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Value of Islet 1 and PAX-8 in Identifying Metastatic Neuroendocrine Tumors of Pancreatic Origin

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Background: Neuroendocrine tumors (NETs) can present as liver metastases before discovery of the primary tumor. Immunohistochemical (IHC) staining with TTF-1 and CDX2 are currently used to identify NETs of pulmonary and gastrointestinal (GI) origin, respectively. Only recently have markers for NETs of pancreatic origin been proposed, including Islet 1 and PAX8. The purpose of this study was to (1) compare the utility of Islet 1 and PAX-8 in distinguishing pancreatic NETs from tumors of other sites; and (2) determine the usefulness of an IHC panel including TTF-1, CDX2, Islet 1, and/or PAX-8 in identifying metastatic pancreatic NETs.

Methods: A total of 110 primary NETs and 73 metastatic NETs were studied. Immunohistochemistry was performed using antibodies against Islet 1, PAX8, TTF-1 and CDX2. Tumors showing moderate to strong nuclear staining of at least 5% of cells, or tumors showing weak nuclear staining of at least 10% of cells were considered positive.

Results: Islet 1 and PAX8 were positive in 82% and 88% of primary pancreatic NETs, respectively, and negative in all primary ileal NETs. Immunoreactivity results for metastatic NETs are summarized below:

Primary Site	n	Islet 1 (%)	PAX8 (%)	TTF-1 (%)	CDX2 (%)
Pancreas	28	19 (68)	15 (54)	0	1 (4)
Pulmonary	5	0	0	1 (20)	0
Ileum	37	0	0	0	33 (89)
Other GI	3	1 (33)	0	0	1 (33)

A four-stain IHC panel including Islet 1, PAX8, TTF-1, and CDX2 identifies 75% of metastatic pancreatic NETs, which was significantly better than a three-stain panel of PAX8, TTF-1, and CDX2 and slightly better than a three-stain panel of Islet 1, TTF-1, and CDX2.

Conclusion: Both Islet 1 and PAX8 are reliable IHC markers for NETs of pancreatic origin and would be useful adjuncts to other markers (TTF-1, CDX2) currently used to work up a metastatic NET of unknown primary.