

# Different Scenarios for Hormone-Release Control Before Invasive Procedures in Endocrine Malignancies

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## Disclosures Wouter W. de Herder

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  - Endocrine-Related Cancer.
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  - Nederlands Tijdschrift voor Geneeskunde.

# Perioperative Procedures are Sometimes Necessary to Control (Potential) Hormonal Hypersecretion

**GI NET - Bronchial Carcinoid**

**Pancreas NET**

**Pheochromocytoma/Paraganglioma**

**Carcinoid Syndrome**

**Insulinoma**

**Gastrinoma**

**VIPoma**

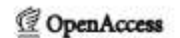
**Glucagonoma**

**Ectopic ACTH Secretion (Cushing's)**

**PTHrp Secretion**

# Procedures in Hormone-secreting Neuroendocrine Tumors can Sometimes cause Hormonal Crises

Eur J Nucl Med Mol Imaging (2008) 35:749–755  
DOI 10.1007/s00259-007-0691-z



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**J. R. T. C. Roelandt**

ORIGINAL ARTICLE

**Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [<sup>177</sup>Lu-DOTA<sup>0</sup>, Tyr<sup>3</sup>]octreotate**

Bart de Keizer • Maarten O. van Aken •  
Richard A. Feelders • Wouter W. de Herder •  
Boen L. R. Kam • Martijn van Essen •  
Eric P. Krenning • Dik J. Kwekkeboom

**Carcinoid crisis during transesophageal echocardiography**

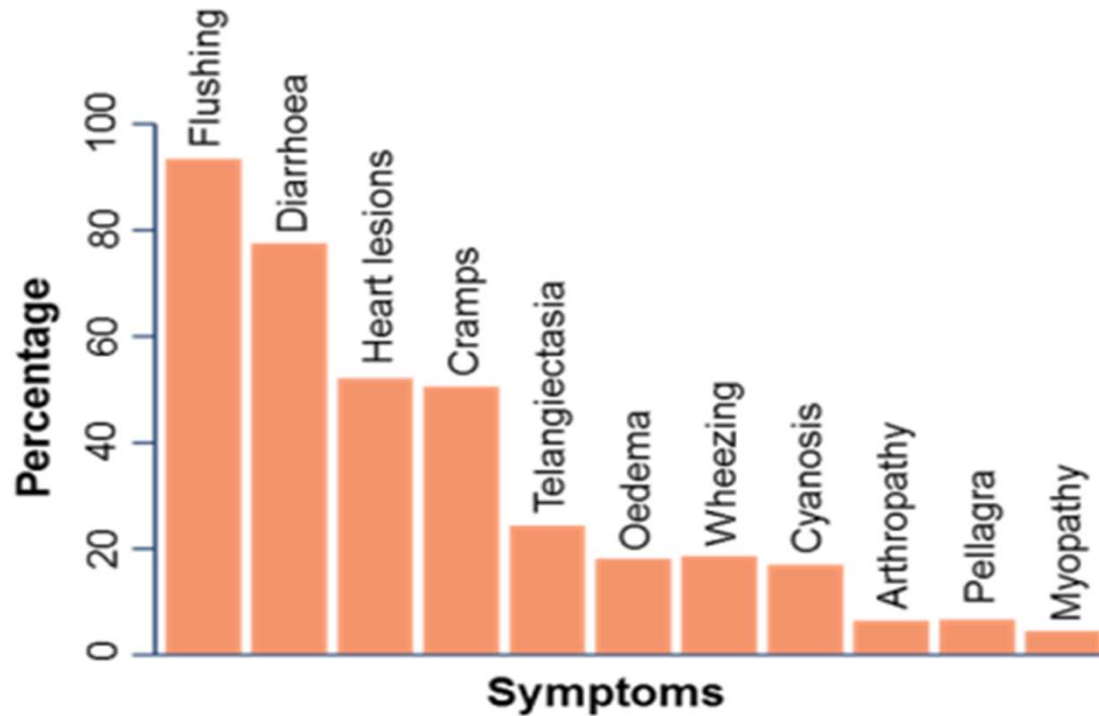
Accepted: 1 December 1999

**Case of carcinoid crisis following a fine-needle biopsy of hepatic metastasis**

Vikram Sinha<sup>a</sup>, Philip Dyer<sup>b</sup>, Shuvro Roy-Choudhury<sup>b</sup>, J. Ian Geh<sup>b</sup> and Sharad Karandikar<sup>b</sup>

