

Comprehensive diagnosis and individualized treatment of multiple primary lung cancer: A case report

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Abstract. With the popularity of low-dose CT, the detection rate of multiple primary lung cancer (MPLC) has gradually increased. However, to the best of our knowledge, no unified standard for diagnosing MPLC currently exists. Therefore, the differentiation of this tumor type from lung cancer intrapulmonary metastasis (IM) can aid the diagnosis of MPLC. The treatment strategies and prognosis of these two tumor types are different. The present report documents the case of a 45-year-old female patient with MPLC with >20 lesions in both lungs. Enhanced chest CT imaging indicated IM, prompting admission to the hospital for clarification of the pathology of the lung lesions and for receiving drug therapy. However, whole-body PET-CT revealed an anterior left upper lobe lesion with increased F¹⁸-fluorodeoxyglucose (FDG) metabolism (maximum standardized uptake value=7.3). No abnormal increases in FDG metabolism were found in the other multiple lesions. The data led to a diagnosis of MPLC. Following multidisciplinary discussions, an individualized treatment plan for this patient was developed. The patient was treated with a two-stage surgery (first surgery on the left lung, second surgery on the right lung) according to the protocol,

coupled with adjuvant chemotherapy (700 mg pemetrexed combined with 45 mg lobaplatin) between surgeries. For 56 months after the first surgical treatment, the patient did not experience disease progression. The patient's disease-free survival period is ongoing. In this case, the multiple lesions did not show significant similarities in their histopathological and genomic characteristics. The integration of radiological, histopathological and genomic features by a multidisciplinary team facilitated a more accurate diagnosis of MPLC. This has the potential to become an option for the differential diagnosis of MPLC in the future. In addition, an individualized treatment design would be more beneficial to patients with MPLC, especially those with a large number of lesions in both lungs. The present study reports a case of the diagnosis and individualized treatment of MPLC with multiple lesions in both lungs, which provides a reference for the diagnosis and treatment of similar patients.

Introduction

According to global cancer epidemiological data (GLOBOCAN 2020 statistics), the incidence and mortality of lung cancer rank first among all malignant tumors (1). The incidence of multiple pulmonary nodules ranges 5-20% in studies of different sample sizes and populations (2,3). With the increasingly common use of low-dose CT, the detection rate of multiple primary lung cancer (MPLC) has gradually increased. The number of cases diagnosed with simultaneous multiple lung lesions is increasing annually, where the majority of cases are finally confirmed as simultaneous MPLC. Global data shows that the incidence of MPLC ranges from 0.8 to 8.4%, and is on a continuous upward trend (4). Epidemiological studies in China report an incidence of MPLC ranging from 0.52 to 2.45% (5), while a cohort study of surgical patients showed that 12% of patients with lung cancer were pathologically diagnosed with MPLC (6). The diagnosis of MPLC requires a combination of histopathology and molecular characteristics. Clinically, 12-18% of patients with multiple pulmonary nodules are ultimately confirmed to have synchronous MPLC (6,7). MPLCs can be easily misdiagnosed as metastatic cancers when more than two nodules appear in the lungs. The distinction of

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Abbreviations: MPLC, multiple primary lung cancer; FDG, fluorodeoxyglucose; IM, intrapulmonary metastases; NGS, next-generation sequencing; LUL, left upper lobe; RUL, right upper lobe; RLL, right lower lobe; TMB, tumor mutation burden; AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; IA, invasive adenocarcinoma; PD-L1, programmed death-ligand 1; TTF-1, thyroid transcription factor 1; FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; GGN, ground glass nodules

Key words: MPLC, diagnosis, molecular detection, next-generation sequencing, treatment

MPLC from intrapulmonary metastases (IM) is critical but challenging. The former is mainly treated by surgery and the prognosis is favorable, whereas the latter involves systemic chemotherapy and exhibits a poor prognosis (8). For patients with synchronous MPLC undergoing bilateral staged surgery, if the lesions are completely resected, the 5-year survival rate can reach 60-80% (9-11).

Multiple lung cancer types typically present as anatomical pulmonary nodules on imaging (12,13). This has persistently been a challenge for pathologists and thoracic surgeons due to their important implications for treatment and prognosis as a result of the accurate staging of these nodules. However, current tumor staging systems mainly rely on histological and pathological features, which lack definitive criteria for diagnosing MPLC. This condition can lead to ambiguous cases, where pulmonary nodules are histologically, pathologically identical or highly similar (2,14). Next-generation sequencing (NGS) has been garnering attention as a valuable adjunct to the existing histopathological diagnostic workup, notably in lung cancer (15). Molecular typing can aid in treatment selection. In the present case, a patient with MPLC with >20 lesions in both lungs is reported, highlighting the critical role of the combination of imaging, pathological and molecular features obtained from each tumor lesion in the diagnosis of MPLC. The data can be shared with individualized treatment programs.

Case report

A 45-year-old female patient was admitted to the Affiliated Hospital of Guangdong Medical University (Zhanjiang, China) in August 2020 following detection of multiple nodules in both lungs during a CT scan (Fig. 1). The purpose of the visit was to clarify the pathology of lung lesions and provide adequate treatment. The patient had no specific medical symptoms, such as cough, sputum or fever. The patient did not smoke and had no family history of cancer. Chest-enhanced CT indicated a solid mass shadow (4.6x4.0 cm) in the irregular part of the anterior segment of the left upper lobe with blurred edges, visible lobulation, spiculation and cavitation signs, local pleural traction signs, irregular bronchial stenosis and occlusion in the lesion. Enhanced scanning indicated apparent enhancement of the solid component of the lesion (Fig. 2A). Multiple ground-glass nodules (GGN) and mixed ground-glass nodules were scattered in both lungs (Fig. 2B-H). No apparent abnormalities were noted by brain enhanced MRI. The levels of carcinoembryonic antigen, squamous cell carcinoma antigen, neuron-specific enolase and cytokeratin fragment were all within the normal range. Pulmonary function retest indicated forced expiratory volume in 1 sec (FEV₁) of 2.37 l, FEV₁% (measured value/predicted value) of 91.62%, forced vital capacity (FVC) of 2.88 l, FVC% (measured value/predicted value) of 94.46% and FEV₁/FVC 82.84%. Whole-body PET-CT revealed an anterior left upper lobe lesion with increased F¹⁸-fluorodeoxyglucose (FDG) metabolism [maximum standardized uptake value (SUV_{max})=7.3] (Fig. 3A and B). No abnormal increase in FDG metabolism was found in the other multiple lesions (Fig. 3C-H). Peripheral lung cancer in the anterior segment of the upper lobe of the left lung was considered. The results suggested the presence of MPLC, and no distant metastasis was noted. The patient

was only 45 years old and their son was young and required care. The patient was anxious after learning that they may have late-stage lung cancer and urgently sought diagnosis and treatment. Following multidisciplinary discussions, a high possibility for a primary tumor was considered and surgical treatment was recommended. The patient and their family agreed to receive surgical treatment.

