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Editorial

Lung Cancer Screening–A Paradigm Shift

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Lung cancer remains the most lethal malignancy in the world and is the most common cause of cancer related death in the United States [1], in large part due to our inability to eliminate smoking altogether and failure to detect the tumor at an early stage. Even with advances in therapy, 5-year survival rates are around 15% on average for all individuals with lung cancer [2]. In fact, only 15 % of lung cancers are diagnosed at early stage and 50% die within one year of diagnosis. Yet, our spending on lung cancer research has lagged woefully (one-tenth that of breast).

Low Dose Computed Tomography (LDCT) screening of the chest has shown a 20% reduction in mortality in select high-risk patients (smokers between the ages of 55 and 74 years who have smoked a minimum of 30 pack years and quit for no more than 15 years) when compared to chest roentgenogram in the landmark National Lung Screening Trial (NLST) [3]. Nonetheless, there are several caveats to its widespread use. It has a poor specificity (high false positive rate). 96.4% of the nodules detected on LDCT screen in the trial were non-malignant. LDCT has poor sensitivity particularly for non-smokers (10-15% of lung cancers develop in non – smokers) and endobronchial tumors may not be easily detected by LDCT. Furthermore, only about ~30% of current lung cancers patients in the US meet the NLST criteria [4]. Cost (not yet paid by Medicare and other insurances), radiation and potential for increased morbidity and even mortality secondary to further diagnostic procedures are other concerns. Finally, there remains the haunting question of what to do after 3 years. For these reasons, there is a need to explore further screening and diagnostic techniques and lung cancer biomarkers have so far shown promise to bridge this gap in future. Several risk models exist to predict future development of lung cancer in high-risk patients [5-7]. While these models have not been studied as an entry point for LDCT screening, they are important tools for clinicians for thorough bedside assessment.

Early detection techniques may be applied either in the respiratory tract or in the peripherally collected blood or serum specimens. Modalities used in the respiratory tract include airway epithelial gene expression (the airway transcriptome), bronchial epithelium proteomic signature, exhaled breath condensate analysis for volatile organic compounds (VOCs) and auto fluorescence bronchoscopy [8-10]. The airway transcriptome is a set of RNA molecules that can be detected in bronchial, nasal or buccal cells. Proteomic signature is an assay of an individual or a set of proteins that can help distinguish lung cancer from controls and may be tested in bronchial epithelium as well as blood. The rationale for testing VOCs in exhaled breath is that presence of tumor cells result in peroxidation of cell membrane and release of somewhat different organic compounds than normal individuals, which can be detected by various techniques, most commonly by gas chromatography – mass spectrometry. Autofluorescence bronchoscopy is able to detect pre-invasive lesions (dysplasia and metaplasia) with much higher sensitivity than conventional white light bronchoscopy.

Early detection of lung cancer by techniques applied in peripheral specimens like blood, serum or even urine include serum autoantibodies, serum microRNAs, DNA methylation analyses, cell-free circulating DNA and circulating tumor cells. Serum autoantibodies against tumor-associated antigens have been vastly studied, however, they tend to have a low sensitivity. MicroRNAs are class of small non-coding RNA thought to regulate gene expression and are abnormally expressed in many cancers. Being relatively more stable than messenger RNA in blood, they are an attractive approach to early detection. DNA methylation is an epigenetic mechanism that affects gene expression, and methylation of several genes has been associated with lung cancer. DNA methylation studies can be performed on blood cells, cell-free DNA, sputum and airway epithelial specimens. The measurement and detection of early lung cancer from peripheral specimens tend to be least invasive and likely more reproducible since inter-rater reliability is a lesser issue. Nevertheless, there is no compelling data to prefer one to the other strategy and they may ultimately be integrated [9].

Any screening or diagnostic test must satisfy certain quality standards. Not only such a test should be reproducible with high positive and negative predictive values, it should also prove a meaningful clinical utility, be cost-effective and easily applicable. Therefore, in spite of abundant groundwork, none of the available biomarkers have been adopted for current clinical use. Biomarkers for early detection and/or screening for lung cancer are undergoing active investigation with promise. Several of these techniques have been explored as diagnostic biomarkers for pre-invasive and invasive lesions rather than early detection.

Several potential roles of biomarkers in lung cancer can be hypothesized based on available literature. They have a potential to enhance the specificity of LDCT screening by helping to select the highest risk patients who meet the LDCT screening criteria. Biomarker profile may also be useful in decision- making process after an LDCT screening shows lung nodule to stratify high-risk patients who should proceed to biopsy earlier. Because of their reproducibility, they can conceivably be utilized for disease monitoring after therapy as well as to detect recurrence. Because many of these biomarkers have a poor sensitivity, their use as a primary screening modality may not be justified yet. At present, there is no published literature showing outcomes by combining LDCT with a biomarker and studies are underway.

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There is no single intervention better than prevention. The emphasis on smoking cessation cannot be overstated. This is probably the single most important factor with potential to reduce a vast majority of the burden of healthcare related costs, morbidity and mortality. Smoking cessation efforts have been partially successful in the west [11] and will bear fruit in the long term. Whereas, in the short term, lung cancer will remain a major burden worldwide and early detection will be critical to improving outcomes and optimal screening strategy will most likely involve a combination of approaches.

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