Medical Management and Prevention of Carcinoid Crisis during Bland Embolization for Neuroendocrine Tumor

Ghassan El-Haddad, MD

Associate Member, Interventional Radiology and Cancer Physiology

Moffitt Cancer Center and Research Institute

Associate Professor, Interventional Radiology, and Oncologic Sciences

University of South Florida

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No relevant financial interests with any commercial interest to disclose.

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Hepatic Artery Embolization for mNET

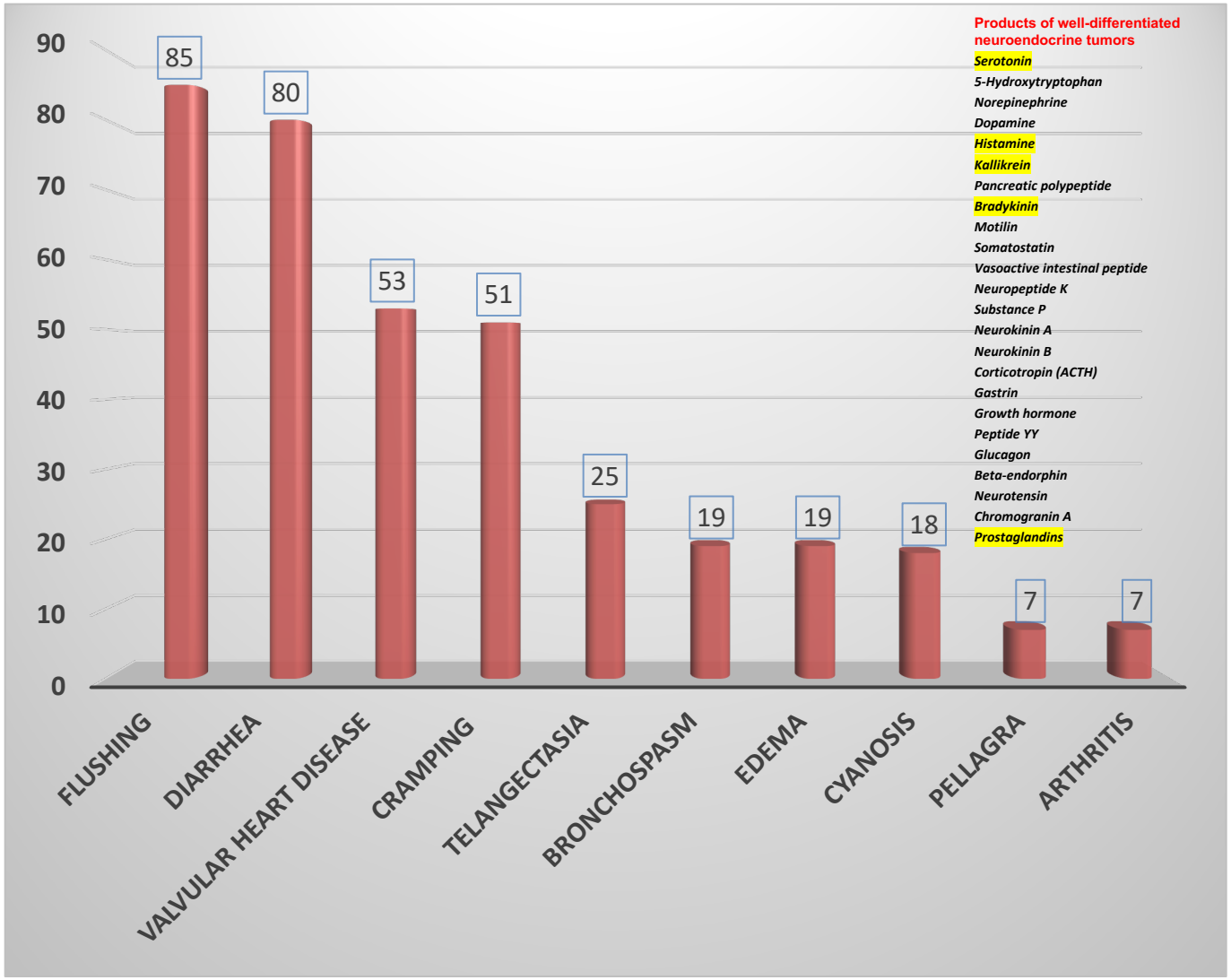
Pre TAE

Post TAE

- NCCN, NANETS, and ENETS guidelines
  - symptomatic or progressive hepatic metastases (level 2B-3 evidence)
- Clinical and imaging response rates: 70%-90%
- Post embolization syndrome

