Received: 30 May 2023 | Accepted: 7 December 2023 | Published on: 4 January 2024

DOI: 10.1111/ajco.14042

REVIEW

WILEY

Overdiagnosis and overtreatment of ground-glass nodule-like lung cancer

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Funding information
Yunnan Provincial Nature Foundation, Grant/Award Number: 202301AY070001-057

Abstract

Lung cancer has had one of the highest incidences and mortality in the world over the last few decades, which has aided in the promotion and popularization of screening for lung ground-glass nodules (GGNs). People have great psychological anxiety about GGN because of the chance that it will develop into lung cancer, which makes clinical treatment of GGN a generally excessive phenomenon. Overdiagnosis in screening has recently been mentioned in the literature. An important research emphasis of screening is how to reduce the incidence of overdiagnosis and overtreatment. This paper discusses from different aspects how to characterize the occurrence of overdiagnosis and overtreatment, how to reduce overdiagnosis and overtreatment, and future screening, follow-up, and treatment approaches.

KEYWORDS
ground-glass nodules, lung cancer, overdiagnosis, overtreatment, screening

1 | INTRODUCTION

Lung cancer has long been regarded as one of the most threatening malignancies to human health and life. It has the highest death rate of all cancers.[1] Based on population projections, China will have the largest number of new cases of lung cancer.[2] Because lung cancer is typically asymptomatic in the early stage, many patients present with advanced disease, and treatment goals often fall short of expectations. Lung cancer, both past and present, is awful news for individuals and families.

Primary lung cancer is classified as either non-small cell lung cancer (NSCLC) or SCLC, with roughly 85% of patients diagnosed with NSCLC. Lung adenocarcinoma is the most common subtype of NSCLC observed.[3] It accounts for 50% of all lung cancer diagnoses, and its incidence is on the rise.[4-6] Computed tomography (CT) imaging shows early lung adenocarcinoma as ground-glass nodules (GGNs), allowing for the early detection and diagnosis of GGN-like lung cancer.

In 2011, the National Lung Screening Trial reported that low-dose CT (LDCT) screening was used instead of standard chest X-rays. LDCT significantly improved the detection rate of early lung cancer and, more importantly, revealed a 20% reduction in mortality.[7] The main reason is that the early detection of lung cancer and subsequent treatment reduces lung cancer mortality.[8,9] Since then, LDCT screening for lung cancer has been highly embraced. While LDCT detects early lung cancer, it also detects a large number of GGNs, which are often considered manifestations of early lung cancer. This leads to overdiagnosis. Most patients are terrified and anxious to begin active treatment after being diagnosed with precancerous lesions of early lung cancer. This eventually led to overtreatment.

Overdiagnosis and overtreatment have had unanticipated repercussions. It causes a series of social, psychological, and economic problems

for the patients.[10,11] The focus of the present study is on how to mitigate these impacts.

1.1 | Overdiagnosis

The first thing we need to understand is what overdiagnosis is. Overdiagnosis in medicine arises because of disease redefinition, increased use of imaging technologies, and screening for early disease diagnosis. These factors result in millions of patients being diagnosed with conditions that may have never progressed to clinical significance.[12,13] Now that we have defined overdiagnosis, we need to know how it is defined in cancer. It exists under the following three conditions: the presence of microfocal disease, a long natural history, and screening tests directed at early detection.[12,14]

Most cancers, particularly GGN-like lung cancer, currently exist to meet the three conditions mentioned above. GGN, also known as ground-glass opacity (GGO), is screened by LDCT. GGN is classified radiologically into two types: pure GGN (pGGN), which has no solid component, and part-solid GGN, which has both a pure GGN region and a consolidated region (also known as mixed GGN [mGGN]).[15] However, in many cases, GGNs do not always develop into lung adenocarcinoma. According to Sakamoto et al.,[16] GGNs with KRAS mutations may not develop into invasive lesions and may even subside. This evidence suggests that GGNs may be static or even spontaneously subsiding in genetic terms.

