Advancements in the diagnosis and treatment of sub-centimeter lung cancer in the era of precision medicine (Review)

XIAO WANG[1], JINGWEI SHI[2] and ZHENGCHENG LIU[1]

[1]Department of Thoracic Surgery, Nanjing Drum Tower Hospital, Clinical College of Nanjing Medical University; [2]Department of Thoracic Surgery, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, Jiangsu 210008, P.R. China

Received September 16, 2023; Accepted January 10, 2024

DOI: 10.3892/mco.2024.2726

Abstract. Lung cancer is the malignancy with the highest global mortality rate and imposes a substantial burden on society. The increasing popularity of lung cancer screening has led to increasing number of patients being diagnosed with pulmonary nodules due to their potential for malignancy, causing considerable distress in the affected population. However, the diagnosis and treatment of sub-centimeter grade pulmonary nodules remain controversial. The evolution of genetic detection technology and the development of targeted drugs have positioned the diagnosis and treatment of lung cancer in the precision medicine era, leading to a marked improvement in the survival rate of patients with lung cancer. It has been established that lung cancer driver genes serve a key role in the development and progression of sub-centimeter lung cancer. The present review aimed to consolidate the findings on genes associated with sub-centimeter lung cancer, with the intent of serving as a reference for future studies and the personalized management of sub-centimeter lung cancer through genetic testing.

Correspondence to: Dr Jingwei Shi, Department of Thoracic Surgery, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, 321 Zhongshan Road, Nanjing, Jiangsu 210008, P.R. China
E-mail: shijingwei555@126.com

Dr Zhengcheng Liu, Department of Thoracic Surgery, Nanjing Drum Tower Hospital, Clinical College of Nanjing Medical University, 321 Zhongshan Road, Nanjing, Jiangsu 210008, P.R. China
E-mail: lzclzc0928@foxmail.com

Abbreviations: AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma *in situ*; *ALK*, anaplastic lymphoma kinase; *BRAF*, V-raf murine sarcoma viral oncogene homolog B1; CALGB, cancer and leukemia group B; CTR, consolidation-to-tumor ratio; *EGFR*, epidermal growth factor receptor; FISH, fluorescence *in situ* hybridization; GGN, ground glass nodules; IAC, invasive adenocarcinoma; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; LCSG, Lung Cancer Study Group; mGGN, mixed GGN; MET, mesenchymal-epithelial transition factor; NCCN, National Comprehensive Cancer Network; OS, overall survival; pGGN, pure GGN; RATS, robot-associated thoracic surgery; RET, rearranged during transfection proto-oncogene; *ROS1*, ROS proto-oncogene 1 receptor tyrosine kinase; SCLC, small cell lung cancer; SN, solid nodules; VATS, video-associated thoracic surgery; VDT, volume doubling time

Key words: sub-centimeter lung cancer, gene mutation, pulmonary nodules, genetic testing

Contents

1. Introduction

Lung cancer remains the leading cause of cancer-related deaths, with 2.3 million newly diagnosed cases worldwide in 2020 according to the International Association of Research on Cancer (1-3). It ranks second in terms of incidence and first in terms of mortality among malignant tumors (4,5). The World Health Organization classifies primary lung cancer as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) based on histological criteria. NSCLC accounts for >80% of lung cancer cases, and is mainly divided into adenocarcinoma, squamous cell carcinoma and large cell carcinoma (6). Imaging examination is used to determine the primary tumor site, histopathological examination to verify the tumor type and molecular pathology examination to formulate treatment plans. Patients with early-stage lung cancer are often asymptomatic and are commonly identified through routine medical examinations, such as chest computed tomography (CT) examinations (7,8). Symptoms tend to manifest in medium and advanced stages, leading to missed

opportunities for surgical intervention, resulting in a 5-year overall survival (OS) rate of 39% on average for patients with lung cancer (9,10).

The popularization of medical examination and low-dose CT technology has led to an increase in the proportion of patients with early-stage lung cancer. This benefits numerous patients with lung cancer by enabling detection and treatment at an earlier stage, thereby improving the survival rate of those affected (8). However, this has also resulted in the identification of a significant number of sub-centimeter lung lesions. Traditional qualitative diagnostic methods are of limited value in these cases, which has led to an inconsistency in the diagnostic protocols (11). Furthermore, a large number of studies in previous years have established an association between gene mutations and tumor development, leading to the emergence of targeted drugs based on gene mutations in the era of precision medicine for lung cancer treatment (12-14). Despite these advancements, the diagnostic and therapeutic options for sub-centimeter lung lesions remain controversial (15-18). Determining the best target and timing of drug treatment for patients with sub-centimeter lung cancer continues to be a matter of debate (19-21). The objective of the present review was to summarize the current status of the diagnosis and treatment of sub-centimeter lung cancer and to provide novel ideas and a scientific basis for improving the diagnosis and treatment strategies for this condition.

2. Sub-centimeter pulmonary nodules

Recently, a large number of pulmonary nodules, especially those with a small diameter, have been detected in patients, raising concerns about pulmonary health (8,22,23). Notably, pulmonary nodules are identified in ~1.6 million patients annually in the USA, and the cases in China exceed 100 million (24). A sub-centimeter pulmonary nodule, defined as a small growth in the lung with a diameter of <1 cm, can be observed on a CT scan (25). The solid component of a nodule is the area that completely covers the bronchus and blood vessels (26). Based on the proportion of solid components, sub-centimeter pulmonary nodules can be classified as pure ground glass nodules (pGGN), subsolid nodules or mixed ground glass nodules (mGGN), and solid nodules (SN) (27). Since the vast majority of sub-centimeter pulmonary nodules are benign or cannot be unequivocally diagnosed as lung cancer, regular review is a safer option, particularly for patients diagnosed for the first time. The National Comprehensive Cancer Network (NCCN) and the Fleischner Society have recently published a follow-up strategy for the first discovered solitary sub-centimeter pulmonary nodules, as presented in Table I. However, discrepancies exist in the guidelines due to differences in national conditions and epidemiological characteristics. For example, the British Thoracic Society has set the mGGN distinction limit at 5 mm (28). Furthermore, with regard to screening age, the American College of Chest Physicians and NCCN recommend 55 years (29,30), while the Chinese Medical Association recommends 45 years (31).

Assessment of the malignant probability of pulmonary nodules detected by chest CT is mainly based on the diameter, consolidation-to-tumor ratio (CTR), imaging signs and volume doubling time (VDT). The CTR is defined as the ratio of the maximum consolidation diameter to the overall maximum diameter of the nodule (32). Nodules with a small diameter and few solid components are often associated with low malignancy, typically associated with early clinical stage malignancy. The imaging signs of pulmonary nodules mainly include lobulation, burr, vacuolation, pleural indentation, vascular collection, spinous processes and inflatable bronchi (33-36). Additionally, imaging signs of nodule malignancy are harder to detect in comparison with large nodules. The VDT, defined as the time required to double the three-dimensional volume of the lung nodule (37), is also considered as an indicator. Due to the small basic size of sub-centimeter lung nodules, the changes in diameter reflected on the images are difficult to capture when their volume is doubled and 3D imaging techniques are required for evaluation when necessary (37).

