

### Editor's Note:

In the era of personalized medicine, a critical appraisal new developments and controversies are essential in order to derived tailored approaches. In addition to its educative aspect, we expect these discussions to help younger researchers to refine their own research strategies.

## Controversies on Lung Cancer: Pros and Cons

# Rebuttal from Professor Sanja Dacic

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First of all, I would like to thank Dr. Helmut H. Popper for his discussion on controversial areas in the 2015 WHO classification of mucinous lung adenocarcinomas. Many points are related to the fact that mucinous adenocarcinomas are less common than non-mucinous lung adenocarcinoma and our knowledge about this subset of lung carcinoma is still relatively limited.

The definition of mucinous adenocarcinoma in situ (AIS) is essentially the same as the pathological definition of former mucinous bronchioloalveolar carcinoma. I agree that is hard to follow the literature on mucinous non-invasive lesions before the 2015 WHO classification, mainly because the pathologists were the only one using a very strict definition outlined in the WHO book. On the other hand, the definition that our clinical colleagues used frequently included invasive lepidic predominant adenocarcinomas that can mimic, particularly on imaging studies, non-invasive adenocarcinoma. Therefore, the major accomplishment of the 2015 WHO classification is that it represents a multidisciplinary classification which is a result of many fruitful discussions between experts in thoracic pathology, radiology, surgery and oncology. A recent literature clearly demonstrates a shift in the clinical definitions of AIS.

Professor Popper goes into great details about statements in regards to mucin production and patterns associated with mucinous adenocarcinoma. I agree with the statement that

quantification of mucin is challenging in lung carcinomas, and that the definition is rather vague (i.e., “abundant”). The main issue is that the literature is limited on this issue, and some statements in the WHO classification are based on personal experiences rather than scientific evidence. Furthermore, some criteria cannot be always precisely quantitated and therefore more descriptive terms have been used. Use of mucin may be challenging and sometimes misleading on small biopsy specimens, while the adenocarcinoma classification on the resection specimen is rarely an issue. The use of different MUC antibodies was also discussed, but from my own experience, these are not very helpful in separating mucinous from non-mucinous lung adenocarcinoma. Most of the cases of a primary mucinous versus non-mucinous adenocarcinoma can be easily separated based on morphology alone and no other ancillary studies are needed. In contrast, mucinous adenocarcinomas can be very challenging to separate from metastatic mucinous adenocarcinoma such as pancreas.

An idea of solid adenocarcinoma being classified as mucinous adenocarcinoma is challenging particularly if mucin is considered to be one of the main criteria for such proposal. Intracellular mucin can be identified in many types of lung carcinoma including squamous cell carcinoma, large cell carcinoma and carcinoids. This well-known observation argues against mucin as diagnostic criteria for classifying

tumor as adenocarcinoma. The 2015 WHO classification of lung carcinoma for the first time in addition to morphology also uses tumor immunophenotype. For example, former large cell carcinomas with TTF-1 expression and with negative mucin are classified as solid adenocarcinoma.

Professor Popper has also challenged some less clear terminology issue that could be particularly difficult to apply if taken out of context such as use of the term “lepidic predominant adenocarcinoma” which is reserved for non-mucinous adenocarcinoma; while invasive mucinous adenocarcinoma is recommended for mucinous adenocarcinoma. These issues are better discussed in the original 2011 IASLC/ATS/ERS lung adenocarcinoma classification.

*KRAS* mutations are the most predominant genomic abnormality in lung adenocarcinomas in Western population (1,2). Recent publications comparing mucinous and non-mucinous adenocarcinomas indicate differences in the amino acid substitutions between mucinous and non-mucinous adenocarcinoma. Furthermore, a correlation with immunophenotype has been reported. Invasive mucinous adenocarcinomas with *KRAS* mutations and frameshift or nonsense mutations of *NKX2-1* are negative for TTF-1 (also called Nkx2.1) (3). However, they express gastrointestinal markers such as CDX2. It is also interesting that 73% of primary lung mucinous adenocarcinoma show *KRAS* mutations G12D and G12V that are frequently observed in mucinous colorectal and pancreatobiliary adenocarcinoma. This is in contrast to non-mucinous lung adenocarcinoma that more often show G12C *KRAS* mutation (4,5). The prognostic value of *KRAS* mutations is still controversial, with many reports indicating negative prognostic value and some reports challenging this observation. The prognostic role of *KRAS* remains to be investigated in prospective studies.

I agree with the statement that signet ring adenocarcinoma and cystadenocarcinoma should be kept in the WHO classification. Signet ring adenocarcinoma of the lung is frequently associated with *ALK* gene rearrangements and

occurs in younger patients with no history of cigarette smoking. Therefore, I believe that it should be kept as a subtype of mucinous adenocarcinoma, rather than cytological variant. Similarly, cystadenocarcinoma has distinct clinical, prognostic and morphological features that would justify its classification as a distinct entity.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

### References

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