Virtual NET Cancer Patient Conference

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Patient M.D.G.

36 y/o male presented with three-year history of constant facial flush, 4-5 “loose stools” daily, R. flank pain, SOB

- Liver biopsy (2012) established metastatic NET WHO Grade 1
- OctreoScan (2012): Somatostatin receptor (SST2R) avid liver, nodal lesions
- Cardiac Echo: (+) tricuspid and (+) pulmonary regurgitation
- Surgery of primary tumor (2013): Dr. James R. Howe
- CT Scan (5/21/2014): 60% liver tumor burden
- S/P four cycles of PRRT (^{177}Lu-DOTATATE)
- **Liver Transplant: 9/23/2017**

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Case Report – Pt. M.D.G.

- 36 y/o, M: Carcinoid tumor syndrome with METs to liver

	Pre-Liver Transplant*	Post-Liver Transplant*	3/3/2020
Serotonin	1,975	249	217
CgA	2,111	118	160 (Nl < 160)
Pancreastatin	15,251	61	95
NK A	953	28	31
Subst P	1,292	109	198

* Mean of three values between January 2015 – April 2018

Neuroendocrine Cells (Specific Characteristics)

- Take up hormone precursors (Tryptophan)
- Synthesize, store, release amines and neuropeptides (serotonin, insulin)
- Express specific receptors and transporters (**SST2A receptors**, norepinephrine transporter)
- Express specific genes - neuropeptides that can predict tumor activity and behavior (**pancreastatin**, Neurokinin A)
- **Can be distinct cytology and CgA/Synaptophysin IHC**

Modified from Karel Pacak, with permission

Problems With Neuroendocrine Tumor Therapeutic Intervention(s)

- Decisions made primarily based on the “Gold Standard” CT, MR, Ultrasound demonstration of disease progression
- Both “symptomatic” and “asymptomatic” changes are **subjective** and clinical signs, like art, are often in the eye of the beholder
- Tumor-secreting amines and neuropeptides may be episodic initially and sustained later with tumor progression

Functioning Neuroendocrine Tumors

BASIC PRINCIPLES:

- Syndromes and symptoms (e.g., hypoglycemia) are due to sudden or sustained elevations of circulating amines (e.g., serotonin, catecholamine, or neuropeptides [e.g., insulin, VIP]).
- Documentation of elevated amines and neuropeptides should be done whenever possible.

Biomarkers and Neuroendocrine Tumors

TUMOR	BIOMARKERS	
Carcinoid, Sm. Intest (Mid-Gut)	• **[Serotonin]** • CgA – Pancreastatin	• Neurokinin A • (Substance P)
Carcinoid, Lung (Fore-Gut)	• **[CgA]** – Pancreastatin • Serotonin (3-5%)	• Substance P (?) • PP
N/E Pancreas (Fore-Gut) Non-functional (70%) Functional (30%)	• [**CgA** – Pancreastatin] • PP, Calcitonin • Serotonin (?) • Insulin, Gastrin, etc	

Biomarkers, Regulatory Function, Acute-Chronic Excess

BIOMARKER	FUNCTION*	ACUTE EXCESS	CHRONIC EXCESS
Serotonin	Hormone	Hypotension, Tinnitus, Flush	Diarrhea, Perspiration
Subst P	Neuro-Mod	Flush, Hypotension	Secret Diarrhea
Gastrin	Hormone	Flush, Reflux	Atyp Ulcers, Rugal Thick
Insulin	Hormone	Sympt Hypoglyce	Neuroglycopenia
Glucagon	Hormone	Hyperglycemia	Dermopathy, Wt Loss, DVT
VIP**	Neuro-Mod	Hypotension, Flush	Watery Diarrhea Syndrome
PP†	Hormone	None	None
Somatostatin	Multi-Regul	None/hypoglyce	Fat Malab, Gallstones

* All functional Tumor Biomarkers are Patho-Hormonal when elevated

** VIP = Vasoactive Intestinal Peptide

† PP – Pancreatic Peptide

Serotonin and Carcinoids

- Mid-gut carcinoids are **rich** in serotonin containing granules and are **frequently** associated with carcinoid syndrome
- Foregut carcinoids (stomach, lungs) have **few** serotonin granules
- Hind-gut carcinoids have **very few** serotonin granules
- Pancreatic NETs?