Janssen M, *et al.* Intensive Care Med. 2000;26(2):254. de Keizer B, *et al.* Eur J Nucl Med Mol Imaging. 2008;35(4):749-55.  
Sinha V, *et al.* Eur J Gastroenterol Hepatol. 2009;21(1):101-3

## Carcinoid Syndrome Frequency of Symptoms



Mamikunian G, *et al.* (eds). Neuroendocrine tumours: A Comprehensive Guide to Diagnosis and Management, 4th Edition, 2009.

## **Carcinoid Crisis Surgery (n = 16/46)**

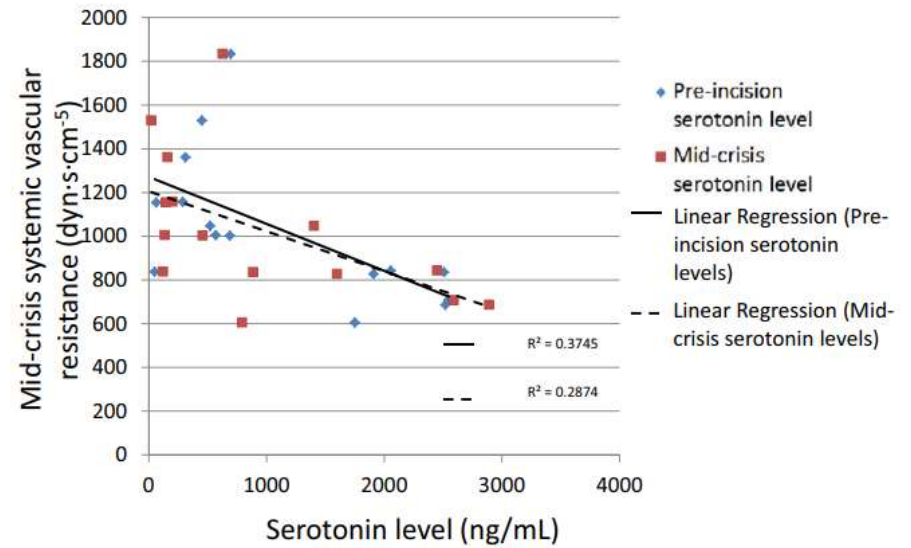
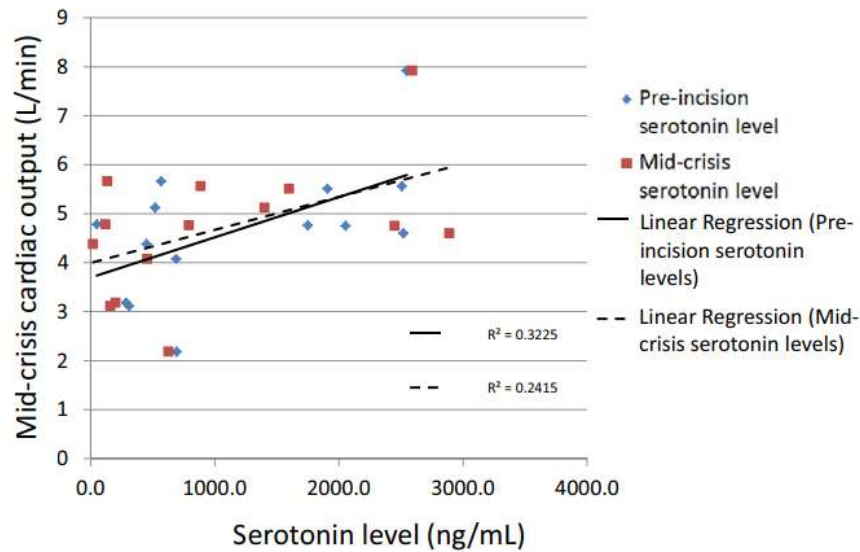
**Clinics:** Abrupt onset of hemodynamic instability in patients with the carcinoid syndrome undergoing an intervention

**Cause:** Stress +/- tumor manipulation  
Massive secretion of Serotonin, Histamine, Kallikrein & Bradykinin?  
No “typical” hormone profiles found

**Findings:** >> Preincision serotonin levels in patients who had crisis

**Pathophysiology** ≈ distributive shock = Intracardiac hypovolemia / decrease in pulmonary artery pressure / decreased systemic vascular resistance

# Carcinoid Crisis Surgery (n = 16/46)



Condrón ME, et al. Clin Surgery. 2019;165(1):158-165.

