Systemic Therapy for Pheos/Paras:
Somatostatin analogues, small molecules, immunotherapy and other novel approaches in the works.

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Disclosures

♦ I have no competing conflicts of interest

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NETs: A Diverse group of malignancies

- NETs can be either functioning and non-functioning (hormone secreting) tumors, which leads to different symptoms and presentations
  - Gastrointestinal NETs
  - Pancreatic neuroendocrine tumors
  - Multiple endocrine neoplasia (MEN), type 1 and type 2, medullary thyroid carcinoma
  - Pheochromocytoma/paraganglioma
  - Poorly differentiated/ small cell/ atypical lung carcinoma
  - Small cell carcinoma of the lung
  - Merkel cell carcinoma
  - Adrenal gland tumors
Paraganglioma/ Pheochromocytoma

PRIMARY TREATMENT

<table>
<thead>
<tr>
<th>Resectable</th>
<th>SURVEILLANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha blockade with aggressive volume repletion ± alpha-methylyrosine ± beta blockade preoperative (beta blockade only after alpha blockade) + Resection (laparoscopic preferred when safe and feasible)</td>
<td>3–12 mo postresection:</td>
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<tr>
<td>Locally unresectable</td>
<td>3–12 mo postresection:</td>
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<tr>
<td>RT + alpha blockade ± alpha-methylyrosine ± beta blockade ± cytoreductive (R2) resection, if possible</td>
<td>&gt;1 y postresection up to 10 y:</td>
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<tr>
<td>Continuous alpha blockade ± alpha-methylyrosine ± beta blockade (optional) ± cytoreductive (R2) resection when possible or Clinical trial or Systemic chemotherapy (eg, dacarbazine, cyclophosphamide, vincristine) or 131I-MIBG (requires prior positive MIBG scan with dosimetry)</td>
<td>Years 1–3: every 6–12 mo Years 4+ up to 10 y: annually Consider CT or MRI or FDG-PET scan Genetic counseling and testing as clinically indicated</td>
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| Distant metastases | Years 1–3: every 6–12 mo Years 4+ up to 10 y: annually Consider CT or MRI or FDG-PET scan Genetic counseling and testing as clinically indicated |

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1. Phenoxybenzamine or doxazosin can be considered.
2. Other effective agents can be used for alpha and beta blockade. Rapid-acting intravenous alpha-adrenergic antagonists (eg, phenolamine) and rapid-acting intravenous beta blockers (eg, esmolol) are primarily used in the operating room. Selective alpha1-blocking agents, such as prazosin, terazosin, and doxazosin, are alternative medications when long-term therapy is required for metastatic pheochromocytoma. Noncardioselective (propranolol, nadolol, or labetalol) or cardioselective (atenolol and metoprolol) beta blockers can be used after initiation of alpha blockade. Dihydropyridine calcium channel blockers may be used to provide additional blood pressure control or may be substituted in patients who cannot tolerate beta blockers. The endpoint of alpha blockade is orthostasis.
3. Earlier, if symptoms.
Current Systemic Treatment Options for Patients With Advanced PC/PG

- Somatostatin analogues
- MIBG-therapy
- Molecular-targeted therapies
- Peptide receptor-targeted therapy
- Chemotherapy
- Clinical trials
MIBG scan

Diffuse metastatic pheochromocytoma

123-I-meta-iodobenzylguanidine scan from a 41-year-old woman shows diffuse metastatic pheochromocytoma.

Courtesy of William F Young, Jr, MD.
Paradigm shift

- The traditional morphological and pathologic anatomical classification of cancer cannot accurately predict its biological and clinical behavior, prognosis or response to treatment.
- It is not only important to identify the clinical stage, but also to use biologic or molecular markers that determine outcome (i.e., prognosis) and therapy (i.e., prediction);
- Classic paradigm: Phenotype → Genotype
- Novel paradigm: Genotype ↔ Phenotype
Introduction to targeted therapies

- Targeted cancer therapies: Drugs, molecules and proteins designed to interfere with specific cellular pathways necessary for tumor growth and progression.
- Traditional cytotoxic chemotherapies: Usually kill rapidly dividing cells in the body by interfering with cell division.
- A primary goal of targeted therapies is to fight cancer cells with more precision and potentially fewer side effects.
Therapeutic monoclonal antibodies target specific antigens found on the cell surface, such as transmembrane receptors or extracellular growth factors. In some cases, monoclonal antibodies are conjugated to radioisotopes or toxins to allow specific delivery of these cytotoxic agents to the intended cancer cell target.

Small molecules can penetrate the cell membrane to interact with targets inside a cell. Small molecules are usually designed to interfere with the enzymatic activity of the target protein.
Additional abdominal lesion detected with SRS. (A) SRS image shows uptake in left neck (red arrow, grade 3) and in abdomen, suspected to be due to carcinoid tumor (blue arrow, grade 3). (B) On MIBG scan, neck lesion appears much smaller (red arrow, grade 2) and abdominal lesion shows no uptake (grade 1). (C) SRS and MRI fusion image shows neck lesion.
Pathophysiology
Significance of Somatostatin Signaling

• Somatostatin (SST) receptors are highly expressed on the surface of NETs
  – More than 80% of all NETs express SST receptors

• Overexpression provides basis for regulation by SST

• SST receptor activation inhibits secretory and proliferative activity

   Image source:5[Faivre2006, 685Figure 6]
Peptide receptor radionuclide therapy (PRRT) with 90Y- or 177Lu-labeled octreotide derivatives is a treatment for inoperable or metastatic, well or moderately differentiated neuroendocrine tumors (NETs)

Second line and beyond therapies in NETs: CAP/TEM

• