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One-stage resection of four genotypes of bilateral multiple primary lung adenocarcinoma: A case report

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Abstract

BACKGROUND

The incidence of multiple primary lung cancer (MPLC) in China is 0.52%-2.45%. Most primary lung cancer cases have reported two lesions or three in rare cases. We report a rare case of bilateral simultaneous multiple primary lung adenocarcinoma of four different genotypes.

CASE SUMMARY

A 58-year-old woman was admitted to our hospital on June 29, 2021, and upon physical examination, four multiple pulmonary nodules were identified in both lungs. Further computed tomography (CT) images revealed the presence of ground glass nodules, predicted to be high-risk cancer lesions by artificial intelligence. With the guidance of three-dimensional reconstruction of preoperative CT images, the nodules were resected under thoracoscopy. Postoperative pathological investigation revealed that the nodule types were adenocarcinoma *in situ*, invasive alveolar adenocarcinoma, and microinvasive adenocarcinoma. The excised nodules were further sequenced using high-throughput sequencing (semiconductor sequencing method) of 26 lung cancer genes to confirm that the four lesions were not homologous. The patient was discharged on postoperative day 8, that is, on July 15, 2021. One month later, she returned to the hospital for follow-up and reexamination. Chest CT examination showed that she had recovered well, and no obvious exudation and effusion were found in both pleural cavities. Evaluation of postoperative pulmonary function showed that her forced vital capacity was 1.40 L (preoperative value, 2.27 L) and forced expiratory volume was 1.24 L (preoperative value, 2.23 L).

CONCLUSION

The surgical plan for multiple pulmonary nodules should be carefully considered.

For carefully selected patients with concurrently occurring multiple lung nodules in both lungs, sublobectomy is a safe and feasible plan for concurrent bilateral resection of the lesions. Genetic sequencing is necessary for MPLC diagnosis and treatment.

Key Words: Multiple primary lung adenocarcinoma; Three-dimensional reconstruction; Sublobar resections; High-throughput sequencing; Case report

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Core Tip: In this case, nodules in bilateral four lobes were resected simultaneously *via* video-assisted thoracic surgery. Postoperative pathological and genetic analyses revealed that the types of nodules were left upper lobe adenocarcinoma *in situ* [epidermal growth factor receptor (EGFR) exon 21], left lower lobe invasive adenocarcinoma (Erb-B2 receptor tyrosine kinase 2 exon 20 and tumor protein p53 exon 8), and right upper lobe microinvasive adenocarcinoma (EGFR exon 19), and right lower lobe microinvasive adenocarcinoma (EGFR exon 18). Genetic examination is of decisive significance in the identification of multiple lung cancers and metastatic cancers.

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INTRODUCTION

Lung cancer has a high incidence and mortality rate, and is one of the major malignant tumors that pose a threat to human health and life. In the past 30 years, lung cancer has ranked first among malignant tumors in China with regard to its incidence and mortality rates[1]. With the development of multilayer spiral computer scanning technology and the popularization of lung cancer screening, a greater number of lung nodules are being discovered, many of which are multiple pulmonary nodules. Some of these nodules are pathologically confirmed as multiple primary lung cancers after surgery. Multiple primary lung cancer (MPLC) refers to the concurrent or successive occurrence of primary lung cancer lesions of at least two different sources at different sites of a patient's lungs. These lesions can develop in one or two lungs. Two types of MPLCs have been described: simultaneous MPLC (sMPLC) and metachronous MPLC (mMPLC). At 0.52%-2.45% [2], the incidence of MPLC in China is lower than that of primary lung cancer.

The prognosis and treatment of primary lung cancer and lung cancer with intrapulmonary metastasis (IM) are significantly different[3]. Therefore, it is important to accurately distinguish between MPLCs, especially sMPLCs and IMs. The traditional methods used for differential diagnosis have many limitations. For example, immunohistochemistry can only be used to differentiate between MPLC and metastatic lung cancer, and percutaneous lung biopsy, which is often used to diagnose lesions that are suspected of being lung cancer, has a high false-negative rate, and carries the risk of pleural implantation and metastasis[4]. Therefore, surgical resection of the lesions to the greatest extent possible is one of the important choices of thoracic surgeons. However, the current standard guidelines do not provide clear instructions on how to choose between simultaneous surgical resection and staged resection of all lesions. With the rapid development of gene sequencing technology, there is increasing evidence to support the independent clonal origin of MPLC[5]; therefore, gene sequencing may be useful for the differential diagnosis of IM and MPLC. According to reports, most cases of primary lung cancer present with two lesions, and three lesions are found in rare cases.