3. Sub-centimeter lung cancer

Either the imaging or the pathological size of pulmonary lesions is always an essential element to assess the stage of lung cancer development. The tumor-node-metastasis stage, developed by the Union for International Cancer Control and the American Joint Committee on Cancer, represents the primary tumor extent, the degree of regional lymph node involvement and the extent of distant metastasis (38). Sub-centimeter lung cancer mainly appears at the early stage and is commonly determined to be no later than pT1aN0M0. Nevertheless, there are still limited data in surgical and pathological reports regarding early pulmonary lesions classified as pT1N0M0, especially those ≤1 cm in size, which are defined as sub-centimeter lung cancer with no sign of nodal involvement and metastasis (39). There is emerging evidence revealing that sub-centimeter lung cancer exhibits distinctive characteristics. Patients with sub-centimeter lung cancer are found to have a younger median age in the lung cancer population. Furthermore, the pathological type is mostly proved as adenocarcinoma, among them, the incidence of atypical adenomatous hyperplasia (AAH), adenocarcinoma *in situ* (AIS), and minimally invasive adenocarcinoma (MIA) is generally high (27,40). However, it is still possible that they may evolve into invasive adenocarcinoma (IAC), invade the pleura and develop into lymph node metastasis (33,34). Independent risk factors for the progression of invasive lung cancer include tobacco use, tumor history, mGGN or SN and tumor diameter >5 mm (11-13,27). There are numerous predictive models for pulmonary nodules; however, their diagnostic accuracy remians limited in sub-centimeter lung nodules, especially for lesions with a diameter of 1-5 mm (34-36,41).

Surgical resection is the gold standard for sub-centimeter lung cancer treatment. In 1995, the Lung Cancer Study Group (LCSG) identified in the LCSG821 clinical trial that lobectomy was the standard surgical mode; however, the definite conclusion about the optimal mode of surgery remains unknown (42). Jiang *et al* (43) and Bai *et al* (44) found that among patients with stage IA1 sub-centimeter lung cancer, patients who underwent sub-lobar resection, including anatomical segmentectomy and wedge resection, had a similar 5-year OS compared with patients who underwent lobectomy. Sub-lobar resection is expected to be a novel standard surgical procedure for stage IA lung cancer that meets specific requirements, based

Table I. Follow-up strategy for sub-centimeter pulmonary nodules.

Characteristics	National comprehensive cancer network				Fleischner society	
	Maximum diameter					
Type	<6 mm	6-8 mm	>8 mm	<6 mm	6-8 mm	>8 mm
Solid nodules	1 year	6 months	3 month or PET-CT	No follow-up required or 1 year	6-12 months	3 month or PET-CT
Mixed ground glass nodules	6 months	3 month or PET-CT	Enhancement CT or PET-CT	No follow-up required	3-6 months	3-6 months
Pure ground glass nodules	1 year	1 year	1 year	No follow-up required	6-12 months	6-12 months

PET-CT, positron emission tomography-computed tomography.

on the release of the outcomes of clinical trials designed by the Japan Clinical Oncology Group, West Japan Oncology Group, and Cancer and Leukemia Group B (CALGB). Minimally invasive surgery, such as video-associated thoracic surgery (VATS), has replaced the traditional thoracotomy surgery and is currently the mainstream surgical method (32,45,46). In recent years, Da Vinci system robot-associated thoracic surgery (RATS) has developed rapidly. Compared with VATS, RATS offers superior imaging quality, a hand fibrillation filtration system, and increased flexibility and freedom. The advantages are particularly evident in intricate procedures like lymph node sampling and lung sleeve resection (47-49). In addition, thermal ablation therapy has received increasing attention as one of the supplements for patients with inoperable sub-centimeter lung cancer.

4. Gene mutation and targeted therapy in sub-centimeter lung cancer

The most representative lung cancer-related gene mutations, including epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), V-raf murine sarcoma viral oncogene homolog B1 (*BRAF*), mesenchymal-epithelial transition factor (*MET*), ROS proto-oncogene 1 receptor tyrosine kinase (*ROS1*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), rearranged during transfection proto-oncogene (*RET*) and *TP53* mutations, have led to the development of constantly updated treatment means for advanced lung cancer through the identification of driver genes and the advance of targeted therapies. However, the lack of clinical trials for targeted therapy for patients with sub-centimeter lung cancer remains a challenge. Most sub-centimeter lung cancers, due to being in early clinical stages, are not included in studies, which undermines the specificity of the results for sub-centimeter lung cancer.

EGFR is a member of the tyrosine kinase receptor family, situated in the short arm of chromosome 7 and considered to be the most pivotal driver gene in patients with NSCLC (50-52). Previous studies have demonstrated that the incidence of *EGFR* mutation is higher in Asian non-smoking women and mutations are predominantly found in adenocarcinoma (53-55). Targeted medicines, such as osimertinib, gefitinib, almonertinib and afatinib, known as *EGFR* tyrosine kinase inhibitors, are recommended for patients at an advanced clinical stage who are *EGFR* mutation-positive (56-61). In the case of brain metastases, osimertinib is the recommended treatment, given that a clinical study has demonstrated its capability to reduce the risk of brain metastasis by 82% (62). For non-classical *EGFR* mutations, afatinib is the preferred option (56).

ALK is located in the short arm of chromosome 2, crucial in neural development and associated with neuroblastoma (54,63). The typical *ALK* mutation, the fusion of echinoderm microtubule associated protein like 4 and *ALK*, is caused by chromosome translocation. In cases where the fusion gene is identified during chemotherapy, guidelines suggest targeted therapy with alectinib, ensartinib or crizotinib (64,65). In a randomized clinical trial, ensartinib was associated with superior progression-free survival and efficacy compared with crizotinib, thereby becoming a novel first-line treatment option for *ALK*-positive patients with NSCLC (66).

BRAF is positioned in the long arm of chromosome 7 and is the driver gene for various tumors, including melanoma, thyroid cancer and lung cancer (15,67-69). The most common *BRAF* mutation is the V600E point mutation, with an approximate mutation rate of 3% in lung adenocarcinoma (16). For patients with the *BRAF* V600E point mutation, the current preferred treatment is dabrafenib plus trametinib, which exhibits marked antitumor activity and a manageable safety profile (70-74).

MET is known as the hepatocyte growth factor receptor and is located at the long arm of chromosome 7 (75). *MET* contributes to nerve and muscle formation and is involved in embryogenesis and wound healing. *MET* mutations lead to tumor cell proliferation and angiogenesis. Savolitinib has been demonstrated to be an effective targeted medicine with an acceptable safety profile (76).

ROS1 is rarely mutated in NSCLC, is situated in the long arm of chromosome 6 and tends to form a fusion gene (54,69,71). Crizotinib is the only targeted medicine unanimously approved for patients with *ROS1* mutations (16,77).

