

C-40

The Clinical Utility of Blood Neuroendocrine Gene Transcript Measurement in Defining Surgical Resection and Residual Disease in Bronchopulmonary Neuroendocrine Tumors

Pier Luigi Filosso¹; Mark Kidd²; Matteo Roffinella¹; Kyung-Min Chung²; Anna Lewczuk³; Agnieszka Kolasinska-Cwikla⁴; Jaroslaw Cwikla⁵; Anna Malczewska⁶; Margot Tesselaar⁷; Beata Kos-Kudla⁸; Mauro Papotti¹; Lisa Bodei⁹; Ignat Drozdov²; Irvin Modlin¹⁰

¹Medical University of Torino; ²Wren Laboratories; ³Medical University of Gdansk; ⁴Marie Curie Cancer Institute; ⁵University of Warmia and Mazury; ⁶Yale University; ⁷Netherlands Cancer Institute; ⁸Medical University of Silesia; ⁹Memorial Sloan Kettering Cancer Center; ¹⁰Yale University Medical School

BACKGROUND: Management of bronchopulmonary neuroendocrine tumors (BPNETs) is difficult since imaging, histology and biomarkers have limitations for diagnosis, predicting outcome and defining therapeutic efficacy. We evaluated a NET multigene blood test (NETest) to diagnose BPNETs, assess disease status and evaluate surgical resection.

METHODS: A. Diagnostic Cohort: BP carcinoids (n=118); typical (TC) n=67; atypical (AC) n=51; other lung NEN (LCNEC and SCLC: n=13); n=18; adenocarcinoma n=26, squamous cell carcinoma (SCC) n=23; controls (n=90); and COPD (n=18). B. Surgical Cohort: n=28: BP carcinoids (n=16:TC 12; AC: 4); LCNEC: n=3; lung adenocarcinoma: n=8, SCC: n=1. Sampling pre- and post-surgery 30d. Transcript levels were measured by qPCR and calculated as activity scores (0-100% scale: normal <14%) and compared to CgA (ELISA; normal

<109ng/ml). Analysis: Fisher's test, 2-tailed Mann-Whitney U-test, and ROC-statistics.

RESULTS: NETest was significantly elevated ($48.7\pm 27\%$) in carcinoids versus controls ($6\pm 6\%$, $p<0.0001$) with metrics: sensitivity 93%, specificity 89%, PPV 92% and NPV 91%. Levels were elevated in SCLC/LCNEC ($59\pm 10\%$); somewhat increased in COPD and lung cancers (18-24%). The NETest ($49.5\pm 28\%$) differentiated patients with image-positive disease from R0 resections ($10\pm 5\%$, $p<0.0001$, AUC: 0.99). In post-surgical BPNETs, transcript levels were decreased by 60% (POD30; $p<0.0002$). Two carcinoids with elevated scores at POD30 subsequently developed disease recurrence. In comparison to the transcript levels, CgA was elevated in only 40% of carcinoids, but 45% of COPD and in 10-14% of other lung neoplasia. In the BPNET cohort, surgery did not significantly decrease CgA.

CONCLUSION: Blood NET gene levels accurately identified BPNETs (100%) and differentiated controls, benign and malignant lung disease. NET disease could be identified and complete surgical resection or residual disease verified. CgA had no clinical utility. Monitoring NET transcript levels in blood will facilitate management by detecting residual tumor and identifying recurrent disease.