Touzios JG, et al. *Ann. Surg.* 2005;241(5),776–783. Roche A, et al. *Eur. Radiol.* 2003;13(1),136–140. Moertel CG, et al. *Ann. Intern. Med.* 1994;120(4),302–309. Mavligit GM, et al. *Cancer.* 1993;72(2),375–380. Loewe C, et al. *AJR Am. J. Roentgenol. 2003;*180(5),1379–1384. Iwazawa J, et al. *World J Radiol. 2010;*2(12), 468–471. Pavel M, et al. *Neuroendocrinology.* 2012;95:157-176. Boudreaux JP, et al. *Pancreas.* 2010;39:753-766. Kulke MH, et al. *Pancreas.* 2010;39:735-752.

Carcinoid syndrome



- Elevations in **serum serotonin** or its metabolite **urinary 5-HIAA**
- > 90% of patients with carcinoid syndrome have **metastatic disease, typically involving the liver** (primarily from midgut tumors)
- Rare exceptions: bronchial and ovarian NETs (release hormones directly into systemic circulation)

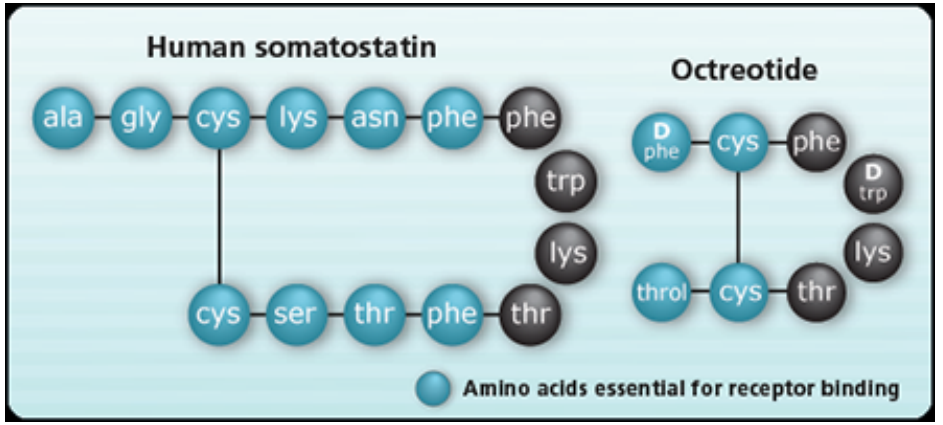
Carcinoid Crisis

- Definition varies: **wide blood pressure fluctuations** with a **predominance of hypotension, flushing, bronchospasm, tachycardia**
- Can be life-threatening
- At risk: carcinoid syndrome, high serotonin/5-HIAA
- *Hypothesis:* Overwhelming release of biologically active compounds from NET, but still largely unknown
- Triggered by tumor manipulation:
  - **<u>Hepatic arterial embolization (even contrast injection)</u>**
  - Surgery
  - Anesthesia
  - Radiofrequency ablation
  - PRRT

Howe JR, et al. *Pancreas*. 2017;46(6):715-731. Kaltsas G, et al. *Neuroendocrinology*. 2017;105(3):245-254. Condron ME, et al. *Surgery*. 2019;165(1):158-165. Kwon DH, et al. *Pancreas*. 2019;48(4):496-503.

Prevention of Carcinoid Crisis or "Flattening The Curve"

- No strict guidelines, lack of definitive studies to support preprocedural octreotide
- **Prophylactic** octreotide prior to TAE for ***carcinoid syndrome*** and/or elevated urinary ***5-HIAA***
- Octreotide pre-TAE (**300 to 500 mcg intravenously or subcutaneously**) at least 1 hour before (trend for better control of hemodynamic instability/carcinoid crisis than surgical resection and/or ablation)
- Different protocols: Octreotide 100-500 mcg/hr gtt x 4-6 hrs. and octreotide 150 mcg SQ
- +/- H1 and/or H2 blockers
- Patients with tumors that do not produce serotonin (eg, rectal NETs, most pancreatic NETs) may not require prophylactic octreotide
- **Carcinoid crisis can still occur despite the use of pre-embolization prophylactic octreotide**