KRAS is located at the short arm of chromosome 12 and mutations are predominantly found in exons 1 and 2, leading

to uncontrolled cell proliferation. A total of ~20% of all *KRAS* mutations occur in patients with lung cancer (22,78,79). It has been observed that patients with resistance to *EGFR* tyrosine kinase inhibitors are prone to *KRAS* gene mutations (71,80,81).

RET is present in the long arm of chromosome 10, and mutations typically occur in the form of fusion genes (82,83). Although novel *RET* inhibitors are under development, there is still a gap in the efficacy of *RET* fusion-targeted therapy compared with other gene mutation types (83).

TP53 is a tumor suppressor gene regulating the cell cycle, associated with patients who are smokers, and predominantly linked to squamous cell carcinoma and SCLC (84-86). There are currently no available targeted therapies for *TP53* mutations in patients with lung cancer.

5. Genomic characterization of sub-centimeter lung cancer

Throughout the entire life of humans, genomic instability is serving a crucial role in carcinogenesis (87,88). Studies on the genomics of lung cancer have made marked progress over the decades. This encompasses genomic variation that includes, but is not limited to, gene mutations, gene amplifications, gene deletions and gene rearrangements. Most current research has focused on genetic mutations in lung cancer, making it the focal point of discussion. Mutated genes, such as *EGFR*, *BRAF*, *KRAS*, *ALK* and *TP53*, have a higher incidence rate in sub-centimeter lung cancer. Early lung cancer progression to the advanced stage relies on the impact of several oncogenes, including *EGFR*, *KRAS* and *TP53* (89-92). A number of studies have demonstrated an association between the mutated gene *KRAS* and the solid components and diameter of the tumor (93,94). Furthermore, gene mutations, such as *ALK* mutations, suggest a poor prognosis of patients (95-97). In addition, mutated genes in lung cancer are associated with various factors, such as the living area (98,99), age (100), sex (101) and smoking history (102) of patients. In sub-centimeter lung cancer, *BRAF* mutation is classified as a special subtype, potentially serving a specific role in the early stages of lung cancer. Research has revealed that *BRAF* has a higher mutation frequency and clonal index in sub-centimeter lung cancer and is mostly present in AAH and AIS (102,103) and is potentially related to the overall low malignancy of sub-centimeter lung cancer. It has been demonstrated that *BRAF* mutation could stimulate proliferation and induce hyperplasia but is rarely associated with the development of malignancy, unlike *EGFR*, *TP53* and *KRAS* mutations, which indicate malignant transition (102). There is also evidence of mutual exclusivity between *BRAF* and *KRAS* mutations (103).

Supporting the theory of genome evolution, Hu *et al* (90) hypothesized that lung cancer develops from the early stage to IAC. Sub-centimeter lung cancer, known for its small diameter, is evaluated based on the CTR, which serves as a crucial imaging reference index for determining its malignancy. Chen *et al* (94) revealed a lower tumor mutation burden in pGGN compared with mGGN, suggesting that the former exist in a balanced state with a less active metabolism and immune environment, leading to their identification as inert nodules. Additionally, Li *et al* (26) confirmed that mGGN exhibited a lower somatic mutation count, genomic alteration count and intratumor heterogeneity compared with SN. Furthermore, research has demonstrated that, as the GGN solid component increases, the mutation frequency of *EGFR*, *KRAS* and *TP53* increases (93). Notably, *KRAS* mutations are associated with a higher rate of $CD8^+$ T cell infiltration, stronger proliferative and immunosuppressive signals (92,102,104). *ALK* mutations are more frequently observed in young adults and are mainly diagnosed at an advanced tumor stage (100,105,106). It is worth mentioning that *ALK* mutation is associated with *EGFR* mutation, suggesting an increased malignant potential leading to decreased OS of patients (105). Supporting this notion, Campbell *et al* (107) found that *ALK* was more detectable in SN.

6. Genetic testing technology and its application

Genetic testing is recommended for patients with sub-centimeter lung cancer with clinical stage IB or above, in accordance with the current clinical consensus (16,95). The mostly adopted methods for lung cancer genetic testing at present are fluorescence *in situ* hybridization (FISH), PCR, microarray technology and DNA sequencing technology (108-110). FISH is the gold standard for detecting *ALK* and *ROS1* gene rearrangements in lung adenocarcinoma, as it is capable of obtaining chromosome information that cannot be detected by conventional techniques (69). It is a technique that hybridizes fluorescein-labeled probes to cellular nucleic acid. PCR technology, characterized by high sensitivity, high specificity and high yield, can amplify small amounts of DNA fragments in large quantities (111). Real-time PCR technology, also known as quantitative PCR technology, can dynamically monitor the number of products in the reaction process, eliminating the interference of product accumulation in the quantitative analysis, and effectively detecting gene mutation and the expression of oncogenes. Microarray technology is particularly suitable for the analysis of gene expression differences in separate tissues, with the advantage of low sample size requirement and the disadvantage of inferior specificity (108,110). DNA sequencing technology aims to determine the order of the four bases in a stretch of DNA molecule (111). High-throughput DNA sequencing technology, also referred to as next-generation sequencing technology, is commonly used (108). The specimen for genetic testing comes from the tumor tissue resected during the operation, and the results are more accurate than those obtained using other methods such as detection in peripheral blood (54). Additionally, the concentration of DNA extracted from the specimen continuously decreased over time, indicating biased results and potential under-detection of mutated genes with lower mutational abundances if the testing is not performed in a timely manner. Therefore, timely genetic testing for patients who require subsequent treatment is recommended, as taking targeted medicines in conjunction with timely follow-up can reduce the risk of recurrence and avoid delaying the treatment.

Gene mutations in primary and metastatic lung cancer are often discrepant (96). Currently, the preoperative application of genetic testing technology is principally used to determine the source of the tumor and to provide guidance for subsequent treatment (67,111,112). Determination of the distinctive tumor gene mutations can help identify the source of the tumor and contribute to selecting suitable adjuvant therapy. Neoadjuvant

therapy refers to a novel clinical treatment approach for patients with potential operative indication (16,95). It aims at reducing the size of the tumor bed, removing small lesions in the circulatory system and reducing the clinical stage to ultimately achieve improved surgical efficacy. Targeted medicines can specifically block the biological functions generated by driver genes, inhibiting or even blocking the growth and metastasis of malignant tumors at the molecular level (69,113). The current commonly used techniques for obtaining tissue specimens include transchest wall lung puncture, bronchoscopy and transbronchial needle aspiration. Sepesi *et al* (114) conducted a clinical trial of neoadjuvant therapy with nivolumab in 44 patients with early lung cancer and the results indicated that neoadjuvant therapy was generally safe and effective, with postoperative morbidity and mortality comparable with those of untreated patients. Genetic testing can distinguish driver gene-positive patients from driver gene-negative patients, thus contributing to selecting suitable adjuvant therapy. Currently, neoadjuvant therapy is mostly used in patients with stage III lung cancer; however, to the best of our knowledge, its optimal treatment mode has not been established.

