Chief's CORNER

ANIL K. RUSTGI, MD

T. Grier Miller Professor of
Medicine and Genetics
Chief, Division of Gastroenterology

GREG G. GINSBERG, MD:
Dr. Ginsberg is the president-elect for the ASGE for May 2010-May 2011, and will be ASGE President for May 2011-May 2012. He recently served as president of the Delaware Valley Society for GI Endoscopy (2008-2010).

ANDREW D. RHIM, MD
Dr. Rhim is the recipient of an NIH K08 career development grant in pancreatic cancer and past recipient of an AGA grant.

BEN Z. STANGER, MD, PhD:
Dr Stanger is the recipient of the 2010 AGA/GRG Investigator Award in Basic Science Research, and has been elected to the American Society of Clinical Investigation.

The following Penn Gastroenterologists/Hepatologists were voted as "Top Docs" by *Philadelphia* magazine for 2010:

- GREGORY G. GINSBERG, MD
- TIMOTHY C. HOOPS, MD
- JAMES D. LEWIS, MD, MSCE
- GARY R. LICHTENSTEIN, MD
- DAVID C. METZ, MD
- K. RAJENDER (RAJ) REDDY, MD

Penn Medicine
3600 Market Street
Suite 210
Philadelphia, PA 19104

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Penn Medicine

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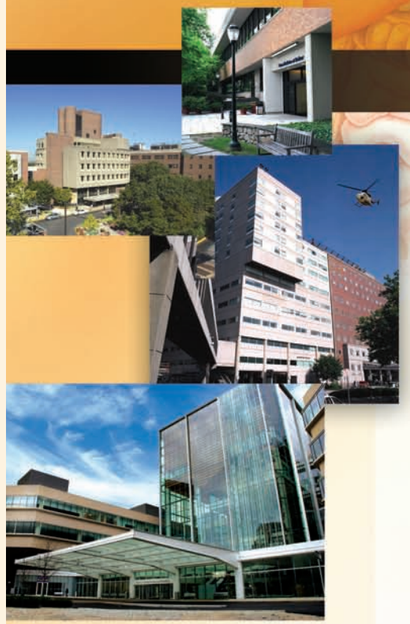
NET TREATMENT PROGRAM

GASTROENTEROLOGY NEWSLETTER



LOCATIONS

The Ruth and Raymond Perelman Center for Advanced Medicine
3400 Civic Center Boulevard
Philadelphia, PA 19104
215.349.8222

Penn Presbyterian Medical Center
38th and Market Streets
218 Wright-Saunders Building
Philadelphia, PA 19104
215.662.8900

Penn Medicine at Radnor
250 King of Prussia Road
Module B
Radnor, PA 19087
610.902.1500

Penn NET Treatment Program
Abramson Cancer Center
Philadelphia, PA
215.615.4646

PENN NEUROENDOCRINE TUMOR TREATMENT PROGRAM

A collaboration between Penn Gastroenterology and the Penn Renal, Electrolyte and Hypertension results in an interdisciplinary program to diagnose, stage and treat neuroendocrine tumors

The Penn Neuroendocrine Tumor Treatment Program was developed under the direction of Debbie Cohen, MD (Nephrology) and David Metz, MD (Gastroenterology), shown above with NET Program patient coordinator Bonnie Bennett, BSN.

The Penn Neuroendocrine Tumor Treatment Program provides a comprehensive, inter–disciplinary approach to the diagnosis, staging, and medical and surgical treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and pheochromocytomas.

GEP-NETs are a rare (~2 percent of all GI tumors), heterogeneous group of malignancies occurring in the digestive tract. Pheochromocytomas are tumors of neuroendocrine chromaffin cells, and are found in both the adrenal glands and in extra-adrenal locations. They are rarer (~2/100,000 persons) than GEP-NETs. With early diagnosis and treatment, tumors in both neuroendocrine classes are potentially curable and manageable for the long term.

Originating in cells having both nervous and endocrine properties, GEP-NETs are classified by histology as either alimentary tract carcinoid lesions (NETs) or pancreatic endocrine tumors (PETs) and subcategorized by whether or not they secrete neuroamines, hormones or peptides at levels sufficient to cause a syndromic response. A recent standard WHO classification has proposed that GEP-NETs be assigned to one of three categories (well-differentiated tumor, well-differentiated carcinoma, and poorly differentiated carcinoma) based on histology, size and proliferative indices.

A Foundation in Experience: The Penn NET Treatment Program

As a result of the rarity and indolent character of GEP-NETs and pheochromocytomas, their early diagnosis depends largely on the experience and expertise of treating clinicians and access to advanced imaging and laboratory facilities—a combination of advantages unique to Penn in the Philadelphia region.

Both Dr. Metz and Dr. Cohen have researched and published on NETs and both have wide experience in the long-term management of NET patients within their respective specialties. In addition, the Penn

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Each patient in the Penn NET Treatment Program is linked to a central physician who is the primary contact for both the patient and the treatment team.

