



Multiple primary lung cancer: a rising challenge

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Abstract: With the use of high-resolution chest imaging system and lung cancer screening program, patients with multiple primary lung cancers (MPLCs) are becoming a growing population in clinical practice worldwide. The diagnostic criteria for MPLCs has been established and modified by three major lung cancer research institutes. However, due to the fact that the differential diagnosis between MPLCs and a recurrence, metastatic, or satellite lesion arising from the original lesion remains ambiguous and confusing, there is still insufficient evidence to support a uniform guideline. Newly developed molecular and genomic methods have the potential to better define the relationship among multiple lesions and bring the possibility of targeted therapy. Surgical resection remains the first choice for the treatment of MPLCs and detailed strategy should be carefully planned taking characteristics of the tumor and status of patients into consideration. For those who are intolerant to surgery, a new technology called stereotactic body radiation therapy (SBRT) is now an optional therapeutic strategy. Furthermore, multiple GGOs are unique MPLCs that need special attentions in the clinical practice.

Keywords: Multiple primary lung cancers (MPLCs); diagnosis; surgery; stereotactic body radiation therapy (SBRT); ground-glass opacity (GGO)

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With the use of high-resolution chest imaging system and lung cancer screening program, patients with multiple primary lung cancers (MPLCs) are becoming a growing population in clinical practice worldwide (1-3). The crucial issue regarding multiple lung cancers is whether they should be diagnosed and treated as separate primary lesions or metastasis, on which both the stage classification and the planning of subsequent treatments are based (3,4). Histological differences between the multiple tumors are reliable indicators of MPLCs, but it would be rather challenging to differentiate a second primary cancer from a satellite, metastatic, or recurrent lesion of the original tumor if the multiple tumors are histologically same or similar. According to the 8th TNM staging system, the patients should be staged as T3 with additional tumor(s) within the

same lobe; T4 with an ipsilateral lesion in a separate lobe, and M1a with a contralateral tumor in a separate lobe (5). However, this staging system could probably cause inaccurate assessment and treatment of patients with actual MPLCs, who are considered to have a local disease and may benefit the most from surgical resections (3,6).

Currently there are no unambiguous guidelines available for the diagnosis and treatment of MPLCs. Although there are some cases reported to The Surveillance, Epidemiology, and End Results (SEER), National Cancer Database (NCDB), and databases in Europe and Asia and recommendations for the management of MPLCs have been published by three major lung cancer research institutes [Union for International Cancer Control (UICC), American Joint Committee on Cancer (AJCC),

Table 1 Criteria for the definition of second primary lung cancer

Martini and melamed criteria (7)

Synchronous MPLC

- A. Tumors physically distinct and separate
- B. Histological type
 - 1. Different
 - 2. Same, but in different segment, lobe or lung if
 - a. Origin from carcinoma *in situ*
 - b. No carcinoma in common lymphatics
 - c. No extrapulmonary metastases at the time of diagnosis

Metachronous MPLC

- A. Histologically different
- B. Histologically identical, if
 - 1. Free interval between cancers ≥ 2 years, or
 - 2. Origin from carcinoma *in situ*
 - 3. Second cancer in different lobe or lung, but:
 - a. No carcinoma in common lymphatics
 - b. No extrapulmonary metastases in at time of diagnosis

Antakli and colleagues Modifications (8)

- A. Different histological conditions
- B. Same histological condition with two or more of the following
 - 1. Anatomical distinct
 - 2. Associated premalignant lesion
 - 3. No systemic metastases
 - 4. No mediastinal spread
 - 5. Different DNA ploidy

MPLC, multiple primary lung cancer.

and International Association for the Study of Lung Cancer (IASLC)], controversies still exist due to inter-individual varieties among patients. The primary objective of our review is to get a global understanding of current information and, taking various clinicopathological and genetic features into consideration, present diagnosis, classification, and multidisciplinary management strategies in patients with MPLCs. We will also make an effort to illuminate the rising challenge faced by physicians and surgeons worldwide regarding the optimal strategies of diagnoses and management of patients with MPLCs and try

to draw some useful conclusion.

The definition and classification of MPLCs

Clinicopathological criteria

The clinical and pathological criteria for the diagnosis of MPLCs were first established by Martini and Melamed (7) in 1975 and then revised by Antakli and colleagues (8). The American College of Chest Physicians (ACCP) developed the criteria of diagnose in the year of 2007 with further clinical evaluations including lymphatic spread and systemic metastasis and extended the interval between metachronous MPLC as at least 4 years (9,10).

