Blood Gene Transcript Analysis Diagnoses Bronchopulmonary NETs and Identifies Progressive Disease

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Principal Message

A blood-based measurement of neuroendocrine tumor transcripts (NETest) accurately identified BPNETs with disease (100%) and differentiated neoplastic and non-neoplastic lung disease. The NETest accurately identified clinico-histological groups and can be used to facilitate TC/AC clinical characterization.

Background

Broncho-Pulmonary (BP) NETs comprise ~30% of all NETs and are classified into four groups: typical carcinoid (TC), atypical carcinoid (AC), large cell NEC (LCNEC) and small cell lung cancer (SCLC). Differentiating TC and AC can be challenging as these tumors comprise a spectrum of indolent to aggressive behavior. Imaging, histology (Ki67 and high grade NECs) and biochemistry e.g., circulating chromogranin A levels, are limited in defining malignancy or progression.

Aim

To assess the NETest in BP-NETs and evaluate its role in delineating progressive disease.

Methods

Neuroendocrine lung neoplasia (*n*=125; BPNETs (*n*=114), LCNEC (*n*=6), SCLC (*n*=5)); lung neoplasia (adenocarcinoma (*n*=7), squamous cell carcinoma (*n*=5); non-neoplastic lung disease (COPD: *n*=18) and healthy controls (*n*=90). Measurements were blood NETest by qPCR; CgA by ELISA (EuroDiagnostica, normal <109ng/ml); disease status was by imaging. BPNETs were typical TC: *n*=64, atypical AC: *n*=44 and complete remission (CR *n*=6). Seventy-four with disease were classified as stable (SD); progressive disease (PD *n*=34). 56% AC were PD, 23% TC were PD. Clinico-histological groups were AC/SD or AC/PD; TC/SD or TC/PD by RECIST. Analysis was by 2-tailed Mann-Whitney U-test, Chi^2 tests and ROC-statistics.

Results

NETest was positive in all BPNETs (100%) irrespective of TC or AC. CRs were all low (<14%), within the normal range. Non-neoplastic lung disease exhibited the highest values of controls (24±2.5%). All NE-neoplasia exhibited significantly elevated NETest (p<0.005). The AUC for differentiating BPNETs from lung disease controls was 0.90±0.03, p<0.0001. NETest predicted clinical status (SD: 38±3% or PD: 74±4%, p<0.0001) irrespective of histological type (AUC: 0.86±0.04, p<0.0001). CgA was non-informative. While it was significantly elevated in COPD (151±37ng/ml) and BPNETs (804±240ng/ml) (both p<0.002 versus healthy controls), the AUC for differentiating BPNETs from lung disease controls was only 0.58±0.05, p=NS. In addition, CgA levels were not able to differentiate PD (397±207ng/ml) from SD (mean: 1016±371ng/ml; p=0.71) (AUC: 0.51±0.06, p=NS).

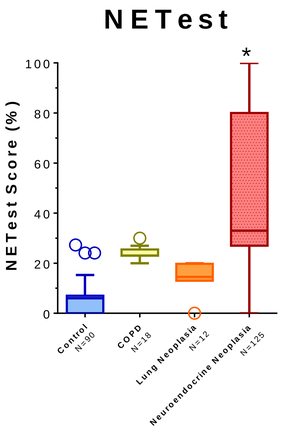

Figure 1: NETest in controls, lung disease (non-neoplastic: COPD; and neoplastic) and neuroendocrine neoplasia.
Levels were significantly increased in neuroendocrine neoplasia compared to COPD, lung neoplasia and healthy controls (p<0.0001).
Box and whisker plot (Tukey).
Circles reflect samples that fall outside of the normal distribution

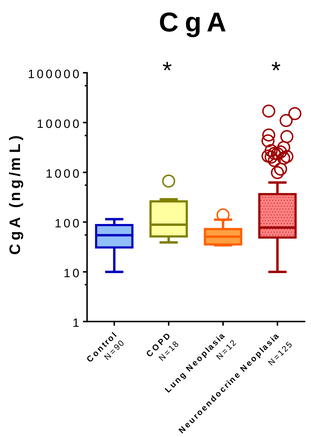

Figure 2: Chromogranin A (CgA) in controls, lung disease (non-neoplastic: COPD; and neoplastic) and neuroendocrine neoplasia.
Levels were significantly increased in COPD and neuroendocrine neoplasia compared to lung neoplasia and healthy controls (p<0.05).
Box and whisker plot (Tukey).
Circles reflect samples that fall outside of the normal distribution