Due to the presence of >20 lesions in each lobe of both lungs, it was impossible to remove all lesions completely. Following multidisciplinary discussion, it was decided to perform surgery in two stages.

As the main lesion was in the left upper lung, in September 2020, the patient underwent a thoracoscopic left upper lobectomy, left lower lung wedge resection and hilar-mediastinal lymph node resection.

Frozen sections (-20°C) of the lesions were prepared by cutting 5- μ m thick tissue sections. The sections were then rapidly fixed with 95% ethanol and stained with hematoxylin-eosin. Tissues were fixed in 10% formalin for 12 h at 20°C, embedded in paraffin and serially sectioned into 5- μ m-thick sections. The sections were then stained with hematoxylin for 10 min (at 20°C) and eosin for 20 sec (at 20°C), before being observed under a light microscope. Pathologically, adenocarcinoma *in situ* (AIS) tumor cells would proliferate along the alveolar wall without destructive interstitial invasion (16,17). By contrast, minimally invasive adenocarcinoma (MIA) of the lung primarily grows adherently but also has an invasive component of \leq 5 mm (16-18). Invasive adenocarcinoma (IA) has an invasive component of >5 mm or involves lymphatic, vascular or pleural invasion (17,19).

The pathological results of the frozen sections indicated that the left upper lung (LUL) lesion, denoted as 1 (main lesion), was IA whereas the LUL lesions 2, 3, 4, 5 and 6 were MIAs. LUL lesion 7 and the left lower lung lesions were AIS. LUL lesion 8 was a benign fibrous nodule. Postoperative pathology indicated that the LUL lesion 1 was IA (100% papillary subtype; T2bN0M0; IASLC 8th edition (20); Fig. 4A and B). The results of the other lesions (lesion 2-7) were consistent with the results of the frozen section pathology analysis (Fig. 5A-F).

Immunohistochemistry was then performed using the EnVision two-step assay according to standard protocols. Antibodies used included Ki67 (cat. no. 8605580), carcinoembryonic antigen (cat. no. IR051-5), cytokeratin 7 (cat. no. IM061-5), Napsin A (cat. no. IM469-5), thyroid transcription factor 1 (TTF-1; cat. no. IR301-5) and programmed death-ligand 1 (PD-L1; cat. no. 22C3; Dako; Agilent Technologies, Inc.). The aforementioned primary antibodies were used at a dilution of 1:100 and incubated at 4°C for 12 h.

The results of the immunohistochemical detection (Fig. 5G-K) indicated detection of Napsin A (+), cytokeratin 7 (+), Ki-67 (10%), PD-L1 (tumor cells-, interstitial macrophages+, 50%) and TTF-1 (+). Co-expression of Napsin A and TTF-1 is a typical characteristic of lung adenocarcinoma, while CK7 positivity rules out the possibility of adenocarcinoma from other sites. These immunohistochemical stains supported the diagnosis of lung adenocarcinoma.

The 9-gene test utilizes the clinically validated LungCore[®] panel, encompassing the following nine common lung cancer gene mutations: *EGFR*, *ALK*, *MET*, *KRAS*, *ERBB2*, *BRAF*, *ROS1*, *PIK3CA* and *RET*. For LUL lesion 1, Library preparation

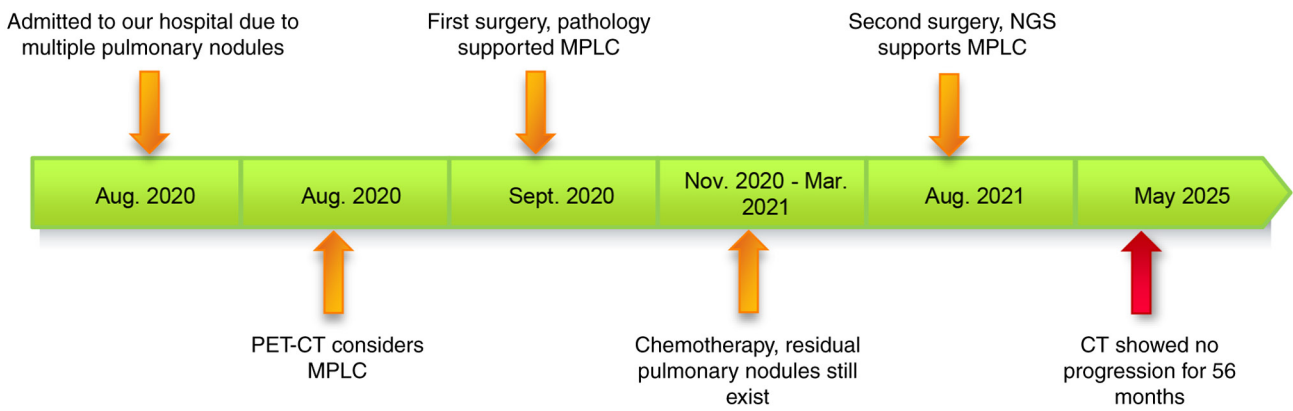


Figure 1. Timeline of the present case report. MPLC, multiple primary lung cancer; NGS, next-generation sequencing.

