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New Pulmonary Nodules. Tip of Iceberg

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Abstract— *Lung cancer remains the most common cause of cancer-related death. Lung cancer starts as a small growth and can be identified as a nodule on CT scans. In the last ten years, several large trials have shown the benefit of screening for lung cancer using low dose CT scan in high-risk individuals. Not all nodules are cancers, although the risk increased exponentially with the size of nodules. There are several published guidelines for management of lung nodules. Most nodules detected either incidentally or during lung cancer screening are less than one centimeter long and will only need follow up CT scan to identify growth. In follow up CT scans new nodules, which are not present in the previous scan can be detected and care called new pulmonary nodules. These nodules are considered to be fast growing and have more potential for being lung cancer. There is a lack of literature about optimal management of these new pulmonary nodules. In this article, we review the incidence of new nodules and the risk of lung cancer from these new nodules.*

Keywords— *Lung cancer. Solitary pulmonary nodules. Incidental pulmonary nodules. Screen-detected pulmonary nodules.*

I. INTRODUCTION

Almost 35 years back, Fleisher society defined pulmonary nodule as "Any pulmonary or pleural lesion represented in a radiograph by a sharply defined, discrete, nearly circular opacity 2-30 mm in diameter". It was considered synonymous to coin lesion [1]. Lesions larger than 30 mm are considered as mass lesions. Lung nodules can be an incidental finding on the CT scan done for nonrelated reasons and are called incidental-pulmonary nodules (IPN). They can also be actively sought for in lung cancer screening program with low dose CT scan and are called screen-detected nodules. The incidence of coin lesion was less than 1% of all chest x-ray done. With the invention of computed tomogram (CT) in 1976 and its subsequent excessive use in daily clinical practice, the prevalence of lung nodules has been growing enormously. Based on the analysis of data from Kaiser Permanente health care nearly 1.6 million pulmonary nodules will be detected every year in United States during CT scans done for unrelated reasons [2]. Low dose CT scans done for screening lung cancer can show nodules in up to 30% of patients and with the rapid adoption of the lung cancer screening program in the community, there will be a significant increase in the burden on pulmonary nodules in the coming years. Most the nodules detected either incidentally or during screening are less than one centimeter and require to follow up CT scan to rule out any growth with time to rule out lung cancer. This approach has created another public health problem new pulmonary nodule (NPN) and is likely to grow in the future.

New nodules can be detected during the follow-up CT scans for both incidental, and screen-detected nodules. Unlike the IPDs and SDNs where their age is not definite, these nodules are new and hence defined as new pulmonary nodules. As these nodules develop in short interval from either three months to one year, they are considered to be fast growing and at high risk for lung cancer. Also, patient's particular genotypic and phenotypic characteristics predisposing them to have incidental or screen-detected nodules can also put them at high risk for lung cancer. Despite the growing healthcare burden, there is a lack of literature about new pulmonary nodules. In this article, We would like to review the new pulmonary nodules and report our experience of treating patients with lung nodules.

II. THE INCIDENCE OF NEW PULMONARY NODULES

The exact incidence of NPN is difficult to determine given the difference in intervals of follow up CTs used in different lung cancer screening trials. Also, even in patients with IPN, the intervals of follow up CT scan depend on the size of the baseline nodule and can vary from three months to eighteen months. Overall, the risk of new nodules during follow up imaging is reported to be 2.5% to 14% in lung cancer screening programs [3-8]. In the NLST trial two annual follow up CT scans showed NPN in 2.6% [3]. In the Nelson trial, the follow-up CT scans were done at one and three years after the baseline CT scans, and they showed NPN in 5 to 7% [4]. In the Mayo Clinic trial, three annual follow CT scan was used and the risk of new nodules at second and third scan was 14% and 9% respectively [5]. In the I-ELCAP trail annual follow up CT scan (7 to 18 months) showed nodules 5.2% of patients [6]. In the ELCAP trial and PluSS trial, the risk of new nodules at one year follow up CT scans was 2.5 and 7.5% respectively [7]. The risk of new nodules includes both patients with and without SDNs at baseline CT scan. None of the screening trails explicitly reported the risk of development of NPN in patients with SDN. In the NLST trials, of the 644 subjects with NPN at the T1 screen, 33.7% also had a pre-existing nodule located anywhere in the lung. Of the 628 subjects with NPN at the T2 screen, 34.6% had pre-existing nodule located anywhere in the lung. Similarly, in the Nelson trial, 46% of patients with NPN in the follow-up scan had SDN in the initial scan.

Literature is scarce about the development of NPN in patients with IPN. In our experience, the risk of development of NPN is new around 12% [9]. This risk is at par with other lung cancer screening trials but higher than others trials. However, our cohort is significantly different from other lung cancer screening trial patients. We followed only patients with

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incidental nodules the duration of follow up CT scan was variable from 3 months to 12 years.

