



MET immunochemistry: a reliable screening tool for MET exon 14 skipping mutations in non-small cell lung cancer?

Melinda A. Pruis^{1,2}, Jan H. von der Thüsen³, Hendrikus Jan Dubbink³

¹Department of Pulmonary Diseases, ²Department of Medical Oncology, ³Department of Pathology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

Correspondence to: Dr. Hendrikus Jan Dubbink. Department of Pathology, Erasmus MC Cancer Institute, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. Email: h.dubbink@erasmusmc.nl.

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Worldwide, lung cancer kills more people than any other cancer (1). The median survival of patients with advanced lung cancer is approximately 9 months (2,3). However, the discovery of actionable driver mutations and subsequent development of targeted therapy has dramatically improved the survival of a subset of lung cancer patients (4,5). Amongst the newer driver mutations in non-small cell lung cancer (NSCLC) is the MET exon 14 skipping mutation, which leads to a more stable active MET receptor and affects about 2–5% of non-squamous NSCLC (6,7). Patients with this mutation are generally older and have a smoking history (7). No significant gender predilection has been determined. Especially for this elderly population, it is compelling to consider targeted anti-cancer therapy rather than intense chemotherapy regimens, and in several studies targeting MET exon 14 skipping mutations showed promising results (7-10). The surge of development of MET inhibitors has led to a need for reliable and feasible diagnostic tests and predictive biomarkers.

For detection of MET exon 14 skipping mutations different strategies can be applied. Tumor RNA analysis is potentially the most accurate, because it allows for detection of all resulting MET exon 13–15 fusions independent of the underlying DNA mutation (11). However, acquiring sufficient tumor tissue for RNA analysis is often difficult (11). An alternative is tumor DNA-based analysis, which detects the specific genomic alterations leading to exon 14 skipping. Exon 14 skipping can, however, be caused by a variety of mutations, including point mutations or small

deletions involving the corresponding splice sites, large intron-exon or exon-intron spanning mutations and large, entirely intronic, deletions present in the adjacent introns, so a dedicated DNA panel is required to cover all these mutations (12). While DNA testing is highly specific and sensitive, it is relatively expensive with a limited availability in routine diagnostic laboratories (7). Also, large deletions can easily be missed by DNA-based next generation sequencing (NGS), but alternatively might be detected by fragment length analysis (FLA) (12,13).

In the brief report of Baldacci *et al.* they investigated if MET overexpression is predictive for the presence of MET exon 14 skipping mutations (14). This could be relevant as a screening tool for MET exon 14 skipping mutations. For their research, they used the IFCT-PREDICT.amm cohort, which consists of 843 patients with treatment-naive advanced NSCLC, who were prospectively observed in a longitudinal cohort study from 2013–2014. For the analysis, 91 patients with a high MET overexpression (MET 3+ immunoscore) were included. MET exon 14 skipping mutations were investigated by combining DNA-based NGS and FLA as described by Descarpentries (13). Two out of 91 patients in the MET immunohistochemistry (IHC) high group had a MET exon 14 skipping mutation. In addition, they analyzed a group of 131 patients with no or low MET expression. In this group, also 2 patients had a MET exon 14 skipping mutation. They conclude that the rate of MET exon 14 skipping mutations is similar in patients with no or low *vs.* high MET expression.

Combined mutation and gene copy number analysis in the high MET overexpression patients demonstrate that only 10% of these patients showed a MET exon 14 mutation or a MET gene amplification. The majority of high MET overexpression seems therefore not be directly linked to a genetic aberration of the MET gene. Also, their results indicate that high MET overexpression is not mutually exclusive with other oncogenic driver mutations, like activating EGFR or KRAS mutations.

As the detection of MET exon 14 skipping mutations poses difficulties, the researchers in this study by Baldacci *et al.*, opt for MET IHC as a screening tool for MET exon 14 skipping mutations (14). They combined NGS with FLA, so probably no MET exon 14 skipping mutations were missed and indeed the prevalence of 2.2% is in accordance with current literature (7,14). While 2 patients is a small number to base firm conclusions on, Guo *et al.* performed a similar study in 2019 and they came to the same conclusion as Baldacci *et al.*: MET IHC is not suitable as a screening tool to detect MET exon 14 skipping mutations (15). In 2018, Lambros *et al.* also described MET IHC as a very weak tool for screening purposes and they report that MET IHC might even decrease the probability of predicting MET exon 14 skipping mutations in a multiclass model (16). This can be explained by several reasons. First of all, not all MET exon 14 skipping mutations are IHC MET positive, probably due to technical issues with MET IHC assessment, and heterogeneity in scoring systems and interpretation (17). In addition, large validation studies for the Ventana SP44 antibody, which is widely used for measuring MET expression, are lacking and SP44 might be less reliable for detecting MET protein products in reducing conditions (17). Baldacci *et al.* also suggest that some phenotypical variations of MET exon 14 skipping mutations might not result in MET overexpression (14,18). Secondly, in this study, only 10% of the lung cancer patients with high MET expression displayed an underlying genetic alteration of MET. This indicates that there might be other causes of MET upregulation, making MET overexpression a very non-specific screening tool for MET gene aberrations (19). Another limitation of MET IHC is that the measured MET expression does not always correlate with p-MET (activated MET receptor) and therefore does not reflect MET activation (20,21). The usefulness of MET IHC in the selection of MET amplification is also dubious. Many studies do find a correlation between MET amplification and MET IHC positivity, as is to be expected (22-25).

More recently, however, Guo *et al.* reported no association between MET IHC positivity and MET amplification measured by NGS or fluorescence in situ hybridization (FISH) and also Schuler *et al.* showed no correlation between MET amplification by FISH and MET expression by IHC (15,26).

In addition, several trials have investigated the possibility of MET IHC as a predictive biomarker for targeted MET therapy (27,28). Unfortunately, the disappointing results of these studies unambiguously demonstrated that MET IHC is a weak biomarker for MET inhibitors (26-28).

Based on these results, we believe that, currently, there is no place for MET IHC as screening tool or as biomarker for MET exon 14 skipping mutations. Therefore, detection of MET exon 14 skipping mutations remains dependent on RNA and DNA analysis.

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