According to Martini-Melamed, a second tumor with different histological type from that of the primary one meets the criteria to be diagnosed as metachronous multiple primary lung cancer (mMPLC). When identical or similar histology occurs, at least one of the following circumstances should be satisfied to differentially diagnose a new primary cancer from recurrence: at least a 2-year disease-free interval between the two tumors; development of the new lesion from an *in situ* carcinoma, or existence of the second tumor in another lobe or the other lung; ruling out extra pulmonary metastases and lymphatic spread common in both tumors (7). Antakli and colleagues then proposed a revised set of criteria (8), which were further extended by the ACCP guidelines (11), elongating the disease-free interval up to 4 years (Table 1).

Coexisting primary lung cancers are called synchronous multiple primary lung cancer (sMPLC). Based on Martini-Melamed criteria, the coexisting tumors should be physically separate and can present either same or different histology. When histology is identical or similar, tumors located in different segments, lobes, or lungs should originate from carcinomas *in situ* and, at the time of diagnosis, evidence of systematic metastases or lymphatic spread should be excluded (12) (Table 1).

Although the diagnostic criteria have been greatly improved, the diagnosis and classification of MPLCs still has not reached consensus amongst UICC, IASLC and AJCC (13). The 2012 UICC manual suggests that a tumor in the same organ with different histology should be diagnosed as a new tumor while IASLC suggests that the maximum T category and staging should be assigned and in addition the number of tumors should be mentioned (14,15). The combination of all tumors with consistent TNM designation should be used when staging sMPLC. The

IASLC guide-line suggests that the TNM staging system can be functional in both same and different histology between primary and secondary tumors (9,14). The diagnosis and classification and therefore the planning of treatment are still difficult clinical decisions for physicians and surgeons due to the lack of high-level, evidence-based studies.

Molecular biomarkers

To better define the relationship among multiple lesions in lung, alternative approaches using novel molecular testing, such as immunohistochemical and molecular analysis, have been proposed by more recent studies (12,16). The clonality of multiple lesions can be demonstrated based on the array comparative genomic hybridization analysis, the loss of heterozygosity (LOH) analysis or the occurrence of somatic mutations in tumor suppressor genes or oncogenes (*Table 2*).

LOH, the loss of one allele at a specific locus caused by a deletion mutation or loss of a chromosome from a chromosome pair resulting in abnormal hemizyosity, represents 1 of the 2 hits required for tumor suppressor gene inactivation (43,44). LOH analysis is based on the comparing between tumor DNA and matched control DNA obtained from normal tissues or between single nucleotide polymorphism or microsatellite genotypes (27,45). Huang and colleagues reported that with the use of LOH array, the metachronous and synchronous primary lung tumors with identical histology could be successfully distinguished from intrapulmonary metastases (22). Shimizu and colleagues reported that the use of the combination of LOH and *p53* mutation analysis could significantly increase the sensitivity and specificity in the identification of MPLCs (46). Despite the significant variability in genetic profiles among multiple primary lesions, some studies observed higher rates of LOH pattern accordance among multiple lesions (27).

Array-based comparative genomic hybridization (aCGH), mainly focused on the identification of copy number changes throughout the genome, is a robust method for undertaking comprehensive genomic level researches (47,48). With very high confidence rates, it is an attractive method that can be used to distinguish recurrent lesions from multiple tumors (49). Arai and colleagues reported that the use of aCGH assessment could improve the accuracy of the clinicopathological diagnosis of MPLCs (4). Similar conclusions could be found in Girard's study (25). However, Girard and colleagues has also demonstrated that aCGH is costly, time consuming and requires relatively large amount

of sample DNA, which is disadvantageous to use aCGH in clinical practices (25,26). It is also more practical to use aCGH in synchronous tumors since fresh frozen tissue is a crucial requirement (12).

