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RECEIVED 28 February 2024

ACCEPTED 13 August 2024

PUBLISHED 01 October 2024

CITATION

Dong H, Tian Y, Xin S, Jiang S, Guo Y, Wan Z
and Han Y (2024) Diagnosis and management
of multiple primary lung cancer.
Front. Oncol. 14:1392969.
doi: 10.3389/fonc.2024.1392969

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Diagnosis and management of multiple primary lung cancer

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Multiple primary lung cancer (MPLC), can be categorized as synchronous multiple primary lung cancer (sMPLC) and metachronous multiple primary lung cancer (mMPLC), which are becoming increasingly common in clinical practice. A precise differential diagnosis between MPLC and intrapulmonary metastases (IPM) is essential for determining the appropriate management strategy. MPLC is primarily diagnosed through histology, imaging, and molecular methods. Imaging serves as an essential foundation for preoperative diagnosis, while histology is a critical tool for establishing a definitive diagnosis. As molecular biology advances, the diagnosis of MPLC has stepped into the era of molecular precision. Surgery is the preferred treatment approach, with stereotactic radiotherapy and ablation being viable options for unresectable lesions. Targeted therapy and immunotherapy can be considered for specific patients. A multidisciplinary team approach to evaluation and the application of combination therapy can benefit more patients. Looking ahead, the development of more authoritative guidelines will be instrumental in streamlining the diagnosis and management of MPLC.

KEYWORDS

multiple primary lung cancer, diagnosis, management, surgery, histology

1 Introduction

Multiple primary lung cancer (MPLC) refers to the presence of multiple primary lung cancer lesions in the lung, which can be classified as synchronous multiple primary lung cancer (sMPLC) and metachronous multiple primary lung cancer (mMPLC) according to the time of lesion occurrence. In recent years, with the widespread use of low-dose computed tomography (LDCT), an increasing number of MPLCs have been diagnosed, attracting the attention of clinicians. The differentiation between MPLC and intrapulmonary metastasis (IPM) is particularly important, as different diagnoses imply completely different stages and treatment plans. However, the complexity and uncertainty of the onset of MPLC make its diagnosis and management a problem that troubles clinical doctors.

Diagnostic criteria for MPLC is updated over time. Martini and Melamed (M-M) (1) established the earliest histologic diagnostic criteria in 1975, which laid the foundation for the diagnosis of MPLC (2, 3). Up to now, several organizations have published their own diagnostic criteria (2, 3). However, there is still a lack of universal and authoritative diagnostic criteria for standardized clinical practice. With rapid development in the field of molecular biology research, the diagnosis of MPLC has also entered the era of molecular diagnosis. Therefore, the diagnosis of MPLC is in dire need of an authoritative update.

According to the latest NCCN guidelines (version 5.2024), the treatment of MPLC should be customized by a multidisciplinary team, including thoracic radiology, pulmonary medicine, thoracic surgery, medical oncology, and radiation oncology. Surgery is the mainstay of MPLC treatment and the choice of surgical modality often confuses clinicians. Whether to perform simultaneous resections of multiple foci or multiple surgical resections, and whether to operate on *de novo* foci, etc. Stereotactic body radiation therapy and image guided thermal ablation are currently the treatment for inoperable MPLC, with favorable outcomes. The use of targeted therapy and immunotherapy in patients with MPLC is still in the exploratory stage, and long-term prognostic information is not yet available. Treatment options for MPLC still need to be further standardized.

In this review, we will focus on advances in the diagnosis and management of MPLC to provide a strong reference for the clinical diagnosis and management of MPLC.

2 Diagnosis

2.1 Histopathological diagnosis

2.1.1 1975 M-M

In 1975, Martini and Melamed (1) first proposed histological diagnostic criteria for MPLC based on information from 50 patients with multiple primary lung cancer. M-M is the first proposed diagnostic standard for MPLC and is therefore widely cited. However, its establishment mainly relied on the diagnostic

Abbreviations: MPLC, multiple primary lung cancer; sMPLC, synchronous multiple primary lung cancer; mMPLC, metachronous multiple primary lung cancer; LDCT, low-dose computed tomography; IPM, intrapulmonary metastasis; M-M, Martini and Melamed; ACCP, American College of Chest Physicians; AJCC, American Joint Committee on Cancer; GGO, ground glass opacity; CHA, comprehensive histological assessment; SPLC, second primary lung cancer; GG/L ground glass/lepidic; GGN ground-glass node; PSN, part solid node; CI, confidence interval; PET/CT, positron emission tomography/computed tomography; SUV, standardized uptake value; SNP, single nucleotide polymorphisms; MSI, microsatellite instability; CNV, copy number variations; LOH, loss of heterozygosity; NGS, next-generation sequencing; aCGH, array comparative genomic hybridization; WGS, whole genome sequencing; WES, whole exon sequencing; MPR, multiple pulmonary resection; SBRT, Stereotactic body radiation therapy; NSCLC, non-small cell lung cancer; IGTA, Image guided thermal ablation; PD-L1, programmed cell death-ligand 1; PD-1, programmed cell death-1; ICI, Immune checkpoint inhibitor.

experience of clinicians at that time, which was a relatively rough diagnostic criterion. Subsequent research (6) found that the M-M standard has significant limitations in identifying IPM and has a poor ability to distinguish prognosis (7).