Genetic testing can detect the lung cancer-related genes expressed in patients with advanced lung cancer in order to evaluate whether targeted medicines are required (78,115). The continuous emergence of novel targeted medicines with improved efficiency and tolerable toxicity is prolonging the survival time of patients detected to be lung cancer driver genes-positive, thus highlighting the importance of genetic testing in targeted drug therapy for non-surgical treatment of lung cancer (69,113). Tsutani *et al* (116) performed a clinical study based on *EGFR* gene mutations in 475 patients with stage I high-risk NSCLC. The results suggested a clear advantage of adjuvant chemotherapy for patients who were *EGFR* mutation-negative or unknown, but not for patients who were *EGFR* mutation-positive. This trial also demonstrated that genetic testing should be individualized, enabling each patient to get the optimal treatment option.

Tissue specimens are obtained by needle biopsy and other techniques for patients with advanced sub-centimeter lung cancer and drug treatment based on this is the preferred treatment plan. However, the guidelines do not routinely recommend genetic testing and adjuvant targeted therapy for the vast majority of patients with postoperative sub-centimeter lung cancer in stage I, which is not consistent with the current clinical practice. Patients with pathological risk factors, including low differentiation, vascular invasion, dirty layer pleural invasion and air cavity dissemination, have a worse OS and need more radical treatment, with lobectomy as the standard surgery. The need for postoperative adjuvant treatment requires further exploration in the future.

7. Discussion and outlook

Lung cancer poses a significant threat to human health due to factors such as environmental pollution, smoking, dust, respiratory infections and genetic mutations (69,74,81). Intercepting the progression of lung cancer at an early stage is critical. In order to improve the relapse-free survival rate for patients developing IAC at the sub-centimeter level, it is urgent to conduct clinical trials with a larger sample size to determine the independent risk factors and guide early clinical management (12). The prediction model of sub-centimeter lung cancer based on clinical data requires continuous improvement (2). Therefore, different countries and regions can make efforts to develop guidelines that align with their actual epidemiological situation. Future guidelines should include a reasonable follow-up time, precise reexamination content and detailed treatment measures, to effectively address the challenges associated with lung cancer (117-119).

As aforementioned, the mutations of *EGFR*, *TP53* and *KRAS* could be one of the explanations for the positive associations between the solid ingredients and the malignancy degree in pulmonary nodules. Exploration of genomics aims to identify the deep mechanism underlying the progression of sub-centimeter lung cancer (15). *BRAF* mostly appeared in AAH and AIS and it may serve an extraordinary role in the early stage of lung cancer development. Existing findings require further confirmation as genetic mutations vary in diverse regions, sexes and lung cancer types. In addition, *ALK* mutation might be a sign of suboptimal prognosis. The potential relationship of antagonism and synergy between different genes suggests that studies should not be limited to a certain class of oncogenes but should be designed to examine a variety of oncogenes (15).

Despite the fact that postoperative genetic testing and adjuvant targeted therapy are not typically recommended for sub-centimeter lung cancer without cut-end failure, it is worth noting that the 5-year disease-free survival of patients with stage IA lung cancer was 64.1% even after lobar resection according to the results from CALGB140503 (46). This unexpected finding suggests the need to include patients with stage IA NSCLC in future trials on postoperative adjuvant targeted therapy, especially with the increasing proportion of patients with sub-centimeter lung cancer. By incorporating patients with stage IA NSCLC, future research efforts could help reduce the recurrence rate of patients with risk factors associated with recurrence and metastasis, ultimately contributing to an improved prognosis. This is important, since the majority of clinical trials on these aspects do not typically include patients with stage IA NSCLC, despite the potential benefit. The combination of genetic testing technology and targeted therapy has greatly improved the prognosis of patients with middle and advanced lung cancer, highlighting the potential impact of including patients with stage IA NSCLC in future research on postoperative adjuvant targeted therapy.

Increasing novel gene alterations are being identified by researchers, in addition to the well-studied genetic mutations (120-122). The future research focus is the development of effective targeted medicines for rare gene mutations and polygene mutations. Some mutations previously recognized to exist only in other malignancies might also be future directions of research in lung cancer. High applicability and low toxicity are aims in the generation of novel targeted medicines.

Genetic testing technologies have the potential to add unique value to the accurate diagnosis and treatment of sub-centimeter pulmonary nodules when combined with imaging methods, given the high incidence of such nodules. This combination can improve the diagnosis quality of sub-centimeter lung cancer and aid in identifying nodules

with a high risk of recurrence. The refinement of prediction models resulting from genetic testing can provide suggestions for surgical method selection, prognosis prediction and the need for subsequent treatment. It is anticipated that future research will focus on increasing the sensitivity of gene detection techniques, exploring the molecular mechanism and raising awareness of the importance of a comprehensive evaluation approach for sub-centimeter pulmonary nodules. The increasing popularity and advancement of genetic testing technology can lead to the integrated management of diagnosis and treatment methods for patients with sub-centimeter lung cancer, incorporating gene testing and targeted therapy.

8. Conclusion

Over the years, the number of patients with sub-centimeter lung nodules has increased. Qualitative diagnostic and treatment strategies for these nodules, which may develop into lung cancer, pose significant challenges in clinical practice. In the era of precision medicine, genetic detection technology and targeted therapy for genetic alterations are increasingly crucial in the diagnosis and treatment of lung cancer. Genomic studies have continuously unraveled the molecular mechanisms contributing to the malignancy progression of sub-centimeter lung cancer. It is anticipated that, in the future, combining genetic information with other clinical data will lead to the development of a comprehensive evaluation system for sub-centimeter pulmonary nodules.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

