ORIGINAL RESEARCH

Synchronous Multiple Lung Cancers with Lymph Node Metastasis and Different EGFR Mutations: Intrapulmonary Metastasis or Multiple Primary Lung Cancers?

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Background: There is no consensus on whether patients with synchronous multiple lung cancers (SMLC) who present with lymph node metastasis (LNM) but whose epidermal growth factor receptor (EGFR) mutations are different are considered to have intrapulmonary metastases or multiple primary lung cancers. Few studies on these patients have been reported.

Methods: The electronic medical records of patients with surgically resected multiple lung cancers between February 2016 and July 2019 were retrospectively reviewed, focusing on the clinical characteristics and prognosis of patients with LNM and different EGFR mutations.

Results: A total of 125 patients were diagnosed with SMLC, and only 8 patients had LNM and different EGFR mutations. Their mean age was 61.43 ± 8.08 years (range 47–69 years). EGFR detection suggested that 4 patients had completely different mutation types, and 4 patients had mutations in only 1 tumor. Only 1 of the 17 total lesions was squamous cell carcinoma, the rest were adenocarcinoma. All patients underwent adjuvant therapy after surgery. Except for 1 patient who underwent chemotherapy, the rest received tyrosine kinase inhibitor-targeted therapy. As at 15 October 2020, the average follow-up time was 28.68 ± 10.74 months (range 10.5–40.5 months), and all patients were alive except 1 who died from extensive pleural metastasis.

Conclusion: The current study highlights the clinical importance of EGFR detection in SMLC, especially in patients with LNM. SMLC with LNM and different EGFR mutations should be considered multiple primary lung cancers rather than intrapulmonary metastases, and comprehensive treatment based on surgery may be preferable in these patients due to a good prognosis.

Keywords: EGFR, epidermal growth factor receptor, IPM, intrapulmonary metastasis, LNM, lymph node metastasis, MPLC, multiple primary lung cancers, SMLC, synchronous multiple lung cancers

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Introduction

With the advancement of imaging technology and the enhancement of people's health awareness, more cases of synchronous multiple lung cancers (SMLC) are being diagnosed. The incidence of SMLC in previously reported studies[1] ranges from 1% to 7%, and the detection rate is rapidly increasing. The diagnosis of such patients is critical because the stage assessment and treatment options for multiple

primary lung cancers (MPLC) and intrapulmonary metastasis (IPM) are completely different. MPLC is considered to be a local disease and surgery is the first choice, whereas IPM is considered to be a systemic disease and chemotherapy and other adjuvant treatments are the first choice. Differentiating between MPLC and IPM is based largely on clinicopathological features, however, there is still no definitive guideline or algorithmic approach. Therefore, distinguishing between MPLC and IPM is challenging for clinicians when tumor histology indicates similar subtypes.

The earliest criteria used to define MPLC was the Martini and Melamed standard in 1975, which stated that for patients with MPLC of similar histology, their common lymphatic drainage system must be free of tumor metastasis.[2] In contrast, the Antakli criteria[3] proposed in 1995 indicates that the absence of lymph node metastasis (LNM) is not a requirement for MPLC of similar histology, as long as two or more of the following five criteria are met: (1) anatomically distinct; (2) associated premalignant lesion; (3) no systemic metastases; (4) no mediastinal spread; (5) different DNA ploidy. It was mentioned there for the first time that different molecular genetic characteristics can also be used as the basis for a diagnosis of MPLC. Since then the American College of Chest Physicians (ACCP) has revised and updated the Martini and Melamed criteria in 2003, 2007, and 2013.[4–6] The criteria propose that patients with the same histology must have no N2 or N3 LNM, and emphasize the importance of molecular genetic diagnosis. With the development of next-generation gene sequencing technology in recent decades, many studies[7–12] have demonstrated the role of genomics in the diagnosis of MPLC. Notably however, to date no definitive consensus has been reached on the various issues related to the diagnosis, treatment, and prognosis of SMPLC.

The current study investigated patients with LNM and different EGFR mutations who had been diagnosed with SMLC and undergone surgical resection. To the best of our knowledge, there are still few reports on such patients. To address the issue of whether such patients should be diagnosed with MPLC or IPM, clinicopathological features, EGFR mutations, and follow-up observations in these patients were analyzed.