2.1.2 2007/2013 ACCP guidelines

The 2nd clinical practice guidelines released by the ACCP in 2007 proposed new diagnostic criteria for MPLC, stating that the diagnostic interval for mMPLC should be ≥ 4 years (3). The ACCP guidelines indicate that a time interval of less than 2 years is more likely to be associated with pulmonary metastasis, and the incidence of new primary tumors and pulmonary metastasis within 2-4 years is equivalent. When the time interval is ≥ 4 years or more, the lesion should be considered a primary tumor. The 3rd edition published in 2013 (8) followed the content of the 2nd edition without significant differences. A meta-analysis reviewing 22 studies between 1975 and 2013 found that the median tumor-free interval of mMPLC (n=883) was 24-71 m. It is evident that there is uncertainty in the timing of the second primary lung cancer (SPLC) in mMPLC. A rigid time standard poses the risk of missed diagnosis and misdiagnosis.

2.1.3 2017 AJCC

The 8th TNM staging published by AJCC in 2017 proposed the use of comprehensive histological assessment (CHA) to distinguish sMPLC from IPM (9), and a separate staging was performed for MPLC (2). CHA distinguishes between multiple primary and intrapulmonary metastases by sequentially comparing the histologic types, tissue subtypes, and cytologic and mesenchymal features and has shown good diagnostic performance among pathological experts; the consistency with molecular evaluation results can reach 91% (10). However, CHA is based on a limited number of cancer patients and is not the so-called gold standard. Studies (11–16) have shown that the histologic diagnosis is unclear in approximately 15–29.8% of patients, especially IPM, which is prone to misdiagnosis.

There is other pathologic feature can predict prognosis of MPLC patients. A recent retrospective study showed that spread through air spaces (STAS) has an impact on the postoperative recurrence-free survival of patients with MPLC. STAS (+) had a significantly higher recurrence rate than STAS (-) (34% vs. 0%, $p < 0.05$) (17).

As of today, there are no recognized diagnostic criteria for MPLC. Histology is the gold standard for cancer diagnosis, but there is still a risk of misdiagnosis for some MPLC. Discovery of new pathologic features associated with MPLC is needed to clarify the pathologic diagnosis and prognosis of MPLC.

2.2 Molecular diagnosis

With the rapid development of molecular biology research and the continuous upgrading and iteration of sequencing technology, the diagnosis of MPLC has moved into the era of molecular diagnosis. Researchers began to test genetic features to explain whether there is a clonal relationship between multiple lesions. The ACCP 2nd guidelines first proposed the inclusion of molecular genetic features

in the diagnostic criteria in 2007 (3). It is generally believed that the primary and metastatic lesions originate from the same clone, so there are shared molecular features between the two, while there is no significant correlation between multiple primary lesions. Subsequent studies have confirmed that different primary lesions in the same patient have different genomic characteristics (18) and a 96% concordance between driving mutations in primary and metastatic lesions (11). Despite heterogeneity within tumors, approximately 70–76% of mutations are shared across all sites, and a single biopsy analysis at an appropriate depth may be sufficient to identify most known cancer-related gene mutations in lung cancer (19, 20).

In previous studies, scholars have attempted to distinguish MPLC and IPM by detecting single nucleotide polymorphisms (SNPs), microsatellite instability (MSI) (21, 22), cancer-related gene mutations (6, 7, 11–16, 18, 23–36), copy number variations (CNVs) (18, 24, 29, 37) loss of heterozygosity (LOH) (38), chromosomal rearrangements (13, 18, 29, 39, 40), and chromosomal inactivation.

2.2.1 Cancer-related gene mutation detection

Researchers first began to detect mutations in the oncogene P53 in tumor tissue from lung cancer patients with two lesions (27, 28), which occurred before metastasis and were conserved during metastasis. Most (95–98%) are found in exons 5–9. P53 mutations were detected in approximately 35% to 56% of participants, and there were three mutation patterns: A) mutations in only one tumor, B) different P53 mutations in two tumors, and C) the same P53 mutation in two tumors. The first two mutation patterns are considered MPLC, and the last one is IPM.

In addition, more studies began to detect multiple cancer gene mutations in lesions for molecular diagnosis (Table 1). In the study by Asmar et al., 45 patients with primary tumors and metastases (cohort 1) and 69 patients with multiple tumors (cohort 2, 154 tumors) were included, and their samples were tested for *EGFR*, *KRAS*, *ALK*, and *BRAF* gene mutations (11). Sharing driver mutations between multiple tumors was considered metastasis and multiple primary tumors if different driver mutations were present. The results showed a 96% compliance rate of driver gene mutations between primary tumors and metastases in cohort 1 and a 29.8% discordance rate between molecular and histological diagnoses in cohort 2. Zheng et al. showed that a 4-gene (*EGFR*, *KRAS*, *BRAF*, and *NRAS*) next-generation sequencing (NGS) panel better differentiated MPLC and IPM, while conventional histology misdiagnosed 4 groups of lesions (4/18, 22.2%) (16). Goodwin et al. examined mutations in more than 50 genes (*ALK*, *BRAF*, *EGFR*, *KRAS*, *MET*, *TP53*, etc.) in patients with double primary lung cancer (n=40), which resulted in a match with the clinicopathological diagnosis in 82.5% (33/40) of patients (13). In the study by Mansuet-Lupo, mutations in 22 genes (*KRAS*, *EGFR*, *BRAF*, *TP53*, etc.) were examined in patients with multiple lung adenocarcinomas (n=120), and the results showed that mutations were detected in 91% of the patients (14). Twenty-seven percent of cases (30/109) were inconsistent with the histologic diagnosis. In addition, 341–468 genes and somatic mutations and structural

