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INSIGHTFUL INVESTIGATIONS INTO INDETERMINATE LUNG NODULE SCREENING FOR EARLY DETECTION OF LUNG CANCER: DR. MOHAN RUDRAPPA

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KEYWORDS :

Each year, more than 1 million persons worldwide are found to possess a lung nodule that carries a risk of being malignant. In reality, the large majority of lung nodules are benign, whether identified by screening or incidentally. The consequences of delaying or missing the diagnosis of lung cancer can be enormous, as can be the consequences of invasive techniques on patients with benign lung nodules. The challenge for the clinician caring for these patients is to differentiate between benign and malignant nodules with the least harm possible. Dr. Mohan Rudrappa is showing us new directions in tackling these clinical ambiguities.

We are currently overwhelmed with an excess case load of indeterminate pulmonary or lung nodules (IPN/ILN), found incidentally during routine radiologic imaging, but also through the increased use of CT screening programs targeting high-risk individuals for lung cancer following the initial results of the National Lung Screening Trial (NLST) and the United States Preventive Services Task Force (USPSTF) recommendations. The large majority of IPNs are, however, benign. The obvious question arises: how aggressively should we screen them? Can they be cancerous in the future? However, current predictive tools to discriminate benign from malignant nodules are not rigorous, leading to many follow-up CTs, unnecessary invasive biopsies with attendant morbidity and rare mortality, anxiety, and wasted healthcare spending. Although the optimal approach to the management of patients with IPNs is evolving, key questions in determining individual probabilities of disease, given their history or findings on CT, remains highly challenging from a routine clinical perspective. Recent work by Dr. Mohan Rudrappa, an attending Pulmonary physician at Mercy Hospital, Rogers, has brought about the opportunity for formulating pithy guidelines related to lung cancer screening. The analyses was performed during his tenure at eh Overton Brooks VA Hospital in Shreveport, Louisiana.

In a landmark original study, Dr. Rudrappa for the first time has demonstrated that the new pulmonary nodules are not to be taken lightly but rather necessitate parallel disease mapping, especially chronic lung diseases (1). In the NLST trial , the risk of cancer from new nodules has been demonstrated as 6 %, compared to about half the risk for screen-detected baseline nodule. What it implies is that the people with co-existed lung diseases have a greater risk of these nodules progressing to cancer. These lung diseases may include chronic inflammatory diseases like asthma or even other lung conditions like fungal infections like histoplasmosis. What this also implies is that patients with co-existent human immunodeficiency virus (HIV) infection are at greater risk for the conversion of these spotty lesions to pre-cancerous and cancerous conditions. The whole nature of finding by Dr. Rudrappa is practice changing, as his reanalysis of the existing trials have given us fresh insights regarding discrete pathways of what we should do in the face of ambiguity. Dr. Rudrappa's clinical inferences for the first time proves beyond doubt that low dose CT scan is not an excess but given the specific conditions, there should be minimal clinical inertia for repeat screening for ruling out "nastiness" of a suspicious lesion. The sheer reason for this is the aggressive downhill course of a lesion frankly progressing to lung cancer. Dr. Rudrappa's findings are a clear step in the practice of precision medicine of one of the commonest cancers facing the United States, as well as globally.

IPNs are those that have traditionally been defined as carrying some risk of cancer risk. They are noncalcified biologically, 7 to 20 mm in diameter, and with a risk of malignancy between 5% and 60%. The risk is less than for suspicious nodules (>60%) and greater than for nonsuspicious ones (<5%). There is still controversy around the definition of an IPN, and all clinicians are well aware how challenging the evaluation of an IPN can be. IPNs fall under the broader picture covering noncalcified nodules (NCN).

Some NCNs may be predicted as cancer precursors based on the analysis of the CT screening data of the NLST. Although the majority of NCNs are not cancer precursors, NCNs are strongly associated with short-term cancer risk and weaker long-term risk. The presence of an NCN confers significantly elevated long-term lung cancer risk ratios at the person, lung, and lobe levels. Ground glass opacity (GGOs) were associated with long-term lung cancer risk but inversely associated with short-term risk. This clearly signals that some NCNs and some GGOs represent cancer precursor lesions that eventually function very differently than benign ones, depending on their biologic features and morphology. As risk biomarkers, the NCN size, attenuation, margins, and persistence (and suspected volume doubling times) provide different odds for cancer. Dr. Rudrappa's findings emphasize that individualistic attention to each case is important, but disease overlap with other chronic conditions, especially lung diseases, is a driving factor for the frequency of the scanning. Likely, this will not increase the incidence but rather figure out specific high-risk lesions.