Patients and Methods
Patients
Clinical data derived from patients with SMLC who had nodal metastasis but different EGFR mutations who were treated at the department of thoracic surgery, Wuhan Tongji Hospital from February 2016 to July 2019 were retrospectively analyzed. The inclusion criteria were (1) ≥ 2 tumors, (2) acceptable cardiopulmonary function, (3) no previous history of tumors, (4) all lesions tested for EGFR and the mutations were different, and (5) no distant metastasis on preoperative examinations, including chest computed tomography (CT), abdominal CT or ultrasonography, brain CT or magnetic resonance imaging, and whole body bone scans. The exclusion criteria were (1) incomplete patient data, (2) adjuvant treatment before surgery, and (3) no LNM detected after surgery. The study was approved by the institutional review board of Tongji Medical College of Huazhong University of Science and Technology, China, and it was also conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Surgical Procedure
All surgical procedures were performed with combined intravenous-inhalation anesthesia plus double lumen endotracheal intubation. The surgery was performed using a 3-cm small single-port approach. A 3-cm incision was made between the 5th ribs in the mid-axillary line of the surgery side to place a thoracoscope, an elbow laparoscopic suction device, and electrocoagulation hooks, and a bipartite clamp was placed to hold the lung lobe if necessary. In bilateral surgery, one side of the surgery was completed then the contralateral surgery was performed in the same way. Specific procedures and strategies used to determine the extent of surgical resection were as previously described.[13,14]

Tissue Samples and EGFR Mutation Analysis
Genomic DNA was extracted from fresh tissues using the QIAamp DNA Tissue Kit (Qiagen, Germany). EGFR mutations were detected using commercially available kits from YZY Medical (Wuhan, China) based on amplification refractory mutation system real-time polymerase chain reaction technology. Twenty-nine different EGFR mutations in exons 18–21 were detected in the lesions of the patients in the current study.

Follow-Up
Follow-up was performed by outpatient or telephone. Follow-up times were calculated from the day after

surgery, and included observations up to 15 October 2020. In the first year after surgery, chest CT, tumor markers, and abdominal ultrasound were reviewed every 3 months. In the second year after surgery the same indicators were reviewed every 6 months. Thereafter they were reviewed annually.

Results
Clinical Characteristics of Patients and Lesions

A total of 125 patients with SMLC underwent surgery at the department of thoracic surgery, Wuhan Tongji Hospital between February 2016 and July 2019, of which 8 met the inclusion criteria. They included 5 males and 3 females, and their mean age was 61.43 ± 8.08 years (range 47–69 years). All the males had a history of smoking, and 5 patients had comorbid hypertension. Of the 8 patients, 5 were found to have tumors as a result of health examination by chest CT and 3 were found to have tumors when they presented with respiratory symptoms. All patients had normal tumor markers. Cardiopulmonary function was acceptable in all patients. The 8 patients had a total of 17 lesions, with a mean diameter of 29.91 ± 12.21 mm, including 8 ground-glass opacity (GGO) lesions and 9 solid lesions. Two patients had lesions in both lungs. One patient had 3 lesions, and the rest had 2 lesions. There were 5 lesions in the right upper lobe, 4 in the right middle lobe, 3 in the left upper or lower lobe, and 2 in the right lower lobe. Only 1 patient's lesions were located in the same lobe. The clinical characteristics of the patients and lesions are shown in Tables 1 and 2 respectively.

Surgical and Postoperative Pathology Data

All patients underwent simultaneous single-port thoracoscopic surgery, including 2 patients who underwent bilateral surgery. Three patients underwent lobectomy plus wedge resection, 2 underwent lobectomy plus segmentectomy, 2 underwent combined lobectomy, and 1 underwent single lobectomy. All operations were successful. The mean operation time was 210.76 ± 65.23 mins, the mean intraoperative blood loss was 184.78 ± 82.70 mL, and the mean postoperative hospital stay was 11.72 ± 2.38 days. No severe postoperative complications or deaths occurred. Only 3 patients had different histopathological types, including 1 with minimally invasive adenocarcinoma and