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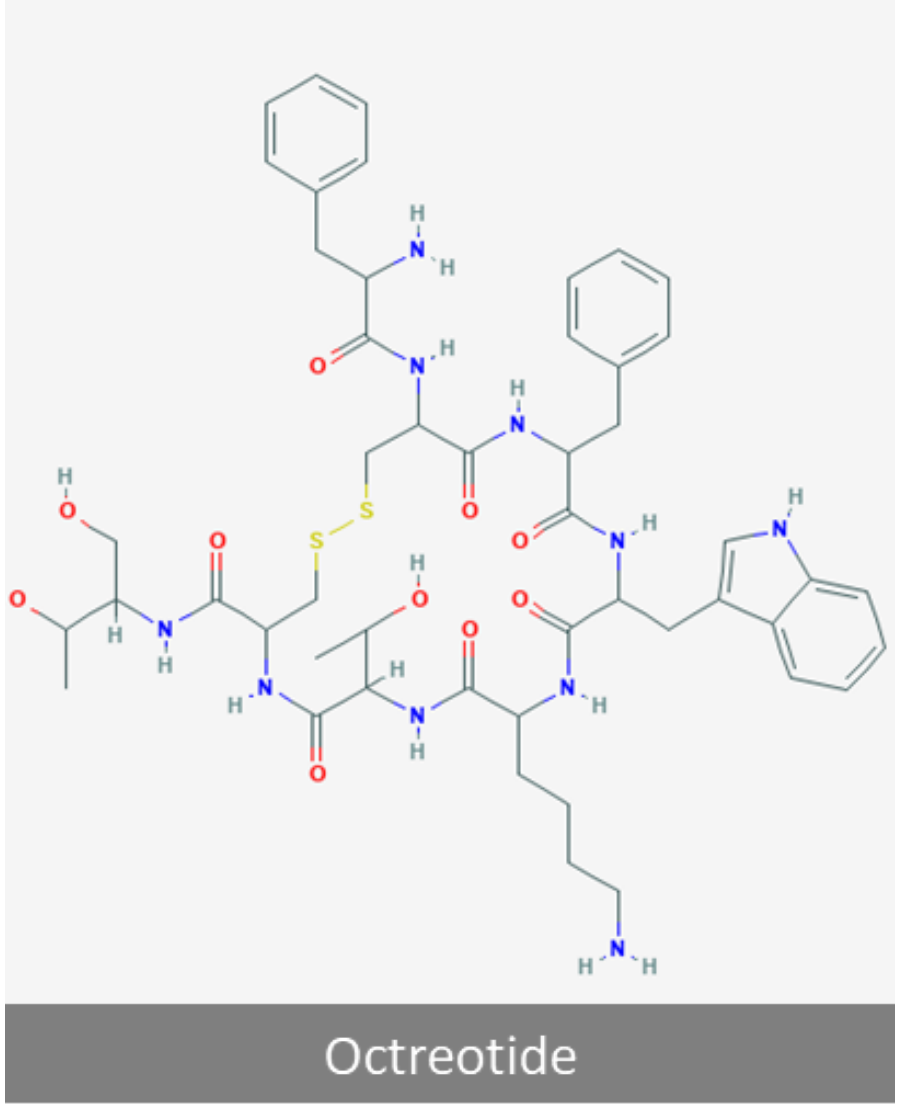
Management of Carcinoid Crisis

- Hypotension(rare with TAE): fluid resuscitation and potentially vasopressors (phenylephrine, ephedrine, vasopressin)
- Hypertension tachycardia more common post-TAE
- Blood pressure should be supported by infusion of octreotide
  - **500 to 1000 mcg intravenously or a continuous IV drip at a rate of 50 to 200 mcg/hour**
- Low toxicity profile of octreotide