NET Treatment Program incorporates the full armamentarium of services, procedures and technologies at Penn into the management of NETs, engaging the diagnostic services of the Divisions of Gastroenterology, Hematology-Oncology (Weijing Sun, MD, Director of GI medical oncology), Renal Electrolyte and Hypertension, Interventional Radiology and Medical Genetics, as well as the capabilities of the Abramson Cancer Center. Thus, Dr. Cohen explains, at Penn patients with NETs have the advantage of a clinical environment capable not only of familiarity with these rare and idiosyncratic tumors, but also of heightened diagnostic scrutiny.

The diverse goals of the Penn NET Treatment Program include accurate diagnosis and staging, effective symptom control, curative surgery (when possible), prevention of tumor progression (using medical, radiological and surgical approaches), genetic counseling (when indicated), and individualized long-term patient management depending on disease progression. Patients enter the program by being referred to a gastroenterologist, nephrologist, oncologist, surgeon or endocrinologist at Penn. This specialist then refers the patient for further diagnostics, which may involve biochemical measurements and imaging studies, or treatment via surgery, medical or radiation oncology and nuclear medicine.

"Each patient has a central physician," Dr Metz says. "This specialist, who might be a gastroenterologist, an oncologist or a nephrologist, is the primary contact for both the patient and the treatment team."

Clinical Diagnosis and Management of GEP-NETs at Penn

Secreting (functional) alimentary tract NET lesions represent only a small portion of carcinoids and are associated with a variable and nonspecific array of symptoms collectively termed the carcinoid syndrome. These symptoms include intense flushing, diarrhea, abdominal pain, heart rate variability and blood pressure lability and are typically caused by the vasoactive neurotransmitter serotonin among others. Functional pancreatic NETs (PETs) produce a variety of clinical syndromes in association with the substances they secrete (e.g., Zollinger-Ellison syndrome [gastrin], insulinoma syndrome [insulin], glucagonoma syndrome [glucagon], VIPoma syndrome [vasoactive intestinal polypeptide], etc). Several inherited conditions are associated with PETs. These include multiple endocrine neoplasia-type 1 [MEN1] and von Hippel-Lindau syndrome. Nonfunctional GEP-NETs are clinically silent and indolent. Most are identified late in their course when tumor bulk or metastases to the liver cause abdominal pain and other symptoms.

Surgery can be curative, and is typically the first-line treatment for resectable patients with GEP-NETs. At Penn, surgery is offered through the divisions of Gastrointestinal Surgery and Endocrine and Oncologic Surgery. In patients with unresectable lesions, hormonal therapy with octreotide, a somatostatin analogue, is used to inhibit tumor growth (MIBG therapy is particularly suited to patients with malignant, unresectable pheochromocytomas). Patients with resectable PETS are candidates for surgery. Patients with unresectable lesions may benefit from debulking surgery. Surgery in patients with MEN-1 is used in some, but not all, situations. Biotherapy is usually the first modality employed for patients with metastatic PETs because it is generally well tolerated. Typically, systemic or regional therapies are reserved until symptoms occur or tumor growth accelerates. Patients with advanced disease may have access to newer agents and receptor-directed radiotherapy, as well as interventional radiologic procedures. As in GEP-NETs, CgA appears to be the most useful serum marker for diagnosis, staging and monitoring.

Clinical Diagnosis and Surgical Treatment of Pheochromocytomas at Penn

The Penn NET Treatment Program is a major regional source of referrals for patients with pheochromocytomas. The elevated catecholamines induced by these tumors can cause a variety of diverse (and often confusing) symptoms, including (but not limited to) the classic triad of headache, palpitations and sweating. Many patients will have hypertension, which can be labile.

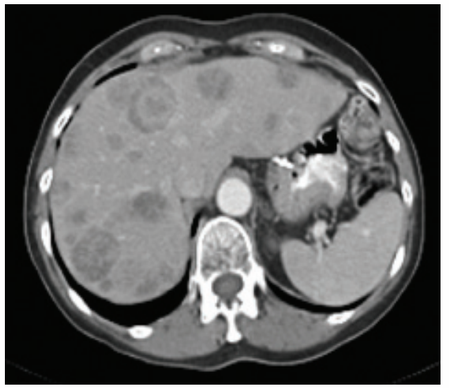
Patients with pheochromocytoma entering the Penn NET Treatment Program are diagnosed and treated by an interdisciplinary team of clinicians within the Renal-Electrolyte and Hypertension Division and the Division of Endocrine and Oncologic Surgery. Typically, initial therapy focuses upon relief of the symptoms caused by hormone over-secretion.

Coordinating Treatment for GEP-NETs and PETs

A nurse coordinator at the Abramson Cancer Center provides an important element of both patient care and confidence, overseeing diagnostics and treatment plans, coordinating visits and follow-up and administering central scheduling for all patients. The nurse coordinator also serves as the liaison for research should appropriate clinical trials become available to patients. According to Dr. Metz, the dedicated nurse coordinator is at the core of the process, ensuring cohesion in the treatment plan, involving the patient at every step and providing updates to the treatment team about important developments. Octreotide, MIBG and other necessary medications are administered through the divisions of Gastroenterology, Hematology-Oncology, Renal Electrolyte and Hypertension, Interventional Radiology and Nuclear Medicine and Medical Genetics.