Modified: AC Deacon. *Ann Clin Biochem* 1994:31;215-232

Thoughts Regarding Whole Blood Serotonin

- Several commercial, CLIA-approved and College of American Pathology (CAP) approved assays in US
- Positive predictive value of 89% and negative predictive value of 93% of midgut carcinoids (Meijer WG, et al. *Clin Chem* 2000;46:1588)
- Elevated in 96% of mid-gut (ileal) carcinoids (Kema IP, et al. *Clin Chem* 1994; 40:86-95)

Carcinoid Tumors
Small Bowel (mid gut)

- **Serotonin** EDTA (Plasma + ascorbic acid)
  - Most sensitive, episodic
  - Collection critical for preservation
  - Commercially available
- **5-HIAA** (5-hydroxy-indoleacetic acid, urine) formed by metabolism of serotonin by monoamine oxidase
  - Almost **NEVER** elevated without liver METs (usually 15-20% burden)
  - Plasma 5-HIAA correlates (R=0.8) with urine 5-HIAA

Pancreas 2013:42(6):937-43

Chromogranin A (CgA)

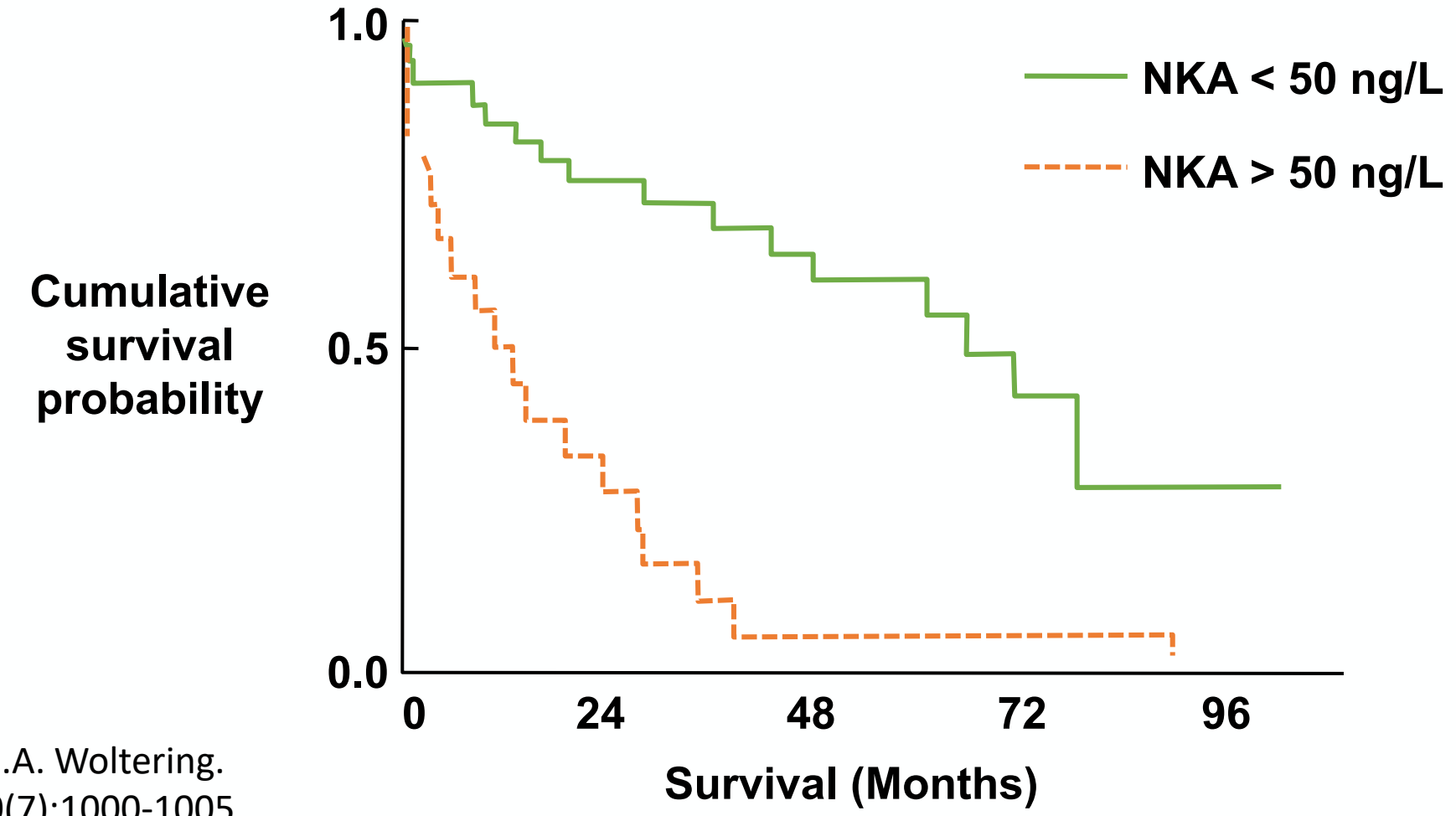
- Acidic, water soluble, secretory glycoprotein (ng/ml)
- Stored in matrix of secretory granules of nervous and neuroendocrine cells / tumors
- **Cleaved by prohormone convertase 1 (PC-1) to pancreastatin (pg/ml)**
- An accurate “marker” of neuroendocrine tumor burden and metastasis

