



Clinical and pathological characteristics of 11 NSCLC patients with c-MET exon 14 skipping

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Background: The aim of the present study was to summarize the clinical and pathological characteristics of 11 non-small cell lung cancer (NSCLC) patients with mesenchymal-epithelial transition factor exon 14 skipping (METex14).

Methods: From 2018 to 2021, medical records of 763 NSCLC patients were reviewed and 11 patients carrying METex14 were identified from the Affiliated Hospital of Guangdong Medical University. Their clinical data were subsequently examined for pathological and related clinical information including symptom and diagnosis, imaging and follow-up.

Results: The METex14 cohort includes 9 males and 2 females and the age range was 69–85 years, with a median age of 77 years. Of the patients one is diagnosed with stage IVB lung adenocarcinoma, 7 with lung adenocarcinoma (1 with stage IIIA and 6 with stage IV), and 3 with stage IV lung sarcomatoid carcinoma. 3 reached stable disease until the end of follow-up and 4 died within a year due to multiple metastases. In 4 cases, the patients received selective MET inhibitor treatment all lived longer than 7 months. There were 4 heterozygous point mutations and 1 deletion of the MET gene in this cohort, as follows: c.G3028T (p.D1010Y); c.G3028A (p.D1010N); c.G3005C (p.V1002A); c.3022C>G and MET c.3021_3028+20del (E14).

Conclusions: According to the data that we collected, the incidence of NSCLC carrying METex14 is low and male outnumber female in our sample pool. Selective target therapy had better prognosis than multitargeted tyrosine kinase inhibitor (TKI) such as crizotinib or standard therapy.

Keywords: Non-small cell lung cancer (NSCLC); c-MET exon 14 skipping; target therapy

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Introduction

In China, non-small cell lung cancer (NSCLC) is the most frequently diagnosed cancer and the leading cause of death (1). NSCLC is a heterogeneous disease harboring numerous gene mutations and often found in NSCLC

are Epidermal growth factor receptor (*EGFR*) mutations with prevalence of 35% worldwide (2). To compare, the incidence of *MET* mutations is low in all human cancers and the number is around 3% (3). Awad *et al.* reported in their study that among 933 non-squamous NSCLC (873

cases of adenocarcinoma), 28 cases (3%) had *MET* gene mutations (4), while the incidence of *MET* gene mutation in Chinese NSCLC patients recently has been reported 1.1% (5).

The receptor tyrosine kinase, cellular-MET (*c-MET*), essential for embryonic development, organogenesis and wound healing, is a transmembrane receptor with autonomous phosphorylation activity encoded by the *MET* gene (6), is a single-chain precursor. The precursor is proteolytically cleaved at a furin site to yield a highly glycosylated extracellular α -subunit and a transmembrane β -subunit, and the two subunits are linked by a disulfide bridge (7). *MET* is later found to be an oncogene in NSCLC (8). Located in the 7q31 locus of chromosome 7, *MET* gene contains 21 exons and is also a receptor for hepatocyte growth factor (*HGF*) (9,10). *MET* gene mutation causes the pathological activation of its downstream signal pathways, which promotes cellular transformation, tumor motility, and invasion (10). The most common alterations in *MET* are *MET* Mutation (1.90%), *MET* Amplification (0.69%), *MET* Exon 14 Mutation (0.23%), *MET* c.1078-c.1345 Missense (0.15%), and *MET* X1010_splice (0.13%) (11). And *MET* mutations can be classified into point mutations in the tyrosine kinase domain, gene copy gains, less frequently, by alterations affected the splicing of exon14 which resulted in *MET* exon14 skipping (*MET*Tex14) after translation (12,13). Besides the abnormal gene, another *MET* aberration is protein overexpression, which in unselected NSCLC ranges from 15% to 70% (14,15).