To refer a patient to the Penn NET Treatment Program, call 215.615.4646 or 800.789.7366 or visit PennMedicine.org/referral.

Case Study 1: A 49-year-old female with metastatic carcinoid tumors of the liver

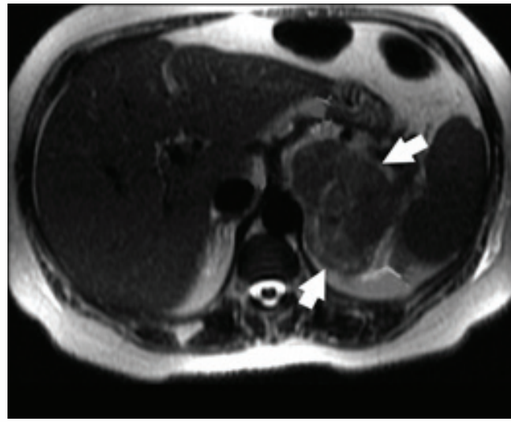


CT scan with contrast of the abdomen of a patient with neuroendocrine tumors (NETs) demonstrating metastases to the liver.

Mrs. G, a 49-year-old female, was referred to the Penn Neuroendocrine Tumor Treatment Program for carcinoid tumor surgery. Several months before presenting at Penn, she had developed lower leg edema, flushing and diarrhea. These symptoms led her to visit her ob/gyn, who ordered an abdominal CT scan that found widely dispersed tumors in her liver. At Penn, a 24-hour urine test for 5-hydroxyindolacetic acid (5-HIAA), the main urinary metabolite of serotonin, measured >150 mg/day (normal=<6 mg/day); an assessment of chromogranin A (CgA), a NET marker, found levels >100 u/L (normal range = 2-18 u/L). An octreoscan identified a primary tumor in the terminal ileum and an extensive tumor burden in the right lobes of her liver but no metastases beyond the liver. Mrs. G was diagnosed with widely metastatic carcinoid tumors in her liver and carcinoid syndrome and began octreotide LAR, 20 mg/month, which improved, but did not resolve her symptoms. Her dose was increased to 30mg/month and following an interdisciplinary review of her tests and scans, it was recommended that Mrs. G have chemoembolization of the tumors in her right liver followed by debulking surgery. Following two visits to interventional radiology for chemoembolization, she had liver resection surgery in the division of gastroenterological surgery. She recovered from these procedures without incident. At this time, her 5-HIAA and CgA levels were within normal levels. Six months post-surgery, a CT scan revealed no new hepatic lesions and no new metastases. At one year, Mrs. G's status remains stable on octreotide maintenance therapy.

Case Study 2: Bilateral adrenal pheochromocytoma

Mr. R presented at age 12 with headaches and diarrhea; he was diagnosed with a right adrenal pheochromocytoma and underwent right adrenalectomy. At age 37, Mr. R was seen at the Penn Center for Complex Hypertension with recurrence of diarrhea and headaches. His BP was 132/80 mm Hg and he was not on any antihypertensive medications. He was found to have a left adrenal mass consistent with pheochromocytoma and was scheduled for a second adrenalectomy. He was treated with dibenzylene for preoperative alpha blockade and alpha methyl-tyrosine. A left-sided adrenalectomy was performed; now unable to produce endogenous steroids, Mr. R began a regimen of hydrocortisone and fludrocortisone. Because certain genetic mutations are associated with bilateral adrenal pheochromocytoma, Mr. R was referred for genetic testing. Genotyping studies were positive for Von Hippel Lindau V84L mutation, an autosomal dominant trait with a 50 percent risk of inheritance. Mr. R's 18-year-old son, JW, was also found to be carrying the vHL mutation. JW had no symptoms; supine and sitting BP were 120/78 mm Hg and 118/82 mm Hg. Standing blood pressure was 96/74 mm Hg with a heart rate of 120 beats/minute. Urine studies show elevated normetanephrine levels. MRI of the abdomen showed a left adrenal mass and laparoscopic adreno-cortical sparing surgery was performed. While his BP remained normal with home BP monitoring, JW's plasma and urine metanephrines never "normalized." A repeat MRI performed a year later revealed a new tumor in the right adrenal gland and a second adrenal cortex sparing surgery for his second pheochromocytoma was performed. Both Mr. R and JW remain disease-free several years later with yearly surveillance with blood tests and imaging for recurrent pheochromocytoma.



MRI scan of a left adrenal pheochromocytoma (arrows). Penn is a major regional source of referrals for patients with pheochromocytoma, who are diagnosed and treated by an interdisciplinary team of clinicians with the renal electrolyte and hypertension division and the divisions of medical genetics and endocrine and oncologic surgery.