invasive adenocarcinoma, 1 with squamous cell carcinoma and invasive adenocarcinoma, and 1 with adenocarcinoma in situ and invasive adenocarcinoma. Apart from the 1 squamous cell carcinoma, all the other lesions were adenocarcinomas. Of the 2 patients with bilateral lesions, 1 underwent systemic lymph node dissection on both sides, and the other only underwent lymph node sampling because the left lesion exhibited pure GGO. The remaining patients underwent systemic lymph node dissection. The mean total number of lymph nodes dissected was 26.17 ± 10.72, the mean number of N1 lymph nodes dissected was 9.59 ± 4.04, and the mean number of N2 lymph nodes dissected was 17.72 ± 7.06. Two patients had N1 metastasis, 4 had both N1 and N2 metastasis, and 2 only had N2 metastasis. Patients with bilateral lesions only had metastases in the right thoracic lymph nodes. Detailed surgical and postoperative pathology data are shown in Table 3.

EGFR Mutations in the 8 Paired Lesions

EGFR detection indicated that 4 patients had completely different mutation types, and 4 had mutations in only 1 tumor. Four lesions had no mutations, and 13 lesions had mutations. L858R was the most common mutation (6/13), followed by 19DEL (3/13), and the rest were rare mutations (two L861Q, one G719X, and one S768I). Details of the EGFR mutations are shown in Table 4.

Postoperative Treatment and Follow-Up

Details of postoperative treatment and follow-up are shown in Table 5. All 8 patients underwent adjuvant therapy after surgery. One patient underwent chemotherapy, and the rest received tyrosine kinase inhibitor-targeted therapy. As at 15 October 2020, the average follow-up time was 28.68 ± 10.74 months (range 10.5–40.5 months). Only 2 patients had distant metastasis. One patient was found to have brain metastasis 25 months after surgery, and another patient was found to have pleural metastasis 6 months after surgery. All patients remain alive except 1 who died of extensive metastases. The patient who presented with distant metastasis was the same patient who developed N2 skip metastasis.

Discussion

In clinical practice we encountered SMLC patients with postoperative LNM but different EGFR mutations. Such patients can easily be diagnosed with IPM in clinical practice, causing them to miss the best treatment opportunity. In the current study analysis of clinical data derived

Table 1 Clinical Characteristics of Patients

Case Number	Sex	Age	Main Complaint	Smoking History	Family History of Tumor	Comorbidity	EF (%)	p-FEV1 (%)	FEV1 (L)
1	M	62	HE	Y	N	None	58	88.34	2.67
2	F	47	HE	N	N	Hypertension	67	86.32	3.23
3	F	69	HE	N	Y	None	55	71.87	1.64
4	M	48	RS	Y	N	Hypertension	65	99.78	2.78
5	M	57	RS	Y	N	None	63	84.35	1.97
6	F	69	RS	N	Y	Hypertension	52	78.35	2.01
7	M	61	HE	Y	N	Hypertension	57	105.35	2.89
8	M	69	HE	Y	N	DM&Hypertension	53	87.65	2.46

Abbreviations: F, female; M, male; HE, health examination; RS, respiratory symptoms; Y, yes; N, no; DM, diabetes mellitus; EF, ejection fraction.

Table 2 Clinical Characteristics of Lesions

Case Number	Lesions Number	Location of the Lesion	Maximum Diameter of Lesions (mm)	Type of Lesions	Pleural Invasion
1	2	RUL/LLL	40/17	mGGO/pGGO	Y
2	3	RUL/RML/RML	21/14/9	mGGO/pGGO/pGGO	N
3	2	RML/RLL	25/35	SN/SN	Y
4	2	RLL/LUL	25/20	SN/SN	Y
5	2	RUL/RUL	21/14	SN/mGGO	N
6	2	LUL/LLL	12/50	mGGO/SN	N
7	2	RUL/RML	8/40	mGGO/SN	Y
8	2	LUL/LLL	37/21	SN/SN	Y

Abbreviations: RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, Left lower lobe; SN, solid nodule; pGGO, pure ground-glass opacity; mGGO, mixed ground-glass opacity; Y, yes; N, no.

