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MET IHC is a Poor Screen for *MET* Amplification or *MET* exon 14 mutations in Lung Adenocarcinomas: Data from a Tri-Institutional Cohort of the Lung Cancer Mutation Consortium

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Abstract

Background: *MET* amplification and *MET* exon 14 alterations (*MET*ex14) in lung cancers impart sensitivity to MET kinase inhibitors. Fluorescence *in situ* hybridization (FISH), next-generation sequencing (NGS), and IHC, have been used to evaluate MET dependency. Here, we determined the association of MET IHC with *MET*ex14 mutations and *MET* amplification.

Methods: We collected data from a tri-institutional cohort from LCMC2 (Lung Cancer Mutation Consortium). All patients had metastatic lung adenocarcinomas and no prior targeted therapies. MET IHC positivity was defined by H-score ≥ 200 using SP44 antibody and *MET* amplification by copy number fold change ≥ 1.8x using NGS or *MET*/CEP7 ratio > 2.2 using FISH.

Results: We tested tissue from 181 patients for MET IHC, *MET* amplification, and *MET*ex14 mutations. Overall, 71/181 (39%) were MET IHC positive, 3/181 (2%) were *MET* amplified, and 2/181 (1%) harbored *MET* exon 14 mutations. Of *MET*-amplified cases, 2 cases were FISH

positive with *MET/CEP7* of 3.1 and 3.3, 1 case was NGS positive with fold change 4.4x, and 1/3 of the cases were MET IHC positive. Of IHC positive cases, 1/71 (1%) were *MET* amplified and 2/71 (3%) were *MET*ex14 mutated. Of MET IHC negative cases, 2/110 (2%) were *MET* amplified.

Conclusions: In this study, nearly all MET IHC positive cases are negative for *MET* amplification or *MET*ex14 mutations. MET IHC can also miss patients with *MET* amplification. The limited number of MET amplified cases in this cohort makes it challenging to demonstrate an association between MET IHC and *MET* amplification. Nevertheless, IHC appears to be an inefficient screen for these genomic changes. *MET* amplification or *MET*ex14 mutations can best be detected by FISH and a multiplex NGS panel.

Keywords

MET exon 14; MET amplified; Lung cancer; Next-generation Sequencing; FISH; immunohistochemistry

Introduction

The hepatocyte growth factor receptor (MET) has been shown to be an oncogenic driver in lung cancers. MET pathway activation, either by *MET* amplification or a splice site alteration in exon 14 (*MET*ex14), facilitates lung cancer growth, survival, and metastasis[1, 2]. In lung cancers, both *MET* mutation and amplification are primary oncogenic drivers. *MET* amplification is also a mechanism of acquired resistance to EGFR- and ALK-targeted therapies.

MET pathway activation by *MET* amplification occurs by constitutive signaling through protein expression and kinase activation. De novo *MET* amplification occurs in 1% to 5% of lung cancers, depending on the assay and positivity cut-point used[2]. A global consensus regarding the appropriate cut-off for *MET* amplification based on gene copy number has yet to be reached[3]. One classification scheme by Camidge et al. proposed various categories of *MET*/*CEP7* ratio as follows: low: ≥ 1.8 to ≤ 2.2; intermediate: > 2.2 to < 5; or high: ≥ 5 (although a later classification changed the intermediate cut-point to > 2.2 to < 4 and high cut-point to ≥ 4) and has been applied in clinical settings when treating patients with MET inhibitors[3].

*MET*ex14 mutations produce a skipping alteration that prevents the MET receptor from being degraded, resulting in increased MET activity. *MET*ex14 mutations occur in 3% to 4% of patients with lung adenocarcinomas based on studies employing hybrid capture NGS[4]. These mutations impart sensitivity to MET tyrosine kinase inhibitors (TKI), including cabozatinib, crizotinib, tepotinib, and capmatinib[2, 5].

Some have suggested that MET IHC can serve as a potential predictive marker for MET kinase inhibitor activity. However, studies that used IHC for MET-targeted therapies have been unsuccessful thus far[6, 7]. Moreover, there is growing evidence that MET IHC may not be a good screening test for *MET* amplification or *MET*ex14 mutation in lung cancer[8].

The Lung Cancer Mutation Consortium 2 (LCMC2) was a multi-institutional effort established in 2010 to investigate the frequency of oncogenic drivers in lung adenocarcinoma[9]. Using a tri-institutional cohort derived from the LCMC experience (University of Colorado, Dana Farber Cancer Institute, Memorial Sloan Kettering), we set out to determine the association of MET IHC testing with *MET* amplification or *MET*ex14 mutation status in patients with metastatic lung adenocarcinomas.