## Carcinoid Crisis Octreotide Prophylaxis (n = 173/179)

- It works (crisis in 3%, n = 179)

Development of effective prophylaxis against  
intraoperative carcinoid crisis<sup>☆</sup>



Eugene A. Woltering MD<sup>a,\*</sup>, Anne E. Wright BS, BSN<sup>b</sup>, Melissa A. Stevens MPH<sup>a</sup>,  
Yi-Zarn Wang MD<sup>a</sup>, John P. Boudreaux MD<sup>a</sup>, Gregg Mamikunian MS<sup>c</sup>,  
James M. Riopelle MD<sup>d</sup>, Alan D. Kaye MD, PhD<sup>d</sup>

- It doesn't work (crisis in 30%, n = 150)

Continuous infusion of octreotide  
combined with perioperative  
octreotide bolus does not prevent  
intraoperative carcinoid crisis

Mary E. Condron, MD,<sup>a</sup> SuEllen J. Pommier, PhD,<sup>b</sup> and Rodney F. Pommier, MD,<sup>b</sup> Portland, OR

# **Carcinoid Crisis Octreotide Prophylaxis ENETS Guideline**

**Patients with carcinoid syndrome (+/-CHD) and/or increased 5-HIAA levels in urine:**

- **If patients already receive octreotide or other somatostatin analogs, this medication should be continued while awaiting surgery.**
- **Perioperative treatment:**
  - Intravenous octreotide: 12 h before anesthesia - 50–100 µg/h using dose titration until resolution of the symptoms (mean dose 100–200 µg/h).**
- **Carcinoid crisis:**
  - Caution with adrenergic drugs.**
  - Octreotide iv at doses as high as 500 µg/h.**

## Perioperative Management Functioning Pancreatic NET ENETS Guideline

- **Insulinoma**
  - Diazoxide not recommended (fluid retention & edema).
  - Dextrose / intravenous glucose infusion.
  - Somatostatin analog / iv Octreotide?
- **Gastrinoma**
  - PPI (adequately high doses) during and 3 months after surgery.
  - Somatostatin analog / iv Octreotide?
- **Glucagonoma**
  - Amino acids / antibiotics for necrolytic migratory erythema.
  - Somatostatin analog / Octreotide.
  - Prophylactic high-dose molecular heparin.
- **VIPoma**
  - Resuscitation from life-threatening fluid losses and electrolyte abnormalities.
  - Somatostatin analog / Octreotide.

## Therapy Ectopic ACTH Syndrome

- **Bi-adrenalectomy**
- **ACTH inhibitory agents:**
  - Somatostatin analogs (Octreotide, Lanreotide, Pasireotide).
  - Dopamine agonists (Cabergoline).
- **Adrenolytic agents:**
  - Ketoconazole.
  - Metyrapone.
  - Mitotane.
  - Aminoglutethimide.
  - Etomidate.
  - LCI699.
  - COR-003 – Levoketoconazole.
- **Glucocorticoid receptor antagonists:**
  - Mifepristone.

## Hypercalcemia in NEN Patients

- **MEN-1 syndrome:**  
(coexistent primary hyperparathyroidism [PHP]).
- **Local osteolytic hypercalcemia:**  
increased bone resorption by osteoclasts mediated by (metastatic) tumor cells, which are in direct contact with bone.
- **Humoral hypercalcemia of malignancy (HHM)**  
hypersecretion of PTH or PTHrP into the circulation by tumor cells.