Here, we report a rare case of primary lung adenocarcinoma of four different genotypes that was treated at the Second Affiliated Hospital of Nanchang University.

CASE PRESENTATION

Chief complaints

A 58-year-old woman was admitted to the hospital with a 10-mo history of pulmonary sarcoidosis.

History of present illness

Pulmonary sarcoidosis was first discovered accidentally during a chest computed tomography (CT) scan 10 mo prior. Chest CT examination revealed tiny nodules in both lungs; the largest nodule measured 4.6 mm. No symptoms such as cough and expectoration, chest pain, dyspnea, fever, night sweats, fatigue, or anorexia were present. Upon further follow-up and clinical evaluations, enhanced chest CT findings in the hospital's outpatient department indicated the presence of multiple ground glass nodules in both lungs (Figure 1). These nodules were predicted to be high-risk nodules by artificial intelligence.

History of past illness

She had a previous history of breast nodules and thyroid nodules, which were not indicative of a history of diseases such as tuberculosis and diabetes.

Personal and family history

The patient denied having a family history of malignant tumors. The patient had no smoking or drinking history.

Physical examination

No obvious abnormalities were found after a cardiopulmonary examination.

Laboratory examinations

No obvious abnormality was found in the blood routine examination results, liver and kidney function, or electrolyte and serum tumor markers (lung cancer marker combination: carcinoembryonic antigen, carbohydrate antigen-199, squamous cell carcinoma associated antigen, neuron-specific enolase, and cytokeratin-19 fragment).

Imaging examinations

Pulmonary function was uneventful, forced vital capacity (FVC) was 2.27 L, and forced expiratory volume (FEV1) was 2.23 L or 78.41% of the predicted value. The enhanced chest CT (Figure 1) findings showed that the bilateral lung markings were enhanced. Density shadows of nodular soft tissues were found in the lower lobe of the left lung near the hilum; the density was uniform. No calcifications were present. The diameter of the nodule was about 12 mm. The nodule had clear boundaries. The enhanced scan showed obvious and uniform enhancement. Scattered ground glass nodules were present in both lungs, especially in the right lung. The diameter of the larger nodule was about 9 mm; enhanced scanning showed no obvious enhancement. The trachea and bronchus were unobstructed, and no clear enlarged lymph nodes were present in both the hila and mediastinum. No obvious thickening of bilateral pleura and no effusion in pleural cavity were observed.

FURTHER DIAGNOSTIC WORK-UP

After excluding surgical contraindications, three-dimensional reconstructions of CT images were performed (the synapse 3D software) before surgery, as shown in Figure 2. After careful preoperative evaluation and consideration of the patient's lung function test results and position of the nodules, a bilateral thoracoscopic one-stage sublobectomy was adopted. The postoperative pathological diagnosis is depicted in Figure 3. Immunohistochemical investigations of the lower left lung cancer revealed positive staining for cytokeratin (CK), thyroid transcription factor-1, napsin A, CK7, and Ki-67 (30% positive staining) and negative staining for p40 and anaplastic lymphoma kinase (ALK)-D5F3. No cancer metastasis was found in lymph node groups 5, 6, and 10. The excised nodules were sequenced using high-throughput sequencing (semiconductor sequencing) of 26 lung cancer genes. Genetic test results revealed that the four lesions were not homologous (Table 1).

FINAL DIAGNOSIS

The patient was eventually diagnosed with sMPLC.