Octreotide

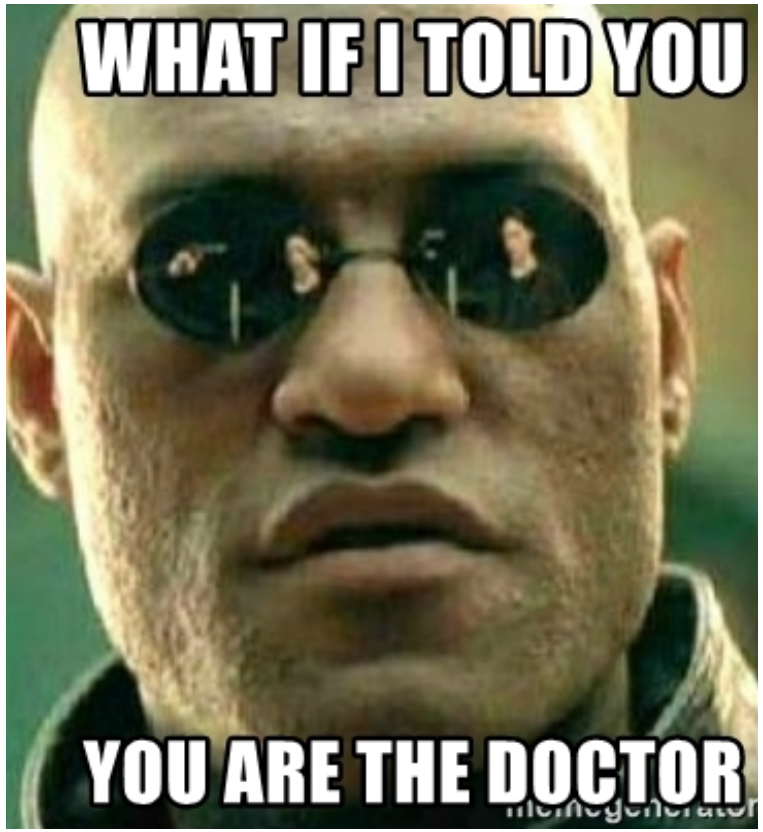
Blood Pressure Categories

American Heart Association.

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

Hypertensive Crisis

- **Hypertensive urgency: SBP > 180 mm Hg or DBP > 120 mm Hg**
- **Hypertensive emergency if combined with symptoms suggesting organ damage**
  - **headache, lightheadedness, altered mental status, anxiety, chest pain, or dyspnea**



Whelton PK, et al. 2017, ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.

Treatment of Hypertensive Crisis

Table. Guideline-Directed Treatments of Hypertensive Urgency and Hypertensive Emergency[1,5]

Treatment Guideline	Hypertensive Urgency	Hypertensive Emergency
2013 ACEP	Reduce blood pressure and/or initiate therapy for long-term control; refer for outpatient follow-up.	None
2013 ESH/ESC Arterial Hypertension	Reinstitute or intensify existing antihypertensive regimen.	Reduce blood pressure by <25% within 1 hour; use IV and oral drugs recommended for malignant hypertension.
2017 ACC/AHA	No indication for immediate reduction of blood pressure in emergency department or hospitalization.	In hour 1, reduce systolic blood pressure by ≤25%; for the next 2 to 6 hours, target 160/100 mm Hg; and for the next 24 to 48 hours, cautiously reduce blood pressure to normal.

Abbreviations: ACC, American College of Cardiology; ACEP, American College of Emergency Physicians; AHA, American Heart Association; ESC, European Society of Cardiology; ESH, European Society of Hypertension; IV, intravenous; MAP, mean arterial pressure.

- Parenteral antihypertensives: hydralazine, nicardipine, metoprolol, atenolol, esmolol, nitroglycerine, and nitroprusside are all possible choices
- Clonidine
- Patients with significant bradycardia, beta blockers and calcium channel blockers should be avoided

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Moffitt Protocol Post TAE Carcinoid HDI/Crisis/Storm

- Octreotide 500 mcg subq about an hour pre-procedure, then 400 mcg subq Q8H starting 8 hours after first dose
- During procedure, if change in vital signs:
  - *SBP < 100 mm Hg OR > 160 mm Hg*
  - *DBP < 60 mm Hg OR > 110 mm Hg*
  - *Pulse < 60 bpm*
  - *Flushing – intense*
- **1000 mcg IV push over 3 min. (may repeat in 5- to 10-minute intervals x 3 doses)**
- Hydralazine (5 to 10 mg IV q 15 min), clonidine 0.2 mg, atenolol, metoprolol for persistent hypertension
- If adequate response not achieved within 30 to 60 minutes, then nicardipine drip

Conclusion

- Lack of strong data, but recommendations for pre-embolization octreotide
- A carcinoid crisis can occur despite preemptive use of octreotide
  - need for vigilance and the availability of octreotide for up to 48 hours post-procedure
  - **Post-TAE hemodynamic instability or carcinoid crisis for mNET is very common** (**definition of carcinoid crisis as hypotension** is too narrow)
- Hard to distinguish post-TAE hyperadrenergic responses from carcinoid crisis, particularly in the context of postprocedural pain
  - make sure the bladder is empty
  - notify the nurse before you start embolizing
  - analgesics ready (PCA pump)
- Exclude other causes
    - allergic reaction (tongue swelling, difficulty breathing)
    - vasovagal reaction

Strosberg JR, et al. *Cancer Control.* 2006;13(1):72-8.