variants were detected in patients with multiple lung cancers using (MSK-IMPACT) NGS in Chang's study (12). Zhanget al. used the NGS panel to detect 425 tumor-related genes and found that approximately 15–17% of cases did not match the results of the CHA (15). At present, there are no results on the optimal number of genes to be detected, and some studies suggest that a panel needs at least 100 genes to confirm the cloning relationship of 95% of adenocarcinoma (41). Of note, if multiple lesions share only one hotspot mutation, such as *EGFR* p.L858R (which occurs in approximately 40% of Asian lung adenocarcinoma patients (42)), the presence of other shared somatic mutations should be cautiously reviewed to determine the clonal relationship between multiple tumors (12, 18).

The NGS platform has been widely used in the clinical diagnosis of MPLC in recent years (6, 12–16, 32, 34, 35). One study (13) found that compared to traditional histology (M-M), NGS may be a more accurate diagnostic and prognostic tool. Several studies (12, 14, 15) have compared the diagnostic efficacy of NGS and CHA and have shown that comprehensive NGS can clearly differentiate clonal relationships between different lesions compared to standard histopathologic methods, which are adequate in most cases but have considerable limitations in identifying IPM. The limitations of NGS itself mainly lie in the implementation cost and the need for personnel in bioinformatics, data analysis, and other fields, and it requires a longer time than pathological examinations. The diagnosis of histological evaluation remains necessary until NGS results are available. Comprehensive NGS can be used as complementary information to histology to achieve a robust identification of MPLC. Therefore, researchers have proposed new algorithms that integrate histologic and molecular approaches to diagnosis, which can substantially improve the discrimination ability for MPLC and IPM, saved about 15.5–22% of MPLC from being misdiagnosed (12, 14, 15).

2.2.2 Chromosome variation

Array comparative genomic hybridization (aCGH) can identify genomic copy number variations. The study (24) showed that two tumors in one patient had deletions and amplifications of chromosome arms at the same location, and closely matched allelic changes were found on eight separate chromosome arms, resulting in a diagnosis of IPM. The study released by the Mayo Clinic in 2014 detecting chromosomal rearrangements in multiple tumors using NGS showed shared chromosomal rearrangement events between primary tumors and metastases, while no shared breakpoints were found between different tumors (40). In the study published in 2019 (29), using mate pair sequencing (MPseq) NGS to detect somatic mutations, chromosome copy number variants, and chromosomal rearrangements in tumor samples from patients with multiple lung cancers, the results showed that there were a large number of shared chromosomal rearrangements and somatic mutations as well as overlapping chromosome copy number variants in both tumors from patients with IPM, with no associated chromosomal variants between primary tumors and a large number of unique somatic mutations in each.

TABLE 1 Applications of NGS in diagnosis of MPLC.

First author, time	Patients	Histopathologic approach	Molecular methods	Mutations	Results	Conclusions
Chang, 2019 (12)	patients with >1 surgically resected tumor (n=60), 70 tumor pairs	CHA	(MSK-IMPACT) NGS	341–468 genes, somatic mutations, structural variants	Histologic prediction was discordant with NGS in 17 cases (22%), particularly in the prediction of IPMs (44% discordant).	Comprehensive NGS allows unambiguous delineation of clonal relationship among NSCLCs. Standard histopathologic approach has notable limitations in the recognition of IPMs.
Mansuet-Lupo, 2019 (14)	Multiple primary adenocarcinomas (n=120)	CHA	NGS	22 genes (KRAS, EGFR, BRAF, PIK3CA, AKT/ AKT1, ERBB2, PTEN, NRAS, TK11, MAP2K1, ALK, DDR2, CTNNB1, MET, TP53, SMAD4, FBXW7, FGFR3, NOTCH1, ERBB4, FGFR1, FGFR2)	Molecular mutations in 91% of tumor pairs (109 of 120), 27% discordant cases (30 of 109).	Combined histomolecular algorithm represents a relevant tool to classify multifocal lung cancers, which could guide adjuvant treatment decisions.
Goodwin, 2021 (13)	Two primary cancers (n=40)	M-M	NGS	Over 50 genes: ALK, BRAF, EGFR, FGFR1, KIT, KRAS, MET, NRAS, PIK3CA, PTEN, RET, and TP53, and rearrangements	33 of the 40 cases concordance with clinicopathologic diagnosis (82.5%).	Gene sequencing technologies are potentially a more accurate diagnostic and prognostic tool compared with traditional histopathologic evaluation in patients with MPLC.
Zheng, 2019 (16)	Multifocal NSCLC(n=18), 41 tumors	IASLC subtypes	NGS	4 genes (EGFR, KRAS, NRAS, and BRAF)	Eight synchronous primary lung cancers (8/18, 44%) were downstaged when compared with their original diagnosis.	Using a 4-gene NGS panel allows for better distinction between sMPLC and IPM than histopathology alone.
Zhang, 2022 (15)	45 pN0M0 MLA patients	CHA	NGS	425 cancer-relevant genes	14 IPM lesion pairs were diagnosed in the study group, with at least 7 misdiagnoses.	Developed an NGS-based algorithm that could accurately distinguish IPMs from MPLAs in MLA patients.
Pei, 2021 (6)	30 MPLC	M-M	NGS	EGFR, TP53, RBM10, ERBB2, CDKN2A	The prospective Martini histologic prediction of MPLC was discordant with the molecular method for three patients (16.7%), particularly in the prediction of IPM (91.7% discordant).	Comprehensive molecular evaluation allows the unambiguous delineation of clonal relationships among tumors. The Martini and Melamed criteria have notable limitations in the recognition of IPM.

