Using Artificial Intelligence and Noninvasive Methods to Diagnosis Pulmonary Nodules Smaller than 8 mm in Diameter: Two Case Reports

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Abstract
The malignancy risk of pulmonary nodules is strongly associated with nodule size. The current clinical guidelines recommended long-term follow-up for patients with nodules smaller than 8 mm; however, the current diagnostic tools are insufficient for evaluating the malignancy risk of nodules of this size. Some patients might feel anxious because of the uncertainty of the malignancy risk during the follow-up process. We reported two cases in which Artificial Intelligence (AI) technology for CT images, as well as liquid biopsy, was used to improve the diagnostic power for small nodules; this approach resulted in higher patient satisfaction since the malignancy risk of the nodules was determined in a short period.

Keywords: Artificial intelligence; Liquid biopsy; Case report; Lung cancer diagnosis; Patient satisfaction; Pulmonary nodules

Introduction
Pulmonary nodule size is one of the important aspects that determines the likelihood of malignancy [1]. The probabilities of malignancy are less than 1% for nodules that are< 5 mm and 2.3% to 6% for nodules that are< 9 mm on low-dose CT images [2,3]. The current clinical guidelines, including the Evaluation of Pulmonary Nodules Clinical Practice Consensus Guidelines for Asia and the American College of Chest Physicians (CHEST) clinical practice guidelines, recommended patients with solid pulmonary nodules ≤ 8 mm and nonsolid pulmonary nodules ≤ 5 mm undergo long-term surveillance with Computed Tomography (CT) to evaluate their lung cancer risk [4,5]. However, during the follow-up period, some patients with pulmonary nodules in this size range might suffer from anxiety and depression because of the uncertainty of the malignancy risk of their nodules. However, the current clinical tools are insufficient for predicting the malignancy risk of pulmonary nodules ≤ 10 mm Ost et al. [6]; therefore, there is a need for diagnostic instruments that can assist in the evaluation of small pulmonary nodules to reduce the psychological stress of patients.

We report 2 cases in which Artificial Intelligence (AI) technology for CT images and liquid biopsy were used to improve the efficiency of recognizing the malignancy risk of pulmonary nodules ≤ 8 mm in diameter.

Case 1
A 53-year-old male discovered a pure Ground-Glass Nodule (pGGN) that was approximately 5 mm in diameter in the upper lobe of the left lung during an annual physical exam in June 2019. The patient had no reported history of cancer, no history of smoking and drinking, and no family history of cancer. Because the patient had no typical clinical characteristics, we evaluated the nodule to have a low risk of malignancy and suggested that the patient schedule a follow-up CT after 6 months. In March 2020, the CT results showed that the diameter of the nodule increased by an estimated 1 mm, from 5 mm to 6 mm in 6 months. We then suggested that the patient continue to be followed up for changes by CT at 3 and 6 months, since no significant changes of the nodules were observed on the CT image.

On April 2nd, the patient returned to the clinic, reported increased anxiety in the past month, and required further diagnosis of the nodule. We decided to analyze his CT image with new (AI) technology that was just introduced to the hospital because the malignancy rate is very low for pulmonary nodules of this size. This technology is based on a self-learning algorithm and has been trained by more than 100 thousand lung CT images with histopathology examination results [7]. Surprisingly, AI identified 5 pulmonary nodules from the CT image and indicated that the malignancy risk of the largest nodule, which was the nodule that we found previously, was 90%. With the 3D reconstruction, the AI predicted that the size of the nodule was 8.0 mm x 7.2 mm, slightly larger than what we visually estimated in the clinic (Figure 1). Furthermore, we suggested that the patient undergo a Circulating Abnormal Cell (CAC) test, a diagnostic technology that uses a Fluorescence in Situ Hybridization (FISH) assay to identify genomic abnormalities of chromosomes 3 and 10 in the peripheral blood of early lung cancer patients [7,8]. With cutoff value of 3 CACs [9], the test showed 6 CACs in the patient’s peripheral blood, which indicated a high risk of lung cancer.

On April 7th, after preoperative examinations that included a cardiopulmonary function evaluation, the patient underwent thoracoscopic radical resection of the pulmonary nodules undergeneral anesthesia. During the operation, local adhesions, horizontal fissures, and oblique fissures of the lung were observed. Next, a wedge-shaped portion of the upper lobe of the right lung was removed, with positioning guidance from a puncture needle. The maximum diameter of the removed nodules was approximately 5 mm, and the nodule

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had a soft texture. A tendency towards noninvasive adenocarcinoma was shown by intraoperative rapid freezing procedures. However, the final diagnosis result of the paraffinized biopsy section indicated that the removed specimens were microinvasive adenocarcinoma. The patient’s condition was stable after the surgery, and he was discharged from the hospital on April 13th.