Differentiating the minority of malignant from benign IPNs represents one of the most urgent clinical problems in early detection of lung cancer, particularly on the eve of widespread advocacy and adoption of lung cancer screening in the United States. The problem is comparable to finding a "needle in a haystack". When managing IPNs, most diagnostic errors occur in the intermediate probability group. This is due to a lack of intricate knowledge of structural features of IPNs and the absence of validated diagnostic biomarkers for accurate disease categorization. Dr. Rudrappa has provided the basis for specific approaches under such conditions of equivocality. In a landmark "one of its kind" study, he elaborated the characteristics of lung cancer from secondary lung nodule in subjects with preexisting solitary nodule. Intriguingly, Dr. Rudrappa's study revealed that the incidence of secondary nodule detected during nodule surveillance program is as high as 12 % (1,2). This is significantly higher than what has been reported in previous trials and actually not mentioned in the Fleischner guidelines. For the first time, with Dr. Rudrappa's pioneering clinical revelations, the balance has been set right that the secondary nodule should be aggressively followed up.

Although most IPNs represent benign disease, significant morbidity and cost are associated with their management—a study reported nearly $28 billion per year in the United States. Incorrect evaluation of IPNs causes risks that encompass patient and family anxiety, to a high rate of unnecessary surgeries and invasive approaches for benign nodules, to missed chances for cure during follow-up, resulting in the fatal outcomes of death. Chest CT, truly is capable of providing the improved diagnostic accuracy needed. Individualization of acre, based upon the novel recommendations

of Dr. Rudrappa, is required for having an above-average approach to this highly challenging clinical scenario.

IPNs may be solitary or multiple and are extremely common, with the reported prevalence between 8% and 69% depending on the clinical context (i.e., screening or prevalent disease, age, and endemic area for fungal disease. Despite using a lower diameter of 4 mm for IPN in the early results of the NLST, a 20% relative reduction in lung cancer-specific mortality was found, though with 39.1% of the individuals having at least one positive result. The vast majority of IPNs are benign, with a false-positive (FP) rate in this high-risk cohort of 96%. The management of lung nodules follows the American College of Chest Physicians (ACCP; and very similar National Comprehensive Cancer Network (NCCN) guidelines, which recommend that for nodules >8 mm in diameter, when the chances of lung cancer is <5%, a follow-up CT be repeated at 3 months. Should the probability be between 5% and 60%, the ACCP recommends a PET CT or tissue diagnosis. Should the probability be >60%, a tissue diagnosis is suggested at discovery. Despite attempts at bringing uniformity of IPN follow-up, controversy persists.

The differentiation of benign from malignant IPNs is based on the nodule shape, density, size, and changes in these features over time, particularly in growth rate as shown by the timing of nodule volume doubling (VDT). Volumetric analysis of nodules has improved significantly with the rates of change of the volumes (growth rates) being some of the best predictors of malignancy. Yet growth rate cannot provide the answer the patients want at the time of discovery because calculation of growth rate requires follow-up studies. Automated approaches for volumetric analysis are being increasingly eamined and are facing the challenges of nodules of low density, those overlapping the pleura or the mediastinum, those close to the vasculature, and, very importantly, the challenge of addressing methods to determine accurately and reproducibly the smallest change. Tumor volume estimation should lead to improving current guidelines of the management of IPNs. Rather than relying on imaging-based biomarkers, Dr. Rudrappa has given us a diagnostic model-based approach. These include factoring for age smoking history, asbestos exposure, but also other co existent diseases like fungal infection and COPD (chronic obstructive pulmonary disease). The demonstration of these unique correlation of what makes Dr. Rudrappa's finding a highly relevant to the field. His visionary approaches to the screening of lung cancer emanates from his lifelong commitment in the field of pulmonary and critical care medicine. Dr. Rudrappa has stressed the need for precision-based approaches to accurately biopsy the lung lesions using Veran system. Though overdiagnosis is a serious problem in screening-detected lung cancer, Dr. Rudrappa has shown us a path to identify indolent cancers by striking the right balance between careful surveillance and aggressive management. The need for clinical surveillance is obvious. Determination of lung nodule malignancy is pivotal, because the early diagnosis of lung cancer could lead to a definitive intervention. Dr. Rudrappa's findings have emphasized that the clinical context should not be overlooked in determining the probability of malignancy. The entire lung cancer screening field has important lessons to learn from paradigm shifting findings from Dr. Rudrappa 's original study. The pioneering work of Dr. Rudrappa has taken down the uncertainty facing the field by an exponential step and given hope for millions of patients facing the dilemma for appropriate lung cancer screening.

Figure 1. Dr. Mohan Rudrappa

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