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Chromogranin A is an Inadequate Circulating Biomarker for Bronchopulmonary Neuroendocrine Neoplasia Management

Anna Malczewska[1]; *Mark Kidd[2]; Somer Matar[2]; Anna Lewczuk[3]; Agnieska Kolasinska-Cwikla[4]; Jaroslaw Cwikla[5]; Lisa Bodei[6]; Beata Kos-Kudla[7]; Irvin Modlin[8]*

[1]Yale University; [2]Wren Laboratories; [3]Medical University of Gdansk; [4]Marie Curie Cancer Institute; [5]University of Warmia and Mazury; [6]Memorial Sloan Kettering Cancer Center; [7]Medical University of Silesia; [8]Yale University School of Medicine

BACKGROUND: Chromogranin A is the default biomarker for managing gastroenteropancreatic NET and bronchopulmonary carcinoids despite concerns regarding the metrics of the assay and the lack of rigorous clinical utility studies. We evaluated the clinical utility of CgA as a circulating biomarker for lung neuroendocrine neoplasia, determining its diagnostic capability, comparing it in other lung diseases including non-neoplastic disease (COPD), other neuroendocrine neoplasia (NEC), adenocarcinoma and squamous cell carcinoma.

METHODS: Blinded and prospective blood samples were obtained from: bronchopulmonary carcinoids (n=118 [typical (TC) n=67; atypical (AC) n=51; RECIST stable disease (SD): n=74; Progressive disease (PD): n=34]); other lung NEC (LCNEC and SCLC: n=13); adenocarcinoma n=34, squamous cell carcinoma (SCC) n=24); controls (n=90); and COPD (n=18). CgA was measured using ELISA (EuroDiagnostica); normal <109ng/ml. Analysis: Fisher's test, 2-tailed Mann-Whitney U-test, ROC-statistics and Decision Curve Analysis (DCA).

RESULTS: CgA was elevated in only 37% (44) of BP carcinoids compared to 2 (2%) of healthy controls. In the elevated group, levels were statistically different (887±247ng/ml vs. 58±30ng/ml, p<0.0001); AUC was 0.68±0.03. Metrics: sensitivity: 36%, specificity: 92%, PPV: 96% and NPV: 55%. CgA was elevated in 42% of AC compared to 35% of TC (p=NS). Levels were higher in SD (966±350ng/ml) than PD (548±171ng/ml) but did not attain statistical significance; the AUC for differentiating clinical status was 0.52. Four (31%) of NEC had elevated CgA. False positive CgAs were identified in COPD (44%), Adenocarcinoma (18%) and SCC (22%). DCA demonstrated CgA to be of clinical value in <20%.

CONCLUSION: CgA exhibits poor metrics as a diagnostic for bronchopulmonary carcinoids. Greater than 50% BPNETs are CgA-negative and have no correlation with tissue histology (TC versus AC). Levels cannot differentiate progressive versus stable disease. Furthermore, a significant number with other lung pathologies exhibit elevated CgA. A prospective assessment of circulating CgA indicates it to be non-specific and of low clinical utility.