Methods

Patient recruitment, enrollment, and IRB approval

Data was collected from three of the institutions that participated in LCMC2[9]. All sites obtained Institutional Review Board approval for this study. Patients undergoing further evaluation for the diagnosis or treatment of stage IV or recurrent lung adenocarcinomas were prospectively enrolled if they provided written informed consent, as previously described[9]. In addition, patients were eligible if they had no prior treatment with targeted therapy, a diagnosis of metastatic disease between May 2012 to January 2016, and adequate tissue for molecular analyses. All subjects enrolled were provided written informed consent. Epidemiologic and clinicopathologic data including age, sex, and cigarette smoking history were collected.

Pathology evaluation

Molecular testing and the diagnosis of lung adenocarcinoma was confirmed by pathologists at each institution. The diagnosis of lung adenocarcinoma was confirmed centrally with the pathology report and review of a hematoxylin- and eosin-stained histology slide or a scanned whole-slide image (Leica Biosystems Inc.). All testing was done in Clinical Laboratory Improvement Amendments (CLIA) laboratories.

IHC and FISH detection

MET amplification was determined by *MET* FISH (Roche/Ventana) and NGS. FISH assays were performed with laboratory-developed reagents as previously described[10]. Amplification by FISH was considered present when the *MET*/*CEP7* ratio was > 2.2.

IHC for MET (clone SP44, Roche/Ventana) was independently validated at each site. MET IHC was defined as positive if the sample had an H-score ≥ 200, following a previously established method[11]. Pathologist training and interlaboratory proficiency testing were used for IHC scoring (Supplemental Methods).

Mutational analyses

Mutational analyses were performed using methods previously described[9]. Mutations included in these studies include *AKT1*, *BRAF*, *EGFR*, *ERBB2*, *KRAS*, *MAP2K1*, *MET*, *NRAS*, and *PIK3CA*. During the course of this study, many diagnostic laboratories converted from single gene testing to NGS methods. NGS technologies at each site are provided (Supplementary Table S2). They were independently validated for both wet-bench and bioinformatics components and were also centrally reviewed. *MET* exon 14 testing was performed at selected LCMC sites. *MET* amplification by NGS was considered to be

amplified from NGS when copy number fold change (log_2 ratio) is ≥ 1.8x assuming 50% tumor content. At least a 50X mean target coverage was needed for a sample to pass analysis.

Statistical Analysis

Mann-Whitney Test was used to compare categorical values. All reported p-values are for two-sided hypothesis tests conducted at the 0.05 level.

Results

One hundred eighty-one patients from three institutions had tissues tested for MET IHC, *MET* amplification, and *MET*ex14 mutation with FISH or NGS. The median age at diagnosis was 65 years, 57% (104/181) were women, and 71% (129/181) were current or former smokers (Table 1). The prevalence of *MET* amplification by FISH or NGS was 2% (3/181, 95% CI: 3.4 to 5.0%) (Figure 1). Two *MET* amplified cases were detected by FISH and 1 by NGS. MET IHC by H-score was negative in 2/3 of the patients (Table 2). MET IHC status was unchanged by MetMab scoring criteria. Two of these MET IHC negative patients also had a concurrent *KRAS* G12C mutation.

*MET*ex14 was seen in 1% (2/181, 95% CI: 0% to 4.2%) (Table 1). The two patients with *MET*ex14 mutation were 73 and 83 years of age, female, and former smokers. MET IHC was positive in both of these cases (Table 2). Of note, neither case had concurrent *MET* amplification.

MET IHC was positive in 39% (71/181, 95% CI: 32 to 47%) (Table 1). Of the patients with MET IHC positive lung cancer, 1% (1/71) had *MET* amplification by FISH and 3% (2/71) had *MET*ex14 mutation by NGS. MET IHC was negative in 61% (110/181) of cases and, of these, 2% (2/110) were *MET* amplified (Figure 1B). Of the cases without amplification, MET IHC was positive in 39% (70/181). Two of these seventy MET IHC positive cases also had *MET*ex14 mutations.

A total of 85 cases (47%) had both MET IHC and *MET* FISH performed. The median *MET/CEP7* ratio of MET IHC negative cases (1.1, n = 49) was not different from that of MET IHC positive cases (1.14, n = 36; Mann-Whitney test, p = 0.57) (Figure 2). The median *MET* FISH copy number was also not different between MET IHC negative (3.3, n = 49) and that of positive cases (3.5, n = 36; Mann-Whitney test, p = 0.20) (Figure 2B). Using a higher cut-off to define IHC positive (H-score 300) did not select for *MET* amplified cases (Figure 2C).