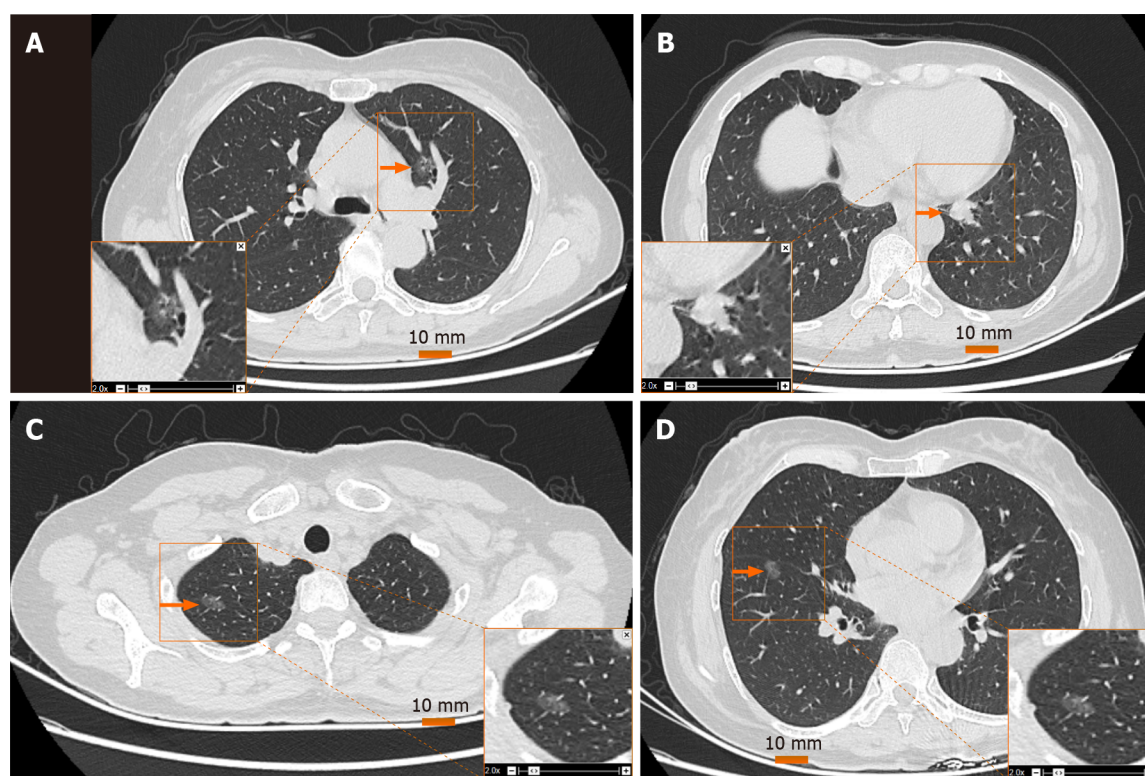
TREATMENT

The surgical plan was left anterior lobe resection + left lower lobe wedge resection + right upper lobe apical resection + right lower lobe wedge resection. For an invasive cancer with a predicted FEV1 value of 78.41%, which is less than 80%, no further lobectomy is required, according to previously published

Table 1 Gene sequencing of four primary lung adenocarcinoma lesions

Nodule location	Mutant gene	Detection result	Abundance/NDF, %
Upper lobe of left lung	EGFR	Exon 21 c.2573T>G p.L858R	4.05
Lower lobe of left lung	ERBB2	Exon 20 c.2310_2311insGCATAC GTGATG p.E770_A771insAYVM	25.40
	TP53	exon 8 c.796G>A p.G266R	2.84
Upper lobe of right lung	EGFR	Exon 19 c.2238_2252delATTAAG AGAAGCA AC p.L747_T751 del	10.24
Lower lobe of right lung	EGFR	Exon 18 c.2156G>C p.G719A	8.89

EGFR: Epidermal growth factor receptor; ERBB2: Erb-B2 receptor tyrosine kinase 2; TP53: Tumor protein p53. NDF is the logarithmic value of the ratio of the number of fusion-supported reads at the site to the total number of reads in the sample (log value). NDF < 0, the larger the NDF value, the more the number of supported fusion reads is detected.