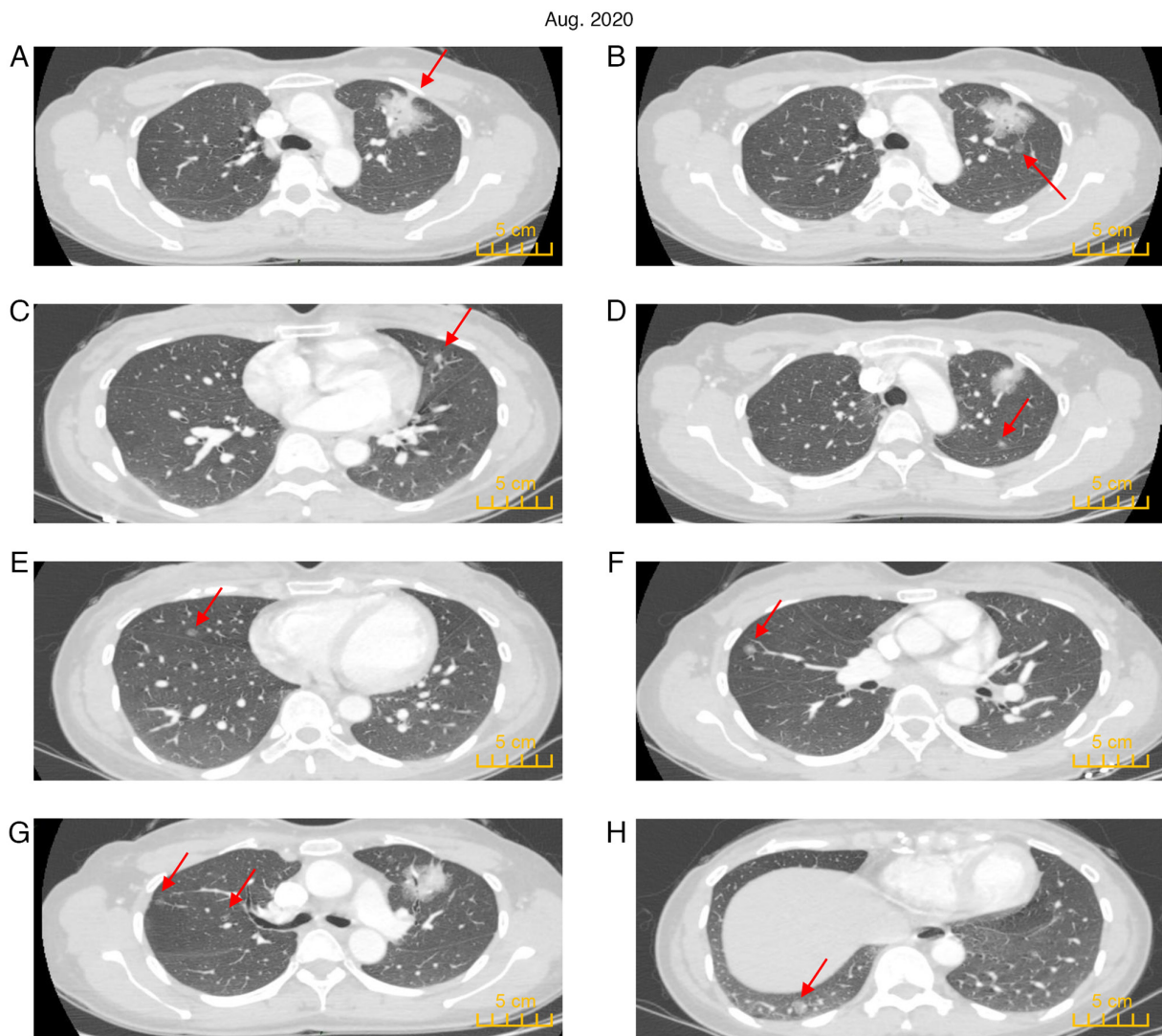


Figure 2. Patient CT images. (A) The main lesion in the lungs (left upper lobe lesion 1); a solid mass shadow in the irregular part of the anterior segment of the left upper lobe with blurred edges, visible lobulation, spiculation and cavitation signs, local pleural traction signs, irregular bronchial stenosis and occlusion in the lesion. (B-D) The main remaining lesions (GGNs) of the left upper lung. (E and F) Main lesions (GGNs) of the right middle lung. (G) Main lesions (GGNs) of the right upper lung. (H) Main lesions (GGNs) of the right lower lung. GGNs, ground-glass nodules.

and hybridization capture were performed using the LungCore® Next-Generation Sequencing Kit (Guangzhou Burning Rock Medical Laboratory Co., Ltd.) and sequencing was performed

on the Illumina MiSeqDX platform (Illumina, Inc.). All experimental procedures strictly followed the standard operating procedures certified by Burning Rock Biotech under ISO 15189,

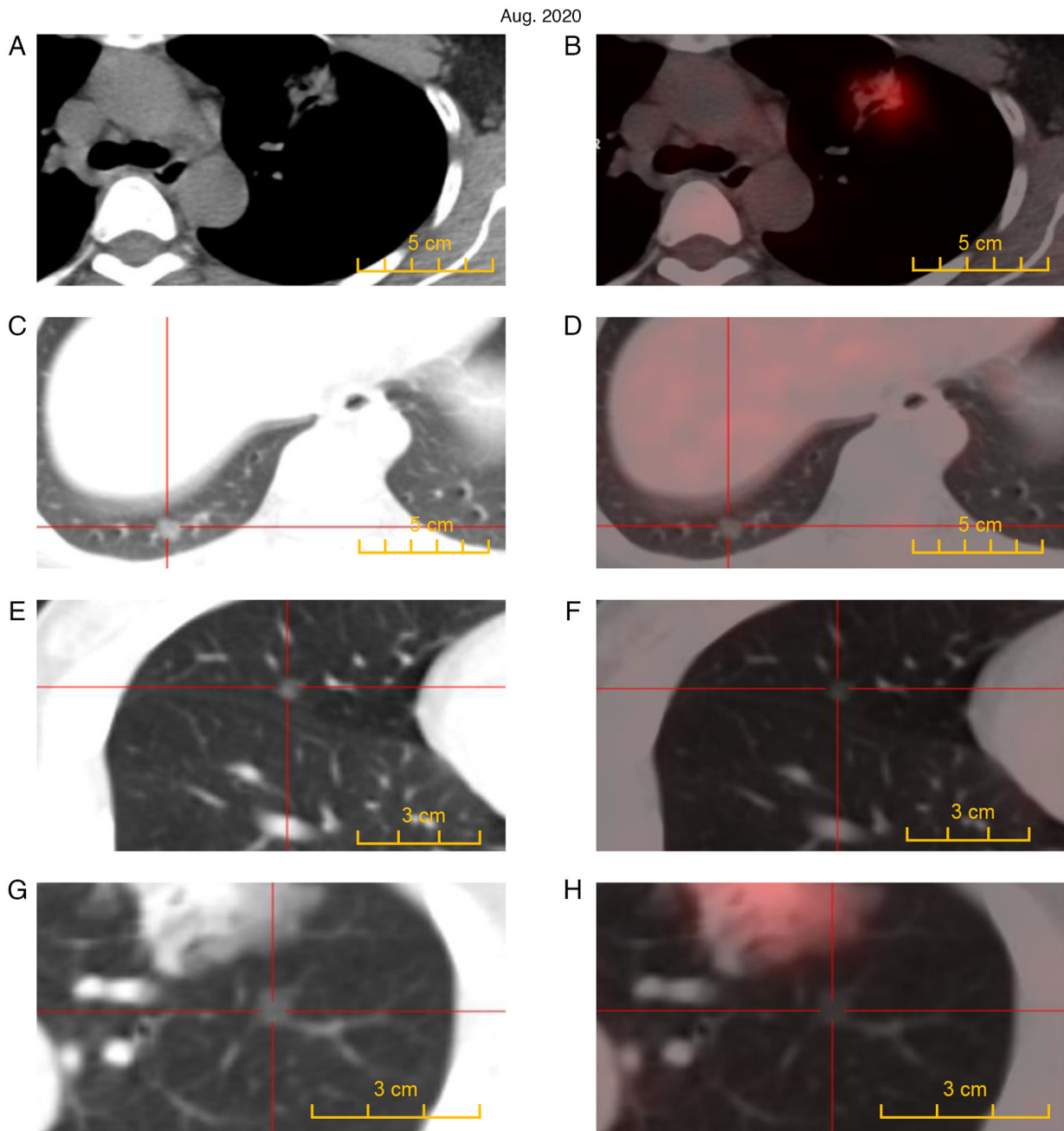


Figure 3. PET-CT images of the patient. (A and B) Hypermetabolism was observed in the left upper lung lesion (maximum standardized uptake value=7.3). (C-H) No abnormal increase in F^{18} -fluorodeoxyglucose metabolism was found in the other multiple lesions.

including DNA extraction, hybridization capture, sequencing and bioinformatics analysis. An overview of Burning Rock Biotech's LungCore[®] 9-gene testing panel is available online at <https://www.brbiotech.com/service/c4> (accessed on 2026-1-10).

