

Neuroendocrine Tumor Blood Transcript Analysis, the NETest, Predicts Gastroenteropancreatic Neuroendocrine Tumor Disease Status and is Prognostic for Progressive Disease

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Background: A key issue in GEP-NET management is early identification and prediction of disease progression. Clinical strategies are insensitive; no accurate biomarkers exist and imaging is limited (variable sensitivity/disease indolence). We evaluated whether a blood-based multigene transcript analysis (NETest) was a predictive and prognostic marker of progression in a long-term, follow-up study.

Methods: Well-differentiated GEP-NETs (n=34): small intestine (n=24), pancreatic (n=7), MEN-ZES (n=2), CUP (n=1) followed longitudinally for a median of 4 years (2.2-5.4). Grade I: n=15, Grade II: n=17; (no grade in 2). Baseline imaging and biomarkers were available in all. Subsequent imaging (restaging median 7 times; 3-15) and blood sampling (median 3 times: 2-5) were acquired (clinical management protocols). Progression was defined by RECIST 1.0 criteria. NETest measurement utilized qPCR and multianalyte algorithmic analysis: risk scale 0-100% with low (<40%) and high activity risk cutoffs (>80%). CgA was measured by RIA (normal <150µg/l, abnormal >300µg/l). PFS was assessed by Kaplan-Meier curve analysis and Cox-proportional modeling was undertaken.

Results: At baseline, all were NETest positive; CgA was positive in 50%. Median PFS was 2.59 years. Neither grade nor baseline CgA were associated with progressive disease (PD). Baseline NETest>80% was significantly associated (p=0.01) with PD: median PFS=0.68 years vs. 2.78 years (NETest<40%). NETest was the only predictive marker by multivariate analysis (p<0.012). Alterations in NETest were more informative than CgA for PD (96% vs 40% p<2x10⁻⁵, X²=18.1) and exhibited an earlier time-point change (1.02±0.15 years vs 0.72±0.11 years, p=0.03). CgA levels >300ng/ml were non-informative. Low NETest values (<40%) accurately predicted disease stability over a 5 year period (p=0.05, Chi²=3.8 vs. CgA).

Conclusion: A blood-based NET multigene analysis measurement correlates with clinical disease status in well-differentiated GEP-NETs. Elevated levels accurately predicted GEP-NET progression occurring ~1 year before image-based evidence of disease progression. The NETest has predictive and prognostic utility for GEP-NETs.