Moreover, patients were not excluded based on smoking history, age or presence of other comorbid conditions. As noted in the several previous trials, nodules can appear and disappear spontaneously in CT scans. The more frequent the follow-up CT scans, the more is the chance of identifying the nodule. The higher risk noted in the study compared to other trials is likely due to varying patient population and difference in the follow-up CT scan regime.

In the coming years, with excessive use of CT scans in daily clinical practice and the pursuit of LDCT in lung cancer programs along with growing awareness of nodules among both public and physicians, the detection of NPN will explode. Considered a 10% risk of NPN in follow up of nearly 1.5 million incidental lung nodules annually, approximately 150000 new pulmonary nodules can be detected every year. Also, at present lung cancer screening program significantly underutilized and less than 5% of eligible 7 million smokers in united stated are screened for lung cancer. Considering half of the eligible smoker gets LDCTs, and the risk of NPN in a screening program of around 5% every year, 350000 new pulmonary nodules can be detected every year. Half a million NPN every year is unquestionably a gross overestimate but does raises concerns for the epidemic of NPN in future.

III. New Pulmonary Nodules and The Risk Of Lung Cancer

New pulmonary nodules are at high risk for lung cancer compared to preexisting nodules. In the lung cancer screening trials, the risk of cancer from new pulmonary nodules is reported between 1.5% to 5.7% [3-8]. The different trail's design of screening trials makes accurate comparison difficult, but overall the risk of cancer from new nodules is around 5%. In the NSLT trial, the risk of cancer from new nodules in both follow-up scans was 5.7% compared to 2.7% risk of cancer from screen-detected baseline nodule [3]. Similarly, in the Nelson trial, 6% of new nodules detected during follow up scans were diagnosed as cancer compared on 4% chance of cancer from baseline screen-detected nodule [4]. In the ELCAP trail, the risk of cancer from new nodules is 10% compared to 7.4% risk of cancer from screen-detected nodules [7]. However different results have been reported in other trials. In Mayo clinic study, the risk of cancer from detected nodules was 4.6% which is higher than the risk from new nodules during follow up at 3.3% [5]. Unlike other screening trials, the Mayo Clinic study was done in Histoplasma endemic area and had a higher incidence of screen-detected nodules of 56% at baseline screen, and the incidence of NPN is also reported to be high at 12%. In our patient cohort with incidental lung nodules, the risk of cancer from new nodules is 7.4% compared to 6.5% risk from preexisting nodules [9].

IV. Characteristics Features of New Pulmonary Nodules

Not all screening trial reported the characteristics of the new nodule. Most new nodules are smaller than one centimeter in size, and in the majority of patients, only one new nodule was detected. In the NLST trial, 53% of new nodules were less than 6 mm in size and 18% of nodules were more than 10 millimeters in size. Half of the nodules had a smooth margin, and only 20% were speculated [3]. In the Nelson trial, nodule volume was measured instead of maximum diameter making a direct comparison to other trials which used either largest diameter or mean of width in two axes. Assuming perfect sphere, nodule of 4 mm will have 34 cubic mm of volume and nodule of 10 mm will have 523 cubic mm of volume. 57% of all nodules were less than 50 cubic mm, and only 8% were larger than 500 cubic millimeters. The median size of the new nodule was 41 cubic millimeters [4].

V. Risk Factors of Cancer in New Pulmonary Nodules.

Size of the nodule is the main determined for risk for lung cancer. In the NSLT trial, the risk of cancer increased monotonically from 1.1% for nodules less than 4 mm to 24 % for nodules larger than 20 mm [3]. For nodules of less than one centimeter, the risk of cancer new nodule was significantly higher compared to baseline nodules, but for larger nodules, the risk of cancer from new nodules was less compared to baseline nodules. A similar finding was noted in Nelson study. Screen-detected nodule at baseline CT scan smaller than 100 cubic millimeters had a risk of cancer of about 0.6% compared to 3% risk for similar nodules detected during follow up [4].

VI. Management of New Pulmonary Nodules

As noted in the British thoracic society guidelines for the investigation and management of pulmonary nodules, there is no robust evidence for optimal management for these new nodules [10]. The lung cancer screening trials have clearly shown that new nodules are common and are at high risk for lung cancer compared to screen-detected lung cancer and might require close follow up. The Lung CT Screening Reporting and Data system incorporates the increased risk and assigns a higher score for similar new nodules. New nodules of <4mm, 4 to < 6 mm, 6 to < 8 mm and more than eight mm nodules are scored 2, 3, 4A and 4B respectively which us one lever higher compared to screen-detected nodule at baseline[11]. Fleischner society guidelines and American College of chest physicians recommend that new nodules should be managed similarly to the baseline nodules [12].

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