

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

Tumor cell proliferation, proliferative index and mitotic count in lung cancer

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The rate of cellular proliferation, expressed either as a Ki-67 proliferative index (PI) by immunohistochemistry (IHC) or as a mitotic count by H&E is a reflection of tumor cell division. Although both assess the uncontrolled proliferation of a cancer, they measure different phases of the cell cycle. Like each test, as Drs. Kriegsmann and Warth mentioned, both these parameters are subject to preanalytic and analytic bias, lack of standardized methodology and interobserver variation. Despite all these drawbacks, multiple studies have shown a good correlation between Ki-67 PI and mitotic count (1-12). Before we respond to the comments stated by Kriegsmann and Warth, we have to ask ourselves if any of these tests would impact the prognosis or prediction of patients with lung cancer. The questions are: (I) is there a significant and independent correlation between tumor cell division and the aggressiveness of the lung cancer, prognosis of the patient, loco-regional and distant tumor spread? and (II) Is Ki-67 useful for separating different tumor entities? We initially discussed the value of Ki-67 PI, as a characteristic of tumor cell division in three separate situations: (I) as a prognostic marker in non-small cell lung cancer; (II) as a predictive marker of brain metastasis in non-small cell lung carcinoma; and (III) as a diagnostic characteristic of pulmonary neuroendocrine tumors.

Ki-67 as a prognostic marker in non-small cell lung cancer

In contrast to the immediate clinical value of Ki-67 in pulmonary neuroendocrine tumors, the issue of a proliferative marker in NSCLC is less clear and less practical. We disagree with our colleagues that “meta-analyses reveal that the prognostic and predictive impact of the PI is debatable” (13,14) when in fact both showed that “high Ki-67 values are correlated with a poor prognosis and a shorter disease free survival, shorter recurrence free survival after lung tumor resection”. These findings were demonstrated at least in lung adenocarcinomas in both western and Asian populations. Part of the disagreement comes from the fact that the majority of studies included indiscriminately both lung adenocarcinoma and lung squamous cell carcinoma, since a recent study has shown, for unexplained reasons, opposing effects of Ki-67 PI on prognosis of these two types of lung cancer (15). Ki-67 was a highly significant independent predictor of disease free survival for lung adenocarcinoma, but not for overall survival or disease specific survival. Paradoxically, the authors found that in squamous carcinoma a high PI in squamous carcinoma was correlated with a better overall survival rates. It is doubtful that Ki-67 will be incorporated into the clinical practice as an indicator of prognosis in NSCLC. What remains to

be seen is if the evaluation of mitoses in lung cancer will be incorporated in a grading scheme. Recent published analyses have attempted to incorporate a mitotic count into a more or less simple grading scheme (16,17).

Reports to correlate the number of mitoses in primary lung cancer with the subsequent development of brain metastases have been attempted so far (18).

We agree with our colleagues, Drs. Kriegsmann and Warth that “despite this exhausting amount of literature, the translation of proliferation assessment into daily routine has largely failed”. We partially disagree since counting mitoses on H&E slides and evaluation of necrosis remain the major diagnostic criteria to separate pulmonary neuroendocrine tumors into typical carcinoid tumors (0–1 mitoses per 2 mm²), atypical carcinoid tumors (2–10 mitoses per 2 mm²) and large cell neuroendocrine carcinomas (more than 10, usually 50 mitoses per 2 mm²). This is not a trivial issue since typical carcinoid tumors are considered virtually benign and have a 5-year survival rate higher than 90%, whereas patients with atypical carcinoid tumors have a much shorter overall survival rate (5-year overall survival rates of 50%). Ultimately, patients with large cell neuroendocrine carcinoma have a dismal prognosis (19).

In contrast with neuroendocrine tumors of the gastrointestinal tract where the Ki-67 PI is incorporated in the diagnostic clinical algorithms and is part of the pathology standard of practice, in pulmonary neuroendocrine tumors, Ki-67 PI is not yet incorporated in the standardized clinical practice. Numerous recent studies have shown a great correlation between Ki-67 PI and the three diagnostic categories in pulmonary neuroendocrine tumors (5,12,20). The only unknown remains choosing the cutoff points to separate these three entities and prospective validation studies are needed. Despite these drawbacks, the assessment of Ki-67 in pulmonary pathology for classifying pulmonary neuroendocrine tumors, it's undoubtedly irreplaceable, helpful, and indisputable. The powerful informative value of Ki-67 PI IHC becomes even more evident when assessing small biopsies with a cut surface area smaller than 2 mm². In this instance, the practicing pathologist does not have the opportunity of assessing ten high power fields (40× objective lens magnification, which translates to an assessable surface area of 2 mm²). Therefore, the WHO definition criteria for pulmonary neuroendocrine tumors are not applicable, especially when one deals with a suboptimal biopsy material or with cells with extensive crush artifact. In this instance, IHC for Ki-67 could provide at least an approximate distinction of

typical carcinoid (virtually no Ki-67 expression) versus large cell neuroendocrine carcinoma or small cell carcinoma (with virtually 100% positive Ki-67 tumor cells). This is probably one of the most important diagnostic issues in pulmonary pathology which has immediate therapeutic implications especially for patients with small cell carcinoma who have to be treated immediately (21). Hopefully, future studies will address the incorporation of Ki-67 IHC in the diagnosis of pulmonary neuroendocrine tumors.

Summary

In conclusion, we believe that in addition to mitotic count which is a well-established and incorporated test for the diagnosis of pulmonary neuroendocrine tumors, evaluation of Ki-67 by IHC has an extreme importance and in our opinion may be soon incorporated into the classification scheme of pulmonary neuroendocrine tumors, similar to the classification of the neuroendocrine tumors of the gastrointestinal tract. This finding is practical in small endobronchial biopsies with extensive crush artifact. For other tumor types however, lack of standardization and absence of established cut off points make both mitotic count and Ki-67 less important than other well-known and well validated tumor characteristics, (e.g., tumor stage and tumor histology). Despite meta-analyses which correlated a high Ki-67 PI with a poor prognosis in NSCLC, the most important rationale in treating patients with lung cancer in this era of precision medicine is shifting towards immediately finding genomic targets for personalized therapy.

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Footnote

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

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