

### 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

# Pros: the present classification of mucinous adenocarcinomas of the lung

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## Introduction

Mucinous lung adenocarcinomas are relatively uncommon and represent 2% to 10% of all lung adenocarcinomas. The 2015 WHO classification of lung tumors essentially adopted the International Association for the Study of Lung Cancer proposal for the reclassification of lung adenocarcinomas (1,2). A proposal to reclassify mucinous bronchioloalveolar adenocarcinoma to invasive mucinous adenocarcinoma was based on the observation that majority, if not all, of formerly known mucinous bronchioloalveolar adenocarcinomas are invasive and show more aggressive behavior when compared to non-mucinous bronchioloalveolar adenocarcinoma (3). All mucinous adenocarcinomas are currently classified under variants of lung adenocarcinoma and in addition to invasive mucinous adenocarcinoma also include colloid adenocarcinoma, and enteric adenocarcinoma. The classification into separate variants is based on morphology, immunoprofile, genomic and clinical characteristics. An alternative approach to lung adenocarcinoma, classifies mucinous adenocarcinomas as the non-terminal respiratory unit (TRU)-type because of their origin from the bronchial epithelium or submucosal glands and a gastric-mucin

phenotype (4).

## Morphology

Mucinous adenocarcinomas of the lung show easily recognizable and distinct morphology. The tumor is composed of goblet and/or columnar cells with small basally oriented nuclei and associated with abundant intra- and extra-cellular mucin. Nuclei are frequently bland appearing and occasionally may show mild atypia. Extracellular mucin is particularly abundant in colloid variant. Mucinous adenocarcinomas most often show lepidic growth with focal invasion, and therefore, depending on the size of invasion may be classified as a minimally invasive ( $\leq 5$  mm) or invasive adenocarcinoma ( $> 5$  mm). Mucinous adenocarcinomas with stromal invasion show less cytoplasmic mucin and more cytological atypia. If no invasion is identified, tumors are classified as mucinous adenocarcinoma *in situ*, although it has been recognized that invasion is present in majority of cases. Cytologically, mucinous adenocarcinoma show abundant extracellular mucin with monolayers of bland columnar cells forming “drunken honeycomb”.

The WHO makes distinction between mucinous

adenocarcinoma and adenocarcinoma with mucin production based on the presence of goblet or columnar cells in former. Metastatic mucinous adenocarcinoma of the pancreas and ovary are morphologically similar if not identical to primary mucinous adenocarcinoma of the lung. Frequently the distinction between primary tumor and metastasis is based on clinical presentation and imaging findings rather than on morphology alone. Similarly, colloid adenocarcinoma of the lung may be indistinguishable from intestinal or breast metastases.

Enteric adenocarcinoma are morphologically and immunophenotypically similar to colorectal adenocarcinoma, which is the main differential diagnosis.

### Immunophenotype

Invasive mucinous adenocarcinoma frequently shows a distinct immunoprofile, which is different from the immunoprofile of other major subtypes of lung adenocarcinoma. Common subtypes of lung adenocarcinoma express cytokeratin 7 and in about 75% of the cases TTF-1, while cytokeratin is typically negative. In contrast, mucinous adenocarcinomas in addition to cytokeratin 7, typically co-express cytokeratin 20. TTF-1 and napsin A are usually negative (5,6). Yatabe *et al.* reported variability in intensity of staining for CDX2 and cytokeratin 20 in a large proportion of goblet cells within the same tumor. Authors also noted that the goblet cell morphology and staining patterns were similar to colorectal adenocarcinoma with *KRAS* mutation, pancreatobiliary and ovarian mucinous tumors (7).

Colloid adenocarcinoma may show focal and weak expression of cytokeratin 7 and TTF-1. Furthermore, they tend to show expression of intestinal markers such as CDX2 and MUC2 (6). Similarly, enteric adenocarcinomas express at least one of the markers of enteric differentiation such as cytokeratin 20, CDX2 or MUC2 (8). About half the cases also express cytokeratin 7 and TTF-1, which is a very helpful feature in the distinction from metastatic colorectal adenocarcinoma. Overall, the interpretation of immunohistochemical stains in mucinous adenocarcinoma could be very challenging, and the knowledge of imaging studies and clinical history is essential in distinction between lung primary mucinous adenocarcinoma and metastatic carcinomas.