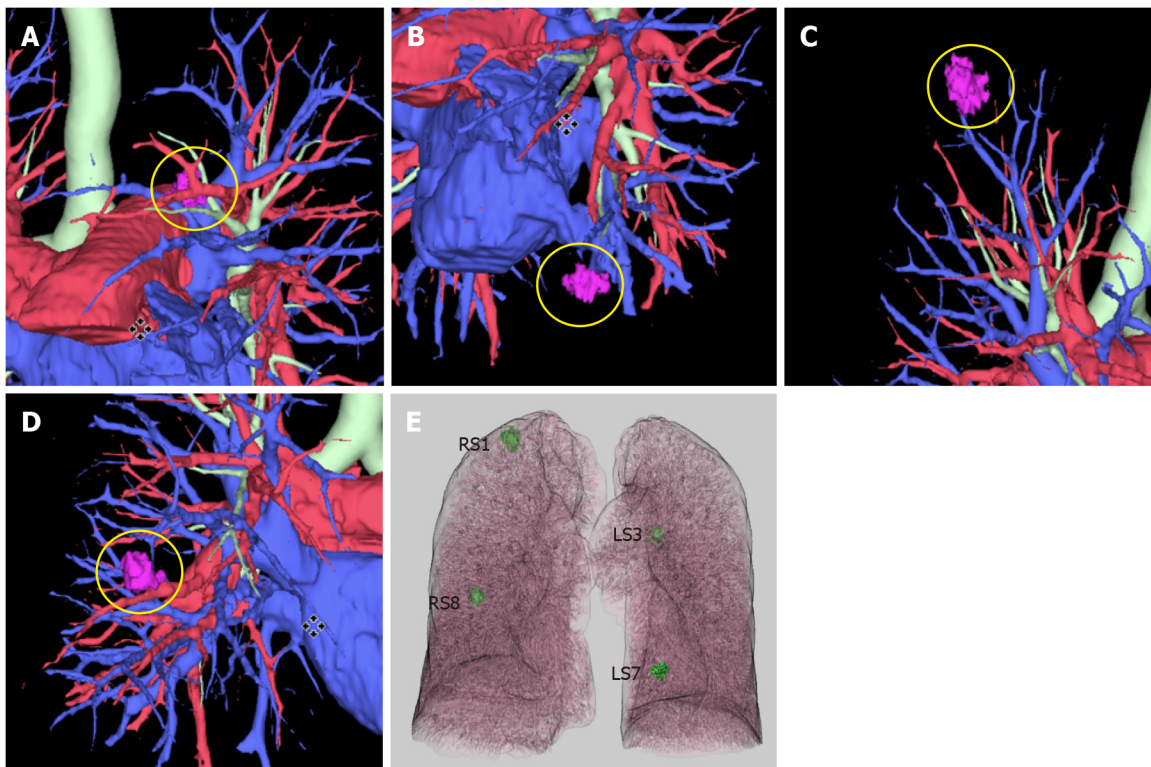
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Figure 1 Computed tomography image of pulmonary nodules. A: Left upper lung nodule (LS3), 11 mm in diameter; B: Left lower lung nodule (LS7), 20 mm × 14 mm × 10 mm; C: Upper right nodule (RS1), 8 mm in diameter; D: Lower right nodule (RS8), 8 mm in diameter. The orange arrow indicates the location of the nodule.

research[6]. After the surgical procedure, the patient was treated with antibiotics and analgesics. Other supportive treatments, such as appropriate nutrition and symptomatic treatment, were also administered.

OUTCOME AND FOLLOW-UP

The patient recovered and was discharged on postoperative day 8. Postoperative evaluation of pulmonary function showed that her FVC was 1.40 L and her FEV1 was 1.24 L or 57% of the predicted value.



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Figure 2 Location of pulmonary nodules in three-dimensional reconstruction. A: Upper lobe of left lung (LS3); B: Lower lobe of left lung (LS7); C: Upper lobe of right lung (RS1); D: Lower lobe of right lung (RS8); E: Three-dimensional imaging projection of pulmonary nodule on the pleura.

