Impact of Gene Expression Profiling using the 92-gene assay on Management of Neuroendocrine Carcinoma of Unknown Primary Site (NEC-UPS)

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Introduction

Neuroendocrine tumors (NETs) are slow growing and can be undetected until patients present with metastasis. Although pathologic examination is adequate for diagnosis, the identification of site of origin can be challenging when patients present with a metastatic focus without an identifiable primary. We aimed to retrospectively analyze the impact of the 92-gene assay, a test that identifies the site of origin in >95% of cases, on management of patients. Specifically, whether management allowed for the use of molecularly targeted therapy, which otherwise would not have been utilized.

Materials and Methods

Forty patients from Louisiana State University and the University of Kentucky with metastatic NET UPS after initial diagnostic evaluation were selected for retrospective analysis. Formalin-fixed, paraffin embedded biopsy specimens were sent to bioTheranostics, Inc. (San Diego, CA) for molecular cancer classification with the 92-gene assay. Patient and tumor characteristics were collected and impact of the 92-gene assay results on clinical therapeutic decision making were evaluated.

Results

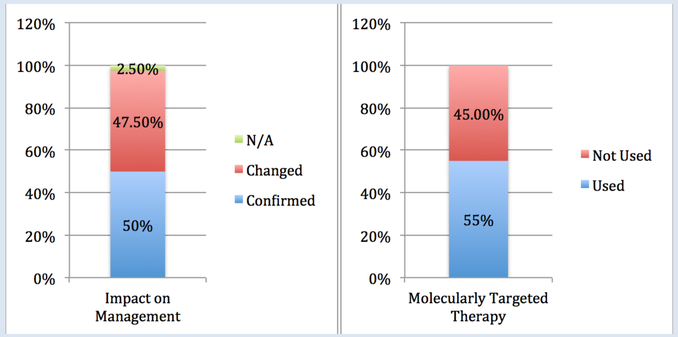
Twenty-one men and 19 women were included in the study, with an age range of 37-75 years and an average age of 61 years and a median age of 63 years. Of the 40 patients 55% presented with only liver metastases; 17.5% had disseminated metastases to the liver and other sites, and 27.5% patients presented with metastases located outside of the liver. The most common presenting symptoms were non-specific: abdominal pain (n=14), and diarrhea (n=7). The most common positive serum biomarkers were 5-hydroxyindolacetic acid (n=17), chromogranin A (n=11), pancreastatin (n=11), neurokinin A (n=5), and serotonin (n=5).

Results

In all cases, the 92-gene assay predicted a neuroendocrine tumor type and site of origin, with 35% of the NET UPS predicted to be gastrointestinal carcinoid, 27.5% pancreatic islet cell, 12.5% small/large cell, and 5% lung carcinoid (see Table 1). Based on the result of the assay, chemotherapeutic regimen was modified in 47.5% of patients and was confirmed in 50%. In addition, 27.5% of patients received molecularly targeted therapy based on the molecular diagnosis of pancreatic islet cell tumor.

	Number of Patients
Number of patients	40
Gender	
Male	21
Female	19
Median age (range)	63 (37-75)
Presenting symptoms	
Abdominal pain	14
Flushing	8
Diarrhea	7
Nausea	5
Weight loss	1
Incidental (e.g. lymphadenopathy, surgery)	3
Mediastinal/myocardial mass	2
Cough	2
Wheezing	2
Pulmonary nodule	2
Back pain	2
Jaundice	1
Syncope	1
Metastatic sites	
Liver only	22
Liver and other sites	7
Outside the liver	11
Tumor marker positivity	
Chromogranin A	12
5-Hydroxyindolacetic acid	17
Pancreastatin	11
Neurokinin	5
Serotonin	5
92-gene Assay Subtype Prediction	
Small/Large Cell Carcinoma	5
Islet Cell Carcinoma	11
Gastrointestinal Carcinoid	14
Lung Carcinoid	2
Breast Adenocarcinoma	2
Other (adenocarcinoma, Merkel cell, etc.)	6

Grade	Number
Low	12
Intermediate	7
High	6
Missing (Different Dx)	12(+3)



Validity of CTID[1]

The CTID can classify 30 main tumor types and 54 histological subtypes, including neuroendocrine tumors and its subtypes (e.g. small cell lung cancer, pancreatic islet cell tumor, Merkel cell carcinoma, lung carcinoid)

	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
30 Main Types	0.87 (0.85-0.88	1.00 (0.99-1.00)	0.87	1.00
54 Subtypes	0.85 (0.83-0.86)	1.00 (1.00-1.00	0.85	1.00

Conclusions

In this retrospective analysis, identifying the site of origin with the 92-gene assay altered treatment regimen in approximately half the patients, and provided molecularly targeted therapy options for more than half of that subgroup.

Treatment regimen was not altered in the high-grade tumors suggesting lack of benefit in genomic profiling for identifying a site of origin.

Three cases were diagnosed as non-neuroendocrine after genomic profiling, and were re-reviewed by a second pathologist who confirmed the non-neuroendocrine nature of these cases. This highlights the importance of working with a pathologist specialized in neuroendocrine carcinoma to prevent interpretation errors.

Analysis of the impact of the 92-gene assay on survival should be evaluated in future studies

References

1. Erlander MG, Ma XJ, Kesty NC, Bao L, Salunga R, Schnabel CA. Performance and clinical evaluation of the 92-gene real-time PCR assay for tumor classification. J Mol Diagn. 2011 Sep;13(5):493-503.