Use of a 92-gene Molecular Classifier to Predict the Site of Origin for Primary and Metastatic Tumors with Neuroendocrine Differentiation

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INTRODUCTION

- A diagnosis of neuroendocrine carcinoma (NEC) is often morphologically straightforward, but the tumour site of origin may remain elusive in a metastatic presentation.
- Neuroendocrine tumour subtyping has important implications for grading, staging, and management, especially as target therapies (everolimus, sunitinib) have been recently approved for use in pancreatic neuroendocrine tumours.
- This study describes the use of a 92-gene molecular cancer classifier (CancerTYPE ID, bioTheranostics Inc.) for predicting neuroendocrine tumour site of origin.

STUDY DESIGN

- Seventy-five (44 metastatic and 31 primary) formalin-fixed, paraffin-embedded tumour samples with neuroendocrine differentiation that were part of a larger validation study of the 92-gene molecular cancer classifier (CancerTYPE ID, bioTheranostics Inc.) for predicting neuroendocrine tumour site of origin.
- All cases submitted for the 92-gene assay were adjudicated between Mayo Clinic, UCLA, and Massachusetts General Hospital by the originating site pathologist and a second institutional pathologist by online whole slide imaging. Clinical and pathologic information was available.
- Clinicopathologic diagnoses were classified as follows:
  - Intestinal NEC (n=12)
  - High-grade pulmonary NEC (small cell or large cell, n=11)
  - Low-grade pulmonary NEC (pulmonary carcinoid, n=11)
  - Merkel cell carcinoma (n=10)
  - Pancreatic NEC (n=10)
  - Pheochromocytoma/paraganglioma (n=10)
  - Medullary thyroid carcinoma (n=11).
- Blinded FFPE tumor sections were submitted and tested using the 92-gene RT-PCR assay.
- Cases were tested using a prespecified classification model that reports computational algorithm results as rank probabilities. The top-ranking tumour type predicted by the classifier was compared to the adjudicated reference diagnosis.

RESULTS

- All 75 neuroendocrine tumours met quality control parameters and were classified by the assay.
- The cohort was comprised of 59% metastatic tumours and 41% primary tumours. The most common biopsy site was liver, followed by lung and lymph node.
- The 92-gene classifier correctly predicted the reference subtype diagnosis in 71 of 75 neuroendocrine cases and had an overall concordance rate of 95%.
- Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for predicting individual subtypes are shown.
- Three of the 4 incorrectly predicted cases were correctly predicted to the neuroendocrine carcinoma level, but were assigned an incorrect subtype.

CONCLUSION

- The 92-gene classifier demonstrated excellent accuracy for prediction of subtype in a heterogeneous cohort of both primary and metastatic neuroendocrine tumours.
- While these results were part of a larger parent study designed to characterize performance of the classifier in a broad range of tumour histologies and did not adjust for neuroendocrine tumour primary site prevalence, these findings show promise for use of the 92-gene assay in classifying neuroendocrine tumours of uncertain primary site.