Discussion

Attempts to use MET IHC as a marker of MET dependency have largely been unsuccessful. Recently, MET IHC was shown to correlate poorly with *MET/CEP7* ratio in all stages of sarcomatoid lung cancer studied[8]. In this tri-institutional cohort of patients with metastatic lung adenocarcinoma, more than 1/3 of cases were MET IHC positive, but only 2% were *MET* amplified. MET IHC also did not detect MET in 2 of the 3 *MET* amplified cases.

Two cases of *MET*ex14-mutated lung cancer were also MET IHC positive. Other studies have also shown that lung cancers with *METex14* mutations are often IHC positive[12–14]. These studies also show that MET IHC is a poor screening strategy for *MET*ex14, considering how frequently MET IHC is positive in lung cancers[9, 13]. In this study, 96% of MET IHC positive cases had no detectable *MET* amplification or *MET*ex14 mutation. Finally, no clear association was observed between IHC and *MET* amplification by FISH in this study. The low number of *MET*ex14 mutations or *MET* amplification by NGS makes it difficult to determine an association with MET IHC. The sensitivity and specificity of H-score for evaluating for a *MET* genomic aberration (either *MET* exon14 mutation or *MET* amplification by FISH or NGS) in this series were both 0.6.

This study was limited by the low number of *MET* amplified and mutated cases. The prevalence of *MET* amplification (2%) in our cohort was similar to earlier reports. However, this prevalence was lower than that reported in LCMC2 as a whole. This discrepancy is likely due to the use of different cut-offs for *MET* amplification in post-hoc analyses between our cohort and that in LCMC2[9]. Furthermore, differences in the prevalence of *MET* amplification between cohorts may be limited by the precision of current methodologies. Recently, it was shown that there was a surprising amount of intratumoral heterogeneity of MET copy number gain and amplification as determined by FISH[15]. In addition, NGS could potentially miss some cases of *MET* amplification that would otherwise be called by FISH. How well *MET* amplification by NGS correlates with *MET* amplification by FISH is not well-understood and needs to be further explored[15].

The prevalence of *MET*ex14 (1%) is also lower than that reported in the literature, which may be related to poor coverage of relevant target regions in *MET*ex14 with earlier versions of the NGS panels used in this study. Issues with *MET*ex14 coverage with older NGS panels has been described and newer generation NGS panels, which were implemented as the study progressed, provide better coverage of these regions[16]. Although the low number of *MET* amplification and *MET*ex14 mutation in this study makes it difficult to draw a strong conclusion about the diagnostic accuracy of MET IHC, the large number of false-positive MET IHC cases in this cohort suggests that MET IHC is a poor screen for *MET* amplification and *MET*ex14 mutation.