### Molecular characteristics

Many studies reported a correlation between lung

adenocarcinoma morphology and genotype. Although correlation between histology and genotype is not absolute some significant associations have been reported. For example, non-mucinous AIS, micropapillary, papillary and lepidic subtypes have been associated with *EGFR* mutations (9). Similarly, V600E *BRAF* mutations have been reported in the association with the same subtypes of invasive lung adenocarcinoma (10). However, the strongest correlation between histologic subtype and genotype was found in invasive mucinous adenocarcinoma. Marchetti *et al.* were among the first to report a correlation between mucinous bronchioloalveolar carcinoma and *KRAS* mutations (11). This observation was confirmed by several studies that reported *KRAS* mutations in about 60% of invasive mucinous and 15% colloid adenocarcinomas (12,13). A correlation between immunoprofile and genotype has also been well documented. Invasive mucinous adenocarcinomas with *KRAS* mutations and frameshift or nonsense mutations of *NKX2-1* are negative for TTF-1 (also called Nkx2.1) (14). 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 (15,16).

Recently, recurrent *CD74-NRG1* somatic gene fusions were discovered in 7–26% of invasive mucinous adenocarcinomas (17,18). *CD74* is the most frequently found *NRG1* fusion partner, but novel *NRG1* partners have been described, such as *SLC3A2-NRG1* and *VAMP2-NRG1*. *NRG1* fusions are mutually exclusive with *KRAS* mutations. Although *NRG1* gene rearrangement are strongly associated with mucinous morphology, recently *RBPMS-NRG1*, *WRN-NRG1*, and *SDC4-NRG1* fusion have been reported in other types of lung adenocarcinoma and squamous cell carcinomas (19). Shim *et al.* performed targeted next-generation sequencing for gene fusions and mutations on *KRAS* wild type mucinous adenocarcinomas. They described a large number of gene fusions, in addition to *NRG1* fusions, *TRIM4-BRAF*, *TPM3-NTRK1* and *EML4-ALK* gene fusions, unexpectedly rare p53 gene (TP53) mutations, and an overall low number of mutations. Potentially targetable gene mutations such as ERBB2 and BRAF were identified; however, no *EGFR* mutations were found (16,20).

## Clinical presentation and treatment

Mucinous lung adenocarcinomas have been associated with poor overall survival and progression-free survival when compared to other subtypes of lung adenocarcinomas. They tend to present at advanced stage of disease that cannot be surgically treated.

## Imaging

Although overlaps in imaging features of mucinous and non-mucinous adenocarcinomas exist, there are some differences that are best appreciated on thin section CT. Furthermore, mucinous tumors tend to be multifocal. Non-mucinous adenocarcinoma *in situ* typically presents as a pure ground glass nodule, while mucinous AIS tend to appear as a solid nodule or consolidation. Imaging features of minimally invasive carcinoma are still not well characterized, but mucinous minimally invasive carcinoma tend to appear as a solid or part-solid nodule while non-mucinous is part solid nodule with significant ground glass appearance. Invasive mucinous and non-mucinous adenocarcinoma show a range of overlapping imaging features such as ground glass opacities and mixed ground glass opacities and solid foci.

## Treatment

Non-mucinous lung adenocarcinomas show a significant number of targetable genomic alterations that provided new approaches to treatment of these carcinomas particular with tyrosine kinase inhibitors. That is in contrast to invasive mucinous adenocarcinomas that frequently do not show targetable genomic alterations and have to be subjected to more traditional cytotoxic chemotherapy options. Therefore, a discovery of *NRG1* fusion represents a promising therapeutic target in mucinous adenocarcinoma. *NRG1* fusions lead to *NRG1* III-b3 isoform expression in invasive mucinous adenocarcinoma. *NRG1* III-b3 binds the extracellular domain of *ERBB3*, causing heterodimerization of *ERBB3* with *ERBB2*. This results in activation of the downstream *PI3K-AKT* and *MAPK* pathways that could be targetable. Preclinical studies demonstrated that *NRG1* fusion-mediated signaling could be effectively suppressed by tyrosine kinase inhibitors such as lapatinib and afatinib.

## Summary

Mucinous adenocarcinomas represent morphologically

distinct group of lung adenocarcinomas. Distinguishing molecular features further support classification of these tumors into separate diagnostic category.

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None.

## Footnote

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

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