MPLC, multiple primary lung cancer; CHA, comprehensive histologic assessment; NGS, next-generation sequencing; IPM, intrapulmonary metastasis; NSCLC, non-small cell lung cancer; M-M, Martini and Melamed; IASLC, The International Association for the Study of Lung Cancer; MLA, multifocal lung adenocarcinoma; MPLA, multiple primary lung adenocarcinomas.

2.2.3 Whole genome sequencing/whole exon sequencing

WGS/WES can help researchers obtain comprehensive genomic information in different tumors and thus perform finer tumor clonal relationship analysis and evolutionary studies. Liu et al. conducted WES/WGS and microarray-based CGH on multiple lesions (15 adenocarcinoma specimens and 1 metastatic lymph node) in 6 patients with synchronous multiple lung cancer (18). The results showed that different tumors from the same patient had different genomic features, including somatic mutations, copy number mutations, and chromosomal structural variations. Approximately 26% of the mutations were shared between the primary lesions and the metastatic lymph nodes. In addition, the investigators discovered

that the same cancer gene showed different mutations in different tumors of one patient (KRAS mutation in P1: T1 p.G12A, T3 p.G12V; EGFR mutation in P4: T1 p.L858R, T2 p.S229C). Maet al. conducted WES sequencing on multiple tumor samples from four treated patients with multifocal lung cancer, and all tumors were confirmed to be primary tumors by constructing a phylogenetic tree (43). They found biological convergence of heterogeneous driving events on the same signaling pathway between different foci in the same patient, suggesting that the evolutionary trajectories of independent tumors in sMPLC may converge, leading to preferential activation of restricted key oncogenic pathways.

Additionally, in various studies, scholars have attempted to use WES to distinguish genomic heterogeneity and clonal relationships

in multiple tumors or multiple GGNs, and only Corsini's study obtained significant results (44). Yang et al. failed to better distinguish between IPM and MPLC in their study (45), and Zhou failed to determine the genetic characteristics and clonal relationships of most multiple GGNs (46). Tian et al. tested samples of MPLC with lymph node metastasis (LNM) and found that the genes with the highest mutation frequencies in this pair were MUC16, FLNA, MUC4, FAT3, SETD2, and CALR, which implied that MPLC with LNM may have a unique mutation spectrum (47).

2.2.4 Others

Yu's study compared differences in genetic, epigenetic, and immunological landscapes between isolated lung cancer and sMPLC (48). The results showed that sMPLC lesions had relatively lower TMB levels than isolated lung cancer, indicating caution when applying immunotherapy to sMPLC patients. Moreover, DNA methylation patterns and associated immune profiles were significantly different between sMPLC and isolated lung cancer, suggesting that they play an important role in the initiation and development of sMPLC. Research showed that MPLC and IPM could be better differentiated according to the differential rates of expression of cancer-associated proteins (p53, p16, p27, and c-erbB2) in the lesions (7). Two groups of patients with MPLC and LNM were included in the study for comparison, and the analysis showed that when the total protein expression difference rate was high, it was MPLC, and when the protein expression difference rate was low, it was IPM. Patients categorized in this way showed a significant difference in the 5-year survival rate.

In conclusion, molecular analysis provides new ideas and methods for the fine diagnosis of MPLC patients. Currently, the most widely used method in clinical practice is large-scale cancer-related gene detection based on NGS panels. Researches on the immune landscape, DNA methylation, and WGS have broad prospects and is still in full swing. It is worth noting that molecular analysis should be used as a supplement to clinical and pathological diagnosis.

2.3 Imaging diagnosis

2.3.1 Chest CT

In the 8th TNM staging (2), multifocal lung cancer is classified into four types: SPLC, separate tumor node (IPM), multifocal ground glass/lepidic (GG/L) nodes, and pneumonic type of adenocarcinoma. SPLC and multifocal GG/L nodes can be considered sMPLC, which are characterized by "two or more distinct masses with imaging characteristics of lung cancer (e.g., spiculated)" and "multiple ground-glass or part-solid nodules." Currently, patients with multiple lung adenocarcinomas are commonly seen in clinical practice. In multiple studies (49, 50), multiple lung adenocarcinoma was categorized into 3-4 types according to the proportion of solid and GGO components, such as pure ground-glass node (GGN), GGO-predominant part solid node (PSN), solid-predominant PSN, and pure solid node. Zhang et al. identified multiple solid tumors as an independent risk factor

for reduced RFS [hazard ratio (HR) 2.941; 95% confidence interval (CI) 1.07-8.08; $P = 0.036$] and poor OS (HR 6.13; 95% CI 1.15-32.63; $P = 0.034$) in patients with multiple lung adenocarcinomas (50). In addition, CT imaging manifestations can assist in distinguishing pathologic subtypes (51), and patients presenting with GGO or mixed GGO are more likely to have EGFR mutations (52). In conclusion, the CT manifestations of SPLC and multiple GGOs or partial solid nodules are referred to as MPLC, and multiple solid tumors are more prone to have advanced disease, which should be diagnosed with caution.

