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It's Time to Rethink Biomarkers for Surveillance of Small Bowel Neuroendocrine Tumors

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BACKGROUND: Tumor biomarkers (TBMs) reflect disease burden and correlate with survival for small bowel neuroendocrine tumors (SBNETs). This study sought to determine performance of chromogranin A (CgA), pancreastatin (PST), neurokinin A (NKA), and serotonin (5HT) during follow-up of resected SBNETs.

METHODS: An institutional database identified patients undergoing surgery for SBNETs. TBM levels were assessed as categorical (normal vs. elevated) and continuous variables for association with progression-free (PFS) and overall survival (OS) by Kaplan-Meier method with Cox multivariable models adjusting for confounders. Sensitivity, specificity, and predictive values of TBM levels in identifying imaging-confirmed progression were calculated.

RESULTS: In 218 patients (44% female, 90% node+, 73% metastatic, 97% G1 or G2), higher levels of CgA, PST, NKA, and 5HT correlated with higher grade and metastatic disease at presentation ($p < 0.05$). Elevated pre- or postoperative CgA, PST, and NKA correlated with lower PFS and OS ($p < 0.01$, median follow-up 49.6 months). In a multivariate model with reverse stepwise selection, only PST remained independently significantly associated with PFS and OS (Table). Biochemical response (postoperative reduction ≥ 50% of preoperative levels) of PST, but not CgA, correlates with longer PFS and OS. Normal CgA, PST, and NKA were present in 23.3, 16.9, and 72.6% of patients with progression, while elevated levels were present in 47.7, 24.8, and 1.3% of patients without progression. Using TBMs to determine progression revealed superiority of PST (78.9% accuracy) over CgA (63.3%) or CgA and PST together (60.3%).

CONCLUSION: While specific for progression, NKA was rarely elevated, limiting its usefulness. Elevated 5HT did not correlate with PFS or OS. Pre- and postoperative PST and CgA correlate with disease burden and survival, with PST providing better discrimination of outcomes. During follow-up, use of PST most accurately detected progression. These results suggest PST should replace CgA for SBNET surveillance.

Stepwise-selected multivariable model to determine independently significant pre-operative variables associated with PFS and OS

	PFS		OS	
Clinical Feature	HR (CI)	P-value	HR (CI)	P-value
Age (per year)	1.01 (1.00-1.04)	0.09	1.05 (1.01-1.71)	<0.01
Node-Positive	1.05 (0.37-2.99)	0.9	5.50 (0.69-43.8)	0.1
Metastasis Present	4.21 (1.67-10.6)	<0.01	4.09 (0.93-17.9)	0.06
Low Grade	0.54 (0.34-0.84)	<0.01	0.37 (0.19-0.69)	<0.01
Log_2-PreOp-PST	1.35 (1.20-1.51)	<0.01	1.43 (1.19-1.71)	<0.01

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