Overdiagnosis in screening results in the identification of non-progressive or very slow-growing cancers. These are referred to as "pseudodiseases." They do not pose a real threat to patients, but cancer diagnosis causes anxiety and other psychological effects, and radical treatments also carry risks.[14,17]

Over the last decade, LDCT screening for lung cancer has reduced lung cancer mortality. However, overdiagnosis owing to screening has been raised. Five studies specifically examined overdiagnosis,[18-22] and seven additional trials were examined for differences in cancer incidence between LDCT and comparison groups.[23-29] Estimates of overdiagnosis ranged from 0% to 67.2% for screen-detected lung cancer.[17,30,33] It can be seen that different definitions of overdiagnosis lead to differences in overdiagnosis rates.[31] One definition of overdiagnosis was proposed in a study in Taiwan. In a paper published by Gao et al.[32] in 2022, the phenomenon of overdiagnosis related to LDCT screening for lung cancer was described in Taiwan. The researchers concluded that the incidence of advanced lung cancer in Taiwan was stable from 2004 to 2018, whereas the incidence of early lung cancer increased with the emergence of LDCT screening. The authors believe that effective cancer screening should include an increase in early cancer and a decrease in late cancer. This increase in early-stage lung cancer is a form of overdiagnosis. Its analysis of lung cancer overdiagnosis in Taiwanese women accounted for 20%. There are inevitable consequences to this overdiagnosis. Using the same definition of overdiagnosis, a study in the inland Shanghai area of China confirmed the existence of the phenomenon of overdiagnosis of LDCT screening.[34] Wang et al. found through statistics that the incidence of lung adenocarcinoma in males and females in the Shanghai area increased from 2012 to 2017. From 2002 to 2017, the rate of early-stage cancer in men increased by 6.9 per 100,000, whereas the rate of late-stage cancer decreased by 5.5 per 100,000. Early-stage rates in women increased by 16.1 per 100,000, but there was no significant decline in late-stage rates. Furthermore, the authors believe that the significant increase in early morbidity but no significant decrease in late morbidity is a sign of overdiagnosis. After the introduction of LDCT screening for lung nodules in inland China in 2011, the incidence of lung cancer in Chinese women increased rapidly, with little change in mortality. Although the early incidence increased significantly, the late incidence did not decrease significantly. This demonstrates the overdiagnosis of LDCT screening. However, the rates of overdiagnosis in these trials vary greatly. Li et al.[35] found in a randomized controlled trial that 39% of the rate of overdiagnosis was related to follow-up time after screening.[14] Estimates of overdiagnosis vary with demographic characteristics, and incidence trends over time vary with histological type.

In a paper on lung cancer overdiagnosis in Taiwan, Bergmann et al.[36] concluded that from 2000 to 2018, the annual number of NHI applications for thoracotomy surgery in women increased from 800 to approximately 8,000, an increase almost entirely attributable to video-assisted thoracoscopic surgery (VATS), and VATS was not used until 2007. This most likely represents one of the most serious consequences of overdiagnosis: the emergence of overtreatment. We can also better understand the consequences of overdiagnosis by studying other disease areas. For example, Rajasekaran,[37] in a letter to the editor, argues that widespread use of magnetic resonance imaging (MRI) early in a patient's clinical course and before nonsurgical treatment is undertaken may harm the patient and impose unnecessary costs on the healthcare system. MRI is the equivalent of LDCT in lung cancer screening, with inevitable consequences when overdiagnosis occurs, including the patient's fear of such a positive test result and the desire to intervene to return to "normal." Therefore, we should actively reduce overdiagnosis and overtreatment of patients.

