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The Failure of Circulating Chromogranin A as a Biomarker of Bronchopulmonary Neuroendocrine Neoplasia: A Meta-Analysis

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BACKGROUND: Management of bronchopulmonary neuroendocrine neoplasia (carcinoids, SCLC, LCNEC) is hampered by the paucity of biomarkers. CgA the default NET biomarker has undergone rigorous reassessment in GEP-NETs. We evaluated CgA in BPNETs to define its clinical utility as a biomarker, assess its diagnostic, prognostic and predictive efficacy as well as its accuracy in the identification of disease recurrence.

METHODS: A systematic review of PubMED was undertaken using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. No language restrictions were applied. Overall, 27 original scientific papers and 3 case reports, which met inclusion criteria, were included in qualitative analysis, and meta-analysis thereafter. All studies except two, were retrospective. Metric comparisons based on standard NIH proposal for biomarkers: sensitivity >80%, specificity >90%.

RESULTS: Nine different CgA assays were reported, without consistency in the upper limit of normal (ULN).

For pulmonary carcinoids (n=12 studies; mean patient inclusion: 30 (range:

3-42)), the CgA diagnostic sensitivity was 62% but ranged from 25-93%. Extensive disease (liver metastases) was associated with the highest sensitivity (93%). Specificity was not documented. No information was available for typical versus atypical carcinoids. Abnormally elevated CgA (>6x ULN) was prognostic for overall survival (n=2 retrospective studies). No information was identified for predicting treatment responses or identifying residual disease.

For SCLC (n=16 studies; mean inclusion: 72 (range: 6-200)), the mean diagnostic sensitivity was 58% (range: 33-100%). Extensive disease exhibited the highest sensitivity: 63±11% versus limited disease 43±14%. Specificity was 76% (62-96%). Elevated CgA was prognostic for overall survival (n=4 retrospective studies).

No prospective studies evaluating predictive benefit or prognostic utility were identified.

CONCLUSION: CgA exhibits major limitations as an effective and accurate biomarker for bronchopulmonary neuroendocrine neoplasia. An assessment of all published data indicates that CgA does not exhibit the required metrics to function as a clinically useful predictive or prognostic biomarker.