Ideal genetic biomarkers for clonality analysis should be independent with frequent somatic mutations, which occurred early and maintained across the development of tumor. With rates up to 50% in non-small cell lung cancers (NSCLC), the *p53* gene mutations are frequently seen in the presence of lung carcinomas (50,51). Most of them are point mutations and distribute throughout the DNA-binding domains of the *p53* gene (51). Therefore, a huge amount of somatic mutations may occur and the chance of two independent lung cancers harboring identical mutations simultaneously is small. Recent studies demonstrated that *p53* mutation analysis could be an effective biomarker for a definitive diagnosis in almost 66% of synchronous and metachronous cancer cases (23,52,53). Kirsten rat sarcoma viral oncogene homolog (*K-ras*) gene and epidermal growth factor receptor (*EGFR*) mutations are early events in the occurrence of lung cancer (54,55). Takamochi and colleagues reported that both *K-ras* and *EGFR* mutations frequently occur randomly in multifocal lung adenocarcinomas. Combined mutation pattern analyses of *EGFR* and *K-ras* may be useful for diagnoses and classification of MPLCs and therefore making decisions regarding treatment strategies (30). Chang and colleagues demonstrated that *EGFR* mutation, either alone or together with *p53*, is a potential biomarker for the clonal origin of MPLCs for differential diagnosis, especially in cases with similar histopathological types (24).

Despite that higher diagnostic rates (up to 83%) of using gene mutation pattern analysis in MPLCs have been described in several studies, it has also been reported that there is significant variability in genetic profiles among metachronous and synchronous primary tumors. Kalikaki and colleagues' study suggested that multiple lesions may have matched mutations while metastasis may have additional mutations (56). It strongly indicated the possibility that subclonal drifts cause monoclonal origin with subsequent genetic tumor heterogeneity. Zhang and colleagues investigated the intra-tumor heterogeneity in 11 lung cancer patients and by multi-region whole-exome sequencing, all tumors showed clear evidence of ITH (57). Chang and Kalikaki's studies demonstrated that *p53* and *EGFR* mutation/overexpression status were distinctive between primary tumors and lymphatic spread in patients with NSCLC (56,58). Other studies also reported

Table 2 Molecular and genomic profiling of MPLCs.

Study (year)	Patients	Molecular biomarker (methods)	Results
Noguchi <i>et al.</i> [1993] (17)	9 patients with MPLCs	<i>p53</i> (IHC and PCR-SSCP)	All of the patients were diagnosed as MPLCs
Sozzi <i>et al.</i> [1995] (18)	5 patients with 11 synchronous lesions	<i>p53</i> , <i>K-ras</i> (LOH/mutations)	The lesions were found to be genetically distinguishable
Mitsudomi <i>et al.</i> [1997] (19)	16 patients with mMPLC	<i>p53</i> (mutations)	9 patients with at least one <i>p53</i> gene mutation; the mutational status was discordant in all cases
Hiroshima <i>et al.</i> [1998] (20)	19 patients with sMPLC and 11 with mMPLC	<i>p53</i> (IHC and PCR-SSCP)	Different genetic changes were detected in 11 sMPLC (57.9%) and 5 mMPLC (45.4%) patients
Matsuzoe <i>et al.</i> [1999] (21)	20 patients with MPLCs	<i>p53</i> (PCR-SSCP/DNA sequencing)	<i>p53</i> gene alternations were found in 7 patients
Huang <i>et al.</i> [2001] (22)	4 patients with sMPLC and 5 with mMPLC	<i>RB</i> , <i>DCC</i> , <i>APC-MCC</i> , <i>p53</i> (LOH/microsatellite alterations)	3 sMPLC lesions and 3 mMPLC lesions were found to be independent
van Rens <i>et al.</i> [2002] (23)	21 patients with sMPLC and 11 with mMPLC	<i>p53</i> mutations	Different <i>p53</i> mutations were detected in 21 patients; identical <i>p53</i> mutations were found in 2 patients
Chang <i>et al.</i> [2007] (24)	58 patients with sMPLC	<i>p53</i> , <i>EGFR</i> (gene expression and mutations)	15 MPLCs were diagnosed as intrapulmonary metastases according to <i>p53</i> alterations; Based on <i>EGFR</i> alterations, 19 MPLCs were diagnosed as intrapulmonary metastases
Girard <i>et al.</i> [2009] (25)	8 patients with sMPLC and 16 with mMPLC	9 genes (aCGH/mutations)	The genetic diagnosis of 4 cases were found to be discordance with Martini-Melamed criteria
Girard <i>et al.</i> [2009] (26)	20 patients with MPLCs	9 genes (aCGH/mutations)	Mutational data led to a diagnosis of multiple primaries in 14 cases and of metastases in 8 cases; 2 cases could not be assessed. This molecular characterization contradicted the Martini-Melamed diagnosis in 7 (32%) of the 22 assessable comparisons.
Wang <i>et al.</i> [2009] (27)	18 patients with sMPLC and 12 with mMPLC	<i>p53</i> (LOH/gene mutations)	23 patients had identical genetic alternations
Moffatt-Bruce <i>et al.</i> [2010] (28)	13 patients with sMPLC and 11 with mMPLC	Comparative mutational profiling	Comparative mutational profiling was found to be useful and reliable to assess the relatedness of multiple cancer lesions
Girard <i>et al.</i> [2010] (29)	7 patients with MPLCs	<i>EGFR</i> , <i>K-ras</i> (mutations)	<i>EGFR/KRAS</i> mutation testing of multiple lung adenocarcinomas can assist in differentiating multiple primary lung adenocarcinomas from metastatic lesions
Takamochi <i>et al.</i> [2012] (30)	31 patients with sMPLC and 5 with mMPLC	<i>EGFR</i> , <i>K-ras</i> (mutations)	The clonality status of multifocal lung adenocarcinomas could be determined in 30 (83%) of the 36 patients
Warth <i>et al.</i> [2012] (31)	78 patients with multiple lung tumors	<i>K-ras</i> , <i>EGFR</i> (LOH/mutations)	36% of multiple NSCLC lesions displayed unique molecular changes
Arai <i>et al.</i> [2012] (4)	12 patients with sMPLC	<i>EGFR</i> (aCGH/mutations)	Pathological diagnosis and molecular classification were the same in 10 out of 12 cases (83%)
Lin <i>et al.</i> [2014] (32)	64 patients with sMPLC	<i>EGFR</i> , <i>p53</i> , <i>K-ras</i> (mutations)	<i>EGFR</i> , <i>p53</i> , and <i>KRAS</i> mutations were detected in 41 (64.1%), 8 (12.5%), and 4 (6.3%) patients, respectively. The high frequency of genetic mutations resulted in a high (68.8%; 44/64) discrimination rate of tumor clonality