# PTHrP in NEN Patients

Therapeutic interventions (TI) after diagnosis of PTHrP-hypersecretion	N		Calcium Response (N)			Response Duration (Months)	
	pts	TI	Normalization	Decrease	None	Normalization	Decrease
<b>Total patients</b>	10	51	27	16	8	0.1-49.0	0.03-1.5
<b>NaCl 0.9%</b>							
24-h	3	3		2	1		0.1-0.2
12-h (intervals)	1	1			1		
<b>Somatostatin analog (SSA)</b>							
Octreotide LAR 20mg/4wk *	1	1	1			35.2	
Octreotide IR	6	7	6	1		1.0-7.7	0.5
<b>Bisphosphonates (B)</b>							
Single short iv infusion	2	4	1	2	1	2.3	0.2-0.4
Repetitive iv infusions	1	1	1			1.6	
						28.2	
						0.1-1.1	
						0.3	
						9.0	
						0.5	
						5.2	0.3
							0.1
							0.2
NaCl 0.9% + SSA IR	1	1		1			0.2
NaCl 0.9% + B iv	4	8	2	5	1	0.8-2.7	0.03-1.3
NaCl 0.9% + SSA IR + B iv	2	2	1	1		0.5	0.1
NaCl 0.9% + B oral + B iv repetitive	1	1	1			10.0	
SSA IR + B iv repetitive	1	1	1			1.2	
SSA LAR + B iv repetitive	1	1		1			1.5
SSA LAR + B iv + G	1	1	1				0.5
S + NaCl 0.9%	1	1	1			3.3	
D + NaCl 0.9% + SSA IR	1	1		1			1.5
PRRT <sup>177</sup> Lu-Octreotate (4 cycl.) + SSA IR	1	1	1			14.5	
PRRT <sup>177</sup> Lu-Octreotate (6 cycl.) + SSA LAR	2	2	2			33.3-49.0	

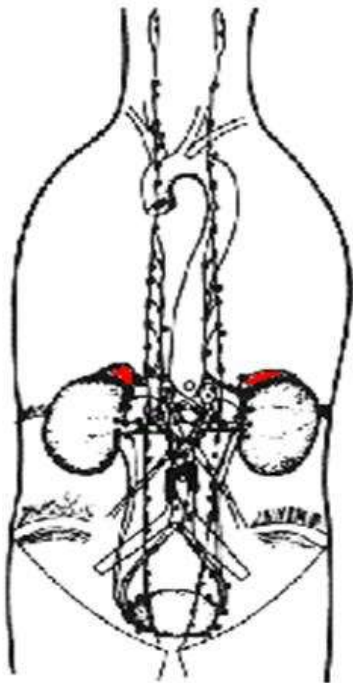
**Isotonic saline and bisphosphonates recommended as supportive therapy.**

**Most successful therapies:**

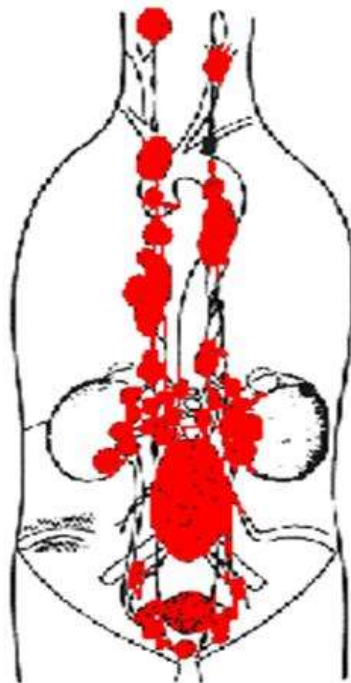
**Somatostatin analogs.**

**Peptide receptor radiotherapy (PRRT)**

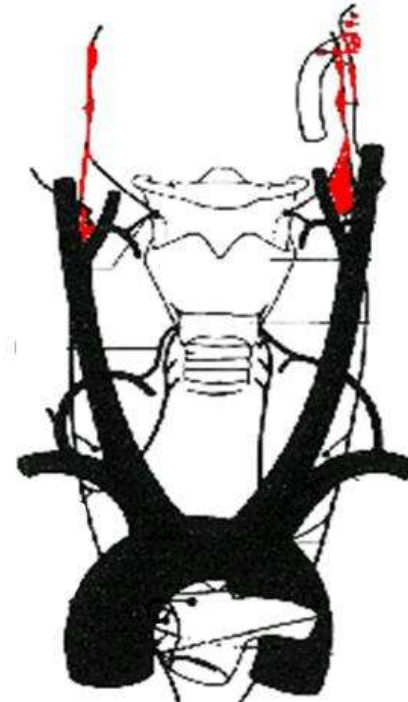
## PPGL – Pheochromocytoma = Paraganglioma