How to reduce overdiagnosis is a challenge we face today. Menkes[38] suggests that doctor–patient communication will be a decisive factor in this battle. How we view our patients matters; the words we use reflect and affect clinical relationships, and it is vital to support high-value interventions while avoiding those that carry an unacceptable risk of overdiagnosis, overtreatment, and iatrogenic harm.[39]

1.2 | Reduce overdiagnosis and overtreatment

Reduced overdiagnosis starts with a clear diagnosis of when GGNs are likely to develop into invasive cancer. This must be considered and evaluated in various ways, including baseline demographics[40–42] and the GGNs themselves.[43–45]

For a long time, smoking as a major cause of lung cancer has been a concern for researchers. An analysis of a real-world study of non-smoking Asian women in Taiwan confirmed that in a population of

women in Taiwan whose smoking rate was less than 5% over the years, there was only an increase in the incidence of early-stage lung cancer, whereas late-stage cancer remained relatively stable, suggesting that LDCT screening results in these nonsmoking women were likely to be overdiagnosed.[32,36] Similarly, the screening test in South Korea confirmed the same hypothesis.[46] Therefore, it is recommended that LDCT screening only focus on smokers. In many other studies, smokers have also been targeted for screening. The screening population for the German randomized trial LUSI[47] included 4,052 long-term smokers (≥15 cigarettes a day for 25 years or ≥10 cigarettes a day for 30 years; smoking cessation ≤10 years). The Cleveland Clinic's lung cancer screening program also recommends lung cancer screening for people between the ages of 50 and 80 who have smoked for at least 20 pack-years, are current smokers or have quit in the last 15 years.[48] Moreover, a recent study in mainland China found that LDCT screening of smokers significantly increased the incidence of lung cancer while decreasing lung cancer mortality and all-cause mortality. The incidence of lung cancer, all-cause mortality, and lung cancer mortality was not statistically significant among nonsmokers.[49] It is further suggested that smoking may be a factor influencing the development of lung adenocarcinoma in GGNs and including smoking as a factor in screening criteria may reduce the rate of overdiagnosis.[50,51] A quantifiable risk assessment model for nonsmokers should be developed for nonsmokers.[46]

Additionally, gender,[52] age, region, and family history of cancer may affect the development of GGN. Roy et al.[53] conducted a retrospective study of all suspected lung cancer patients with GGNs who underwent nodule resection at the same hospital between 2001 and 2017. In this model, GGNs were more likely to be lung adenocarcinomas in older female and Asian patients. Therefore, we investigated whether it would be more beneficial to reduce the rate of overdiagnosis if age, sex, and region factors were included in the screening criteria, which requires further research. On the other hand, the CanSPUC risk scoring system identified 55,428 participants in a study conducted in Henan, China, as being at high risk for lung cancer and recommended LDCT.[54] Participants with one, two, three, and four or more family histories of cancer were 1.9, 2.7, 2.8, and 3.5 times, respectively, more likely to be screened for LDCT than participants with no family history of cancer. The authors suggest that LDCT screening in a population with a family history of cancer may lead to higher LDCT compliance and lung cancer detection rates, thereby improving screening efficiency and cost-effectiveness. Of course, increased physical activity reduces the risk of lung cancer; therefore, screening people who are less physically active is a way to reduce overdiagnosis.[55]

We can begin to identify who requires screening through these discussions, with the goal of minimizing overdiagnosis and finding the best balance of benefits and harms. Furthermore, clarifying GGNs can effectively avoid overdiagnosis.[56]

According to the American College of Radiology, Lung-rads 2022, pulmonary nodules are classified into three types: solid nodules with no visible bronchial vascular structures; pure frosted glass (or nonsolid) nodules with visible bronchial vascular structures; and partial solids with solid and ground-glass part.[57] In most cases, pure GGNs have good survival and no recurrence, regardless of overall lesion size (in fact, they are rarely larger than 3 mm).[58] A study from Japan[59] found that when a GGN is accompanied by solid parts, it is more likely to develop into adenocarcinoma and these solid parts have been shown to be invasive growth parts. This finding suggests that the degree of pathologically aggressive growth of adenocarcinoma can be quantified by the proportion of increased solid density on the CT findings of the lesion. In this study, nodule size had no effect on 5-year recurrence-free survival when the nodule CTR was 0.25 or less. Similarly, Zheng et al.[60] found that CEA (> 5 ng/mL) and CTR (> 0.75) were two important predictors of lymph node metastasis in patients with stage IA3 lung adenocarcinoma. We can reduce overdiagnosis based on the size of the CTR shown on imaging.

