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Phenotyping of Pulmonary Carcinoids and Establishment of a Grading System

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Pulmonary carcinoids (PC) are rare malignant neuroendocrine neoplasms, which are further sub-classified into typical (TC) and atypical carcinoids (AC) based on histological criteria. Separation is vital because AC are more aggressive and treatment modalities differ. Histological differentiation can be subtle, especially in small biopsy specimen. While immunohistochemistry (IHC) is helpful in identifying carcinoids, so far no marker clearly separates AC from TC. This study aimed to provide an integrated approach of PC phenotyping, prognostic evaluation, and prediction. Up to present, this is the first series of PC investigations covering all WHO recommended diagnostic, as well as putative predictive immunomarkers. Furthermore, for the first time, the grading system for gastrointestinal neuroendocrine tumors was applied to PC.

A collective of 200 PC from a single institution, over a period of 22 years, was reclassified according to the current WHO criteria, resulting in 114 TC and 86 AC. Carcinoids were investigated for expression of diagnostic (synaptophysin, chromogranin A, N-CAM (CD56), Leu-7 (CD57), CK18, KL-1, CD117, TTF-1) and putative predictive markers (Her-2/neu, EGFR, ERCC-1, thymidylate synthase (TS), SSTR2A, CD99) by means of tissue microarrays and IHC. In addition, Ki-67 was employed and the proliferative index (PI) was counted on whole slides of resected specimens in areas of average and highest activity.

Immunohistochemical analyses revealed neuroendocrine as well as epithelial markers as highly sensitive diagnostic tools. Synaptophysin and pan-cytokeratins were expressed in almost all specimens, while CD57 and CD117 were of inferior diagnostic value. Notably, nuclear TTF-1 staining was found in more than 70% of PC, which might aid in the separation from tumors with other origin. Finally, Ki-67 was the only marker to significantly differentiate AC from TC.

Besides diagnostic phenotyping, a reliable sub-typing of PC is of utmost importance. In order to optimize distinction of tumors with an aggressive from those with a more

benign behavior, the grading system for gastrointestinal neuroendocrine tumors was adapted to PC. Thereby a modified and novel grading system for PC was established on the basis of mitotic count and PI. This novel grading scheme reflects the biological behavior of PC and serves as a better prognosticator than the currently established separation into TC and AC. In addition to the prognostic assessment, advanced, unresectable, or metastasized PC may require chemotherapy. A screening for selected putative immunomarkers demonstrated SSTR2A expression in 80% of all PC, which may render SSTR as a predictive marker for octreotide-based therapies and for imaging approaches, e.g. initial or postoperative follow-up scintigraphy for specific, early detection of tumor recurrence. EGFR, Her-2/neu, ERCC-1, and TS were expressed to a lesser extent; nevertheless, it may be worth to further investigate the value of these markers for putative therapeutic approaches.

In conclusion, the findings in this study demonstrate that pan-cytokeratin and neuroendocrine markers, particularly synaptophysin, are useful diagnostic panels with a high sensitivity for PC. In addition to PC phenotyping, the herein established grading system based on mitotic count and PI allows for an optimized prediction of the biological behavior of PC and thus the patients' outcome compared to the classification into TC and AC. Furthermore, the majority of PC may be susceptible for SSTR-based scintigraphy and octreotide-based therapies. The findings of this study should be validated in other large series of PC.