Reducing uncertainty to a manageable level: the need for a nuanced and patient-centric approach to lung nodule management in the 21st century

Despite remarkable progress in an indominable struggle with lung cancer, owing to unprecedented recent achievements in smoking cessation efforts, effective novel therapeutics, and implementation of life-saving lung cancer screening strategies, the management of incidentally- or lung cancer screening-identified pulmonary nodules remains fraught with difficulty and risk. One major challenge in lung nodule management is the frequent need to respond to the main patient concern, the actual nature of a suspicious lung lesion ("is it cancer or not?") with a probabilistic outcome ("the probability of lung cancer is such"). The former is an ontological consideration, a "black and white" matter, the latter an epistemological one, declined in shades of grey. This imbalance in expectations and delivery dictates, consequently, the nuanced nature of discussions lung nodule experts have on a daily basis with patients with suspicious but indeterminate lung lesions. With an estimated 1.5 million new lung nodules incidentally identified annually in the United States, novel non- or minimally-invasive strategies are urgently needed to effectively reduce the zone of uncertainty, or intermediate probability of malignancy, and re-classify lesions as low- or high-probability of malignancy in order to facilitate informed decision-making and illuminate patient-provider discussions.

Increasing awareness of the dismal outcomes of lung cancer, still responsible for more cancer-related deaths than colon, breast and prostate cancer combined, has led to considerable investments in research and development in industry and federally-funded research in the past decade, which have attempted to address this issue and radically transformed the landscape of lung cancer diagnosis, staging and treatment. Many of these advances have been slow to percolate into routine clinical practice, but some, like bronchoscopic mediastinal staging and immunotherapy, are now widely considered standard of care. This special issue of the Journal of Thoracic Diseases encompasses a broad range to topics pertinent to this space, authored by recognized international researchers and clinicians involved in lung nodule and lung cancer management, and provides a timely review of recent developments to establish the current state of affairs and hopefully provide insights into what the future of lung nodule management may hold in the coming years.

Advanced diagnostic bronchoscopy has in the past few years advanced to position itself as a viable alternative to transthoracic imaging-based biopsies, as supported by current expert recommendations. Dr. Cicenia and colleagues review the published evidence on electromagnetic navigation, while, Drs. Lentz, Cheng and Murgu discuss recent advances in novel biopsy techniques, advanced real-time imaging with cone-beam computed tomography (CT), and the promising introduction of robotic bronchoscopy, respectively, all technological advances poised to substantially affect the yield of peripheral bronchoscopy. Because technological progress in this field has in some respect outpaced critical evaluation and provider education, Drs. Yarmus, Lamb, and Lee provide their expert opinion on the need for methodologically robust clinical trials to evaluate new interventions, and the challenges of standardizing education in interventional pulmonology in the midst of technological progress. Bronchoscopy has also proved very useful in providing tissue for advanced molecular testing and Dr. Gonzalez provides a sensible review of the evidence supporting its role in suitable specimen acquisition. Non-invasive risk stratification of lung nodules has also received considerable attention in the past few years. The revolution of artificial intelligence using conventional radiomic and deep-learning-based quantitative imaging on available CT datasets is discussed by Dr. Peikert and colleagues, while the current status of other plasma-and tissue-based biomarkers is examined by Dr. Massion. Finally, an integrated Bayesian approach to lung nodule characterization, leveraging all these novel diagnostic approaches to provide accurate and actionable probabilities of malignancy is summarized by Drs. Tanner and Fox.

It is our sincere hope that these state-of-the-art reviews on relevant and debated topics in lung nodule management will stimulate discussions, encourage research and inform clinical decisions to hopefully ultimately improve patient care. We believe that thoughtful and cautious implementation of these novel strategies will eventually contribute to clarify the nature of indeterminate lung lesions, or at least reduce uncertainty to a manageable level.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease* for the series "Novel Diagnostic Techniques for Lung Cancer". The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd.2020.03.65). The series "Novel Diagnostic Techniques for Lung Cancer" was commissioned by the editorial office without any funding or sponsorship. RJL served as an unpaid Guest Editor for the series. FM served as the unpaid Guest Editor of the series and serves as an unpaid editorial member of *Journal of Thoracic Disease* from Aug 2019 to Jul 2021. FM reports grants from Medtronic, personal fees from Medtronic, during the conduct of the study.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
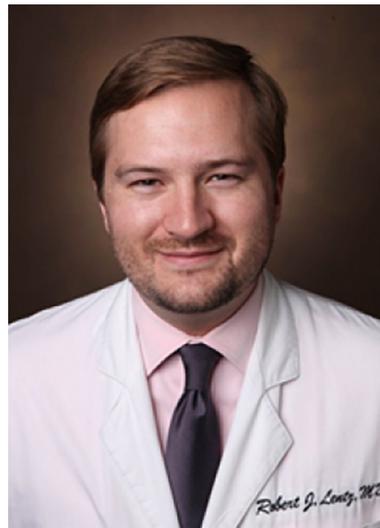
Fabien Maldonado

Robert J. Lentz

Fabien Maldonado[1,2]**, MD**
(Email: fabien.maldonado@vumc.org)
Robert J. Lentz[1,2,3]**, MD**
(Email: robert.j.lentz@vumc.org)
[1]*Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA;* [2]*Department of Thoracic Surgery, Vanderbilt University School of Medicine, Nashville, TN, USA;* [3]*Department of Veterans Affairs Medical Center, Nashville, TN, USA.*