*MET*Tex14 is associated with a mutation in one of the exon 14 splice regions, which results in the translation of a shortened *MET* receptor. In 2014, it was reported in The Cancer Genome Atlas that about 4% (10/230) of *MET*Tex14 were found in lung adenocarcinoma (16). Studies shows that *MET*Tex14 mutations were more frequent in women than men (17,18). *MET*Tex14 is often found as a sole mutation without other mutations and is mostly found in older patients. Some of *MET*Tex14 carriers have and high PD-L1 expression and brain metastases can occur in about 40% of patients (19).

Patients with *MET* mutation *MET*Tex14 had higher recurrence rate than *ALK* fusion patients (17). With the advent of newly- developed small molecule inhibitors, such as capmatinib, tepotinib and cabozantinib, treatment selection of *MET*Tex14 are more diverse. Capmatinib and tepotinib were approved for use by the US Food and Drug Administration in 2020 (20). Tepotinib's approval was based on the results of the VISION study (NCT02864992) which

recruited 99 NSCLC patients with *MET*Tex14 and the overall response rate (ORR) after tepotinib treatment was 42.4% (21,22). tyrosine kinase inhibitors (TKIs) in research or ongoing clinical trials include cabozantinib, glesatinib, and merestinib (23). Results from savolitinib clinical trials (NCT03778229) showed that the ORR was 51.6% (16/31). Savolitinib has been granted conditional approval in China for use in NSCLC patients with *MET*Tex14 who have disease progression after previous systemic therapy or are unable to receive chemotherapy.

The purpose of the present study was to summarize the typical clinical characteristics and report different treatment of both traditional and new drugs as well as outcomes of patients carrying *MET*Tex14 for reference purposes. We present the following article in accordance with the MDAR reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-782/rc>).

Methods

Patients and samples collection

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by institutional ethics board of the Affiliated Hospital of Guangdong Medical University (No. YJYS2010106). A total of 11 NSCLC patients with *c-MET* exon 14 skipping were diagnosed at the Affiliated Hospital of Guangdong Medical University. Samples included formalin-fixed, paraffin-embedded (FFPE) tumor tissue, plasma, and biopsy specimens were obtained from patients who provided signed informed consent. Thick sections cut from tumor tissue samples were used for DNA extraction and plasma were stored in cell-free DNA blood collection tube (Streck, America).

Next-generation sequencing (NGS)

DNA was extracted using the GeneJET FFPE DNA purification kit (#K0881; Thermo Scientific, Shanghai, China) according to the manufacturer's instructions. DNA was then amplified using The In vitro DNA Amplification Kit [Applied Biological Materials Inc (ABM), America] and DNA quality was assessed on a NanoDrop 2000 spectrophotometers (ThermoFisher, America). The targeted DNA fragments were pulldown and exon-wide libraries from genomic DNA were generated Roche SeqCap EZ Exome V3 (Roche Diagnostics, Basel, Switzerland) and TruePrep

DNA Library Prep Kit V2 for Illumina (#TD501, Vazyme, Nanjing, China) as paired-end reads on the using Illumina HiSeq machines (Illumina, Inc., San Diego, CA, USA).

Data analysis and statistics

All statistical tests were conducted in R software (version 3.6.1). Somatic mutation identification and indels were calculated and identified by Mutect and Somatic Indel Detector software, and then annotated through ANNOVAR. $P < 0.05$ was considered significant.

Results

Patient characteristics and outcomes

From 2018 to 2021, medical reports from 763 patients were collected from our hospital, and 11 patients were found to have METex14. Of these 11 patients, 9 were male and 2 were female. The age range was 69–85 years, and the median age was 75 years (Table 1). Patients were diagnosed with lung adenosquamous carcinoma (stage IVB, 1 patient), lung adenocarcinoma (stage IV, 6 patients/stage IIIA, 1 patient), lung sarcomatoid carcinoma (stage IV, 3). Eight patients had metastases; 3 had liver metastasis, 4 had lymph node metastasis, and 1 had chest metastasis and pericardial metastasis. *MET* gene alterations included base substitution, insertion, and large fragment deletion. Of our patients, the alteration varied and included c.3005 A>T, c.3028 G>T/D1010Y, c.3021_3028+20del, c.3005 A>T, c.3028G>A, c.3022C>G, and c.3028 G>T/D1028Y.