Table 2 (continued)

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Study (year)	Patients	Molecular biomarker (methods)	Results
Zhang <i>et al.</i> [2014] (33)	70 patients with sMPLC	<i>EGFR</i> , <i>HER2</i> , <i>K-ras</i> (mutations)/ <i>ALK</i> (fusion analysis)	Histologic subtyping and driver-mutation testing reached almost perfect agreement in diagnostic yields for sMPLC
Wu <i>et al.</i> [2015] (34)	35 patients with MPLCs	<i>EGFR</i> , <i>p53</i> , <i>K-ras</i> , <i>PIK3CA</i> and <i>BRAF</i> (mutations)/ <i>EML4-ALK</i> , <i>ROS1</i> and <i>RET</i> (fusion analysis)	The discordance rate of driver mutations was 80% (24 of 30) in those patients harboring at least one of the detected driver mutations
Zhou <i>et al.</i> [2016] (35)	24 patients with sMPLC	miRNA expression analysis	6 patients showed conflicting diagnoses by miRNA analysis and 14 were given the same classification. miRNA expression profiles is considered to be a useful tool for discriminating SMPLCs from intrapulmonary metastases
Liu <i>et al.</i> [2016] (36)	78 patients with multiple GGOs	<i>EGFR</i> (mutations)	The <i>EGFR</i> mutation rate of invasive adenocarcinoma was higher than that of AAH, AIS and MIA. Of the 38 paired lesions in patients harboring <i>EGFR</i> mutation, the discordance rate of <i>EGFR</i> mutation was 92.1%
Schneider <i>et al.</i> [2016] (37)	60 patients with MPLCs	<i>K-ras</i> , <i>EGFR</i> , <i>BRAF</i> , <i>PIK3CA</i> , <i>ALK</i> , <i>MET</i> , <i>ROS1</i> , <i>PIK3CA</i> and <i>p16</i> (mutations)	Comprehensive genotypic and morphological assessment of surgically treated MPLCs is feasible but not sufficient to establish their clonal relationship and prognosis
Yang <i>et al.</i> [2016] (38)	129 patients with MPLCs	<i>EGFR</i> , <i>BRAF</i> , <i>ROS1</i> and <i>K-ras</i> (gene mutations) and <i>EML4-ALK</i> (gene rearrangement)	Only 30 (32.6%) of the MPLC patients had identical gene mutations. More than half of second primary lung cancers result from different mechanisms compared with primary cancers
Asmar <i>et al.</i> [2017] (39)	69 patients with MPLCs and 45 patients with primary tumors and their metastases	<i>EGFR</i> , <i>K-ras</i> , <i>BRAF</i> , and <i>ALK</i> (mutations)	Oncogenic driver mutations are concordant between primary tumors and metastasis
Patel <i>et al.</i> [2017] (40)	11 patients with MPLCs and 8 patients with primary tumors and their metastases	Gene mutations (NGS)	Primary-metastatic pairs had high mutational concordance. Multiple lung tumors from 8 patients had completely discordant mutations and were predicted to be independent primary tumors
Chen <i>et al.</i> [2018] (41)	96 patients with MPLCs	<i>EGFR</i> , <i>K-ras</i> , <i>HER2</i> , <i>BRAF</i> , and <i>PIK3CA</i> (gene mutations) / <i>EML4-ALK</i> , <i>ROS1</i> and <i>RET</i> (gene fusion analysis)	High discrepancy of 80% among patients with MPLCs were found
Haratake <i>et al.</i> [2018] (42)	59 patients with MPLCs	PD-L1 expression (IHC)	Among 43 patients with MPLCs, 13 patients (30.2%) were PD-L1 positive; and pulmonary metastatic lesions among 16 patients, 7 patients (43.8%) were PD-L1-positive. Among 43 patients with MPLCs, there was disagreement of PD-L1 expression in 12 patients (27.9%). Among 16 patients with pulmonary metastasis, disagreement of PD-L1 expression was observed only in 1 patient (6.3%)