The detection results of these nine target genes indicated that *KRAS* gene exon 2 mutation was detected in both LUL lesions 1 and 5. Except for the main lesion in the LUL, the remaining lesions were not tested for PD-L1 because they did not reach IA staging. Combined with the analysis of imaging and pathological results, the patient was considered for the diagnosis of MPLC. The lesion stage was IIA (IASLC 8th edition) (20) and postoperative chemotherapy was indicated. The patient received four cycles of pemetrexed 700 mg combined with lobaplatin 45 mg adjuvant therapy (every

21 days) from November 2020 to March 2021. No adverse reactions were noted during this period.

Following chemotherapy, the patient still exhibited multiple high-risk nodules in the lungs in July 2021 (Fig. 6A-D) and the desired pulmonary nodule regression was not achieved. At this time, the pulmonary function retest values were as follows: FEV₁, 1.41 l; FEV₁%, 54.15%; FVC, 2.05 l; FVC%, 67.08%; and FEV₁/FVC, 68.97%. The patient exhibited no asthma in their daily life. High-risk residual lesions were recommended for treatment and both surgery and thermal ablation were considered options. However, the patient elected to undergo surgery. As a result, the patient underwent a second surgery in August 2021. Considering that excessive resection of lung tissue may lead

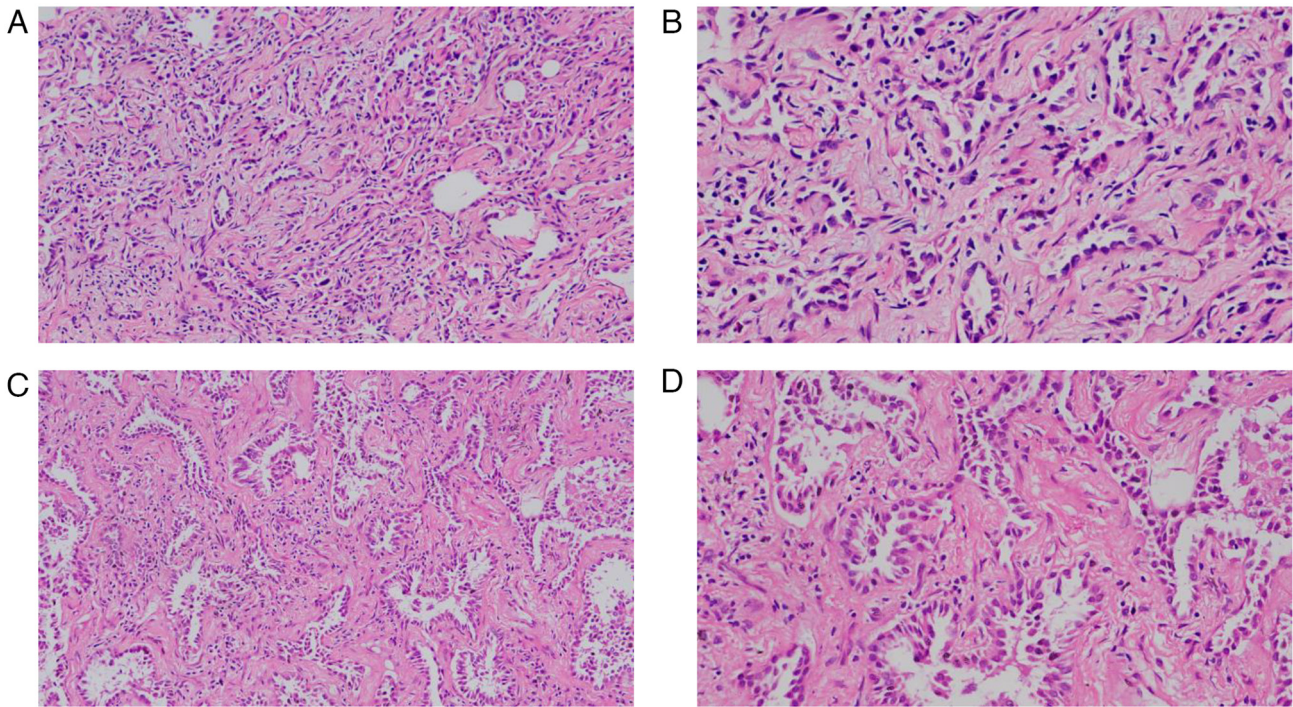


Figure 4. Pathology of the lung lesions. (A and B) Histological examination of the left upper lobe lesion 1 showed 100% papillary subtype adenocarcinoma (H&E). Magnifications, (A) x200 and (B) x400. (C and D) Histological examination of the right lower lung lesion 1 showed predominantly adherent type adenocarcinoma (H&E). Magnifications, (C) x200 and (D) x400.

to insufficient pulmonary functional reserve, wedge resection was performed on each lobe of the right lung.

The pathological results of the frozen sections indicated that the right upper lung (RUL) lesion 1, right middle lung lesions 1, 2 and right lower lung (RLL) lesion 1 were MIAs and that RLL lesion 2 was AIS. RUL lesions 2 and 3 were benign fibrous nodules. Postoperative routine pathological results indicated that RLL lesion 1 was IA (predominantly adherent type; T1bN0M0 IASLC 8th edition (20); Fig. 4C and D). The results of the other lesions were consistent with those of the frozen section pathology. Immunohistochemical analysis (Fig. 5L-P) of RLL lesion 1 indicated the following results: Napsin A (+), PD-L1 (tumor cells-, tissue cells+, >50%), Ki-67 (3%), carcinoembryonic antigen (-) and TTF-1 (+). Except for RLL lesion 1, the remaining lesions were not tested for PD-L1 because they did not reach IA stage.