Case descriptions of patients

Patient 1

Male, 72 years old. Diagnosed in 2018.9 with stage IVB lung adenosquamous carcinoma with liver and brain metastasis. Gene sequencing showed *MET* (D1010Y), *TP53* p.R280G (E8) mutation, and *ALK* negativity. The treatment plan was 250 mg crizotinib twice daily. The tumor response was initially assessed after 1 month of therapy, which showed preferable outcomes with noticeable shrinkage of tumor volume (diameter: from 37.2 to 29.7 mm). However, the patient went through severe drug resistance in July 2019 and rapid progression (progression-free survival: 10 months). Overall survival was 12 months.

Patient 2

Male, 75. First admitted in August 2020 for stage IVB lung

sarcomatoid carcinoma. Three 0.1-cm³ tumor mass were found by magnetic resonance imaging in the lung including pleural metastases and left lymph node transfer. Gene sequencing indicated mutations of *MET* c.3021_3028+2del (E14) and *BRC2* p.Gln1037Ter (E11). The initial treatment plan was 250 mg crizotinib twice daily, but the patient had severe side-effects and was switched to savolitinib. Slight shrinkage of tumor mass could be observed by magnetic resonance imaging after 2 months of treatment. After treatment for 5 months with savolitinib, it was suspected that the tumor had metastasized to the brain. The patient was commenced on crizotinib for a month, and died after 1 month later.

Patient 3

Female, 75 years old. Diagnosed with stage IIA lung adenocarcinoma with a 5 cm × 5 cm tumor mass without metastasis. Gene sequencing showed *MET* exon 14 skipping mutation (c.3005 A>T). The patient received combined therapy of crizotinib and chemotherapy, and a significant decrease in tumor mass was achieved. At June 2019, the patient's condition was stable.

Patient 4

Male, 69 years old. Diagnosed in August 2019 with stage IV lung adenocarcinoma and liver metastasis. Gene sequencing showed *MET* (c.3005 A>T). TMB value was below average, and PD-L1 protein expression was negative. The initial treatment plan was 250 mg crizotinib twice daily. The patient had a good clinical response. Overall survival was 25 months.

Patient 5

Male, 72 years old, 40-year smoking history. In July 2019, this patient diagnosed at our hospital with stage IV lung adenocarcinoma, right lung pleural effusion, and emphysema in both lungs. Enlarged lymph nodes in the mediastinum and left hilar lymph node calcification were observed. After thoracentesis, non-small cell lung cancer-related antigen dropped from 216.7 to 167.7 ng/mL. However, the patient refused to be admitted to hospital and received Chinese medicine for palliative treatment, as requested. Overall survival was 12 months.

Patient 6

Male, 78 years old, smoker. In July 2019, the patient was diagnosed at our hospital with stage IV lung adenocarcinoma. Gene sequencing showed *MET* (c.3022C>G). The patient