IHC, immunohistochemical analysis; NGS, next-generation sequencing; SSCP, single-strand conformation polymorphism; aCGH, array comparative genomic hybridization; LOH, loss of heterozygosity; GGOs, ground-glass opacities.

intra-tumoral heterogeneity of the *EGFR* mutation in NSCLC (59-61). It strongly indicated that the variations and complicates in the definition of synchronous and metachronous primary lung cancers by using molecular biomarkers (2).

Multidisciplinary management of MPLCs

The diagnosis and stage classification of MPLCs

Due to tumor heterogeneity and insufficient understanding of clinicopathological characteristics of MPLCs, there are currently no golden diagnostic criteria for MPLCs. The ACCP recommended that the diagnosis of MPLCs should be based on a careful review that considers all available information by a multidisciplinary tumor board, which should include radiologist, thoracic surgeons, pathologists and pulmonologists (9-11,62).

Stage classification of multiple lesions is crucial for the surgical treatment because it allows consistent diagnosis of patients (63). For patients with MPLCs, however, the staging rules are ambiguous and confusing. Previous studies demonstrated that, for sMPLC, each tumor should be staged and treated as separate tumors and one TNM designation should be assigned in the final stage based on a combination of all tumors. For mMPLC, the second tumor should be staged as a primary original tumor (11,64).

According to ACCP guidelines (11,65), for patients with multiple primary NSCLCs (synchronous or metachronous), when therapeutic surgical resection is considered, invasive LN biopsy (if possible) and extra-thoracic imaging (head CT/magnetic resonance imaging plus whole-body PET or abdominal CT plus bone scan) are recommended (grade 1B). And the possibility of a benign lesion or synchronous primary lung cancer should be considered and excluded in patients with suspected or diagnosed lung cancer and an ipsilateral different lobe nodule (grade 1C). Preoperative bronchoscopy examination could also be beneficial for the evaluation of local tumor extension and surgical treatment. The size and location of the tumors and the patient's general condition should be both carefully evaluated before choosing a surgical approach.

Surgical treatment: lobectomy or sublobectomy?

Despite that surgical resection remains the most employed approach for the treatment of MPLCs, controversies over some issues still exist. Promising survival outcomes of

lobectomy have been demonstrated in previous studies (66,67), however, standard surgical strategies for the treatment of MPLCs have not been established because of the lack of consistent golden diagnoses criteria and prospective clinical trials. The extent of resection is mainly decided by surgeons based on the balance of risk and benefit of surgery, taking characteristics of the tumor and status of patients into consideration, which might have inter-individual differences (16,68,69) (Table 3).