To further analyze the relationship between the lesions, 425 gene-NGS detection was performed in the lesions derived from the two surgical resections of the patient. A pathologist confirmed that all samples contained $\geq 10\%$ tumor. The tissue was fixed with 10% formaldehyde, embedded in paraffin at 20°C for 24 h, and then sectioned. After dewaxing with xylene, genomic DNA was extracted. The genomic DNA was extracted using the QIAamp DNA FFPE Tissue Kit (Qiagen GmbH). DNA fragments library preparation was made using the KAPA hyper library preparation kit (KAPA Biosystems; Roche Diagnostics GmbH). The resulting libraries were sequenced using the Illumina HiSeq 4000 platform (Illumina, Inc.). Sequencing data were analyzed using a validated automated pipeline from Gene Biogene. The bioinformatics analysis platform from Nanjing Shihe Gene Biotechnology Co., Ltd. (<https://zh.geneseeq.com/220801144116.html>) was

used to identify genetic variants, perform variant annotation, variant screening and comprehensive analysis of variant information, including mutations, fusions, amplifications and deletions at 425 loci (21).

The results indicated that two different *KRAS* exon 2 mutations, p.G12D and p.G12C, were noted in the two IA lesions. The other lesion-mutated genes are shown in Table I; no significant common mutated genes were found. All lesions indicated low tumor mutation burden (TMB). NGS results showed no significant common mutated genes across the different lesions in this patient, which supports the diagnosis of MPLC.

Subsequently, low-risk pulmonary residual lesions were regularly reviewed every 6 months and were found to be stable with no progression (Fig. 6E-H). This case did not receive chemotherapy or radiotherapy after the second surgery. The patient remained in recovery without recurrence or progression until the latest follow-up in May 2025 (progression-free survival >56 months continuing). Currently, after the second surgery, the patient experiences mild breathlessness following physical activity, which is relieved by rest. However, their daily life has not been affected.

Discussion

At present, the diagnosis of MPLC has been primarily based on the diagnostic criteria of Martini-Melamed (22). In 2011, the International Association for the Study of Lung Cancer recommended a new classification of lung adenocarcinoma as a factor to be considered in identifying MPLC (23,24). Lung cancer was classified into AIS, MIA and IA. Subsequently, in 2013 the American College of Chest Physicians updated the diagnostic criteria of MPLC to improve the Martini

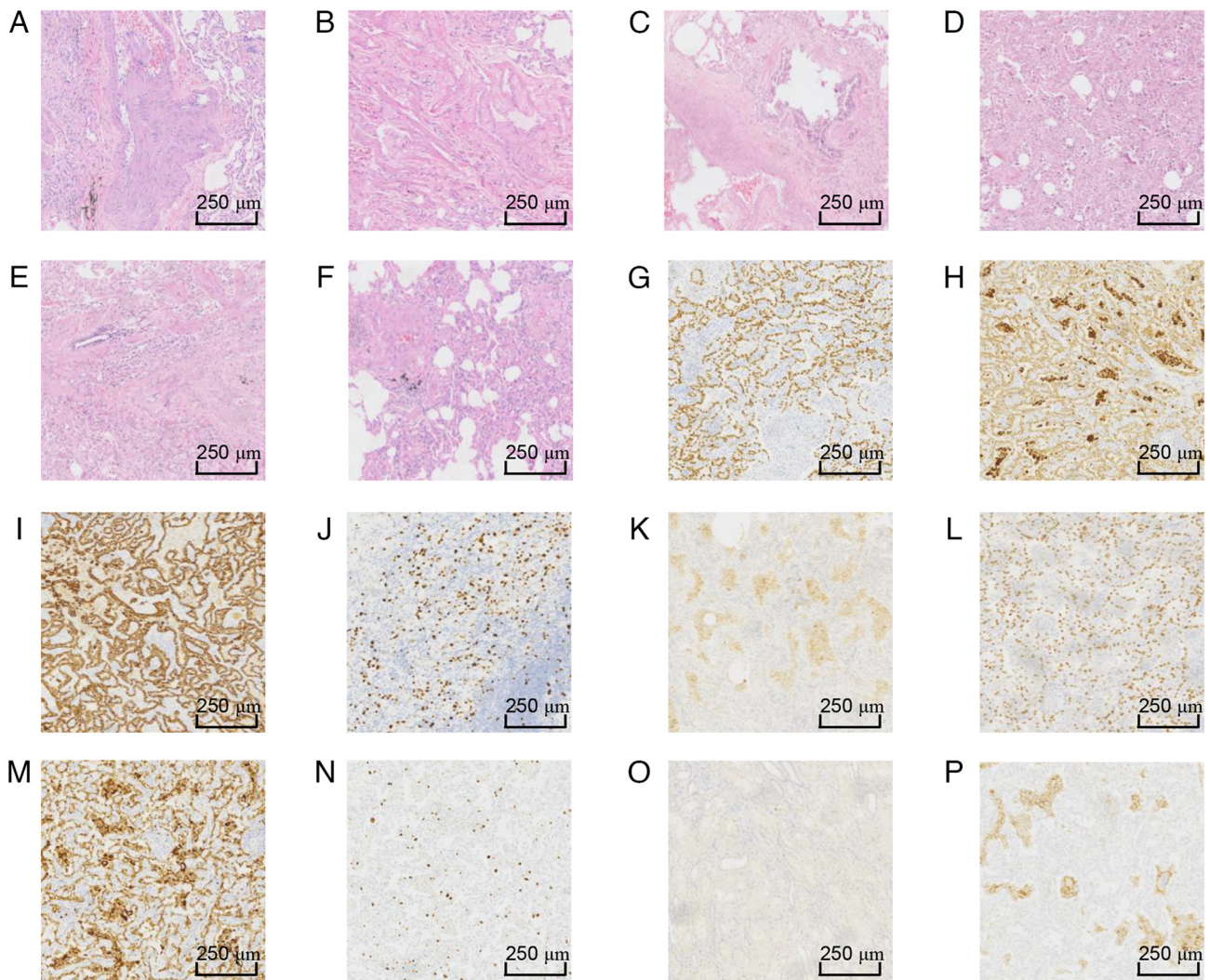


Figure 5. Pathological staining results for samples from both lobes. H&E staining for (A) LUL2, (B) LUL3, (C) LUL4, (D) LUL5 and (E) LUL6. Staining results indicated minimally invasive adenocarcinoma. (F) H&E staining of LUL7 showed adenocarcinoma *in situ*. (G) LUL1 immunohistochemical staining showed (G) TTF-1 (+), (H) Napsin A (+), (I) cytokeratin 7 (+), (J) Ki67 (10%) and (K) PD-L1 (tumor cells-, interstitial macrophages+, 50%). Right lower lung lesion 1 immunohistochemical staining showed (L) TTF-1 (+), (M) Napsin A (+), (N) Ki67 (3%), (O) carcinoembryonic antigen (-) and (P) PD-L1 (tumor cells-, tissue cells+, >50%). LUL, left upper lung; TTF-1, thyroid transcription factor 1; PD-L1, programmed death-ligand 1.

