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Commentary: Pay attention to low-risk populations for lung cancer, but cautiously interpret ground-glass nodules screened by low-dose computed tomography scan

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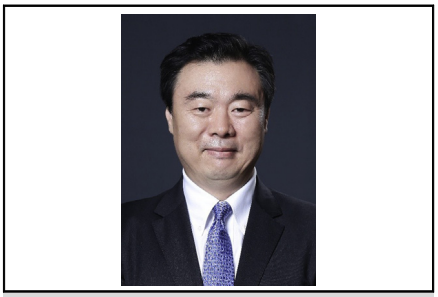

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CENTRAL MESSAGE

The traditional high-risk population for lung cancer has been changing. Nonetheless, it remains important to avoid overdiagnosis and overtreatment of ground-glass nodules.

Traditionally, "high-risk" populations for lung cancer refer to male smokers age 55 to 74 years who have had a malignancy or whose parent(s) had lung cancer. However, due to the widespread application of low-dose computed tomography (LDCT) scanning in China, many young female nonsmokers and those without a history of malignancy or family history have been diagnosed with early-stage lung adenocarcinoma. The nodules manifest as ground-glass nodules (GGNs), which are adenocarcinoma in situ, minimally invasive adenocarcinoma, or lepidic predominant adenocarcinoma pathologically.

Although we are beginning to recognize the authenticity of early-stage lung adenocarcinoma among young females, the phenomenon lacks support from large-sample screening data. Thus, the report by Zhang and colleagues in the *Journal*[1] is a major advance. This multicenter, large-sample study included 8392 hospital employees who were screened by LDCT as part of a regular examination. Lung cancer was confirmed in 179 patients (2.1%), with detection rates of 2.5% in females and 1.3% in males. The incidences in nonsmokers and smokers were 2.2% and 1.4%, respectively. The detection rates were 1.0% in patients age $\leq$40 years, 2.6% in patients age 40 to 55 years, and 2.9% in patients age >55 years.

With substantial data, Zhang and colleagues document that the high-risk population for lung cancer, at least in China, is undergoing change or has already changed, and that LDCT is identifying more lung cancers among the traditional low-risk populations of nonsmokers and young females. This finding merits attention from government, medical professionals, and society at large.

This study may change the traditional view of lung cancer, but it also revealed that 95.5% of the cancer cases

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manifested as GGNs, 98.9% were adenocarcinoma, and 98.9% of the patients underwent surgery with "excellent" outcomes. Thus, we should also take the following factors into consideration when interpreting and treating GGNs screened by LDCT:

- Clarification of GGN TNM staging. The 8th TNM staging for lung cancer clearly notes that the T category is based on the size of solid tumors or solid components in GGNs rather than on GGN size. In the study reported by Suzuki and colleagues,[2] the cases (tumor >30 mm) with a consolidation/tumor ratio (CTR) <0.50 had no lymph node metastases, and 5-year OS and DFS were both almost 100%. Therefore, pure GGNs should be cautiously defined as stage IA, because most of them screened by LDCT are actually stage c0.
- Radiologic classification of GGNs. The classification of GGNs has developed from the 6-type to the 3-type classification based on patient prognoses, that is, pure GGNs, heterogeneous GGNs, and partly solid GGNs. This reclassification scheme is intimately correlated with prognosis, which best reflects the biological behavior of GGNs. Moreover, Suzuki and colleagues reported that in 1029 patients with early-stage lung cancer, the GGN component was an independent favorable prognostic factor (hazard ratio, 0.314; 95% confidence interval, 0.181∼0.529).
- Monitoring GGN growth. Given the indolent growth of GGNs indolent growth, most guidelines recommend CT observation. Surgery should be performed only for patients who experience GGN growth during observation. Sawada and colleagues[3] reported on 15 years of observation for 226 patients with GGNs. Only 0.6% progressed over a period of 4 to 10 years. Furthermore, among those who underwent surgery, only 4% of the GGNs were diagnosed as pathologically invasive adenocarcinoma. Kakinuma and colleagues[4] reported that among patients with pure ground-glass opacities of 10 mm in diameter, only 20% of females and 30% of males experienced growth of 2 mm after 10 years. Therefore, they concluded that it is appropriate to observe GGNs, because very few progress during follow-up.
- Conversely, the radiation dosage of CT is cause for concern. Rampinelli and colleagues[5] estimated incidences of radiation-induced lung cancer and other major cancers (10-year) of approximately 3/10,000 and 5/10,000, respectively. The National Lung Screening Trial reported that 18% of all lung cancers detected by LDCT were overdiagnoses.[6] In addition, although there are no relevant data, the anxiety raised by pulmonary nodule detection and the associated economic burdens have been receiving attention. Therefore, the new American College of Chest Physicians guideline also recommends decreasing the examination frequency for indolent tumors such as GGNs.

In summary, we should recognize that the traditional high-risk lung cancer population has been changing, and young female nonsmokers should receive more attention. At the same time, it is important to cautiously interpret and treat adenocarcinoma manifested as GGNs, to avoid overdiagnosis and overtreatment. The indications for clinical intervention proposed by Detterbeck[7] (>3 cm/>2 mm solid component in mediastinal window/>25% increase annually) might not be accepted by all Asian clinicians; however, persistent ground-glass opacities or ground-glass opacities ≥6 mm observed by LDCT during follow-up should not be the indication for surgery. I do agree with Detterbeck regarding the observation standards of GGNs by CT. Finally, it is highly recommended that multidisciplinary team experts discuss the imaging report negative/positive standard for pure GGNs under thin-section high-resolution CT, to further minimize overdiagnoses and overtreatment.

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