For mMPLC, anatomical removal of the second lesion with lobectomy or bilobectomy was the first choice for surgery in the majority of the previous reports (64,87). However, in other studies, sublobar resections, including segmentectomy or wedge resection, were the mainstream of treatment (86). For sMPLC, which more frequently occurred in the same lung, anatomical resections (single, bilobectomy, or pneumonectomy) are also recommended (85). Chang *et al.* demonstrated that anatomical resection of the first lesion followed by limited resection of the second might be a safer and more beneficial option for synchronous bilateral lesions (73,76,77,80). The initial surgery should be performed on the side with the largest tumor and contralateral resection should then follow, according to recommendation (79). Nakata and colleagues reported bilateral video-assisted thoracic surgery in surgical treatment of cases with bilateral MPLCs might come along with minor postoperative complications and good survival rate also (88). These studies indicated that in patients who are intolerant to an extensive surgical resection, the sublobectomy has been widely accepted as an alternative choice since it allows major conservation of lung function (16). However, it still needs to be addressed that the local recurrence rate after sublobectomy (wedge or segmental resection) is higher than that after lobectomy (46,89,90).

Surgical treatment or stereotactic body radiation therapy (SBRT)?

A certain amount of patients with MPLCs might be intolerant to surgical resections due to impaired cardiopulmonary function or other impaired conditions. SBRT, also called stereotactic ablative radiotherapy (SABR), is a novel radiation modality that has been recommended as an optional therapeutic strategy for patients (91-93). For patients with early stage NSCLC, several groups have reported similar outcomes after SBRT treatment and surgical resections (93-95). For the patients with NSCLCs but intolerant to surgeries, Timmerman and Nantavithya's studies demonstrated the feasibility, safety, and efficacy of

Table 3 Surgical resection and the survival rate of patients with MPLCs

Study [year]	Patients	Surgical resection (n)					Survival		
		W/S	L	biL	P	P/L+W/S	Median (month)	3-year survival, %	5-year survival, %
Deschamps <i>et al.</i> [1990] (70)	36 patients with sMPLC and 44 with mMPLC	12	54	6	11	0	NA	NA	27
Adebonojo <i>et al.</i> [1997] (71)	15 patients with sMPLC and 37 with mMPLC	11	22	6	8	4	43	52	32
Rea <i>et al.</i> [2001] (72)	19 patients with sMPLC and 61 with mMPLC	29	29	3	8	11	NA	NA	51
Aziz <i>et al.</i> [2002] (73)	10 patients with sMPLC and 41 with mMPLC	2	29	3	14	11	40	NA	38
Rice <i>et al.</i> [2003] (74)	49 patients with mMPLC	13	15	0	3	0	NA	NA	NA
Battafarano <i>et al.</i> [2004] (75)	69 patients with mMPLC	34	29	2	4	0	NA	NA	60.9
Trousse <i>et al.</i> [2007] (62)	125 patients with sMPLC	15	41	7	40	22	35	45	34
Chang <i>et al.</i> [2007] (76)	92 patients with sMPLC	10	53	8	6	14	NA	NA	35
De Leyn <i>et al.</i> [2008] (69)	36 patients with sMPLC	32	NA	10	0	23	25.4	NA	38
Rostad <i>et al.</i> [2008] (77)	94 patients with sMPLC	4	30	8	41	11	NA	NA	27
Riquet <i>et al.</i> [2008] (78)	118 patients with sMPLC and 116 with mMPLC	54	103	0	77	0	30	NA	32.7
Finley <i>et al.</i> [2010] (79)	175 patients with sMPLC	48	59	18	3	47	67.4	64	51
Voltolini <i>et al.</i> [2010] (80)	43 patients with sMPLC	4	0	12	3	16	NA	NA	34
Haraguchi <i>et al.</i> [2010] (81)	30 patients with mMPLC	18	7	0	5	0	NA	NA	65
Kocaturk <i>et al.</i> [2011] (82)	26 patients with sMPLC	10	6	0	10	0	40	NA	49.7
Bae <i>et al.</i> [2011] (83)	40 patients with mMPLC	7	7	0	9	0	NA	NA	48
Yu <i>et al.</i> [2013] (66)	97 patients with sMPLC	14	39	8	0	36	38.3	83.1	69.6
Ishigaki <i>et al.</i> [2013] (84)	14 patients with mMPLC	10	4	0	0	0	NA	NA	85.7
Zhang <i>et al.</i> [2016] (6)	285 patients with sMPLC	59	Together 87		0	139	NA	NA	82.4
Dai <i>et al.</i> [2016] (85)	27 patients with sMPLC and 4 with mMPLC	0	0	7	2	18	NA	75.8	75.8
Yang <i>et al.</i> [2016] (86)	101 patients with sMPLC	13	0	39	0	49	NA	84.5	74
Chen <i>et al.</i> [2018] (41)	96 patients with sMPLC	21	19	10	0	46	37.5	82.9	71.3