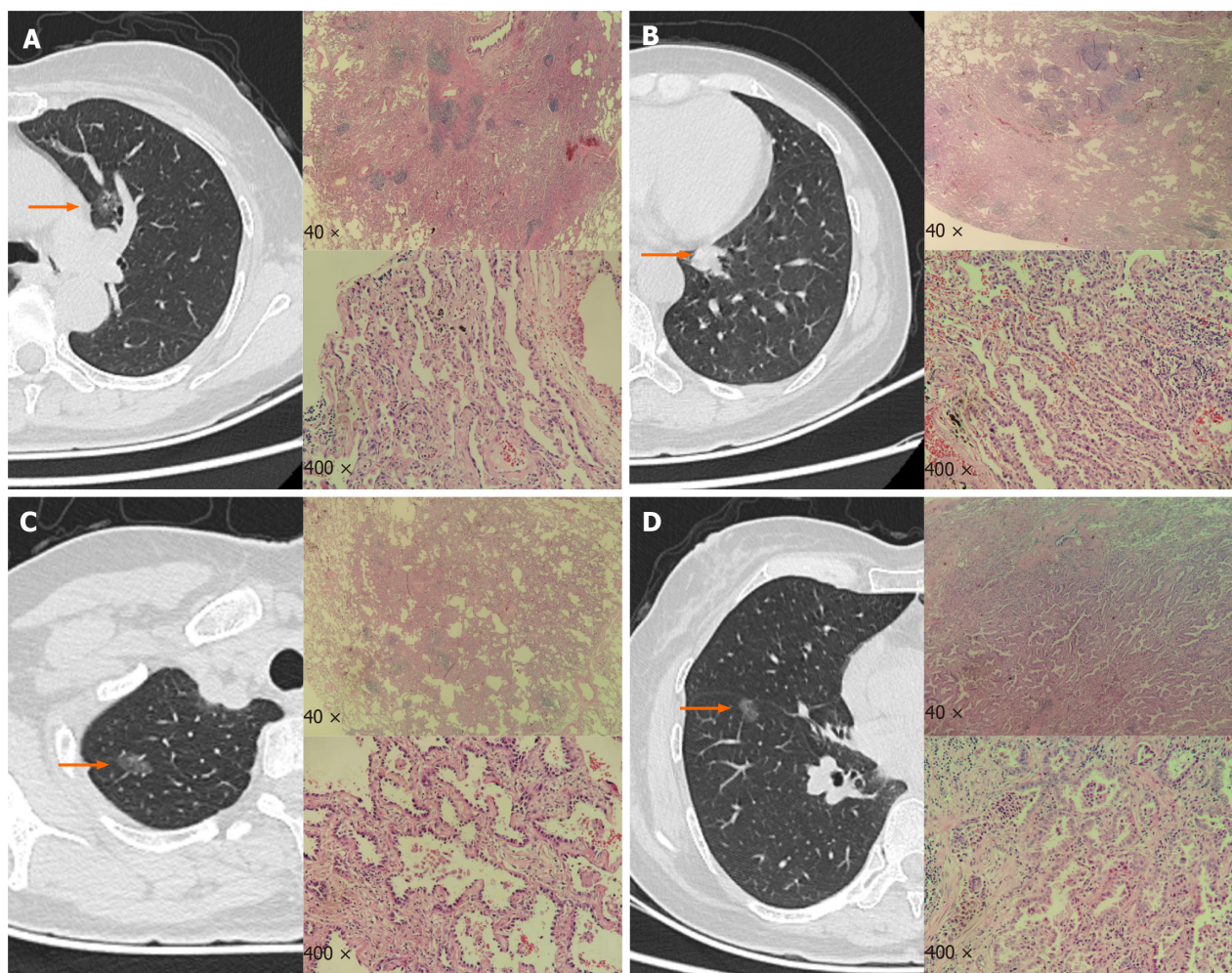
DISCUSSION

MPLC refers to the concurrent or successive occurrence of primary lung cancer of at least two different sources at different sites of a patient's lungs. Two types of MPLC have been described: sMPLC and mMPLC. According to the criteria proposed by Martin and Melamed[7] in 1975 for the diagnosis of MPLC, the lesions must be of different tissue types or originate from different carcinoma *in situ*, if the types are the same. Each lesion must also be located in different anatomical sites with no common lymphatic or extrapulmonary metastatic paths at the time of diagnosis. For mMPLC, an additional tumor-free interval of at least 2 years is required. Compared to the incidence rate of lung cancer, the incidence rate of MPLC is lower at 0.52%-2.45%[2]. Most cases of primary lung cancer have been reported to have two lesions and three in rare cases. In this case, four different lesions were identified. After a comprehensive preoperative evaluation, this case was considered to be a case of high-risk nodules.

Chest CT and other imaging examinations did not indicate intrapulmonary metastasis, and the hilar and mediastinal lymph nodes were not enlarged. However, some nodules were indicative of inflammation in the left lower lung. As percutaneous lung biopsy carries the risk of false-negative results due to the small amount of sampling tissue, as well as the risk of pleural implant transfer, we determined that the most appropriate approach was to surgically resect all the lesions simultaneously. Therefore, single-hole thoracoscopic surgery was indicated. Four nodules in both lungs were also resected. Postoperative pathological examination confirmed our suspicion.