Table 1 Clinical Characteristics and follow-ups of patients carrying METex14

Case	Sex	Age	Clinical manifestation	Smoker	PS score	Mutation Information	Metastase	Treatment	Clinical response	OS
1	Male	72	Stage IVB lung adenosquamous carcinoma	Yes	3	MET (D1010Y) and TP53 p.R280G(E8)	Liver and brain metastases	Crizotinib, one year		12 months
2	Male	75	Stage IVB lung sarcomatoid carcinoma	No	4	MET c.3021_3028+20del (E14) BRCA2 p.Gln1037Ter (E11)	Left hilar lymph node metastasis, Multiple metastases on the left pleura	Crizotinib for 1month, savolitinib for 5 months, then crizotinib for a month		7 months
3	Female	75	Stage IIIA lung adenocarcinoma	No	1–2	MET (c. 3005 A>T)	None	Crizotinib and chemotherapy	SD	Alive
4	Male	69	Stage IV lung adenocarcinoma	No	4	MET (c. 3005 A>T)	Liver metastases	Crizotinib		25 months
5	Male	72	Stage IV lung adenocarcinoma	40-year history	4	MET (c.3028G>A) and TP53 p.E271Q(E8)	Multiple lymph nodes enlargement in the mediastinum, calcification of the left hilar lymph nodes	Chinese medicine palliative treatment		12 months
6	Male	78	Stage IA lung adenocarcinoma	Yes	1–2	MET (c.3022C>G)	None	Capmatinib	SD	Alive
7	Male	85	Stage IV lung adenocarcinoma	30-year history	4–5	MET exon14-skipping mutation (c.3028G>T) TP53 p.Y236C(E7) TP53 p.I162T(E5)	Chest metastasis, pericardial metastasis	Crizotinib for 3 months		4 months
8	Male	79	Stage IVB lung sarcomatoid carcinoma	Yes	1	MET p.D1010Y(E14) PIK3CA p.E542K(E9) TP53 p.V173M(E5)	Lymph node metastasis	Crizotinib, one month, savolitinib for 9 months	PR	14 months
9	Female	81	Stage IVB lung adenocarcinoma	No	3	MET (D1010Y) and TP53 p.R280G(E8)	Right hilar lymph node metastasis, Multiple metastases on the left pleura	Chemotherapy, savolitinib for 6 months,		10 months
10	Male	77	Stage IVA lung sarcomatoid carcinoma	No	2	MET (c. 3005 A>T)	None	Chemotherapy and crizotinib	SD	Alive
11	Male	78	Stage IV lung adenocarcinoma	No	4	MET (c. 3005 A>T)	Liver metastases	Crizotinib		5 months

OS, overall survival; SD, stable disease; PR, partial relief.

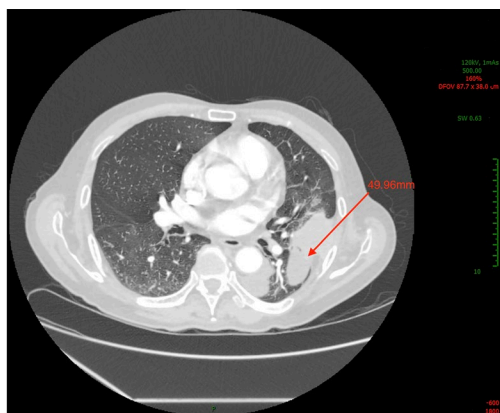


Figure 1 Patient 8: computed tomography before treatment.

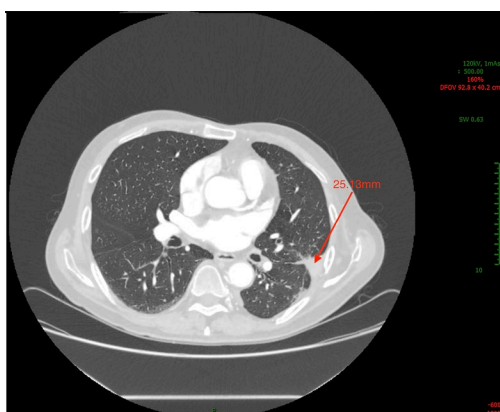


Figure 2 Patient 8: computed tomography after treatment of savolitinib.

commenced capmatinib for 6 months. Symptoms, such as chest pain, were relieved quickly and the patient's condition was stable. At the last follow up, there was no disease progression.

Patient 7

Male, 85 years old, 40-year smoking history. This patient was diagnosed in May 2018 with stage IV lung adenocarcinoma, chest metastasis, and pericardial metastasis. Gene sequencing showed mutations, including *MET* (c.3028G>T), *TP53* p.Y236C (E7), and *TP53* p.I162T (E5). The treatment plan was 250 mg crizotinib twice daily. After 3 months on crizotinib, the disease progressed. Overall survival was 4 months.

