Abstract #224

Molecular classification of neuroendocrine tumors in a large case series of patients with an unknown/uncertain diagnoses

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INTRODUCTION

- Approximately 50% of neuroendocrine tumors (NETs) are metastatic at the time of diagnosis.[1] While histological diagnosis of metastatic NETs can be straightforward, identification of the specific NET tumor type and subtype can be challenging based on morphology alone
- Accurate identification of NET subtype in patients with an unknown or uncertain diagnosis affects grading and staging, and increasingly affects treatment decision-making as new targeted therapies become available
- The 92-gene assay (CancerTYPE ID, Biotheranostics, Inc., San Diego, CA) is a validated gene expression classifier that provides a molecular classification for 28 main tumor types and 50 tumor subtypes, including 7 NET subtypes (Table 1)

Table 1. NET subtypes classified by the 92-gene assay

Small/large cell lung carcinoma	Merkel cell carcinoma
Lung carcinoid	Thyroid medullary carcinoma
Gastrointestinal (GI) carcinoid	Pheochromocytoma
Pancreatic islet carcinoma	

- Clinical validation in a blinded study demonstrated that the 92-gene assay has an overall sensitivity of 95% (71/75; 95% CI 0.87–0.98) to subtype NETs[2,3]
- The objective of this study was to evaluate clinical utility of NET subtype classification in a large cohort of patients with unknown/uncertain diagnoses tested by the 92-gene assay
- Secondary objectives were to examine the distribution of NET subtypes with respect to biopsy site, age, and gender

METHODS

- The study protocol to create a database of 92-gene assay test results and de-identified patient data was approved by an external Institutional Review Board.
- A database of test results and de-identified patient information was created for >24,000 cases that received a reportable test result from the 92-gene assay as part of patients' routine care
- From this larger database, a subset of cases with a test result from one of the 7 NET subtypes was analyzed (Table 1)
- The final subset contained >1,500 de-identified cases with a NET subtype test result paired with data on biopsy site and patient age and gender
- Descriptive analyses were performed for the proportion and distribution of NET subtypes across biopsy sites, age groups, and gender using this subset
- Fisher's Exact test was used to determine the statistical significance of observed differences in the analyses

RESULTS

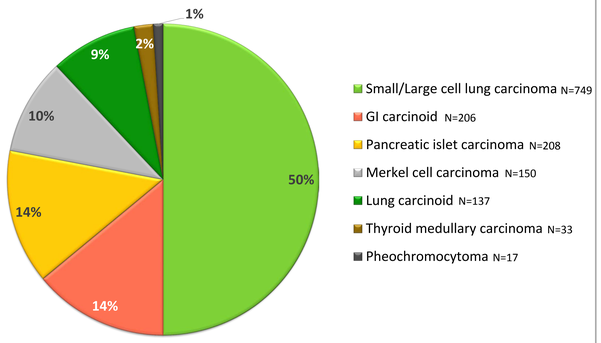
Table 2. Characteristics of cases with a NET subtype* result by the 92-gene assay

Total Cases, N	N=1,500
Age, y, mean (range)	65.2 y (18.1–93.9 y)
Male / Female (%)	(49% / 51%)
Biopsy site distribution (%)	• Liver (40%) • Other# (14%) • Lymph node (13%) • Lung (11%) • Abdomen (5.3%) • Bone (4.3%) • Brain (4.0%) • GI tract (3.3%) • Pelvis (3.0) • Head and neck (2.3%)

*NET diagnoses included small/large cell neuroendocrine carcinoma, lung carcinoid, GI carcinoid, pancreatic islet carcinoma, Merkel cell carcinoma, thyroid medullary carcinoma, and pheochromocytoma

Includes specific organs (e.g. adrenal, kidney, ovary, etc.)