XW wrote the manuscript. JS and ZL provided study materials and revised the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A and Bray F: Cancer statistics for the year 2020: An overview. Int J Cancer: Apr 5, 2021 (Epub ahead of print).
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global CANCER Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
3. Deo SVS, Sharma J and Kumar S: GLOBOCAN 2020 report on global cancer burden: Challenges and opportunities for surgical oncologists. Ann Surg Oncol 29: 6497-6500, 2022.
4. Cao W, Chen HD, Yu YW, Li N and Chen WQ: Changing profiles of cancer burden worldwide and in China: A secondary analysis of the global cancer statistics 2020. Chin Med J (Engl) 134: 783-791, 2021.
5. Wang M, Herbst RS and Boshoff C: Toward personalized treatment approaches for non-small-cell lung cancer. Nat Med 27: 1345-1356, 2021.
6. Mattiuzzi C and Lippi G: Cancer statistics: A comparison between World Health Organization (WHO) and global burden of disease (GBD). Eur J Public Health 30: 1026-1027, 2020.
7. Xi KX, Zhang XW, Yu XY, Wang WD, Xi KX, Chen YQ, Wen YS and Zhang LJ: The role of plasma miRNAs in the diagnosis of pulmonary nodules. J Thorac Dis 10: 4032-4041, 2018.
8. Nooreldeen R and Bach H: Current and future development in lung cancer diagnosis. Int J Mol Sci 22: 8661, 2021.
9. Wen M, Wang L, Wang X, Yang S, Sun Y, Xia J, Zhang Y, Zhang Z, Huang L and Jiang T: Optimal adjuvant therapy in resected stage IIIA-N2 non-small-cell lung cancer harboring EGFR mutations. Oncol Res Treat 43: 686-693, 2020.
10. Zhong WZ, Wang Q, Mao WM, Xu ST, Wu L, Wei YC, Liu YY, Chen C, Cheng Y, Yin R, *et al*: Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC: final overall survival analysis of CTONG1104 phase III trial. J Clin Oncol 39: 713-722, 2021.
11. Colletti PM: Earlier diagnosis of subcentimeter lung cancers is not self-evidently beneficial: Personal experience. AJR Am J Roentgenol 213: 819-820, 2019.
12. Shin KE, Lee KS, Yi CA, Chung MJ, Shin MH and Choi YH: Subcentimeter lung nodules stable for 2 years at LDCT: Long-term follow-up using volumetry. Respirology 19: 921-928, 2014.
13. Heuvelmans MA, Groen HJ and Oudkerk M: Early lung cancer detection by low-dose CT screening: Therapeutic implications. Expert Rev Respir Med 11: 89-100, 2017.
14. Reich JM and Kim JS: Earlier diagnosis not self-evidently beneficial: Natural history of subcentimeter lung cancers. AJR Am J Roentgenol 213: 817-818, 2019.
15. Parikh AR: Lung cancer genomics. Acta Med Acad 48: 78-83, 2019.
16. Imyanitov EN, Iyevleva AG and Levchenko EV: Molecular testing and targeted therapy for non-small cell lung cancer: Current status and perspectives. Crit Rev Oncol Hematol 157: 103194, 2021.
17. Rammal S, Kourie HR, Jalkh N, Mehawej C, Chouery E, Moujaess E and Dabar G: Molecular pathogenesis of hereditary lung cancer: A literature review. Pharmacogenomics 22: 791-803, 2021.
18. Hu B, Ren W, Feng Z, Li M, Li X, Han R and Peng Z: Correlation between CT imaging characteristics and pathological diagnosis for subcentimeter pulmonary nodules. Thorac Cancer 13: 1067-1075, 2022.
19. Ruiz-Cordero R and Devine WP: Targeted therapy and checkpoint immunotherapy in lung cancer. Surg Pathol Clin 13: 17-33, 2020.
20. Miller M and Hanna N: Advances in systemic therapy for non-small cell lung cancer. BMJ 375: n2363, 2021.
21. Schuler M, Bölükbas S, Darwiche K, Theegarten D, Herrmann K and Stuschke M: Personalized treatment for patients with lung cancer. Dtsch Arztebl Int: arztebl.m2023.012, 2023 (Epub ahead of print).
22. Wu F, Wang L and Zhou C: Lung cancer in China: Current and prospect. Curr Opin Oncol 33: 40-46, 2021.
23. Sherry V: Lung cancer: Prevention and early identification are key. Nurse Pract 47: 42-47, 2022.
24. Mazzone PJ and Lam L: Evaluating the patient with a pulmonary nodule: A review. JAMA 327: 264-273, 2022.