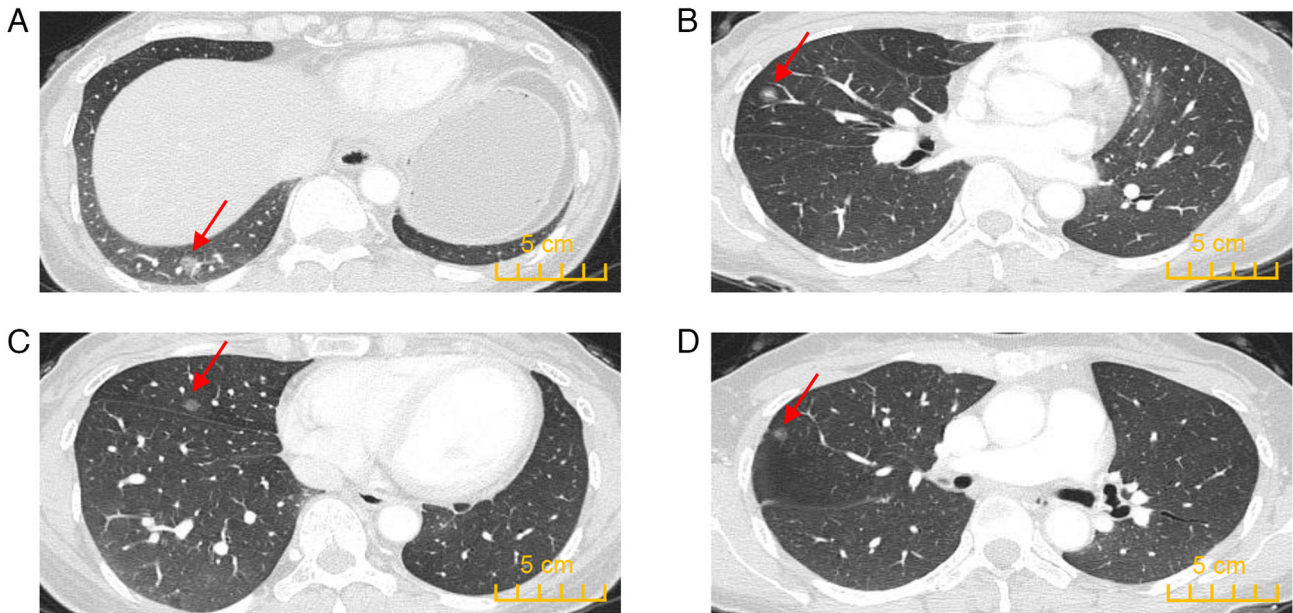
criteria (22) as follows: i) Same histological type, primary in different lung lobes; ii) lack of N2 and N3 lymph node metastases; iii) lack of systemic metastases; iv) different histological types; v) different genetic and molecular biological characteristics, AIS foci with different origins; vi) the same histological type; vii) different onset at the same time; and viii) a >4 year interval between the two onsets.

There has been considerable uncertainty in distinguishing between MPLC and IM (25). It is difficult to obtain all the lesion tissues for pathological examination and genetic testing in patients with multifocal bilateral lungs prior to surgery. Comprehensive imaging analysis is therefore key for the preoperative judgment of these two conditions. At present, the preoperative diagnosis and identification of MPLC mainly rely on chest CT (26). The majority of the cancer lesions in MPLC tend to exhibit the typical CT manifestations of primary lung cancer (27), such as marginal burrs, pleural traction, lobulation, vascular bundle sign, mixed density (such as ground glass or solid), enhancement, lack of lymph node metastasis and distant metastasis. In addition, it is typically difficult to

characterize the initial diagnosis and the follow-up observation of CT is also an essential means of differential diagnosis. Untreated primary lung cancer (following treatment of the main lesion) frequently develops slowly, whilst patients with metastases progress rapidly and the general condition of the patients is poor (28,29). Compared with these aforementioned observations, single or multiple lung metastases are mostly round and oval, generally have smooth edges and rarely have burrs and pleural traction signs (30,31).

CT imaging features provide the core value in the differential diagnosis of MPLC, whilst the metabolic parameters of PET-CT can provide supplementary evidence. Liu *et al* (32) previously demonstrated that the SUV_{max} among MPLC lesions was significantly different ($\Delta SUV \geq 3.0$), whilst the metabolic consistency of intrapulmonary metastatic lesions was high (sensitivity 78.9%). However, it should be noted that the low uptake characteristics of pure GGN may result in false negative results. Following combination of these two examinations, the study by Liu *et al* (32) suggested the diagnosis was biased towards MPLC. According to the recommendations of previous studies,

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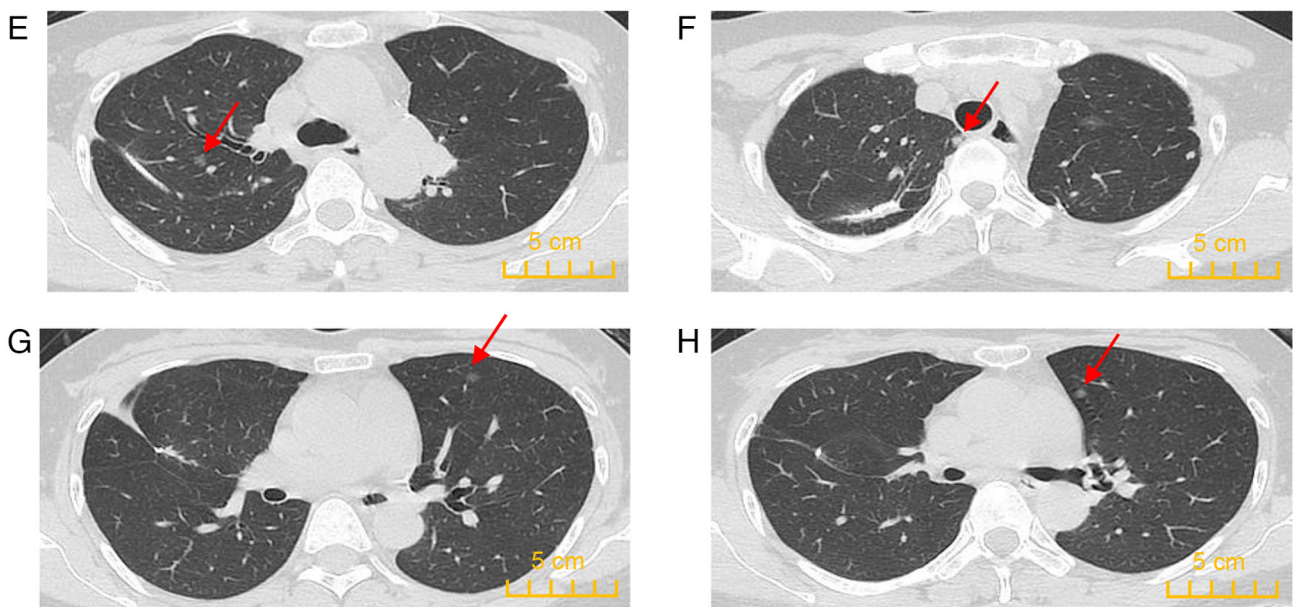


Figure 6. CT images after the two surgeries. (A-D) CT images after the first surgery in July 2021. High-risk residual lung nodules remained in the right lower and middle lungs. (E-H) CT images after the second surgery in May 2025. The residual lung nodules were stable small GGN stable and have not progressed.

