed death ligand 1) antibodies have shown promising results. The most important so far are phase III studies, evaluating anti-PD-1 antibody in patients diagnosed with non-small cell lung cancer who had disease progression after or during treatment with first line chemotherapy. These studies show increased overall survival using the new drug, compared to docetaxel therapy for both squamous and non-squamous tumors, in addition to a more tolerable profile.[7,8] The hope is that soon there will be evidence for the use of such treatments in other clinical situations, as well as a better understanding of the populations most likely to benefit from this therapy.

Another form of treatment that has shown progress is proton therapy. Initially used for treatment of other cancers, this technology has been increasingly studied in the treatment of lung cancer, and data suggests benefit in terms of disease control and toxicity when compared to conventional radiotherapy.[9] Results are still preliminary but a phase III randomized clinical trial is already underway in order to assess whether there is a benefit in survival with the use of this technique.[10]

In Brazil, the National Cancer Institute estimates that in 2016 more than 28,000 cases of lung cancer will be diagnosed.[11] However, most of these cases will be diagnosed in advanced stages, requiring more complex and more expensive treatments. In an audit report of the Brazilian Federal Court of Auditors published in 2010, the delay in the treatment of cancer patients in the country was evident. Only about 15% started treatment within 30 days, much less than in other countries.[12] This demonstrates that greater efforts should be made for early detection and to provide therapeutic resources for a larger portion of the population.

As we can see, the international scientific community has contributed with major discoveries in the fields of cancer screening, diagnosis and treatment. Within the Brazilian context, however, the next step for proper development of this area would be to make the currently existing resources accessible to all. The incorporation of new technologies always tends to be slow, especially in developing countries, but we must remember that this process can occur more rapidly in an increasingly globalized world. It is undeniable that a hierarchical service on a large scale and with easy access to centers specialized in cancer across the country would completely change the way we see the progression of our patients. The Brazilian thoracic oncology will have a bright future when the interval between disease detection and early treatment allows us to provide the best treatments currently available.

References

1. ITMIG | International Thymic Malignancy Interest Group [Internet]. [cited on 3 dez. 2015]. Available from: https://www.itmig.org/.
2. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011; 365(5):395-409.
3. Cui J-W, Li W, Han F-J, Liu Y-D. Screening for lung cancer using low-dose computed tomography: concerns about the application in low-risk individuals. Transl Lung Cancer Res. 2015; 4(3):275-86.
4. Trial data [Internet]. [cited on 3 dez. 2015]. Available from: http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=636.
5. Nelson Infobrochure [Internet]. [cited on 3 dez. 2015]. Available from: http://www.nelsonproject.nl/infobrochure.html.
6. Leighl NB, Rekhtman N, Biermann WA, Huang J, Mino-Kenudson M, Ramalingam SS, et al. Molecular testing for selection of patients with lung

cancer for epidermal growth factor receptor and anaplastic lymphoma kinase tyrosine kinase inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the study of lung cancer/Association for Molecular Pathology Guideline. J Clin Oncol. 2014; 32(32):3673-9.
7. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015; 373(17):1627-39.
8. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. N Engl J Med. 2015; 373(2):123-35.
9. Berman A, James S, Rengan R. Proton Beam therapy for non-small cell lung cancer: current clinical evidence and future directions. Cancers. 2015; 7(3):1178-90.
10. RTOG | Clinical Trials | Study Number 1308 [Internet]. [cited on 11 dez. 2015]. Available from: https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1308.
11. Estimativa 2016 Incidência de câncer no Brasil. [Internet]. [cited on 9 dez. 2015]. Available from: http://www.inca.gov.br/wcm/dncc/2015/index.asp.
12. Auditoria Operacional na Política Nacional de Atenção Oncológica. [Internet]. [cited on 11 dez. 2015]. Available from: http://portal.tcu.gov.br/lumis/portal/file/fileDownload.jsp?inline=1&fileId=8A8182A14E1CA3E4014E1CFCC4D62E43.