Table 3 Surgical and Postoperative Pathology Data

Case Number	Surgical Procedure	Operation Time (min)	Intraoperative Blood Loss (mL)	Postoperative Hospital Stay (Day)	Postoperative Pathology	pT_{max} Stage	pN Stage	pTNM Stage
1	L/W	380	300	14	IA/MIA	T2a	[b]N2	IIIA
2	L/L	140	100	5	IA/IA/IA	T1c	[b]N2	IIIA
3	L/L	175	200	13	SCC/IA	T2a	[a]N2	IIIA
4	L/S	200	200	14	IA/IA	T2a	N1	IIB
5	L	180	100	12	IA/IA	T1c	[a]N2	IIIA
6	S/L	185	100	9	IA/IA	T2b	[b]N2	IIIA
7	W/L	155	100	11	AIS/IA	T2a	[b]N2	IIIA
8	L/W	175	50	10	IA/IA	T2a	N1	IIB

Notes: [a]N2, metastases in only N2 lymph nodes; [b]N2, metastases in both N1 and N2 lymph nodes.
Abbreviations: W, wedge resection; S, segmentectomy; L, lobectomy; IA, invasive adenocarcinoma; SCC, squamous cell carcinoma; MIA, minimally invasive adenocarcinomas; AIS, adenocarcinoma in situ.

from these patients indicated that an absence of LNM may not be a necessary criterion for the diagnosis of MPLC with similar tumor pathology.

Differential histopathology remains the first criterion for the diagnosis of MPLC. From the earliest Martini-Melamed criteria[2] in 1975, to the Antakli criteria[3] in 1995, to the ACCP guidelines[6] in 2013, different histopathology types have been used as primary criteria for the diagnosis of MPLC. In this context different histopathology types refers to completely different pathologies, and only one patient (patient 3) in the present study met this condition, with squamous cell carcinoma and adenocarcinoma. With the advancement of

Table 4 Detail of EGFR Mutation in the 8 Paired Lesions

No.	Primary Lesions	Second Lesions
1[a]	L858R	19DEL
2[a]	L858R	19DEL/L861Q
3[a]	19DEL	L858R
4[b]	Wild	L858R
5[b]	L858R	Wild
6[b]	Wild	G719X
7[b]	L861Q	Wild
8[a]	L858R	S768I

Notes: Lesions with the largest size in diameter were defined as the primary lesions; the others were defined as the second lesions; [a]Different mutation in the primary and secondary lesions; [b]Mutation in only one lesion.

Table 5 Postoperative Treatment and Follow-Up of Patients

Case Number	Adjuvant Treatment	Recurrence Status	New Lesions	Follow-Up Months	Survival Status
1	TKI therapy	NO	None	26	Alive
2	TKI therapy	NO	None	14	Alive
3	CT+TKI therapy	Distant (pleura)	Multiple	20.5	Death
4	TKI therapy	NO	None	40.5	Alive
5	TKI therapy	Distant (brain)	None	40	Alive
6	TKI therapy	NO	None	25	Alive
7	TKI therapy	NO	None	10.5	Alive
8	TKI therapy	NO	None	15	Alive

Abbreviations: TKI, tyrosine kinase inhibitor; CT, chemotherapy.

imaging technology and the popularization of lung cancer screening, more multiple primary lung adenocarcinomas are being diagnosed and they now account for 40.3%–91.3% of MPLC.[15–18] Because there are significant differences in the biological characteristics of lung adenocarcinoma and patient survival associated with different invasive states and different invasive components, the classification of lung adenocarcinoma in 2011[19] and the World Health Organization classification of lung cancer in 2015[20] further subclassify lung adenocarcinomas into pre-invasive lesions and invasive lesions. These can be divided into five categories according to the main components of invasion; lepidic, acinar, papillary, micropapillary, and solid. Subsequently, the American Joint Committee on Cancer 8th TNM staging system included the different pathological subtypes of tumors as criteria for the diagnosis of MPLC.[21] Although both patient 1 and 7 in the present study had lung adenocarcinomas, the invasive states of their lesions differed. Patient 1 had minimally invasive adenocarcinoma and invasive adenocarcinoma, and patient 7 had adenocarcinoma in situ and invasive adenocarcinoma, so they should also be considered cases of multiple primary lung adenocarcinoma.