25. Hansell DM, Bankier AA, Macmahon H, McLoud TC, Müller NL and Remy J: Fleischner Society: glossary of terms for thoracic imaging. Radiology 246: 697-722, 2008.
26. Li H, Sun Z, Li Y, Qi Q, Huang H, Wang X, Zhou J, Liu K, Yin P, Wang Z, *et al*: Disparate genomic characteristics of patients with early-stage lung adenocarcinoma manifesting as radiological subsolid or solid lesions. Lung Cancer 166: 178-188, 2022.
27. Lv Y and Ye B: Advances in diagnosis and management of subcentimeter pulmonary nodules. Zhongguo Fei Ai Za Zhi 23: 365-370, 2020 (In Chinese).
28. Callister ME, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, Franks K, Gleeson F, Graham R, Malhotra P, *et al*: British Thoracic Society guidelines for the investigation and management of pulmonary nodules. Thorax 70 (Suppl 2): ii1-ii54, 2015.
29. Armstrong C: Lung cancer screening recommendations from the ACCP. Am Fam Physician 98: 688-689, 2018.
30. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, Bruno DS, Chang JY, Chirieac LR, D'Amico TA, *et al*: Non-small cell lung cancer, version 3.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 20: 497-530, 2022.
31. Oncology Society of Chinese Medical Association; Chinese Medical Association Publishing House: Chinese medical association guideline for clinical diagnosis and treatment of lung cancer (2022 edition). Zhonghua Zhong Liu Za Zhi 44: 457-490, 2022 (In Chinese).
32. Suzuki K, Watanabe SI, Wakabayashi M, Saji H, Aokage K, Moriya Y, Yoshino I, Tsuboi M, Nakamura S, Nakamura K, *et al*: A single-arm study of sublobar resection for ground-glass opacity dominant peripheral lung cancer. J Thorac Cardiovasc Surg 163: 289-301.e2, 2022.
33. Borghesi A, Michelini S, Nocivelli G, Silva M, Scrimieri A, Pezzotti S, Maroldi R and Farina D: Solid indeterminate pulmonary nodules less than or equal to 250 mm^3: Application of the updated fleischner society guidelines in clinical practice. Radiol Res Pract 2019: 7218258, 2019.
34. Borghesi A, Michelini S, Scrimieri A, Golemi S and Maroldi R: Solid indeterminate pulmonary nodules of less than 300 mm^3: Application of different volume doubling time cut-offs in clinical practice. Diagnostics (Basel) 9: 62, 2019.
35. Zhan Y, Peng X, Shan F, Feng M, Shi Y, Liu L and Zhang Z: Attenuation and morphologic characteristics distinguishing a ground-glass nodule measuring 5-10 mm in diameter as invasive lung adenocarcinoma on thin-slice CT. AJR Am J Roentgenol 213: W162-W170, 2019.
36. Hui H, Yin HT, Wang T and Chen G: Computed tomography-guided core needle biopsy for sub-centimeter pulmonary nodules. Kardiochir Torakochirurgia Pol 19: 65-69, 2022.
37. Chen W, Li M, Mao D, Ge X, Wang J, Tan M, Ma W, Huang X, Lu J, Li C, *et al*: Radiomics signature on CECT as a predictive factor for invasiveness of lung adenocarcinoma manifesting as subcentimeter ground glass nodules. Sci Rep 11: 3633, 2021.
38. Kutob L and Schneider F: Lung cancer staging. Surg Pathol Clin 13: 57-71, 2020.
39. Pasic A, Postmus PE and Sutedja TG: What is early lung cancer? A review of the literature. Lung Cancer 45: 267-77, 2004.
40. Mi J, Wang S, Li X and Jiang G: Clinical characteristics and prognosis of sub-centimeter lung adenocarcinoma. Zhongguo Fei Ai Za Zhi 22: 500-506, 2019 (In Chinese).
41. Shen C, Wu Q, Xia Q, Cao C, Wang F, Li Z and Fan L: Establishment of a malignancy and benignancy prediction model of sub-centimeter pulmonary ground-glass nodules based on the inflammation-cancer transformation theory. Front Med (Lausanne) 9: 1007589, 2022.
42. Ginsberg RJ and Rubinstein LV: Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung cancer study group. Ann Thorac Surg 60: 615-623, 1995.
43. Jiang W, Pang X, Xi J, Chen X, Wang Q, Qian C and Fan H: Clinical outcome of subcentimeter non-small cell lung cancer after surgical resection: Single institution experience of 105 patients. J Surg Oncol 110: 233-238, 2014.
44. Bai W, Zhang J, Wang Y, Zhou M, Liu L, Wang G, Zhao K, Gao X and Li S: Comparative analysis of the long-term outcomes of segmentectomy and lobectomy for stage IA1 lung adenocarcinoma in patients with or without previous malignancy of other organs: A population-based study. Expert Rev Anticancer Ther 22: 215-228, 2022.
45. Saji H, Okada M, Tsuboi M, Nakajima R, Suzuki K, Aokage K, Aoki T, Okami J, Yoshino I, Ito H, *et al*: Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): A multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. Lancet 399: 1607-1617, 2022.
46. Altorki N, Wang X, Kozono D, Watt C, Landrenau R, Wigle D, Port J, Jones DR, Conti M, Ashrafi AS, *et al*: Lobar or sublobar resection for peripheral stage IA non-small-cell lung cancer. N Engl J Med 388: 489-498, 2023.
47. Miyajima M, Maki R, Arai W, Tsuruta K, Shindo Y, Nakamura Y and Watanabe A: Robot-assisted vs video-assisted thoracoscopic surgery in lung cancer. J Thorac Dis 14: 1890-1899, 2022.
48. Qi F, Xiang M, Deng Y, Huang W and Sun Y: Application of Da Vinci Robot and thoracoscopy in radical lung cancer surgery. J Healthc Eng 2022: 2011062, 2022.
49. Shimomura M, Ishihara S and Inoue M: Robot-assisted segmentectomy for lung cancer. Kyobu Geka 76: 79-83, 2023 (In Japanese).
50. Zhang YL, Yuan JQ, Wang KF, Fu XH, Han XR, Threapleton D, Yang ZY, Mao C and Tang JL: The prevalence of EGFR mutation in patients with non-small cell lung cancer: A systematic review and meta-analysis. Oncotarget 7: 78985-78993, 2016.
51. Harrison PT, Vyse S and Huang PH: Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. Semin Cancer Biol 61: 167-179, 2020.
52. Rosell R, Cardona AF, Arrieta O, Aguilar A, Ito M, Pedraz C, Codony-Servat J and Santarpia M: Coregulation of pathways in lung cancer patients with EGFR mutation: Therapeutic opportunities. Br J Cancer 125: 1602-1611, 2021.
53. Chen YJ, Roumeliotis TI, Chang YH, Chen CT, Han CL, Lin MH, Chen HW, Chang GC, Chang YL, Wu CT, *et al*: Proteogenomics of non-smoking lung cancer in east asia delineates molecular signatures of pathogenesis and progression. Cell 182: 226-244.e17, 2020.
54. Chang YS, Tu SJ, Chen YC, Liu TY, Lee YT, Yen JC, Fang HY and Chang JG: Mutation profile of non-small cell lung cancer revealed by next generation sequencing. Respir Res 22: 3, 2021.
55. Tsubata Y, Tanino R and Isobe T: Current therapeutic strategies and prospects for EGFR mutation-positive lung cancer based on the mechanisms underlying drug resistance. Cells 10: 3192, 2021.
56. Yang JC, Sequist LV, Geater SL, Tsai CM, Mok TS, Schuler M, Yamamoto N, Yu CJ, Ou SH, Zhou C, *et al*: Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: A combined post-hoc analysis of LUX-lung 2, LUX-lung 3, and LUX-lung 6. Lancet Oncol 16: 830-838, 2015.
57. Noronha V, Patil VM, Joshi A, Menon N, Chougule A, Mahajan A, Janu A, Purandare N, Kumar R, More S, *et al*: Gefitinib versus gefitinib plus pemetrexed and carboplatin chemotherapy in EGFR-mutated lung cancer. J Clin Oncol 38: 124-136, 2020.
58. Gerber DE, Mayer M, Gagan J and von Itzstein MS: Systemic and intracranial efficacy of osimertinib in EGFR L747P-mutant NSCLC: Case report. JTO Clin Res Rep 3: 100291, 2022.
59. Miyauchi E, Morita S, Nakamura A, Hosomi Y, Watanabe K, Ikeda S, Seike M, Fujita Y, Minato K, Ko R, *et al*: Updated analysis of NEJ009: Gefitinib-alone versus gefitinib plus chemotherapy for non-small-cell lung cancer with mutated EGFR. J Clin Oncol 40: 3587-3592, 2022.
60. Shirley M and Keam SJ: Aumolertinib: A review in non-small cell lung cancer. Drugs 82: 577-584, 2022.
61. Wang J and Wu L: An evaluation of aumolertinib for the treatment of EGFR T790M mutation-positive non-small cell lung cancer. Expert Opin Pharmacother 23: 647-652, 2022.
62. Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, Goldman JW, Laktionov K, Kim SW, Kato T, *et al*: Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med 383: 1711-1723, 2020.
63. Wen S, Dai L, Wang L, Wang W, Wu D, Wang K, He Z, Wang A, Chen H, Zhang P, *et al*: Genomic signature of driver genes identified by target next-generation sequencing in Chinese non-small cell lung cancer. Oncologist 24: e1070-e1081, 2019.
64. Bernabé-Caro R, Garrido P, García-Campelo R, Palmero R, Artal Á, Bayona C, Rodríguez-Abreu D, López-Brea M, Paredes A, Vicente D, *et al*: Alectinib after failure to crizotinib in patients with ALK-positive non-small cell lung cancer: Results from the Spanish early access program. Oncotarget 13: 812-827, 2022.