MPLC is considered a localized pathology and should be treated with radical surgery, contributing to optimal outcomes (7,33). It should not be arbitrarily assessed as an advanced metastatic disease, which can deprive the patients from selecting surgery as a treatment method. Surgical treatment can confer optimal survival benefits to patients with MPLC.

At present, no unified standard exists for the surgical methods of MPLC and the selection of the methods currently used in clinical practice depends on various aspects. The two principles of surgery are to remove as much tumor as possible whilst preserving as much normal lung tissue as possible. Tie *et al* (34) proposed the application of anatomic resection when the lung reserve is sufficient, suggesting the following treatment methods: Lobectomy,

double lobectomy, pneumonectomy and lymph node dissection. When the patient lung function is limited, lobectomy and sublobar resection or sublobar resection alone can be performed. Among them, anatomical segmental resection is the first option for sublobar resection (35). The study by Yang *et al* (36) demonstrated the lack of significant differences in the 5-year survival between patients with MPLC who underwent bilateral lobectomy and lobectomy + sublobar resection. Therefore, it is suggested that bilateral MPLC can be treated with main lesion lobectomy combined with contralateral sublobar resection.

In patients with bilateral lung multiple tumors, single or delayed resection is safer compared with one-stage surgery (7). Accurate identification of MPLC and IM following surgery is

Table 1. Genomic alterations detected by NGS profiling of pulmonary resections from the present case^a.

Characteristics	LUL1	LUL2	LUL3	LUL4	LUL5	LLL	RLL1	RUL1	RUL3	RML1	RML2
Histology	IA	MIA	MIA	MIA	MIA	AIS	IA	MIA	Benign	MIA	MIA
TMB	4.2	1.1	0	4.2	0	0	1.1	3.2	0	2.1	2.1
<i>PD-L1</i> (tumor proportion score)	- (<1%)	/	/	/	/	/	- (<1%)	/	/	/	/
<i>KRAS</i> : Exon 2, p.G12D	+	-	-	-	+	-	-	-	-	-	-
<i>KRAS</i> : Exon 2, p.G12C	-	-	-	-	-	-	+	-	-	-	-
<i>ERBB2</i> : Exon 20, p.Y772_A775dup	-	-	-	-	-	-	-	-	+	-	+
<i>PRKCI</i> : Exon 3, p.L95Qfs*8	+	-	-	-	-	-	-	-	-	-	-
<i>MYC</i>	+	+	-	-	-	-	-	-	-	-	-
<i>TERT</i>	+	-	-	-	-	-	-	-	-	-	-
<i>NKX2-1</i>	-	+	-	+	-	-	-	-	-	-	-
<i>TERC</i>	-	+	-	-	-	-	-	-	-	-	-
<i>ARID1B</i>	-	-	+	-	-	-	-	-	-	-	-
<i>TSCI</i> : Exon 7, p.V172Wfs*38	-	-	-	-	-	+	-	-	-	-	-
<i>ZNF703</i> : Exon 2, p.G224S	-	-	-	-	-	-	-	+	-	-	-
<i>MAP2K1</i> : Exon 3, p.L98_I103del	-	-	-	-	-	-	-	+	-	-	-
<i>EXT2</i> : Exon 2, p.R94H	-	-	-	-	-	-	-	+	-	-	-
<i>MAP3K1</i> : Exon 5, p.R364W	-	-	-	-	-	-	-	-	+	-	-
<i>NFI</i> : Exon 14, p.Q514Rfs*43	-	-	-	-	-	-	-	-	-	+	-
<i>NFI</i> : Exon 16, p.W599Cfs*9	-	-	-	-	-	-	-	-	-	+	-
<i>RHOA</i> : Exon 2, p.G17A	-	-	-	-	-	-	-	-	-	-	+

^aSome lesions were not tested by NGS due to unqualified quality inspection. NGS, next-generation sequencing; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe. TMB, tumor mutation burden; AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; IA, invasive adenocarcinoma; PD-L1, programmed death-ligand 1; +, positive; -, negative; /, not tested.

essential, since it can affect disease staging, treatment decisions and patient outcomes. Ichinokawa *et al* (37) demonstrated that the third or subsequent surgery on the same individual was expected to increase the risk of surgical complications, such as prolonged operation time, increased bleeding and prolonged air leakage. In the present case, the patient exhibited >20 lesions in both lungs, prompting an individualized treatment plan. Pathological diagnosis and genetic testing of the tumor aided the further disease diagnosis, stage and identification of the follow-up treatment plan. In a study of 26 patients with MPLC, a multivariate analysis previously indicated that adjuvant chemotherapy positively improved patient survival (38). The present patient achieved optimal surgical results and high quality of life following undergoing second-stage surgery combined with chemotherapy where no tumor recurrence or progression was noted during the 56-month follow-up period.

Clinically, the differential diagnosis of MPLC and IM is complex. In addition to imaging examinations, the diagnosis should be combined with a comprehensive analysis of pathological and molecular biological features (39). With the development of molecular pathology, it was first proposed to use molecular genetics to diagnose multiple lung lesions of the same pathological type (40). A previous study has shown that sequencing of ~50 genes can be used as an indicator of multiple lung tumors containing different driver mutations. These tumors were characterized as MPLC, where in case only one driver mutation is common, the tumors would be characterized as IM (41). In cases with no clear histopathological distinction or similar histological subtypes, the consistency of genomic alteration profiles among multiple nodules would then provide additional insights into their clonal relationships and therefore guides the diagnosis of MPLC (42,43). A previous study has reported that metastatic lung lesions rarely exhibit discordant mutational patterns (44). Another study of 120 patients by Mansuet-Lupo *et al* (45) indicated that molecular typing could increase the sensitivity of the detection of MPLC compared with histopathological features and proposed an integrated tissue-molecular algorithm for MPLC. When multiple tumors share a frequent hotspot mutation (such as *EGFR* exon 19 deletions, *EGFR* p.L858R or *KRAS* p.G12X), histological algorithms can aid the confirmation of the diagnosis.