With the increasing use of high-resolution low-dose spiral CT in lung cancer screening, the discovery of pulmonary nodules is more common, with 50% of screened patients having multiple pulmonary nodules[8]. MPLC is mostly diagnosed early during physical examination by the identification of pulmonary nodules. Currently, no guidelines have been established for the diagnosis and treatment of MPLC. Therefore, treatment regimen for multiple pulmonary nodules can be adopted for the treatment of MPLC. In National Comprehensive Cancer Network (NCCN) and China's guidelines for the diagnosis and treatment of lung nodules, the treatment of multiple lung nodules is mentioned, but no specific guidelines for the diagnosis and treatment of multiple lung nodules were found in the literature.

However, we decided on a plan based on clinically relevant suggestions in the literature, domestic expert views, and relevant foreign guidelines. With respect to the timing of surgical intervention, from the 2018 version of the guidelines on diagnosis and treatment of pulmonary nodules in China[9] and those on the diagnosis and treatment of early lung adenocarcinoma of ground glass nodules[10] at Shanghai Pulmonary Hospital, experts recommend that each nodule should be evaluated separately.

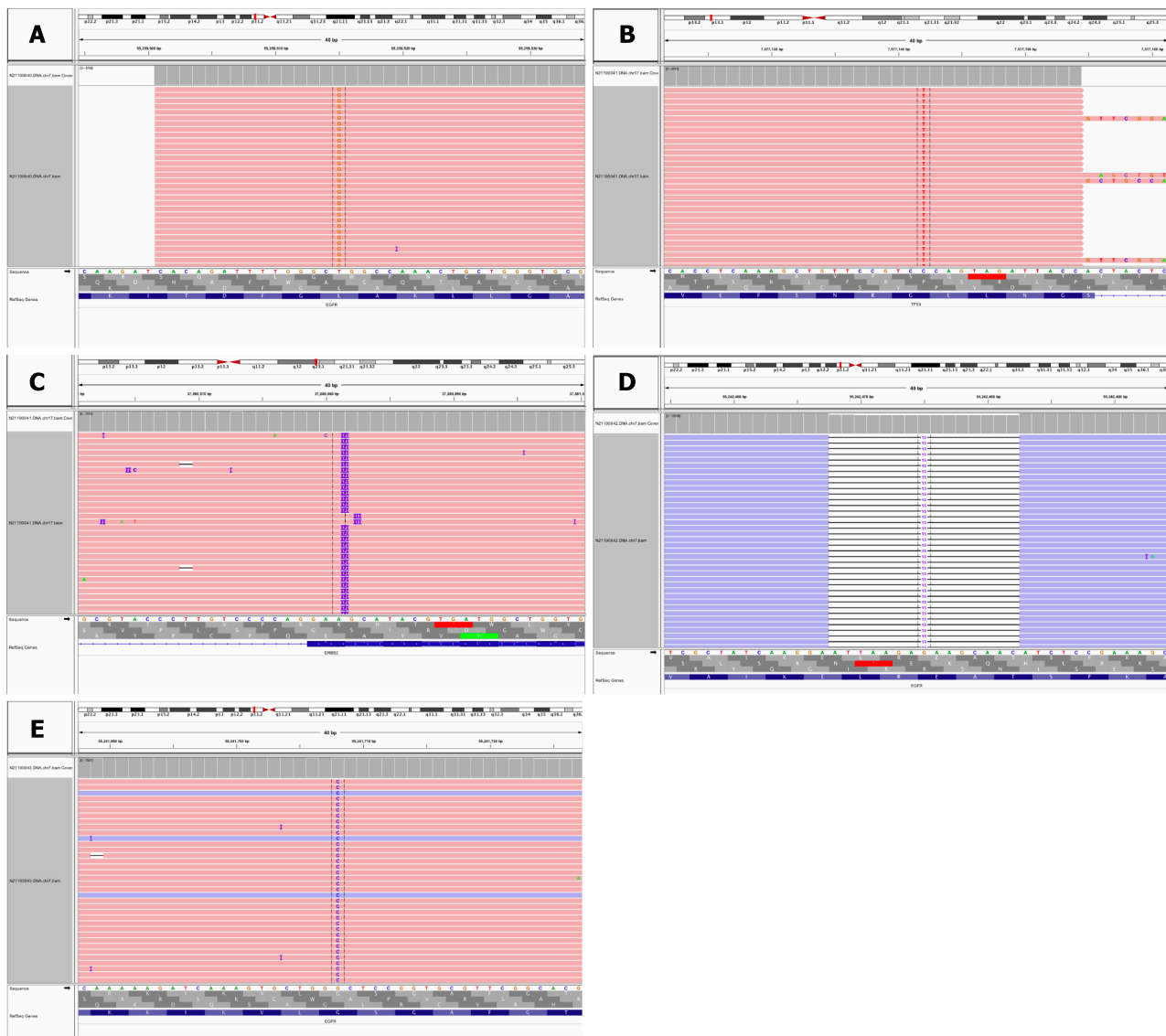


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Figure 3 The left side of the image is a computed tomography image. The red arrow indicates the location of the nodule. The upper right side indicates a low-power microscopic pathological image, and the lower right side indicates a high-power microscopic pathological image. A: The left upper pulmonary nodule is an adenocarcinoma *in situ*, with adherent growth and obvious cell atypia; B: The left lower lung nodule is an acinar adenocarcinoma with glandular arrangement, invasive growth, significant atypia of cancer cells, and proliferation of interstitial fibrous tissue; C and D: The right upper and right lower nodules are microinvasive adenocarcinoma. The cancer cells adhere to the wall; the cell atypia is significant; and the focus shows invasive growth.

They also recommend that major lesions should be prioritized over secondary lesions. Comprehensive evaluation of the lesion's location, size, and effect on lung function should be conducted. Selective local resection of lesions is also recommended. For suspected MPLC, the mediastinal lymph node status should be evaluated. Surgical treatment is not recommended, if mediastinal lymph node metastasis is present. If