Patient 8

Male, 79 years old, non-smoker. The patient was diagnosed

with stage IV lung sarcomatoid carcinoma and multiple lymph node metastases. Lymph nodes throughout the body were not enlarged or swollen (*Figure 1*). Gene sequencing showed mutations, including *MET* (c.3028G>T), *TP53* p.Y236C (E7), and *TP53* p.I162T (E5). The treatment plan was 250 mg crizotinib twice daily. The patient was on crizotinib for one month and then refused to continue taking it. The patient was admitted in August 2020. Head magnetic resonance imaging showed scattered ischemic foci under the cerebral cortex on both sides, as well as brain atrophy. Electronic gastroscopy showed stomach polyps and chronic non-atrophic gastritis. Pathological results confirmed the diagnosis of sarcomatoid carcinoma, and malignant tumor cells were observed in the smear submitted for examination.

On 250 mg crizotinib, the patient developed a taste disorder with obvious bitterness in the mouth, and severe constipation. The patient was found to have level 3 Common Terminology Criteria for Adverse Events. After 1 week, the patient refused to take crizotinib.

In September 2020, the patient commenced 600 mg savolitinib daily. After 2 weeks, the patient regained his taste, and symptoms, such as chest pain and constipation, disappeared. The patient's sleep improved and appetite was restored. The patient claimed that he felt as well as he did before his illness. CT scan showed that the lesion in the upper lobe of the left lung has significantly reduced (22 mm × 24 mm × 27 mm) (*Figure 2*). However, there still were several solid nodules in the oblique fissure of the left lung, with the largest about 5 mm in diameter. The patient had stable disease for over 7 months.

Patient 9

Female, 81 years old. The patient was diagnosed with stage IVB lung adenocarcinoma. Gene sequencing showed *MET* (D1010Y) and *TP53* p.R280G (E8). The patient received chemotherapy, followed by savolitinib, for 6 months, and the disease progressed. Overall survival was 10 months.

Patient 10

Male, 77 years. The patient was diagnosed with stage IVA lung sarcomatoid carcinoma. Gene sequencing indicated *MET* mutations (c.3005 A>T). The patient's PS score was 2, and the initial treatment was chemotherapy and crizotinib. The patient's condition was stable following treatment.

Patient 11

Male, 78 years old, smoker. The patient was diagnosed with

stage IV lung adenocarcinoma. Gene sequencing indicated MET mutations (c.3005 A>T). The patient's PS score was 4, and have severe live metastasis. The patient took crizotinib and in both sites tumor enlarged. The patient's overall survival was 5 months.

Discussion

Lung cancer can be driven by gene mutations (16). *MET* exon 14 skipping mutation is an independent oncogenetic driver gene for NSCLC and usually does not co-exist with other driver gene mutations, such as *EGFR*, *ALK*, and *ROS1*. The incidence of NSCLC carrying METex14 is low. According to the current reports, the clinical manifestation and sequencing information in NSCLC with METex14 skipping mutation are insufficient. To broaden our understanding of NSCLC with MET exon 14, we retrospectively analyzed the clinical and pathological characteristics and therapeutic effects of 11 patients to yield information regarding population profile, treatment, and prognosis.

A previous study has shown that the incidence of METex14 in NSCLC is 1–3% (21). The prevalence rates of METex14 in lung adenocarcinoma ranges from 0.9% to 4% in Asian populations (1,5). The medical reports of 763 patients were collected from our hospital, and 11 patients were found to have METex14. Retrospective studies and clinical research have also indicated that METex14 mutations are more common in elderly patients, males, and advanced NSCLC patients (18–25). Lee *et al.* reported that METex14 is associated with advanced age and acinar or solid histological subtype (17), and METex14 was present in about one-third of Lung sarcomatoid carcinoma patients (26). The findings of the present study are consistent with those of other previously published study (4).