Validation of Neurokinin A (NKA) Assays in the U.S. and Europe

P. Mamikunian, J.E. Ardill, T.M. O'Dorisio…
E.A. Woltering et al.

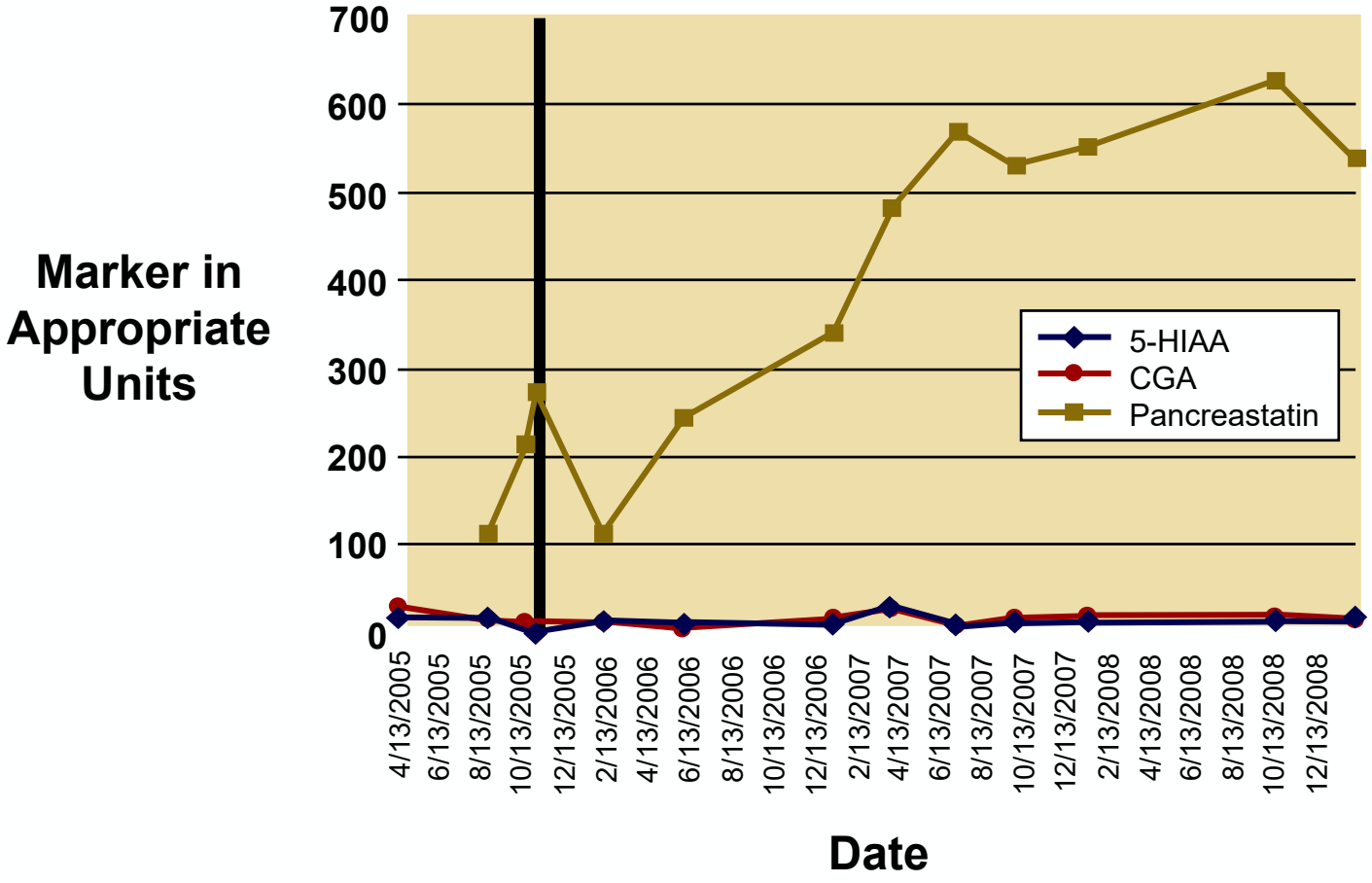
Pancreas 2011;40(7):1000-1005

Kaplan-Meier Survival Curve



P. Mamikunian…E.A. Woltering. *Pancreas* 2011:40(7);1000-1005

Sequential Marker Sensitivity of Pancreastatin



TM O'Dorisio, et al.
Pancreas 2010:39(5);611-616

Pancreastatin Predicts Survival in Neuroendocrine Tumor Patients

- 98 small bowel NETs: 78 pancreatic NETs
- Event times estimated by Kaplan-Meier
- Pre- and postoperative labs for correlation with outcomes
- Multivariant Cox model adjusted for confounders