Case 2

A 59-year-old male patient was found to have multiple pulmonary nodules on both sides of the lung by CT scan in March 2020. The largest nodule was identified as a solitary nodule less than 7 mm in diameter on the left lower lobe. The patient stated that he did not experience any chest pain or other discomfort. Correspondingly, he reported no history of smoking, cardiovascular diseases, or cancer. The malignancy risk of the nodules was classified as “low”, with a less than 3% malignancy likelihood according to the Mayo Clinic Solitary Pulmonary Nodule (SPN) Malignancy Risk Score Model [10].

After 3 months, the patient returned to the clinic for follow-up. The CT image showed no changes in the size of the largest nodule or in any other clinical signs. We suggested that the patient return to the clinic for a follow-up in another 3 months, as the malignancy risk of the nodules was still very low. The patient expressed concern since his two older brothers died from lung cancer and stomach cancer and requested further diagnostic approaches. Therefore, we analyzed his CT image with AI. The AI results indicated that the size of the largest nodule was 5.8 mm x 5.1 mm, with a 25% malignancy risk. To reduce his anxiety, we also suggested that he undergo a CAC test, which only required 10 ml of peripheral blood without invasive procedures [9]. Consistently, the likelihood of malignancy was specified to be “low” based on the findings of only 1 CAC in his blood.

The patient still insisted on surgery after all the diagnostic tests that we performed. The thoracoscopic resection of multiple nodules in the left lung under general anesthesia was successfully performed after two weeks. Multiple carbonized nodules were discovered on the surface of the upper lobe during the operation. The frozen sections of the lung specimens indicated that the largest nodule in the lower lobe was an inflammatory nodule. Reactive lymph node hyperplasia with carbon deposition was the final histopathology diagnosis result.

The patient’s condition was stable, and he was discharged from the hospital 6 days after surgery (Table 1).

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<tr>
<th>Case 1</th>
<th>Case 2</th>
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<tr>
<td>Date of First Discovery</td>
<td>Date of First Discovery</td>
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<tr>
<td>Pulmonary Nodules</td>
<td>Pulmonary Nodules</td>
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<tr>
<td>June 05, 2020</td>
<td>June 21, 2020</td>
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<td>Analyze CT Images with AI &amp; Liquid Biopsy</td>
<td>Analyze CT Images with AI &amp; Liquid Biopsy</td>
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<td>April 02, 2020</td>
<td>June 15, 2020</td>
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<td>Surgery &amp; Histopathology Result</td>
<td>Surgery &amp; Histopathology Result</td>
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<td>April 07, 2020</td>
<td>June 15, 2020</td>
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<tr>
<td>Patient Discharge</td>
<td>Patient Discharge</td>
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<td>April 13, 2020</td>
<td>June 21, 2020</td>
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</table>

Table 1: Patient Care Timeline.

Conclusion

Pulmonary nodules less than 8 mm in diameter, especially pGGNs, are difficult to visually evaluate by CT images; the current diagnostic tools, such as PET-CT, are insufficient in diagnosing this type of nodule [6]. Using deep learning AI to analyze lung CT images might be more effective than visually evaluating small pulmonary nodules because AI can provide a quantitative assessment of the images systematically, which might help experienced physicians to analyze lung CT images that are hard to assess visually [11]. In some populated cities in China, one physician might need to read more than 50 CT images a day because of the high patient flow; deep learning AI might be able to improve the reading capacity and reduce the mistakes made by exhausted physicians. In addition, deep learning AI is trained with thousands of clinical CT images, which might help inexperienced physicians improve their diagnostic ability for lung nodules, especially in rural areas where doctors have less medical training than those in urban areas. Furthermore, in contrast to diagnostic methods such as core needle biopsy and thoracoscopy that might cause side effects such as bleeding and pneumothorax, liquid biopsy can be an alternative tool to noninvasively assess the malignancy risk of pulmonary nodules that are difficult to analyze by CT, which can help to reduce the patients’ physical and mental stress.

In conclusion, the combination of deep learning AI and noninvasive liquid biopsy can provide additional evidence for clinicians to evaluate the malignancy risk of pulmonary nodules less than 8 mm in diameter, which might help to reduce the anxiety of patients during the follow-up process.

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Author’s Contribution

Conceptualization NZ and YW; writing- original draft preparation LY; writing-review and editing XZ.

Conflict of Interests

The authors declare no conflict of interest.

References