2.3.2 PET-CT

¹⁸F-Fluoro-D-glucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) plays an important role in the diagnosis of MPLC and has good diagnostic efficacy in monitoring patients with non-small cell lung cancer for post-treatment recurrence or the development of second primary cancers (53). The most commonly used semiquantitative parameter indicator in PET/CT imaging is the standardized uptake value (SUV), which refers to the ratio of the activity of a unit volume of tissue uptake of a contrast medium to the average activity of the whole-body tissue. The maximum SUV (SUV_{max}) is most used technique because of its better repeatability and is generally applied to identify benign and malignant tumors. Liu's (54) research shows that there is a significant difference in the ratio of SUV_{max} between different lesions in sMPLC and IPM, which can be used to distinguish sMPLC and IPM. The Lv study proposed the use of the dynamic ¹⁸F-FDG PET/CT acquisition mode and Patlak model to fit K_i , representing the ¹⁸F-FDG net uptake rate constant, as well as the corresponding maximum diameter (D_{max}) of the two largest tumors (55). By determining the absolute difference between SUV_{max}/D_{max} and K_i/D_{max} tumors ($\Delta SUV_{max}/D_{max}$; $\Delta K_i/D_{max}$), it was found that there was no significant difference in $\Delta SUV_{max}/D_{max}$ between the IPM group and the sMPLC group, while $\Delta K_i/D_{max}$ in the IPM group was significantly higher than that in the sMPLC group.

In addition, Suh et al. combined CT imaging features with PET/CT and designed a four-step algorithm: CT lesion types (Step 1), CT lesion morphology (Step 2), difference in maximal standardized uptake values on PET/CT (Step 3), and presence of N2/3 lymph node metastasis or distant metastasis (Step 4) (56). The results showed significantly higher specificity and positive predictive value for the diagnosis of IPM in all observers compared to without using the algorithm. Combining comprehensive imaging information is more helpful in improving the accuracy of diagnosing MPLC.

Overall, imaging diagnosis is particularly important for clinicians, especially thoracic surgeons for determining the surgeon's judgment of surgical strategy. Multiple GGOs or partial solid nodules are often MPLC, while multiple solid nodules are difficult to make a clear diagnosis. Cases that are difficult to diagnose definitively can be defined by combining PET-CT and CT, supplemented by other clinical information.

Unlike previous disease diagnoses, the diagnosis of MPLC is more of a "spot the difference," where multiple lesions are compared for similarities to determine whether they are primary

or metastatic. Comparative methods include histology, imaging, molecular biology, etc. Imaging diagnosis is the key first-hand information but does not directly confirm the diagnosis as a preoperative diagnosis. Standard histopathological diagnosis is sufficient in most cases but has obvious limitations in identifying IPM and can only be determined after surgical resection, which should serve as a supplement to clinical information. Molecular biology provides a new direction for the fine diagnosis of MPLC, and its limitations mainly lie in the implementation cost and the need for personnel, such as specialists in bioinformatics and data analysis. It takes a longer time than pathologic examination. Therefore, diagnosis by histologic evaluation remains necessary until molecular diagnostic results are available. The guidelines emphasize that ideally, a multidisciplinary diagnosis should be made by combining all available information, including histopathology, imaging, molecular, and clinical features (9).

Throughout the development of diagnostic criteria for MPLC, the diagnosis of MPLC has become increasingly accurate, from the beginning of the process, which was based on the experience of clinicians only, to the idea of comprehensive diagnosis proposed in the current guidelines. Currently, there is no “one-size-fits-all” diagnostic gold standard that can be applied to all MPLC patients, so we should synthesize all the information that can be collected during the diagnostic process rather than using a single criterion to define MPLC patients.

3 Management

The management of MPLC mainly includes surgery, radiotherapy, and ablation, with targeted therapy and immunotherapy limited to specific patients (57–59). The quantity, location, and size of lesions in MPLC can affect the decision of its management. The NCCN guidelines state that a comprehensive multidisciplinary evaluation should be conducted, including thoracic radiology, pulmonary medicine, thoracic surgery, oncology, and radiation oncology. When the lesion is stable or grows very slowly, regular LDCT follow-up can be performed. If there is evidence of growth in the major nodule, surgery, radiotherapy or image-guided thermal ablation (IGTA) may be an option when there is a possibility of local radical treatment. If there is no possibility of local cure, the disease is treated as recurrent and metastatic.

3.1 Surgical treatment

Surgery is currently the treatment of choice for MPLC (60). The ACCP 3rd guideline (8) recommends a multidisciplinary evaluation of patients with MPLC to exclude mediastinal and systemic metastases and to resect as many lesions as possible if the patient’s lung function permits. PET or PET-CT scanning is recommended for staging and to detect unsuspected metastatic disease (61). In case of CT-enlarged or PET-positive mediastinal lymph nodes require tissue confirmation, tissue confirmation is indicated. Endosonography [endobronchial ultrasonography (EBUS)/esophageal ultrasonography (EUS)] with fine-needle

aspiration (FNA) is the first choice (when available). If negative, surgical staging will be performed (62). The NCCN guidelines (version 3.2023) recommend that anatomic pneumonectomy with parenchymal preservation is preferred in most patients undergoing surgery, especially in patients with insufficient lung function or other comorbidities that preclude lobectomy.