Sherman SK, Maxwell JE, O'Dorisio MS, O'Dorisio TM, Howe JR. *Ann Surg Oncol* 2014; 21:2971

Results (1)
(*Ann Surg Oncol* 2014; 21:2971)

- Preoperative serotonin levels significantly associated with progression free survival (PFS) (p=0.02)
- Postoperative reduction of serotonin by 88 ng/ml or more was significantly associated with PFS (p=0.01)
- Preoperative CgA and preoperative pancreastatin showed significant correlation with PFS and OS ($p<0.05$)

Results (2)
(*Ann Surg Oncol* 2014; 21:2971)

- Elevated preoperative PAN associated with shorter median PFS and OS vs normal PAN
- PFS 1.7 yrs vs 6.5 yrs vs median not reached
- 5 yr PFS 14.9% (high prePAN: 59% [normal PAN])
- Normalization of post-op pancreastatin significantly improved PFS and OS (3.9 yrs and 100%)
- Elevated post-op pancreastatin, 5 yr PFS dropped to 8.6% and OS decreased to 6.5 yrs

Conclusion
(*Ann Surg Oncol* 2014; 21:2971)

- Higher pancreastatin levels are significantly associated with worse PFS and OS in SBNETs and PNETs
- Independent of age, primary tumor site, and nodal or metastatic disease

It Is Time to Rethink Biomarkers for Surveillance of Small Bowel NETs

Tran C., Sherman S., Scott A., Ear P., Chandrasekharan C., Belizzi A., Dillon J., O'Dorisio T., Howe, J.

Annals of Surgical Oncology 2020

https://doi.org/10.1245/s10434-020-08784-0

Subjects and Methods

Ann Surg Oncol. 2020. C. Tran

- 218 small bowel NETs (92% nodal; 73% metastatic)
- Biomarkers: Serotonin (SER), CgA, NKA, Pancreastatin (PAN)

Assessed as categorical (Normal or Elevated) and continuous variable

- Progression Free Survival (PFS) and Overall Survival (OS) via Kaplan-Meier models adjusted for confounders
- Serial CT/MR imaging confirmed progression

Results

Ann Surg Oncol. 2020. C. Tran

- High CgA, PAN, NKA, SER correlated with higher grade and metastatic disease at presentation ($p < 0.05$)
- Higher levels pre and post surgery of CgA, PAN, NKA, SER correlated with LOWER PFS and OS (Median F/U 4 yrs)
- Using Biomarkers to determine progression:
  - **PAN showed superiority with 79% accuracy** vs CgA (63% accuracy) or PAN + CgA (60% accuracy)

Conclusion

Ann Surg Oncol. 2020. C. Tran

- During long-term F/U, PAN accurately detected progression
- **PAN should replace CgA for small bowel surveillance**

Elevated Serum Pancreastatin is an Indicator of Hepatic Metastasis in Patients with Small Bowel Neuroendocrine Tumors

T.M. Khan, M. Gary, R. Warner, J.H. Uh, C.M. Divine

Pancreas, 2015; 45:1032-1035

Patients and Methods

77 Patients Retrospective: 44 (57%) Primary small bowel

49 (64%) Metastasis to liver

Metastatic Markers: Pancreastatin (PAN) and CgA

Sensitivity (%), Specificity (%)

Positive (%)/Negative (%) Predictive Value (PV)

Results

PAN	87% Sensitivity	(+) PV = 71%	(-) PV = 83%
CgA	62% Sensitivity	(+) PV = 64%	(-) PV = 41%

Conclusion

ELEVATED SERUM PANCREASTATIN:

- Sensitive and specific assay for detecting incidence of metastatic small bowel NETs
- Routine measurement of PAN in small bowel NETs is supported

Biomarkers

- CgA levels can reflect total tumor burden (when metastatic) for both pancreatic and mid-gut (ileal) N/E tumors
- Neurokinin A is a **predictor** for aggressive mid-gut (ileal) tumors
- Pancreastatin may be a very **early** marker for liver tumor activity and predicts **PFS, OS, and Progression**

Reference Laboratories in the United States

ARUP, Quest, MAYO, LabCorp, Viracor, Inter Science Institute (ISI), Cambridge Lab, OSU-URL

- **ALL** CLIA (Clinical Laboratory Improvement Act) accredited
- **ALL** CAP (College of American Pathologists) accredited

Serotonin: ARUP, Quest, LabCorp

CgA: ARUP, Quest, MAYO, LabCorp, ISI, Cambridge (?)

Pancreastatin: ISI (published), URL (published), Cambridge (published)

NkA: ISI (published), Cambridge (?)

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