As an auxiliary method for the diagnosis of MPLC, genetic analysis can improve the accuracy of diagnosis. Currently the most widely used technique is next-generation sequencing, which shows solid tumors with tens to hundreds of somatic chromosomal rearrangements, single nucleotide variations, and other molecular variations (eg mutations, CNVs, and fusion heterozygosity). Because it is highly sensitive and can provide genomic data even on specimens with relatively low or very low tumor cell counts, it has been widely used in routine clinical practice.[22] It can be used to select people suitable for targeted therapy, and it can also identify multiple lung cancers. It is now recognized that cancers with different driver mutations in oncogenes have different clonal origins.[23,24] Among them, EGFR and KRAS mutations have proved widely useful for distinguishing SMLC with similar pathological tissue from MPLC or IPM.[12] In the current study, EGFR mutation testing was performed on all lesions in 6 patients with the same tumor pathology, and the EGFR mutations in each patient were different, indicating that the patients had different tumor clonal sources. Therefore, in patients with the same tumor pathology and LNM, if the tumor driver mutation is different, the

metastasis may be local rather than systemic, and they should be considered to have MPLC.

Differences in the radiological appearances of tumors can be useful for distinguishing MPLC. With the application of low-dose computed tomography and positron emission tomography-computed tomography (PET-CT), more multifocal ground glass/lepidic lung cancers are being diagnosed. Multifocal ground glass/lepidic lung cancer exhibits GGO on CT scanning, or appears as lepidic cancer on pathology.[21,25,26] Multifocal ground glass/lepidic lung cancers, including adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic-predominant adenocarcinoma are all considered to be independent primary tumors.[27–29] Matsunaga et al[30] concluded that multifocal lung cancer with at least one GGO should be diagnosed as MPLC due to its favorable prognosis. In addition, PET-CT can distinguish MPLC from IPM based on the difference or ratio of standard uptake values between tumors in each patient.[31,32] Notably however, it may not be sufficient to rely solely on PET-CT or CT to identify MPLC. Suh et al[33] established a new method for the diagnosis of MPLC by combining the standard uptake value from PET-CT with the radiological features on CT, including GGO, spicule sign, and air-bronchogram. MPLCs are diagnosed when any tumor with pure GGO or GGO-dominant features in present, or when both tumors have spiculation or air-bronchogram, or when only one tumor has spiculation or air-bronchogram but tumors have more than two grades of standard uptake values. This method could have been used in the patients in the current study to verify whether they were considered to have multiple primary lung cancers. Of the 8 patients in this study 5 had at least one GGO lesion, and the 3 patients whose lesions were all solid nodules also had spiculation or air-bronchogram on CT.

Surgery is still the first choice for the treatment of MPLC. Because most MPLC is diagnosed at an early stage, surgery should be the preferred treatment.[34] Targeted therapy and immunotherapy have achieved promising results in patients with advanced non-small cell lung cancer,[35,36] but there is still insufficient clinical evidence on whether these two therapies can be applied in patients with MPLC. In one study approximately 45% of MPLC manifesting as GGOs had EGFR mutations.[37] Therefore, targeted therapy may be a treatment option in inoperable MPLC patients with EGFR mutations. Traditional chemotherapy should be considered in patients with LNM. All the patients in the present study underwent targeted therapy after surgery. Because all patients with MPLC have EGFR mutations, targeted therapy may be more suitable for them. All patients survived except 1, who died from extensive pleural metastasis. Therefore, for MPLC with LNM,

comprehensive treatment based on surgery should be the first choice.

In conclusion, the diagnosis of MPLC should be based on detailed evaluation of all available information from multiple oncology-related disciplines, rather than relying merely on clinicopathological features. EGFR mutation testing is extremely important in patients in whom MPLC is suspected, especially in patients with LNM. SPLC with LNM but with different EGFR mutations should be considered MPLC rather than IPM. Comprehensive treatment based on surgery may be preferable in these patients because it is associated with a good prognosis.

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Disclosure

None of the authors have any potential conflicts of interest.

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