Multi-target TKI including tivantinib, foretinib, glesatinib, cabozantinib, and crizotinib are often compared with single target TKI such as tepotinib, capmatinib, and savolitinib in efficacy for single-target MET-TKI has higher MET inhibitory activity in protein bonding (4,27). In this 11 patients cohort, 8 patients died with metastases and among them 4 died within a year. Those 4 patients developed multiple metastases in pleura or metastases in other organs such as liver. Of the 4 patients, two stage IV lung adenocarcinoma patients received only crizotinib lived 4 and 5 months respectively as one had Chest metastasis, pericardial metastasis and another with liver metastases. And the left two survived beyond 6 months were diagnosed with stage IVB lung sarcomatoid carcinoma

and stage IVB lung adenocarcinoma, respectively. Besides chemotherapy or crizotinib, they both received savolitinib treatment as sequential therapy. The mechanism might be its relatively high oral absorption rate and high selectivity (28). But Patient 4 was an example of a patient who had a better prognosis with multitarget TKI, crizotinib.

From the cases and previous studies, we summarize our experience as follows. First, from our small sample pool, we found that METex14 is more common among males, which is in accordance with a previous study (5) but different from two reports (17,18). Second, off-label treatment crizotinib with METex14 NSCLC was found to be effective against *MET* kinase. The PROFILE 1001 trial found that the ORR was 32% [95% confidence interval (CI): 21–45%] for patients with METex14 NSCLC (n=65) and the median duration of response was 9.1 months (95% CI: 6.4–12.7 months) (29). In 5 patients who were treated with crizotinib, progression-free survival ranged from 3 months up to 24 months. For 1 patient who received capmatinib treatment, a previous clinical study demonstrated that METex14 patients who did not receive any other treatment (n=28) had an ORR of 68% (95% CI: 48–84%) and a median duration of response of 12.6 months (95% CI: 5.6 months to not estimable) per blinded independent review committee (BIRC) (29). To date, those patients are still alive. For Tepotinib, treatment-naive METex14 patients (n=69) had an ORR of 43% (95% CI: 32–56%) and a median duration of response of 10.8 months (95% CI: 6.9 months to not estimable) for tepotinib per BIRC (30). In our study, overall survival was less than 6 months, considering the stage of this disease. Acquired *BRCA2* p.Gln1037Ter (E11) was found in 1 crizotinib-resistant patient. Third, the presence of an oncogenic driver could be a contraindication for the use of immunotherapy in metastatic NSCLC by the National Comprehensive Cancer Network, because these patients, even those with high programmed death ligand-1 levels, do not respond to immunotherapy (31). In our cases, most cases had low programmed death ligand-1. The use of immunotherapy in patients with METex14 NSCLC is not definitive, and reported response rates are ambiguous and warrants further research (32). Finally, we used amplicon-based library preparation techniques for targeted sequencing. Jurkiewicz *et al.* reported a METex14 detection rate of 2.5% (16 of 644 lung cancer tumors analyzed) using an amplicon-mediated, targeted, DNA-based NGS panel (33). Given the diversity of alterations that could lead to METex14 and the potential location of these alterations in the *MET* gene, hybrid capture is the preferred approach

to avoid the allele dropout commonly observed with amplicon-based methods.

In patients with METex14, the choices of first-line treatment drugs must take modality, timing, and adverse effect into consideration. We are considering adopting the full management model for first-line treatment with single-targeted therapy. For well-controlled (PR) patients, the following options lie among combination therapy surgery or SBRT. Although drug resistance were not observed in our cases, biopsy and gene sequencing can be instructive in clinical practice.

To conclude, the incidence of MET exon 14 skipping was found to be lower in females in our sample pool. Because most of our patients were elderly and the gene mutations was highly diversified, the clinical response was poor. The best treatment option needs to be carefully considered. With the increasing use of small molecular inhibitors, acquired resistance mechanisms need to be carefully investigated.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-782/tc>

Data Sharing Statement: Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-782/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-782/coif>). All author report that this work has received technical support in gene mutation screening and other data processing from Shanghai Tongshu Biotechnology. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of the Affiliated Hospital of Guangdong Medical University (No. YJYS2010106). Informed consent was taken from all the patients.

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