W/S, wedge resection or segmentectomy; L, lobectomy; biL, bilobectomy; P, pneumonectomy; P/L+W/S, pneumonectomy or lobectomy plus wedge resection or segmentectomy; NA, not available.

this technique (91,96). The local control rate after SBRT is more than 90% (97,98). Moreover, SBRT has also been widely adopted for the treatment of oligometastasis involving the lungs (87,99).

Chang and colleagues reported that the 2- and 4-year local control rates of SBRT treating MPLCs were 97.4%

and 95.7%. The 2- and 4-year overall survival (OS) were 73.2% and 47.5% and progression-free survival (PFS) were 67.0% and 58.0%. Patients with sMPLC had lower OS and PFS than patients with mMPLC (100). Creach and colleagues investigated MPLCs patients in whom SBRT was used for at least one tumor. The 2-year OS was

acceptable and no grade ≥ 3 toxicities were observed (101), which were similar to Matthiesen's reports (102). Varlotto and colleagues described the OS, recurrence rate, and loco-regional control rate of SBRT treatment were acceptable compared with those observed after surgical treatment (103). However, in these studies, most of the patients with MPLCs submitted to SBRT treatment were those who are intolerant to anatomic resection.

It is reported that the regional and overall recurrence rates after SBRT for single early stage lung cancer were up to 10% and 30%, respectively (104). One of the major disadvantages of SBRT without surgery treatment is that exact pathologic mediastinal lymph node histology thus the accurate staging is unavailable. Although PET/CT has quite considerable specificity and sensitivity in the detection of lymph node spread, the false-negative rate is still 13% for NSCLC patients in clinical stage T1-2N0 (105). Takashi and colleagues reported that the regional recurrence rate of patients with MPLCs was about twice as much as that of patients with single early stage lung cancer, indicating the risk of regional node micrometastasis of each lesion and the potential application of adjuvant chemotherapy for eradication of micrometastasis (106). These studies indicated that the clinical application of SBRT in treating MPLCs still needs further research and observation.

Targeted therapy: is there a role for it?

Another potential treatment for the medically inoperable patients with MPLCs is targeted therapy, especially the *EGFR*-targeted tyrosine kinase inhibitors. It has been widely reported that the NSCLC patients carrying activating mutations in *EGFR* might respond to *EGFR*-targeted tyrosine kinase inhibitors (107,108). Nevertheless, as mentioned previously, most of the lesions from MPLCs are histopathologically different or have different molecular alternations. Thus, the gene mutation testing results from biopsied or resected lesions might not fully represented the genetic changes of all the lesions in the lung, which may greatly limit the use of target therapy in the management of MPLCs.

Ye and colleagues reported a successful case of treatment of a sMPLC patient displaying heterogeneous *EGFR* and *K-ras* molecular profiles and different responses to gefitinib. Not feasible for aggressive surgical resection, the patient was initially treated with gefitinib. Considering the different responses among the multiple lesions, a strategy involving continuing gefitinib treatment for the gefitinib-sensitive

bilateral ground-glass opacity (GGO) lesions and surgical resection for the gefitinib insensitive lesion was developed. The patient achieved complete remission and has been free of disease for 1.5 years (109). Their study indicated that the potential role of target therapy in the multidisciplinary management of MPLCs. However, in a study involving 78 patients with multifocal adenocarcinomas presenting as GGO lesions, Liu and colleagues found that matched *EGFR* mutations between the primary lesions and the paired specimen collected from another lesion were identified in only 8% of the patients (36). Ryoo and colleagues' study also showed that the multiple lesions response to *EGFR*-tyrosine kinase inhibitors might be caused by different molecular pathogenesis (110). Given the fact that *EGFR*-targeted tyrosine kinase inhibitors do not restrain growth of tumors without *EGFR* mutations, these results indicated that the genetic heterogeneity of multifocal adenocarcinomas may bring a challenge to get a whole control of disease in all cancer sites (2).

