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Beyond Chromogranin A: Molecular Surveillance with NETest2.0® Improves Detection of Neuroendocrine Tumor Progression

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BACKGROUND

Reliable biomarkers for longitudinal surveillance of neuroendocrine tumors (NETs) remain an unmet clinical need. Chromogranin A (CgA), historically the most widely used circulating biomarker, has limited sensitivity and often correlates poorly with disease progression. We evaluated whether serial molecular assessment using NETest2.0®, a blood-based multigene transcriptomic liquid biopsy, more accurately identifies progression during routine NET surveillance.

METHODS

Patients enrolled in RegisterNET (NCT02270567) with paired blood samples and contemporaneous imaging assessments were analyzed. NETest2.0® scores were generated from a 51-gene RT-PCR transcript signature and compared with serial serum CgA measurements. Disease status at follow-up was determined by CT, MRI, and/or SSTR-PET imaging with RECIST 1.1 criteria applied when appropriate. Longitudinal changes between sequential samples were assessed using predefined NETest2.0® thresholds (>0% and >5%) and compared with the conventional CgA surveillance threshold (>50%).

RESULTS

A total of 191 patients were evaluated, with a median surveillance interval of 6 months. Serial NETest2.0® changes demonstrated significantly superior discrimination of progression compared with serial CgA changes (AUC 0.893 vs. 0.538; $p<0.0001$).

In the primary surveillance analysis, NETest2.0® >0% achieved an AUC of 0.860 and NETest2.0® >5% an AUC of 0.822, both significantly superior to CgA (AUC 0.553; $p<0.0001$ for both comparisons). NETest2.0® >0% demonstrated the highest sensitivity (86.4%), while NETest2.0® >5% provided the optimal balance of performance with 70.5% sensitivity, 93.9% specificity, 77.5% positive predictive value, 91.4% negative predictive value, and 88.5% overall accuracy. In contrast, CgA demonstrated only 18.2% sensitivity and 75.4% overall accuracy. Multivariable and logistic regression analyses identified changes in NETest2.0® as the strongest independent predictor of progression (all

p<0.0001; OR 52.99–61.26), whereas serial CgA changes were not independently associated with progression.

CONCLUSIONS

Serial NETest2.0® assessment significantly outperformed Chromogranin A for identifying progression during NET surveillance. Molecular changes measured by NETest2.0® were strongly associated with clinical outcome and represented the dominant independent predictor of progression. These findings support integration of NETest2.0® into biologically informed follow-up and risk-adapted imaging strategies for NETs.

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