However, IM and MPLC are similar in genetic and immune characteristics, such that genomics alone may not be able to effectively distinguish IM from MPLC (46). Therefore, a comprehensive evaluation of the present case was conducted through imaging, pathological and genetic analyses. Han *et al* (47) indicated that all three nodules in an MPLC case expressed *RET* mutations. However, there was significant heterogeneity in the gene mutations (differences in the number of cellular mutations, substitution composition levels and clustering analysis of the three nodules). Thomas *et al* (48) further indicated that whole genome sequencing can be used to distinguish whether the nodules possess a definite origin. Saab *et al* (49) in another report documented that 65% patients with MPLC could be identified based on clinical manifestations, imaging and morphology. In addition, 94% of patients can be identified by combining patient morphological characteristics and genomics.

For unresected residual nodules, the current consensus recommends individualized monitoring based on their biological characteristics. A prospective study by Shimada *et al* (50) has

indicated that the progression rate of residual GGN following resection of the main lesion was only 8% (median follow-up, 58 months). The incidence of new lesions (23%) and the growth of residual lesions did not affect the patient overall survival [overall survival (OS); P=0.82]. This supports the rationale of the 'main lesion first' strategy. When the residual GGN is pure ground glass density and the diameter is <8 mm, then annual CT follow-up was recommended to be sufficient (51). By contrast, in case of a partially solid nodule or a solid component ≥ 6 mm, then review should be shortened to 6 months (52).

The indications for surgical resection of all lesions should be strictly limited to the following: i) Progression of residual GGN during follow-up (diameter increase >2 mm or new solid components); ii) lesions located in the 'advantageous site' for sublobar resection; and iii) patients with severe anxiety symptoms. For deep small nodules, thermal ablation can be used as an alternative. However, the 5-year local control rate of thermal ablation (42-55%) is still lower compared with that of surgical resection (80-94%) (53).

Regarding thermal ablation, several retrospective studies have demonstrated that for patients with high-risk stage I lung cancer who are not suitable for surgery, thermal ablation treatments, such as radiofrequency ablation and microwave ablation, can achieve a prognosis similar to that of lobectomy (53-55). Currently, the safety and efficacy of thermal ablation for subsolid nodules have been reported and preliminary results comparable to those of surgical resection have been achieved, with a 5-year OS and tumor-specific survival rates of ~95 and 100%, respectively (55-57). Thermal ablation has become one of the treatment options or a supplemental treatment to surgery for multiple ground-glass nodules in the lungs and a consensus has been reached (58,59). In the present case, the patient exhibited residual high-risk lesions in the right lung, which were at the edge of the lobe. When lung function was still acceptable, high-risk residual lesions were recommended for treatment, and both surgery and thermal ablation were options. However, the patient elected to undergo surgery.

NGS-driven comprehensive genomic analysis is reshaping the diagnostic standards for MPLC. Chang *et al* (60) previously reported that NGS could reduce the misdiagnosis rate of MPLC and IM by 22% compared with traditional histological evaluation techniques. Notably, the accuracy of identifying intrapulmonary metastases was improved by 44%. NGS can be used to accurately trace the origin of multiple primary lesions by detecting a number of driver gene mutations, such as *HER2* and chromosomal rearrangements (61). In the field of treatment, in addition to the thermal ablation, immunotherapy combined with radiotherapy has also shown potential. A phase II trial by Chang *et al* (62) indicated that PD-1 inhibitors combined with stereotactic radiotherapy increased the 4-year event-free survival rate of early non-small cell lung cancer to 77%, resulting to an increase of 24% compared with radiotherapy alone. However, targeted therapy is not without limitations. Cheng *et al* (63) reported that the response rate of EGFR-tyrosine kinase inhibitors to multiple GGN residual lesions was only 23.9%, mainly due to the heterogeneity of the mutation spectrum of each lesion (only 7.9% of secondary lesions carry the same driver mutation as the primary lesion).

To the best of our knowledge, the present case report presents the highest number of resections of multiple primary lung cancers (13 lesions) and the highest number of lung cancer

lesions (10 lesions) detected by NGS in a single patient. It was found that all lesions exhibited low TMB, which was consistent with the existing research data on multiple primary lung cancers (21,64). Among them, the LUL lesion 1 and the RLL lesion 1 were both IAs. However, their histological subtypes differed. In addition, *KRAS* gene exon 2 p.G12D mutation was detected in LUL lesion 1, whilst *KRAS* gene exon 2 p.G12C mutation was detected in RLL lesion 1. Combined with pathological results and genetic testing results, MPLC diagnosis was supported. The multiplexed nature of NGS technology results in high throughput and sensitivity, providing an effective complement to current diagnostic efforts. With the development of molecular diagnostic technology, the absorption of higher number of genes and molecular features will aid the development of a more objective basis for identifying MPLC and metastatic cancer, providing scientific and rational standardized diagnosis and treatment for patients with MPLC.

In conclusion, due to the development of novel technologies, the diagnosis and treatment of MPLC have developed rapidly. Using only imaging, pathology and genetic testing to diagnose multiple lung lesions can readily lead to the misdiagnosis of MPLC as IM, which may in turn result in the lack of surgical treatment for the patients. Broad-spectrum NGS can differentiate between MPLC and IM and serves a vital role in the diagnosis and subsequent treatment (identification of driver oncogenes) of MPLC. Integrating radiology, histopathology and integrated genomic features in clinical practice by a multidisciplinary team facilitates a more accurate diagnosis of MPLC, and is expected to become a trend in the differential diagnosis of MPLC in the future. Furthermore, an individualized treatment design is more beneficial to patients with MPLC containing a large number of lesions in both lungs. A case of the diagnosis and individualized treatment of MPLC was provided with ultra-multiple lesions in both lungs, which can be used as a reference for the diagnosis and treatment of similar patients.

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Availability of data and materials

The sequencing data generated in the present study can be found in the Genome Sequence Archive (GSA) database of the China National Center for Bioinformatics (<https://ngdc.cncb.ac.cn/gsa-human>) under accession number HRA003776. Further inquiries can be directed to the corresponding author. The individual name of this patient in the dataset is P24, and the individual accession number is HRI328653. After the application is reviewed by the GSA database, the genetic data of this patient can be downloaded. Unrestricted public access to the NGS data is not possible due to national legal requirements (Regulations on the Management of Human Genetic Resources of the People's Republic of China,

articles 7 and 28; https://www.most.gov.cn/xxgk/xinxi/fenlei/fdzdgnr/fgzc/flfg/201906/t20190612_147044.html). The other data generated in the present report may be requested from the corresponding author.

Authors' contributions

GZ and ZL conceived the study. WW and BD extracted and organized the original data. GZ and YZ wrote the main part of the original manuscript. WW and CC developed the treatment plan and wrote a literature review of the progress in the discussion section. YZ analyzed and interpreted the patient's imaging results, BD and ZL interpreted the patient's pathology results. GZ and ZL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present report was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Guangdong Medical University (approval no. YJLW2022007; Zhanjiang, China).

Patient consent for publication

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in the present case report.

Competing interests

The authors declare that they have no competing interests.

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