Pheo



Sympathetic PGLoma



Parasympathetic PGLoma



## Suggested Presurgical Oral Treatment of Patients With PPGL

Drug	Starting dose	Incremental dose steps <sup>a</sup>	Dose range	Comments
phenoxybenzamine	10mg q.d.	20mg	10-140mg	Preferably started at least 7-14 days prior to surgery, also in case of normotension. Doses higher than starting dose are administered b.i.d.
<i>or</i>				
doxazosin ER	4mg q.d.	4mg	4-56mg	
nifedipine ER	30mg q.d.	30mg	30-90mg	Add-on to $\alpha$ -adrenergic receptor blockade in case of persistent hypertension (BP supine >130/80 mmHg, SBP upright >110 mmHg)
<i>or</i>				
amlodipine	5mg q.d.	5mg	5-10mg	
<i>or</i>				
metyrosine	250mg t.i.d.	250-500mg	750-2000mg	
metoprolol ER	50mg q.d.	50mg	50-200mg	Add-on in case of tachycardia (HR supine >80bpm, HR upright >100bpm). Preferably be started after sufficient preparation with $\alpha$ -adrenergic receptor blockade ( $\geq$ 3-4 days)
<i>or</i>				
propranolol	20mg t.i.d.	20mg	20-240mg	
<i>or</i>				
atenolol	25mg q.d.	25mg	25-100mg	
high sodium chloride diet	$\geq$ 15 grams	-	-	Restoration of intravascular volume depletion; prevention of preoperative orthostatic hypotension and postoperative hypotension
<i>and</i>				
saline 0.9% i.v.	2L /24h	-	-	Intravenous saline should be started 24h before surgery

**Berends AMA, et al. J Clin Endocrinol Metab. 2020;105(9):dgaa441.**

## Suggested Intravenous Treatment of Hypertension and Tachyarrhythmia in Case of PPGL Crisis or

Indication	Drug	Dose	Onset of action	Duration of action (after discontinuation)	
Hypertension	magnesium sulfate <sup>b</sup>	loading dose: 40-60 mg/kg followed by infusion of 1-4 g/h	immediate	30 min	
	Step 1 <sup>a</sup>	phentolamine <sup>c</sup>	bolus: 2.5-5 mg at 1 mg/min, repeated every 3-5min continuous: 100 mg in 500 mL of 5% dextrose 20-100 mg/h	1-2 min	10-30 min
	or				
	Step 2	urapidil	bolus: initial dose: 25-50 mg or continuous: 10-15 mg/h	1-5 min	5-11 h
	Step 3	nicardipine	starting dose: 5 mg/h, increased by 2.5 mg/h every 5 min (if needed), maximum dose 15 mg/h	1-5 min	15-30 min, may exceed 12h after prolonged infusion
	or				
		clevidipine	starting dose: 1-2 mg/h, increase by doubling the dose every 90 seconds (if needed), maximum dose 32 mg/h	2-4 min	5-15 min
	Step 4	sodium nitroprusside	start: 0.5-1.5 µg/kg/min, doses range: 0.5-4 µg/kg/min, stop administration if no results are achieved after 10 min of infusion, maximal dose for 10 min only	immediate	2-3 min
	or				
		nitroglycerine	infusion adjusted according to response within the range of 10-200 µg/min <sup>d</sup>	2-5 min	5-10 min
Tachyarrhythmias	esmolol <sup>e</sup>	bolus: 500 µg/kg in 1 min, repeat bolus after 5 min (if needed) continuous: 25-100 µg/kg/min, increase infusion rate to 300 µg/kg/min (if needed)	1-5 min	15-30 min	
	Step 1	amiodarone	loading dose: 5mg/kg followed by infusion of 15 µg/kg/min	1-30 min	1-3 h
	or				
	Step 2	lidocaine	loading dose (bolus) 1mg/kg, repeat after 5-10 min (if needed). continuous: 2-4 mg/min (1-2 mg/ml), maximum 300 mg/h	< 2 min	15-20 min

Berends AMA, et al. J Clin Endocrinol Metab. 2020;105(9):dgaa441.

# Thank You for Your Attention