Researchers in many previous studies (60, 63–70) have discussed the choice between lobectomy and sublobar resection for the extent of surgical resection, with conflicting conclusions (Table 2). The reasons for the differences in these research conclusions may be due to differences in diagnostic criteria, characteristics of the included patients, and sample size, all of which were derived from retrospective studies. In Yang’s study, propensity score matching was utilized to reduce the potential bias caused by differences in the clinicopathological characteristics of first and second lung cancers, and the results showed that for tumors up to 2 cm in diameter, the prognosis of sublobar resection was comparable to that of lobectomy, and the survival rate of patients who underwent lobectomy for tumors between 2–3 cm was significantly higher than that of patients who underwent sublobar resection ($P < 0.014$) (71). In Niu’s study, patients with sMPLC were divided into sublobar resection and lobectomy groups and compared with single primary lung cancer. The results showed that there was no significant difference in 5-year OS (86.7% vs. 83.9%, $P=0.482$) and DFS (86.7% vs. 83.9%, $P=0.482$) between the lobectomy and sublobar resection groups, and that the sublobar resection group had a lower postoperative complication incidence and shorter postoperative hospitalization (72).

For patients with bMPLC, it is necessary to consider performing one-stage or two-stage operations. In Xu’s study, patients with bMPLC were divided into one-stage group and two-stage group, resulting in shorter operative time, surgical bleeding, pleural drainage, chest tube duration, and postoperative admission duration in the stage 1 group ($P < 0.05$) (73). It can be seen that in patients with bMPLC, simultaneous surgery may have better results when the patient’s cardiopulmonary function permits. In addition, many studies (64, 74–77) believe that surgical intervention for second primary lung cancer is effective. Hamaji’s study included patients with mMPLC who underwent secondary surgery after complete resection (78). The results showed that the 5-year OS rates after the first and second surgery were 87.4% and 60.8%, respectively. Both univariate and multivariate analyses showed that a lower-than-expected percentage of FEV1 and an ipsilateral secondary surgery were associated with an increased risk of postoperative complications. Kang’s study reviewed patients with sMPLC and mMPLC who received multiple pulmonary resection (MPR) and showed that the 5-year disease-free survival rate in the metachronous group was 85.4%, while it was 69.1% in the synchronous group; the 5-year overall survival rates were 86.1% and 84.8%, respectively, indicating that MPR is feasible for MPLC patients (64). Fourdrain et al. proposed that for mMPLC and bilateral sMPLC, long-term survival after secondary surgery is acceptable (3-year survival was 77%), and minimally invasive sublobar resection should be applied as much as possible (75).

Hattori et al. found that the presence of a GGO component in MPLC could differentiate survival, with a significant difference in 5-

TABLE 2 Surgical treatment of multiple primary lung cancer.

First author, year	Research time	s/mMPLC	Surgical resection(n)					Results			Conclusions
			W/S	L	L+L	P	P/L+W/S	Lobectomy	sublobar	P value	
Xiao, 2017 (67)	2004-2015	52 sMPLC	18	5	4	5	20	Median survival time (month) 38	Median survival time (month) 60	0.01	Limited resection might improve the prognosis for patients with a tolerable general condition and pulmonary function.
Yang, 2016 (68)	2001-2014	101 BMPLC(71 sMPLC +30 mMPLC)	13	-	39	-	49	5-year OS (mean, months) lobar-lobar 70.6%	5-year OS (mean, months) lobar-sublobar 56.7%, sublobar-sublobar 36.8%	-	The use of a limited resection procedure for the contralateral second nodule in cases with stage I BMPLC did not have a negative effect on the 5-year overall survival.
Ishikawa, 2014 (63)	1995-2009	93 sMPLC	27	28	10	1	27	5-year OS 92.5%	5-year OS segmentectomy 82.1%, wedge resection 80.4%	0.5086	Lobectomy has a high cure rate and should be performed whenever possible. Sublobar resection should be considered for patients likely to have poor residual lung function postoperatively.
Yu, 2013 (69)	2001-2011	97 sMPLC	14	39	8	0	36	5-year PFS:62.4%; 5-year OS:79.7%	5-year PFS:42.9%; 5-year OS: 64.7%	$P_{PFS} = 0.312$, $P_{OS} = 0.331$	No superior survival outcome among patients who underwent lobectomies compared to sublobar resections.
Zuin, 2013 (70)	1995-2010	23 sMPLC + 98 mMPLC	-	-	-	-	-	5-year OS: 57.5%	5-year OS: 36%	0.016	Lobectomy should still be considered as the treatment of choice in the management of second primary lung cancer, completion pneumonectomy was a negative prognostic factor in long-term survival.
Watanabe, 2022 (66)	2010-2020	85 sMPLC	29	-	9	0	47	5-year survival rate:85.0%; bilateral vs ipsilateral 85.1% vs. 85.0%, $P = 0.916$		Limited resection can preserve pulmonary function while ensuring curability.	
Kang, 2020 (64)	2007-2016	106 sMPLC + 36 mMPLC	18	0	42	0	72	All patients 5-year DFS 73.9%; metachronous vs synchronous: 85.4% vs 69.1%, 5-year OS: 86.1% vs 84.8%		Multiple pulmonary resection is valid for patients with MPLC.	
Kocaturk, 2011 (65)	2001-2008	26 sMPLC	1	-	6	10	9	5-year OS: pneumonectomy vs no-pneumonectomy (27% vs 71.1%), $P = 0.12$		Pneumonectomy was a poor prognostic factor.	
Jung, 2011 (60)	1995-2008	32 sMPLC	2	6	4	5	13	Use of limited resection: 5-year OS: 79.4%, 5-year PFS: 74.5%; Lobectomy or extended 5-year OS: 51.2%, 5-year PFS: 34.2%		The decision of aggressive surgical treatments for synchronous MPLC should be made carefully in the patients with old age and underlying comorbidities due to poor OS and increased surgical mortality.	