mediastinal lymph node metastasis is negative, a specific surgical plan, as to whether to remove the main or all lesions, can be formulated according to lesion status and systemic conditions. The NCCN 2020 guidelines, Fleischner Society 2017 guidelines[11], and American Association of Chest Physicians 2013 guidelines[12] recommend regular follow-up of patients with high-risk nodules. The follow-up frequency and duration are based on the main lesions, and the timing of surgical intervention is subject to the specific evaluation of clinicians, as no specific timing recommendations for surgical intervention are available.

In terms of the surgical plan, surgery is still the first choice for multiple pulmonary nodules with clear pathological results or high-risk nodules. The operation plan is determined according to the number, location, and size of the lesions; pulmonary function; and physical condition of the patient. At present, there is consensus among surgeons with regard to the scope of surgical resection of multiple pulmonary nodules, and these are the general guidelines that are typically followed: (1) If multiple pulmonary nodules are located in the same lobe, lobectomy is preferred; (2) If the nodule is located in different lobes of the ipsilateral lung and the nodule diameter is greater than or equal to 2 cm, lobectomy is recommended. If the diameter is less than 2 cm, wedge-shaped, segmental, or combined segmental resection is recommended according to the location and relationship with adjacent blood vessels[13]. Total pneumonectomy is not recommended for multiple pulmonary nodules; it has a poor prognosis [14]; and (3) If the nodules are located in different lobes of bilateral lungs, the choice of simultaneous surgical resection or secondary surgical resection is still controversial. If the patient has good cardiopul-



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Figure 4 Depiction of the mutations detected in the present case. A: Mutation detected in the upper lobe of the left lung cancer [epidermal growth factor receptor (EGFR) exon 21 c.2573T>G p.L858R]; B and C: Mutation detected in the lower lobe of the left lung cancer (1. Erb-B2 receptor tyrosine kinase 2 exon 20 c.2310_2311i nsGCATAC GTGATG p. E770_A77 1insAYVM, 2. Tumor protein p53 exon 8 c.796G>A p.G266R); D: Mutation detected in the upper lobe of the right lung cancer (EGFR Exon 19 c.2238_2252 delATTAAG AGAAGCA AC p.L747_T751 del); E: Mutation detected in the lower lobe of the right lung cancer (EGFR exon 18 c.2156G>C p.G719A).