Another study used solid components of GGNs to differentiate between adenocarcinoma in situ, micro-invasive adenocarcinoma, and advanced adenocarcinoma. Nodules with a pulmonary window greater than 8 mm or a mediastinal window greater than 6 mm on CT are highly likely malignant.[61] Nodular volume assessment (volumetric method)[62] is consistently recommended in the guidelines for pulmonary nodule management to accurately assess the size of the GGN or the size of the solid components within the GGN. Volume measurement can more accurately reflect the three-dimensional characteristics of pulmonary nodules and can also calculate the volume doubling time or nodule growth, which is a reliable parameter for identifying nodule growth. Evaluation of nodule size and growth can also better differentiate between benign and malignant tumors, reducing overdiagnosis.

On the other hand, many studies have pointed out that LDCT is only an imaging technique for lung cancer screening and the screening mode combined with biomarkers and imaging may be more conducive to early lung cancer diagnosis. Therefore, the search for biomarkers with high sensitivity and specificity will be a future direction for cancer screening. Ritambhara et al. included 127 cases and 120 controls in their study and concluded that the present study demonstrated that XRCC1399 (Gln/Gln), GSTT1, and IL-1RN alleles I and II served as risk genotypes. These genes could be used as biomarkers to predict lung cancer risk.[63] In another study, patients with SOX1 aberrant tumor methylation had a statistically significantly shorter 5-year survival than patients without aberrant tumor methylation.[64] These abnormal biomarkers can be combined with LDCT to provide a more accurate diagnosis of lung cancer, thus reducing the occurrence of overdiagnosis.

1.3 | Overtreatment

Overtreatment is one of the most serious consequences of overdiagnosis. When people detect GGN as a manifestation of early lung cancer through LDCT screening, they tend to feel fear and anxiety, prompting them to seek active diagnosis and treatment measures to intervene in the progression of GGN. On the other hand, most doctors do not take the initiative to consider whether GGNs will definitely affect patients'

quality of life but instead actively intervene only according to patients' requests, resulting in overtreatment.[65,66]

The current treatment for lung cancer is surgical excision. However, no matter how much surgery is developed, the inevitable organ damage that comes with surgical removal is unavoidable. Surgical treatment will cause more unnecessary damage, both psychologically and physically, particularly if lung cancer is overdiagnosed. For example, Altorki et al. monitored 697 patients who underwent lobectomy and sublobectomy over 10 years and found that 5-year disease-free survival was 63.6% after sublobar resection and 64.1% after lobar resection in a discussion over the scope and method of surgery. The 5-year overall survival rate was 80.3% after sublobar resection and 78.9% after lobar resection.[67] This suggests that limiting the scope of surgery does not cause the disease to progress faster or fail to control it. Therefore, for this overdiagnosed early lung cancer, we can consider minimally invasive treatment to reduce the trauma of surgery on the body if patients have a strong sense of intervention. Another study of surgical treatment found a potential for recurrence or metastasis after surgery. There were 239 patients with GGN-dominant lung adenocarcinoma who received surgical treatment, with two cases of postoperative recurrence and metastasis. One patient had peritoneal recurrence after segmental resection, and the other had brain metastases 24 months after lobectomy.[68] Similarly, in a European study of surgical removal of lung nodules, 17.4% of pathological findings were benign, resulting in a 17.4% overtreatment rate.[69] Without active intervention, lung adenocarcinoma dominated by GGN will rarely develop into invasive cancer, and patients are unlikely to develop metastases throughout their lives.

With the advancement of technology, surgery has gradually become less invasive. VATS has recently become a common surgical method for the diagnosis and treatment of GGNs. However, VATS has some drawbacks that make identifying deep nodules intraoperatively challenging. At present, many studies are improving its positioning level, and Matthieu Hanauer et al. claim to use preoperative localization of solitary pulmonary nodules with a CT-guided hook wire. However, there are still many problems, including some common complications. In this study, 71/181 patients (38%) developed pneumothorax after hook wire insertion, which is already a high percentage of postoperative complications.[70] Alternatively, 187 pulmonectomies were performed in 181 patients, but only 107 were subsequently diagnosed with malignant lesions, implying that 74 patients should not have been treated aggressively, resulting in a 40% overtreatment rate. These overtreated patients are likely to suffer inevitable postoperative complications, decreased lung function, anxiety, and reduced quality of life.