s/mMPLC, synchronous/metachronous multiple primary lung cancer; W, wedge resection; S, segmentectomy; L, lobectomy; P, pneumonectomy; OS, overall survival; PFS, progression-free survival; BMPLC, bilateral multiple primary lung cancer.

year OS between all lesions with a GGO component and all with a solid component (97.2% vs. 41.3%, $P < 0.001$), and multiple GGO foci and the absence of lymph node involvement were independent predictors of a good prognosis (79). Therefore, as surgical treatment of MPLC, anatomical resection with preservation of the lung parenchyma as much as possible should be opted for, and the extent of resection should be determined according to the size and location of the tumor. The necessity of surgical intervention should be evaluated for patients with multiple GGOs.

In summary, for MPLC that can be surgically removed, sublobar resection should be preferred based on the location and size of the lesions. For mMPLC and bilateral sMPLC, multiple pulmonary resection can be performed when the patient's lung function permits. Multiple GGOs have a better prognosis and should be evaluated for the need for surgical intervention.

3.2 Radiotherapy

Stereotactic body radiation therapy (SBRT) has become the standard alternative treatment for patients with early-stage inoperable lung cancer (80, 81). It has limited toxicity and achieves satisfactory local control of tumors (82, 83). It has been widely used in MPLC (84), especially in patients with mMPLC (85). The American Society for Radiation Oncology (ASTRO)/American Society of Clinical Oncology (ASCO) guidelines (86, 87) strongly recommend SBRT as a potential curative treatment option for mMPLC patients, including those who underwent pneumonectomy (88). MPLC patients should be evaluated by a multidisciplinary team, and sMPLC patients may also be treated with SBRT as a therapeutic option when available. Research has shown that the PFS, OS, and incidence of local failure of sMPLC patients treated with SBRT are comparable to those in the cohort of patients with isolated early NSCLC (89). In another study, SBRT was found to have limited toxicity for the treatment of sMPLC, but the rate of progression appeared to be relatively high, with 11 patients (61%) experiencing disease progression (90). In iSABR trial, freedom from local recurrence at 1 year was 94% (90%CI, 87%-97%) for group MPLC (91). The RTOG 0618 trial (92) demonstrated that a high rate of intrathoracic control (96%) was achieved with the application of SBRT in patients with early-stage resectable lung cancer, but the guidelines (86) emphasized that surgery is still the recommended treatment for early resectable NSCLC patients and that SBRT should be considered as a potential alternative to surgery for patients at high risk of surgery. SBRT may reduce the risk of treatment in the short term, but the long-term outcome is uncertain over 3 years. Overall, SBRT can be adopted as an alternative treatment option for inoperable MPLC.

3.3 Image guided thermal ablation

IGTA is an option for select patients not receiving SABR or radical radiotherapy. Study has shown that IGTA provides at most temporary reductions in FEV1 and DLCO, with no statistically significant difference from baseline after healing (93, 94). For

patients with high surgical risk (inoperable due to comorbidities), IGTA may be considered after a multidisciplinary evaluation. Ablative therapy may be associated with higher rates of local recurrence and complications when the lesion diameter is over 3 cm (95). Overall, patients with MPLC benefit from a comprehensive multidisciplinary approach combining surgery, SBRT, and IGTA to balance local control and preservation of lung function.

3.4 Targeted therapy

Targeted therapy is mostly used to treat patients with advanced NSCLC and is a potential alternative treatment option for selected MPLC patients whose lesions are not completely eradicated by surgery. YE et al. reported a strategy of continuing treatment of gefitinib-sensitive multiple GGO lesions with gefitinib after surgical resection of gefitinib-insensitive lesions, which eventually led to complete remission in this patient (96). Cheng et al. reported a case of an sMPLC patient who underwent surgical resection of the main lesion with EGFR mutation and received EGFR-TKI treatment for 3 months (97). The largest residual GGO lesion achieved complete remission, while the remaining lesions shrank or remained stable. Combination targeted therapy may be considered when there are different driver mutations between multiple lesions in MPLC. Aredo et al. reported a case of MPLC with different driving mutations in EGFR/RET treated with a combination of osimertinib and alectinib (98), and Chen et al. reported another patient with multiple primary lung adenocarcinoma who simultaneously had CD74-NRG1 fusion, EGFR, and human epidermal growth factor receptor 2 (ERBB2) mutations (99). The patient received a combination of afatinib and pyrotinib and showed a significant therapeutic response. Surgery combined with targeted therapy or targeted drug combination therapy for MPLC is promising, but it is necessary to further clarify the dosage and safety of targeted drugs.

