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Expression of Tryptophan Hydroxylase in Neuroendocrine Tumors

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BACKGROUND: Neuroendocrine tumors (NETs) frequently produce serotonin, the main causative hormone of carcinoid syndrome. Tryptophan hydroxylase (TPH) is the rate limiting enzyme in serotonin production and can be targeted to ameliorate symptoms of carcinoid syndrome. We looked at the tissue expression of TPH and serotonin in NETs to explore correlation with other clinical and histological variables.

METHODS: We used tissue microarrays of 127 surgically resected NETs and studied expression of various proteins using immunohistochemistry (IHC). Staining for TPH was performed using rabbit polyclonal anti-TPH antibody (sab4503029, Sigma-Aldrich), the expression was graded between 0-3 and classified as low (≤1) or high (>1). The samples were also stained for serotonin (present/absent) and Ki67. The IHC expressions were correlated with clinical variables. Comparisons were made using the Mann-Whitney U and Fisher's exact tests at $\alpha = 0.05$.

RESULTS: 95/127 (75%) NETs in our sample showed high or moderate level of TPH staining with SAB4503029 antibody. NETs arising from pancreas and small intestines tended to have higher TPH expression than NETs of lungs, but the association was not significant. There was a significant association between TPH expression and stage at diagnosis, where the high TPH tumors tended to have higher stage at diagnosis. TPH expression was not significantly associated with age, sex, smoking status of the patient, or tissue expression of serotonin or Ki67. (Table) After a median follow up of 9.7y, the median overall survival (OS) was 11.7y in high TPH group and 10.9y in low TPH group (p=0.09). In the propensity adjusted

analyses (based on n=96 patients), OS was found to be statistically significant where patients with high TPH expression tended to have better outcomes (p=0.025, Hazard ratio=0.61, 95% CI:0.40-0.94).

CONCLUSION: TPH is frequently expressed in NETs and may be associated with a better prognosis. This can be due to higher TPH expression in gastrointestinal NETs.

Table 1:

Patient characteristics by TPH expression

Patients	Low TPH, n=32 (%)	High TPH, n=95 (%)	p-value
Age <60/ ≥60	16(50)/ 16(50)	38(40)/ 57(60)	0.41
Males/ Females	7(22)/ 25(78)	38(40)/ 57(60)	0.09
Smoking History – pos/neg	21(66)/ 11(34)	65(68)/ 30(32)	0.66
Stage I/ II/ III/ IV	18/3/8/3	29/20/19/25	0.024
Primary Site – Lung/ GEP/ Other	21(66)/ 7(22)/ 4(12)	38(40)/ 40(42)/ 17(18)	0.17
Serotonin pos/neg*	30(97)/ 1(3)	82(88)/ 11(12)	0.29
Ki67 Low/ High*	27(87)/ 4(13)	77(85)/ 14(15)	1.00

High TPH defined as staining score of >1; Ki67 index defined as low (<3%) or high (≥3%); TPH=Tryptophan hydroxylase; GEP=Gastroenteropancreatic; *Not all samples were evaluable for Ki67 or serotonin expression