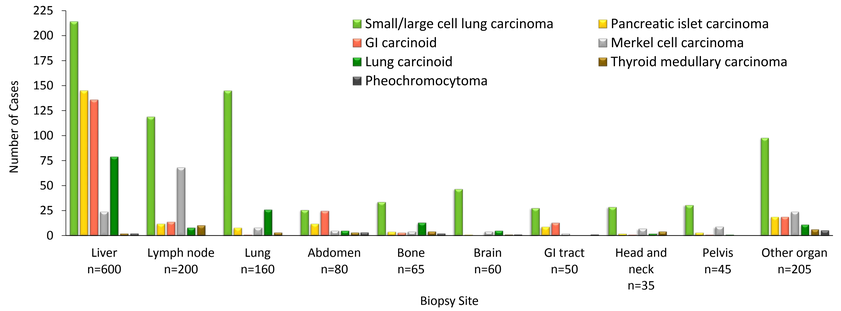
Figure 1. NET subtype results by the 92-gene assay



- All 7 NET subtypes were identified in a large cohort of patients with an unknown or uncertain diagnosis
- Small/large cell lung carcinoma was the the most common NET subtype (50%)
- The majority of NET subtypes (74%) were from tumors that tend to be high grade, such as small/large cell lung carcinoma, or more aggressive, such as Merkel cell carcinoma and pancreatic islet carcinoma
- NET subtype are associated with different molecular targeted therapy or immunotherapy drugs

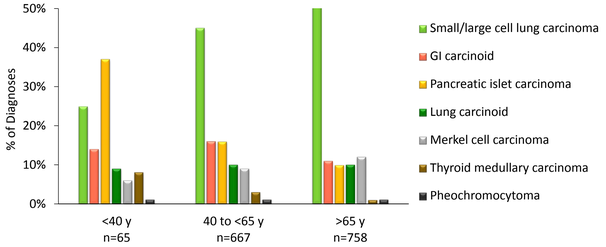
RESULTS

Figure 2. Distribution of NET subtype diagnoses by the 92-gene assay, by biopsy site



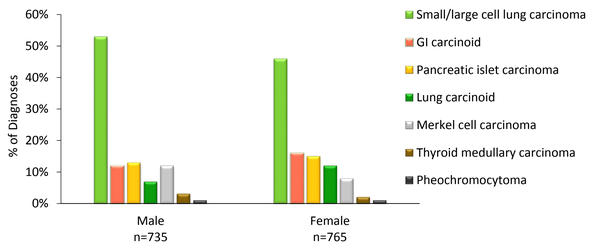
- Liver and lymph node accounted for 54% of the biopsy sites in which a NET subtype diagnosis was rendered by the 92-gene assay
- Each of 7 NET subtypes were identified in cases derived from liver biopsies, including thyroid medullary carcinoma and pheochromocytoma (N=2 for both)
- The majority of GI and lung carcinoid subtypes identified (>85%) were from potential metastatic biopsy sites other than abdomen and lung, respectively
- Small/large cell lung carcinoma was the most common NET subtype identified in potential metastatic locations such as bone, brain, liver, and lymph node

Figure 3. Distribution of NET subtype diagnoses by the 92-gene assay, by age



- A significant difference was observed in the proportional distribution of NET subtypes between age groups (p<0.0001)
- In adolescents and young adults (<40y), pancreatic islet cell carcinoma accounted for more than one-third (37%) of NET subtypes, compared with 16% in patients 40y to ≤65y and 10% in patients >65y
- Small/large cell lung carcinoma was the most common molecular diagnosis in patients ≥40y

Figure 4. Distribution of NET subtype diagnoses by the 92-gene assay, by gender



- The proportional distribution of NET subtypes differed significantly between men and women (p<0.001)
- The 92-gene assay identified a higher proportion of small/large cell lung carcinoma in men (53%) than in women (46%)
- Conversely, a higher proportion Merkel cell carcinoma was identified in women (12%) than in men (8%)

CONCLUSIONS

- The scope of NET subtypes identified at metastatic sites, including a large number of well differentiated NET (GI and lung carcinoid) from the liver, highlight the clinical utility of the 92-gene assay to provide an additive dimension of tumor biology as a molecular correlate for NET stage and grade
- Pancreatic NETs should be considered in adolescents and young adults (< 40 y) with suspected metastatic NET of unknown origin
- Molecular tumor classification by the 92-gene assay identified a substantial proportion of NET subtypes, including well differentiated GI and lung NETs (GI and lung carcinoids), pancreatic islet carcinoma, thyroid medullary carcinoma, and Merkel cell carcinoma with an available targeted or immunotherapy, thus emphasizing the need for accurate NET subtype classification in cases of metastatic tumors of unknown/uncertain diagnosis

REFERENCES

1. Yao, JC, et al. *J Clin Onc*, 2008; 26:3063-3072
2. Kerr et al. *Clin Cancer Res*. 2012;18(14):3952-60.
3. Kerr, et al. *Mod Pathol* 2014; 27:44-54.

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