monary function reserve, bilateral simultaneous surgery can be considered on the premise of strictly grasping the surgical indications. The surgery is safe and feasible, with less trauma, less cost, and faster postoperative recovery than second stage surgery[15,16]. Chen *et al*[17] believe that simultaneous resection and staged resection have a similar prognosis. For patients who cannot tolerate concurrent bilateral surgery, priority can be given to the treatment of the main lesions. The other lesions can be treated during the second stage. Some physicians believe that second stage surgery is safer, more reasonable, and more effective than simultaneous surgery in the treatment of bilateral multiple pulmonary nodules[18]. Multidisciplinary consultation is recommended for the discussion and decision on the timing of surgical intervention and concurrent or secondary surgery. In this case, the patient's bilateral pulmonary nodules were small, and pulmonary function and general condition were acceptable. According to the preoperative plan, double sublobar resection was executed at the same time. Romaszko *et al*[19] believe that the application of a molecular method to accurately determine the cloning source of MPLC may help determine the appropriate therapy and improve the prognosis of patients. In the present study, high-throughput sequencing (semiconductor sequencing) of 26 lung cancer genes in the four nodules was performed after surgical resection, with the human epidermal growth factor receptor, KRAS, BRAF, phosphoinositide 3-kinase, catalytic subunit alpha, ALK, and ROS1 gene mutation detection kit from Tianjin Novogene Bioinformatics Technology Co. Ltd. (Tianjin, China). The experimental method was multiplex PCR capture and semiconductor sequencing. First,

DNA and RNA was extracted and purified from paraffin-embedded pathological tissue specimens of the four nodules. Then the DNA and cDNA fragments in the target area were enriched by multiplex PCR, and the enriched library was quantified and subjected to quality control. Finally, the quantified library was sequenced with a gene sequencer (model DA8600; Daan Gene Co. Ltd., Sun Yat-Sen University, Guangzhou, China) for high-throughput sequencing to obtain the DNA and RNA sequence information of the target region, and the supporting software was used to communicate with the human genome. The information obtained was checked against the Human Genome Database to determine whether mutation or fusion occurs. The results of genetic testing and imaging of the mutations are shown in Table 1 and Figure 4.

Under the guidance of three-dimensional reconstruction, Chu *et al*[20] used a combination of thoracoscopic wedge resection and segmental resection to resect five nodules in different lobes of both lungs. The patients were discharged on postoperative day 8 without complications. Yu *et al*[21] chose video-assisted wedge lung resection, when there were four nodules in different lobes of both lungs. Since the nodules in the right upper lobe were invasive adenocarcinoma, and those in the right middle lobe were micro-invasive adenocarcinoma, further lobectomy with lymph node dissection was performed. Postoperative recovery was acceptable. Sublobectomy has been proven to be an alternative to lobectomy for early lung cancer[22]. Additionally, the development of minimally invasive surgery makes simultaneous multiple nodule resection in both lungs possible. Surgeons can safely and accurately resect multiple nodules under the guidance of three-dimensional reconstruction. Although gene detection was carried out in this case, the gene detection panel was small, and the full exon gene, circulating tumor DNA, molecular residual disease, and other relevant factors were not examined to further identify the primary tumor and metastatic tumor. In addition, as this is a case report, it has several other limitations. At present, domestic reports of MPLC are rare; reports on primary lung adenocarcinoma involving four lesions in both lungs are even rarer. As a result, no clear guidelines for the diagnosis and treatment of MPLC are available. Therefore, more relevant experimental studies and guidelines need to be developed in the future to improve the health of patients with MPLC.

CONCLUSION

On the premise of the careful selection of patients, when considering the diagnosis of multiple primary lung adenocarcinomas, concurrent sublobectomy on both sides is a safer and more feasible option. Molecular sequencing and further genetic analysis of mutations in each nodule are necessary in the investigation of nodules of multiple sources.

FOOTNOTES

Author contributions: Zhang DY reviewed the relevant literature and participated in the drafting of the manuscript; Wei YP and Yu DL participated in the revision of the manuscript; Liu J, Zhang Y, Ye JY, Hu S, and Zhang WX participated in the information collection; Wei YP is the corresponding author; All authors read and approved the revised manuscript.

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