Multiple trials have used MET IHC as a predictive marker for MET-directed therapies, such as onartuzumab, but have largely been unsuccessful[6, 7]. In contrast, ongoing studies with MET tyrosine kinase inhibitors have seen more success with using high *MET* copy numbers (gene copy number >5) and *MET*/*CEP7* ratios as predictive markers[1, 3]. Coupling the results of these trials with growing literature showing that MET IHC inadequately selects for *MET* amplification or *MET*ex14 mutations strongly challenges its use as a screen for *MET* dependency. Multiplex next-generation sequencing panels in use today detect actionable targets (like *EGFR*, *ALK*, *ROS1*, and *BRAF*) and nearly always assess *MET* copy number and *MET* exon 14 mutations. We recommend that tissue should be prioritized for NGS and FISH over IHC to test for actionable *MET* mutations or amplification in lung adenocarcinomas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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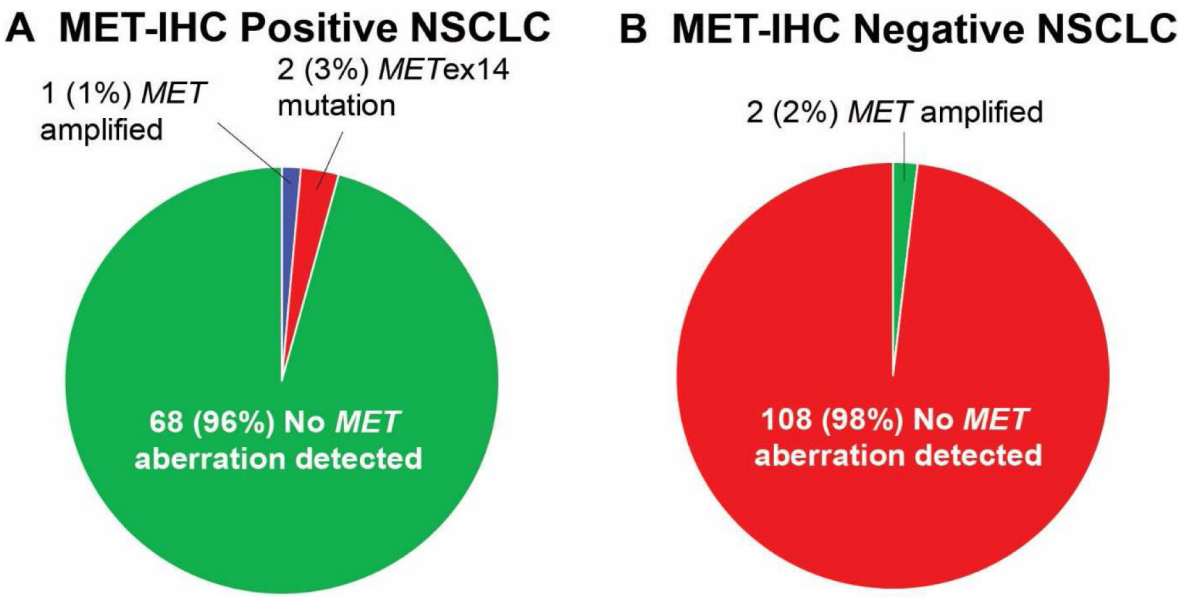

Figure 1. *MET*ex4 and *MET* amplification status in MET IHC positive and negative cases by H-score.

A) Of the MET IHC positive cases by H-score, *MET* amplification or *MET*ex14 was seen in 1% and 3% of cases, respectively. B) Of the MET IHC negative cases, only *MET* amplification was seen in 2% of cases.