Multiple GGOs

One issue worthy to be specially addressed is the multiple ground-glass opacities (GGOs). GGOs, mainly including pure GGO (pGGO) and part-solid GGO, often characterized as a focal area in lung with increased attenuation on CT scan through which normal parenchymal structures can still be visualized (111). Lung cancers growing in a lepidic pattern can present as a GGO because the tumor cells grow only along the alveoli, therefore allowing aeration of the alveoli (2,36). Several studies documented that GGOs often represent benign lesion, or relative lower grade malignant lesions, such as atypical adenomatous hyperplasia (AAH), adenocarcinoma *in situ* (AIS), or minimally invasive adenocarcinoma (MIA). The presence of a solid component in GGO, however, strongly suggests the presence of cancer invasion (111,112). The Fleischer Society believed multiple GGOs should be considered as MPLCs rather than intrapulmonary metastasis which was concordant with IASLC (113), but evidence to reliably identify multiple GGO lesions as clonal or otherwise remains unclear.

Unlike solid nodules, the progression of GGOs is usually very slow. Hiramatsu and colleagues demonstrated that initial size of GGO and a history of lung cancer were independent factors that were significantly associated with GGO growth during follow-up. Their data showed that the growth rate at 5 years was 66% in the GGO lesions with

diameters larger than 10 mm (114). Tsutsui and colleagues demonstrated that most of the pGGO and part-solid GGO are clinically stable, only about 20% of them would decrease, disappear, or advance (115). Additional data showed that worse prognosis was associated with the larger size of the solid component of a lesion. Kim and colleagues demonstrated that for a pGGO lesion larger than 8 mm, resection should be performed to rule out the possibility of malignancy, whereas for a pGGO less than 8 mm, closely followed up using imaging studies is strongly recommended (112).

To our best knowledge, only a few of studies investigated the characteristics of coexisting GGOs and solid nodules. Therefore, clinical controversy over treatment strategies for multiple GGOs still exists. Godoy and Naidich demonstrated that surgical resection could be considered for mixed GGOs, while solitary pure GGO should be followed up until they increase in size or develop new solid component (113,116). Chen and colleagues evaluated both clinical characteristics and genetic alterations of pure GGO, part-solid nodules, and solid-dominant nodules. The 5-year recurrence-free survival was 100% in patients with multiple GGOs, 68% in those with one solid lesion, and 51.4% in those with two solid nodules. The 5-year overall survival was 100% in pure GGO, 80.5% in part-solid nodule, and 59.9% in solid-dominant nodule. A high rate of variability of genetic alterations (89.7%) was observed between cancers within individual patients (41). Similar results were presented in Gu and Castiglioni's studies, which reported the high frequency of genetic heterogeneity among multiple lesions in the same patient (117,118). These studies indicated that, compared to multiple solid NSCLC, the multiple GGOs have their unique clinicopathological characteristics and genetic features. The further explorations should be focused on the potential need to perform collaborative molecular tests in patients with multiple lesions, the possible role of *EGFR* mutation in staging of multiple GGOs and the indication of *EGFR* inhibitors for patients with multifocal adenocarcinomas presenting as GGOs (2,36).

Rising challenge

The growing population of patients with MPLCs is now a rising challenge for physicians and surgeons worldwide. The SEER, NCDB and some other database have been collecting cases of MPLCs but due to the ambiguous criteria for diagnosis and guidelines for the treatment, more effort should be emphasized on it. We summarized the studies now available worldwide (*Tables 2,3*) and found that molecular biomarkers are playing important roles in the

diagnosis of MPLCs and more and more biomarkers would be discovered to make better diagnostic accuracy. Surgical treatment is still the optimal choice for the patients with MPLCs, but it can be a dilemma in some cases and more experience and data analyses will help the surgeons to make better choices. Also, the SBRT and targeted therapy are also innovative and potentially efficient treatment methods which require further research.

Conclusions

With special clinicopathological characteristics and genetic features, MPLCs are increasingly encountered in clinical practice. Comprehensive molecular analysis could be helpful in differentiating multiple primary tumors from metastases. Although surgical resection remains the mainly choice for the treatment of MPLCs, the target therapy and SBRT may have their own roles in the multidisciplinary management of MPLCs. Nevertheless, there are still several controversies exist in the diagnosis, classification, and multidisciplinary management strategies of MPLCs. Multiple GGOs are unique MPLCs that need special attentions in the clinical practice.

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Footnote

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