65. Hotta K, Hida T, Nokihara H, Morise M, Kim YH, Azuma K, Seto T, Takiguchi Y, Nishio M, Yoshioka H, *et al*: Final overall survival analysis from the phase III J-ALEX study of alectinib versus crizotinib in ALK inhibitor-naïve Japanese patients with ALK-positive non-small-cell lung cancer. ESMO Open 7: 100527, 2022.
66. Horn L, Wang Z, Wu G, Poddubskaya E, Mok T, Reck M, Wakelee H, Chiappori AA, Lee DH, Breder V, *et al*: Ensartinib vs crizotinib for patients with anaplastic lymphoma kinase-positive non-small cell lung cancer: A randomized clinical trial. JAMA Oncol 7: 1617-1625, 2021.
67. Negrao MV, Skoulidis F, Montesion M, Schulze K, Bara I, Shen V, Xu H, Hu S, Sui D, Elamin YY, *et al*: Oncogene-specific differences in tumor mutational burden, PD-L1 expression, and outcomes from immunotherapy in non-small cell lung cancer. J Immunother Cancer 9: e002891, 2021.
68. Riudavets M, Cascetta P and Planchard D: Targeting BRAF-mutant non-small cell lung cancer: Current status and future directions. Lung Cancer 169: 102-114, 2022.
69. Tan AC and Tan DSW: Targeted therapies for lung cancer patients with oncogenic driver molecular alterations. J Clin Oncol 40: 611-625, 2022.
70. Kelly RJ: Dabrafenib and trametinib for the treatment of non-small cell lung cancer. Expert Rev Anticancer Ther 18: 1063-1068, 2018.
71. Zhuang X, Zhao C, Li J, Su C, Chen X, Ren S, Li X and Zhou C: Clinical features and therapeutic options in non-small cell lung cancer patients with concomitant mutations of EGFR, ALK, ROS1, KRAS or BRAF. Cancer Med 8: 2858-2866, 2019.
72. Parekh PR, Botting GM, Thurber DB, Boruszczak M, Murphy W and Bertenshaw GP: Predictive biomarkers for response to trametinib in non-small cell lung cancer. Tumour Biol 44: 249-267, 2022.
73. Planchard D, Besse B, Groen HJM, Hashemi SMS, Mazieres J, Kim TM, Quoix E, Souquet PJ, Barlesi F, Baik C, *et al*: Phase 2 study of dabrafenib plus trametinib in patients with BRAF V600E-mutant metastatic NSCLC: Updated 5-year survival rates and genomic analysis. J Thorac Oncol 17: 103-115, 2022.
74. Yang SR, Schultheis AM, Yu H, Mandelker D, Ladanyi M and Büttner R: Precision medicine in non-small cell lung cancer: Current applications and future directions. Semin Cancer Biol 84: 184-198, 2022.
75. Zhu X, Lu Y and Lu S: Landscape of savolitinib development for the treatment of non-small cell lung cancer with MET alteration-A narrative review. Cancers (Basel) 14: 6122, 2022.
76. Lu S, Fang J, Li X, Cao L, Zhou J, Guo Q, Liang Z, Cheng Y, Jiang L, Yang N, *et al*: Once-daily savolitinib in Chinese patients with pulmonary sarcomatoid carcinomas and other non-small-cell lung cancers harbouring MET exon 14 skipping alterations: A multicentre, single-arm, open-label, phase 2 study. Lancet Respir Med 9: 1154-1164, 2021.
77. Shaw AT, Riely GJ, Bang YJ, Kim DW, Camidge DR, Solomon BJ, Varella-Garcia M, Iafrate AJ, Shapiro GI, Usari T, *et al*: Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): Updated results, including overall survival, from PROFILE 1001. Ann Oncol 30: 1121-1126, 2019.
78. Salgia R, Pharaon R, Mambetsariev I, Nam A and Sattler M: The improbable targeted therapy: KRAS as an emerging target in non-small cell lung cancer (NSCLC). Cell Rep Med 2: 100186, 2021.
79. Luo J, Ostrem J, Pellini B, Imbody D, Stern Y, Solanki HS, Haura EB and Villaruz LC: Overcoming KRAS-mutant lung cancer. Am Soc Clin Oncol Educ Book 42: 1-11, 2022.
80. Tsubokawa N, Tsutani Y, Miyata Y, Handa Y, Misumi K, Hanaki H, Hida E and Okada M: Segmentectomy versus lobectomy for radiologically pure solid clinical T1a-bN0M0 lung cancer. World J Surg 42: 2493-2501, 2018.
81. Skoulidis F and Heymach JV: Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. Nat Rev Cancer 19: 495-509, 2019.
82. Drusbosky LM, Rodriguez E, Dawar R and Ikpeazu CV: Therapeutic strategies in RET gene rearranged non-small cell lung cancer. J Hematol Oncol 14: 50, 2021.
83. Gainor JF, Curigliano G, Kim DW, Lee DH, Besse B, Baik CS, Doebele RC, Cassier PA, Lopes G, Tan DSW, *et al*: Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): A multi-cohort, open-label, phase 1/2 study. Lancet Oncol 22: 959-969, 2021.
84. Jiao XD, Qin BD, You P, Cai J and Zang YS: The prognostic value of TP53 and its correlation with EGFR mutation in advanced non-small cell lung cancer, an analysis based on cBioPortal data base. Lung Cancer 123: 70-55, 2018.
85. La Fleur L, Falk-Sörqvist E, Smeds P, Berglund A, Sundström M, Mattsson JS, Brandén E, Koyi H, Isaksson J, Brunnström H, *et al*: Mutation patterns in a population-based non-small cell lung cancer cohort and prognostic impact of concomitant mutations in KRAS and TP53 or STK11. Lung Cancer 130: 50-58, 2019.
86. Xu F, Lin H, He P, He L, Chen J, Lin L and Chen Y: A TP53-associated gene signature for prediction of prognosis and therapeutic responses in lung squamous cell carcinoma. Oncoimmunology 9: 1731943, 2020.
87. Abbosh C, Venkatesan S, Janes SM, Fitzgerald RC and Swanton C: Evolutionary dynamics in pre-invasive neoplasia. Curr Opin Syst Biol 2: 1-8, 2017.
88. Sivakumar S, San Lucas FA, Jakubek YA, McDowell TL, Lang W, Kallsen N, Peyton S, Davies GE, Fukuoka J, Yatabe Y, *et al*: Genomic landscape of allelic imbalance in premalignant atypical adenomatous hyperplasias of the lung. EBioMedicine 42: 296-303, 2019.
89. Chen H, Carrot-Zhang J, Zhao Y, Hu H, Freeman SS, Yu S, Ha G, Taylor AM, Berger AC, Westlake L, *et al*: Genomic and immune profiling of pre-invasive lung adenocarcinoma. Nat Commun 10: 5472, 2019.
90. Hu X, Fujimoto J, Ying L, Fukuoka J, Ashizawa K, Sun W, Reuben A, Chow CW, McGranahan N, Chen R, *et al*: Multi-region exome sequencing reveals genomic evolution from preneoplasia to lung adenocarcinoma. Nat Commun 10: 2978, 2019.
91. Zhang C, Zhang J, Xu FP, Wang YG, Xie Z, Su J, Dong S, Nie Q, Shao Y, Zhou Q, *et al*: Genomic landscape and immune microenvironment features of preinvasive and early invasive lung adenocarcinoma. J Thorac Oncol 14: 1912-1923, 2019.
92. Yu F, Peng M, Bai J, Zhu X, Zhang B, Tang J, Liu W, Chen C, Wang X, Chen M, *et al*: Comprehensive characterization of genomic and radiologic features reveals distinct driver patterns of RTK/RAS pathway in ground-glass opacity pulmonary nodules. Int J Cancer 151: 2020-2030, 2022.
93. Li Y, Li X, Li H, Zhao Y, Liu Z, Sun K, Zhu X, Qi Q, An B, Shen D, *et al*: Genomic characterisation of pulmonary subsolid nodules: Mutational landscape and radiological features. Eur Respir J 55: 1901409, 2020.
94. Chen K, Bai J, Reuben A, Zhao H, Kang G, Zhang C, Qi Q, Xu Y, Hubert S, Chang L, *et al*: Multiomics analysis reveals distinct immunogenomic features of lung cancer with ground-glass opacity. Am J Respir Crit Care Med 204: 1180-1192, 2021.
95. Saito M, Suzuki H, Kono K, Takenoshita S and Kohno T: Treatment of lung adenocarcinoma by molecular-targeted therapy and immunotherapy. Surg Today 48: 1-8, 2018.
96. Schoenfeld AJ, Bandlamudi C, Lavery JA, Montecalvo J, Namakydoust A, Rizvi H, Egger J, Concepcion CP, Paul S, Arcila ME, *et al*: The genomic landscape of SMARCA4 alterations and associations with outcomes in patients with lung cancer. Clin Cancer Res 26: 5701-5708, 2020.
97. Yu Y and Tian X: Analysis of genes associated with prognosis of lung adenocarcinoma based on GEO and TCGA databases. Medicine (Baltimore) 99: e20183, 2020.
98. Li S, Choi YL, Gong Z, Liu X, Lira M, Kan Z, Oh E, Wang J, Ting JC, Ye X, *et al*: Comprehensive characterization of oncogenic drivers in asian lung adenocarcinoma. J Thorac Oncol 11: 2129-2140, 2016.
99. Shi H, Seegobin K, Heng F, Zhou K, Chen R, Qin H, Manochakian R, Zhao Y and Lou Y: Genomic landscape of lung adenocarcinomas in different races. Front Oncol 12: 946625, 2022.
100. Wu SG, Liu YN, Yu CJ, Yang JC and Shih JY: Driver mutations of young lung adenocarcinoma patients with malignant pleural effusion. Genes Chromosomes Cancer 57: 513-521, 2018.
101. Cancer Genome Atlas Research Network: Comprehensive molecular profiling of lung adenocarcinoma. Nature 511: 543-550, 2014.
102. Izumchenko E, Chang X, Brait M, Fertig E, Kagohara LT, Bedi A, Marchionni L, Agrawal N, Ravi R, Jones S, *et al*: Targeted sequencing reveals clonal genetic changes in the progression of early lung neoplasms and paired circulating DNA. Nat Commun 6: 8258, 2015.
103. Sivakumar S, Lucas FAS, Mcdowell TL, Lang W, Xu L, Fujimoto J, Zhang J, Futreal PA, Fukuoka J, Yatabe Y, *et al*: Genomic landscape of atypical adenomatous hyperplasia reveals divergent modes to lung adenocarcinoma. Cancer Res 77: 6119-6130, 2017.