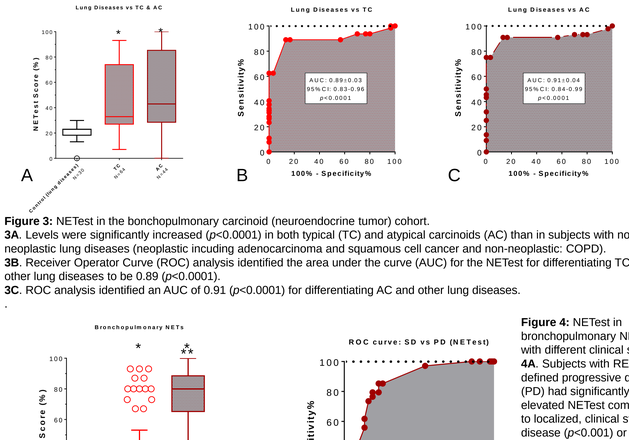

Figure 3: NETest in the bonchopulmonary carcinoid (neuroendocrine tumor) cohort.
3A. Levels were significantly increased (p<0.0001) in both typical (TC) and atypical carcinoids (AC) than in subjects with non-neoplastic lung diseases (neoplastic incuding adenocarcinoma and squamous cell cancer and non-neoplastic: COPD).
3B. Receiver Operator Curve (ROC) analysis identified the area under the curve (AUC) for the NETest for differentiating TC from other lung diseases to be 0.89 (p<0.0001).
3C. ROC analysis identified an AUC of 0.91 (p<0.0001) for differentiating AC and other lung diseases.

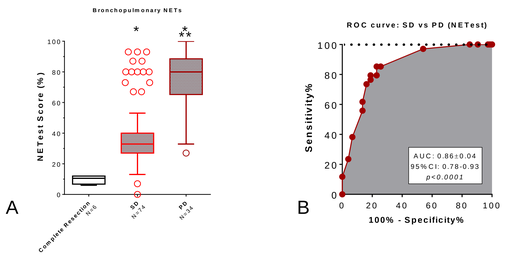

Figure 4: NETest in bronchopulmonary NETs with different clinical status.
4A. Subjects with RECIST-defined progressive disease (PD) had significantly elevated NETest compared to localized, clinical stable disease (p<0.001) or those considered surgical cures (CR). Stable disease was also elevated (p<0.0001) compared to CR.
4B. ROC analysis identified the AUC for the NETest for differentiating PD from SD to be 0.86 (p<0.0001).

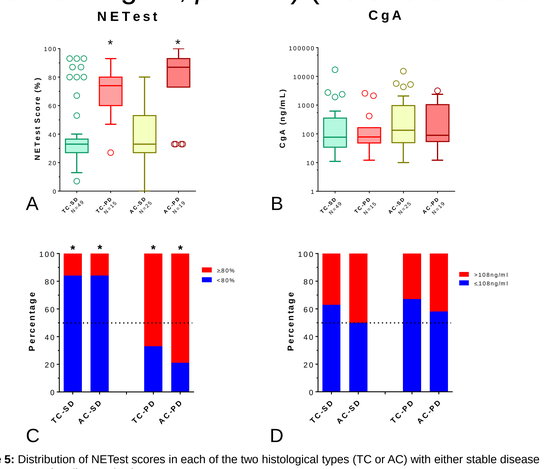

Figure 5: Distribution of NETest scores in each of the two histological types (TC or AC) with either stable disease (SD) or progressive disease (PD).
5A. NETest scores were significantly elevated (p<0.0001) in both TC and AC types in subjects with PD compared to SD.
5B. CgA levels were not significantly different between any of the types grouped by clinical status.
5C. Proportion of BP NETs with low NETest in each of the two histological types (TC or AC: 84% each) with stable disease and elevated NETest (≥80%) in progressive disease (67-79%). Levels were significantly different to CgA (p<0.05).
5D. Proportion of subjects with normal CgA levels in stable disease (50-67%) and abnormal levels (>108ng/ml) in PD (33-42%).

Conclusion

- A blood-based NETest accurately identified neuroendocrine neoplasia lung diseases.
- BPNETs were identified (100%) by the NETest.
- NETest accurately identified BPNETs with PD irrespective of histological status.
- CgA was non-informative.

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