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Meta-Analysis of Prognostic Biomarkers for Pancreatic Neuroendocrine Tumors (PNETS)

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BACKGROUND: PNETs are marked by histological heterogeneity and variable clinical outcomes. Other than Ki67 index, reliable circulating or tissue biomarkers for prognosis do not exist.

METHODS: PubMed was searched through January 31st, 2017. Inclusion criteria were: 1) prospective or retrospective cohort design with a clearly defined source population, boundary dates, and justifications for all excluded eligible cases; 2) assay of primary tumor specimens; 3) clear descriptions of methods, experimental techniques, and choice of positive and negative controls; 4) statistical analysis using multivariate proportional hazards modeling that adjusted for clinical prognostic factors including but not limited to stage or grade; and 5) reporting of the resultant adjusted hazard ratios with 95 % confidence intervals and corresponding P values. Studies with < 50 % PNETs were excluded. Emails were sent to 40 investigators for clarification and responses were received from 16 groups. PNET-specific data was summarized in the table below.

RESULTS: A total of 2958 manuscripts were identified and 462 manuscripts were reviewed in detail. Only 23 multivariate studies met all inclusion criteria. PNET-specific data was summarized in the table. These altogether analyzed 24 unique targets and 14 of them were associated with survival. 1. I-immunohistochemistry, F-fluorescence in situ hybridization, E-enzyme linked immunosorbent assay, M-methylation specific polymerase chain reaction (PCR), P-PCR 2. O-overall survival, F-disease free survival, S-disease specific survival, P- progression free survival.

CONCLUSION: This meta-analysis identified 14 markers associated with survival of PNET patients. Future studies should adhere to the REMARK criteria and incorporate the 2017 WHO grading system for multivariate analysis.

Table 1.

Target	Sample size	Method[1]	HR	P value	End point[2]
α-internexin	257	I	4.285	0.010	O
Alternative lengthening of telomeres	245 (local disease)	F	1.97	0.043	F
	42 (metastatic disease)	F	0.23	0.008	O
	321	F	7.12	<0.001	F
			1.35	0.388	S
ATRX/DAXX	131	I	0.631	0.028	F
Chromogranin A	51	E	6.90	0.014	O
	32	E	5.38	0.16	O
	114	E	0.70	0.27	P
			0.36	0.01	O
CK19	91	I	5.074	0.134	O
	93	I	2.664	0.019	F
			13.882	0.001	S
	145	I	1.89	0.34	O
CRP	149	Turbidimetric assay	4.02	0.007	O
FoxP3	101	I	6.9	0.02	O
hMLH1 methylation	48	M	6	0.03	F
HMOX-1 GTn promoter polymorphism	46	P	3.1	0.01	F

Table 1 (continued)

INK4a/p16 methylation	48	M	4.8	0.029	F
KIT					
	91	I	2.573	0.202	O
	44	I	1.363	0.642	S
	181	I	2.09	0.195	O
LINE-1 methylation	56	P	0.875	0.034	O
MGMT	74	I	3.003	0.212	O
MTOR	90	I	3.947	0.054	O
Neuron-specific enolase	113	Noncompetitive enzyme immunoassay	0.62	0.09	F
			0.60	0.10	O
p21	58	I	2.58	0.219	O
p73 methylation	48	M	4.2	0.117	F
PDGFRA	44	I	2.445	0.320	S
PTEN	90	I	3.268	0.095	O
RASSF1A methylation	48	M	2.3	0.323	F
Survivin	84	I	0.94	0.90	O
Thymidylate synthase	58	I	2.4	0.248	O
Composite score = I (MGMT >0%) + I (NDRG-1 diffuse) + 2x I (NDRG-1 patched) + (PHLDA-3 ≥51%)	92	I	2.68	0.00018	F
			2.67	0.03	O