How to reduce overtreatment or the damage of surgery to the human body is a topic that has to be discussed at present.[71] In terms of other oncology areas, such as urinary oncology, Shariat[72] believes that personalized medicine is essential because it provides the right treatment for the right tumor in the right patient at the right time. Our goal remains to provide the best outcomes and quality of life while minimizing the risks and side effects of treatment. Similarly, in the field of lung cancer, we must practice personalized medicine to the end and select appropriate treatments based on the location and size of the tumor, the patient's overall health status and potential complications, and other factors to improve the patient's survival rate and quality of life. To continue progress, a move must be made from advocating the most tolerable treatment to advocating the least effective one.[73] On the other hand, promoting joint decision-making between patients and physicians[74] will provide new opportunities for addressing surgical overtreatment.

Additionally, other therapeutic measures can be used to reduce the risk of surgical treatment. For example, with low-dose-rate brachytherapy, Rezaei et al.[75] have suggested that using unconventional CT (multinuclear Pt-based CT drugs/regional CT) can reduce the radiation dose to healthy lung tissue and the risk of treatment. Furthermore, image-guided thermal ablation (IGTA) has become the third most popular treatment for local tumors after surgery and radiotherapy. IGTA has certain advantages for treating lung cancer cases with GGO. IGTA provided 1-, 3-, and 5-year survival rates of 97.4%, 72.9%, and 55.7%, respectively, in patients with early NSCLC (tumors 2–3 cm in diameter) who were intolerant to surgery, with a mortality rate of $< 1\%$.[10,76]

2 | CONCLUSION

Although LDCT screening for lung cancer still has a high rate of overdiagnosis and overtreatment, we cannot completely deny its effectiveness,[77] and how to overcome this phenomenon in the future requires extensive research.

We can develop more personalized screening criteria in the future. Extending the interval between low-dose CT scans for some GGN screening participants at low risk for lung cancer can significantly reduce the number of scans per year, the cost of the screening program, and the radiation dose to the individual while reducing the patient's psychological anxiety and stress. Shortening scan intervals, on the other hand, reduces the number of delayed lung cancer diagnoses, which increases lung cancer cure rates.[78] In future GGN screening, stratified lung cancer risk management, and personalized screening intervals are allowed, which will be conducive to reducing screening risk and improving screening efficiency, which is an important focus of future research. However, there is limited data on lung cancer harms, and further trials are needed to determine participant selection and the optimal frequency and duration of screening.[33]

Additionally, AI is taking root in all areas of medicine, including lung cancer screening. Combining AI output with existing guidelines, such as Lung-RADS, could provide an improved framework for nodule management in the future. According to the study of Jiang et al.,[79] the traditional image reconstruction method has the problem of image noise in the low-dose acquisition. This prospective study included patients who underwent non-contrast ULD CT (performed at 0.07 or 0.14 msV, similar to a single chest radiograph) and contrast-enhanced chest CT from April to June 2020. ULD CT images were reconstructed

using filtered back projection, ASIR-V, and DLIR. Deep learning image reconstruction reduces image noise, increases nodule detection rate, and improves the measurement accuracy of ultralow-dose chest CT images compared with adaptive statistical iterative reconstruction-V. However, many studies on artificial intelligence have not been externally verified, that is, they lack strong evidence to determine whether the researchers are correct or not. Research in the field of artificial intelligence still needs to be verified by future researchers to promote its applicability in the field of GGN screening.

ACKNOWLEDGMENTS

This study was supported by Yunnan Provincial Nature Foundation, Grant Number: 202301AY070001-057.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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How to cite this article: Liang X, Zhang C, Ye X. Overdiagnosis and overtreatment of ground-glass nodule-like lung cancer. *Asia-Pac J Clin Oncol*. 2025;21:108–114.
https://doi.org/10.1111/ajco.14042