104. Dejima H, Hu X, Chen R, Zhang J, Fujimoto J, Parra ER, Haymaker C, Hubert SM, Duose D, Solis LM, *et al*: Immune evolution from preneoplasia to invasive lung adenocarcinomas and underlying molecular features. Nat Commun 12: 2722, 2021.
105. Tanaka K, Hida T, Oya Y, Yoshida T, Shimizu J, Mizuno T, Kuroda H, Sakakura N, Yoshimura K, Horio Y, *et al*: Unique prevalence of oncogenic genetic alterations in young patients with lung adenocarcinoma. Cancer 123: 1731-1740, 2017.
106. Han X, Ren P and Ma S: Bioinformatics analysis reveals three key genes and four survival genes associated with youth-onset NSCLC. Open Med (Wars) 17: 1123-1133, 2022.
107. Campbell JD, Alexandrov A, Kim J, Wala J, Berger AH, Pedamallu CS, Shukla SA, Guo G, Brooks AN, Murray BA, *et al*: Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. Nat Genet 48: 607-616, 2016.
108. Van Dijk EL, Jaszczyszyn Y, Naquin D and Thermes C: The third revolution in sequencing technology. Trends Genet 34: 666-681, 2018.
109. Hieggelke L and Schultheis AM: Application of FISH in the diagnosis of lung cancer. Pathologe 41: 582-588, 2020 (In German).
110. Su C, Liu WX, Wu LS, Dong TJ and Liu JF: Screening of hub gene targets for lung cancer via microarray data. Comb Chem High Throughput Screen 24: 269-285, 2021.
111. Morganti S, Tarantino P, Ferraro E, D'Amico P, Viale G, Trapani D, Duso BA and Curigliano G: Complexity of genome sequencing and reporting: Next generation sequencing (NGS) technologies and implementation of precision medicine in real life. Crit Rev Oncol Hematol 133: 171-182, 2019.
112. Xu X, Li N, Zhao R, Zhu L, Shao J and Zhang J: Targeted next-generation sequencing for analyzing the genetic alterations in atypical adenomatous hyperplasia and adenocarcinoma in situ. J Cancer Res Clin Oncol 143: 2447-243, 2017.
113. De Scordilli M, Michelotti A, Bertoli E, De Carlo E, Del Conte A and Bearz A: Targeted therapy and immunotherapy in early-stage non-small cell lung cancer: Current evidence and ongoing trials. Int J Mol Sci 23: 7222, 2022.
114. Sepesi B, Zhou N, William WN Jr, Lin HY, Leung CH, Weissferdt A, Mitchell KG, Pataer A, Walsh GL, Rice DC, *et al*: Surgical outcomes after neoadjuvant nivolumab or nivolumab with ipilimumab in patients with non-small cell lung cancer. J Thorac Cardiovasc Surg 164: 1327-1337, 2022.
115. Nagano T, Tachihara M and Nishimura Y: Molecular mechanisms and targeted therapies including immunotherapy for non-small cell lung cancer. Curr Cancer Drug Targets 19: 595-630, 2019.
116. Tsutani Y, Ito M, Shimada Y, Ito H, Ikeda N, Nakayama H and Okada M: The impact of epidermal growth factor receptor mutation status on adjuvant chemotherapy for patients with high-risk stage I lung adenocarcinoma. J Thorac Cardiovasc Surg 164: 1306-13015.e4, 2022.
117. Mazzone PJ, Gould MK, Arenberg DA, Chen AC, Choi HK, Detterbeck FC, Farjah F, Fong KM, Iaccarino JM, Janes SM, *et al*: Management of lung nodules and lung cancer screening during the COVID-19 pandemic: CHEST expert panel report. Chest 158: 406-615, 2020.
118. Yi QQ, Yang R, Shi JF, Zeng NY, Liang DY, Sha S and Chang Q: Effect of preservation time of formalin-fixed paraffin-embedded tissues on extractable DNA and RNA quantity. J Int Med Res 48: 300060520931259, 2020.
119. Kim YH, Nishimura Y and Funada Y: How should we manage non-small-cell lung cancer 'not-otherwise-specified'? Med Oncol 38: 82, 2021.
120. Liu X, Liu X, Li J and Ren F: Identification and integrated analysis of key biomarkers for diagnosis and prognosis of non-small cell lung cancer. Med Sci Monit 25: 9280-9289, 2019.
121. Shi Y, Zhu S, Yang J, Shao M, Ding W, Jiang W, Sun X and Yao N: Investigation of potential mechanisms associated with non-small cell lung cancer. J Comput Biol 27: 1433-1442, 2020.
122. Wang L, Qu J, Liang Y, Zhao D, Rehman FU, Qin K and Zhang X: Identification and validation of key genes with prognostic value in non-small-cell lung cancer via integrated bioinformatics analysis. Thorac Cancer 11: 851-866, 2020.