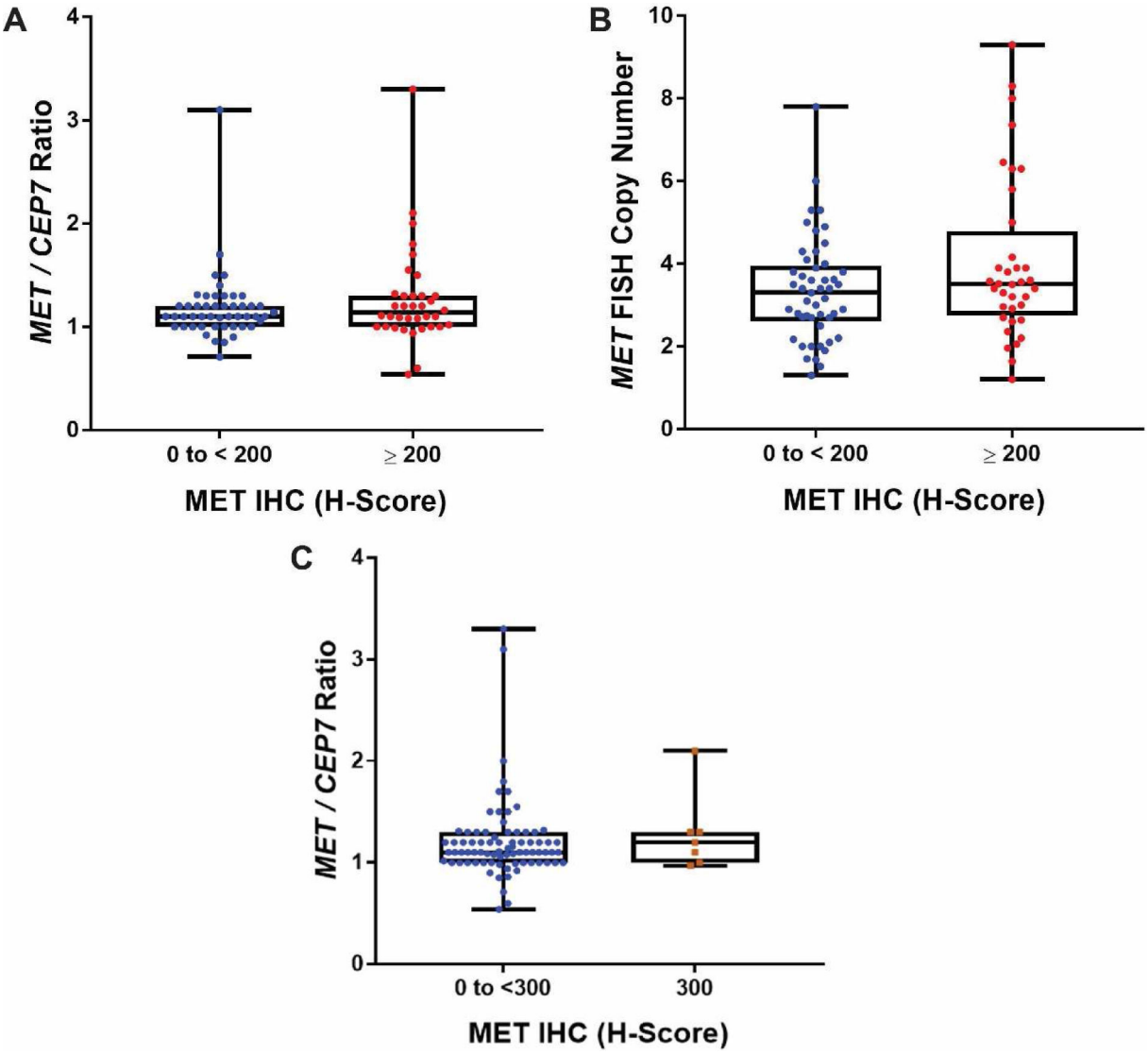

Figure 2. Box plot representations of *MET/CEP7* ratios and MET FISH copy numbers compared to MET IHC H-Score.

Boxes represent the interquartile range, which contains 50% of the values, whereas lines extend the entire range of values. A) Median *MET*/*CEP7* ratios of MET H-scores from 0 to < 200 (1.1, n=49) and ≥ 200 (1.135, n=36) are not significantly different (Mann Whitney test: p=0.57). B) Median *MET* FISH copy number from 0 to < 200 (3.3, n=49) and ≥ 200 (3.5, n=36) are also not significantly different (Mann Whitney test: p=0.2). C) Median *MET*/*CEP7* ratios continue to overlap when comparing MET H-scores from 0 to < 300 (1.1, n=78) and the max score (300) (1.2, n=7) (Mann Whitney test: p=0.58).

Table 1.

Features of patients with metastatic lung adenocarcinomas with MET testing[*].

The clinical characteristics of 181 patients with MET IHC and *MET* FISH or massively parallel sequencing testing are described.

	All patients (n=181)
Age at Diagnosis of Metastatic Disease	
median	64 years
range	(18–90 years)
Sex	
female	104 (57%)
male	77 (43%)
Smoking history	
never smoker	50 (28%)
former smoker	118 (65%)
current smoker	11 (6%)
unknown	2 (1%)
MET IHC by H-Score	181 (100%)
Positive	71 (39%, 95% CI: 32% to 47%)
Negative	110 (61%, 95% CI: 54% to 68%)
MET FISH	85 (47%)
Positive	2 (1%, 95% CI: 0% to 4.2%)
Negative	83 (46%, 95% CI: 39% to 53%)
MET NGS	181 (100%)
MET ex14 mutation	2 (1%, 95% CI: 0% to 4.2%)
MET amplification	1 (1%, 95% CI: 0% to 3.4%)
No *MET* mutation	178 (98%, 95% CI: 95% to 100%)

[*] Percentages may not total 100 because of rounding.

Table 2.

Patients with *MET* amplification or *METex14* mutation.

Five patients with either *MET* amplification or *MET*ex14 mutation are identified. *MET* amplification was detected by FISH in 2/3 (67%) of the patients. Next-generation sequencing detected a concurrent *KRAS* G12C mutation in both. Amplification in case 3 was detected by next-generation sequencing. One out of three patients that were *MET* amplified were also MET IHC positive by H-score. *MET*ex14 was seen in two patients and both were MET IHC positive. These results were unchanged when using IHC status by MetMab scoring criteria.

	***MET* Amplification**	**MET mutation by NGS**	**Other Drivers**	**MET IHC by H-score**
Case 1	Positive by FISH (MET/CEP7 3.1)	None	*KRAS* G12C	Negative
Case 2	Positive by FISH (*MET/CEP7* 3.3)	None	*KRAS* G12C	Positive
Case 3	*MET* amplified by NGS (Fold 4.4)	None	None	Negative
Case 4	None	*MET*ex 14	None	Positive
Case 5	None	*MET*ex 14	None	Positive