3.5 Immunotherapy

Immunotherapy has brought cancer treatment into a new era, especially in advanced NSCLC without driver mutations. MPLC typically exhibits low TMB, low programmed cell death-ligand 1 (PD-L1), and heterogeneous immune infiltration landscapes (100, 101). A total of 13.4% of lesions in MPLC showed positive PD-L1 expression, while 27.9% (12/43) of patients showed inconsistent PD-L1 expression (102). The incidence of PD-L1-negative tumors in MPLC was higher in women and patients who had never smoked or were light smokers (103), and there was a higher incidence of PD-L1-positive tumors in wild-type tumors. This shows that PD-L1 expression levels are heterogeneous in MPLC (4), and the use of neoadjuvant programmed cell death-1 (PD-1)/PD-L1 inhibitors alone may not be the optimal treatment strategy for MPLC.

Lin et al. reported a case of an mMPLC patient with high PD-L1 expression detected after resection of a primary lung adenocarcinoma lesion; neoplastic tumors were found after a period of treatment with pembrolizumab and were later confirmed to be a PD-L1-negative

small cell lung cancer (104). The patient was later treated with atezolizumab and achieved a durable clinical benefit. WES and immunohistochemistry confirmed differences in the distribution of CD8+ and CD4+ T cells in the two tumor tissues. Wu et al. reported a case of a patient with sMPLC who received 3 cycles of pemetrexed plus pembrolizumab upfront and surgical resection of a nearly pure solid lesion, followed by no further treatment (5). After 12 months of follow-up subsequent to termination of immunotherapy, almost all remaining lesions achieved radiographic complete remission due to the trailing effect of the PD-1 antibody of pembrolizumab.

Xu et al. conducted a clinical trial (ChiCTR1900022159) involving treatment of residual GGO lesions with the PD-1 inhibitor sintilimab (105). Of 13 GGOs in 7 patients who underwent secondary surgical resection, major pathologic response (MPR) was achieved in 2 lesions (2/13, 15%). Partial pathologic response (pPR) was found in 6 nodules (6/13, 46.2%), of which 4 GGOs were pPR high (>10% and <50% viable cells) and 2 were pPR low (>50% and <90% viable cells) lesions. pNR was observed in 5 (5/13, 38.5%) GGOs. Immunofluorescence revealed enriched T and B cells associated with pathological tumor regression. Patients who achieved MPR had higher TMB before the application of immunotherapy and were enriched for mutations such as MUC19 and PCDHB5, which have been found to be associated with good immunotherapeutic outcome.

In conclusion, the combined application of immunotherapy has a promising future, especially for PD-L1-positive patients with multiple GGOs who underwent surgery on the main lesion. Immune checkpoint inhibitor (ICI) application is expected to achieve complete remission of the remaining lesions, and further validation of the approach in large-sample clinical trials is currently pending.

4 Conclusions and future perspectives

MPLC is now very common in clinical practice and is characterized by multiple GGOs or subsolid nodules. Clinical diagnosis mainly relies on histopathologic, molecular, and imaging methods. Diagnostic imaging is indispensable as a preoperative diagnosis, histopathologic methods are adequate in most cases, and molecular diagnosis can make up for the lack of histology in differentiating IPM. It is worth noting that there are no universal diagnostic criteria for MPLC, and clinicians should collect as much comprehensive information as possible to make a diagnosis.

Treatment of MPLC should be developed by a multidisciplinary team. For patients who are surgically curable and can tolerate surgery, anatomical lung resection is preferred, preserving as much lung parenchyma as possible. SBRT can be an alternative option for inoperable patients, with better local control and low toxicity. IGTA is an option for selected patients who do not undergo SABR. Targeted therapies and immunotherapy are not yet standard therapies for the treatment of MPLC but have a promising future. Overall, patients with MPLC benefit from combination therapy combining surgery, SBRT,

IGTA, targeted therapy, and immunotherapy to balance local control and preservation of lung function.

Currently, there is still much room for improvement in the diagnosis and treatment of MPLC, and the establishment of authoritative and comprehensive guidelines is needed. The application of AI technology to assist diagnosis is expected to further improve the efficacy of diagnosis in imaging and histopathology. cDNA testing, single-cell sequencing, and spatial transcriptome sequencing, which are molecular tests applied to MPLC, may bring hope for the discovery of new biomarkers or therapeutic targets. Impressive progress has been made in the field of emerging tumor vaccines, such as RNA vaccines, drug delivery through nanorobots and the potential for future applicability to the treatment of MPLC is promising. Multidisciplinary intersections allow for more flexible treatment options for MPLC, benefiting more patients.

Author contributions

HD: Writing – original draft, Writing – review & editing. YT: Writing – original draft, Writing – review & editing. SX: Writing – original draft, Writing – review & editing. SJ: Writing – original draft, Writing – review & editing. YG: Writing – original draft, Writing – review & editing. ZW: Writing – original draft, Writing – review & editing. YH: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was funded by the National Natural Science Foundation of China (82373102 to YH), the Natural Science Foundation of Shandong Province (ZR2022QH146 TO YT) and the China Postdoctoral Science Foundation (2023MT44294 TO YT).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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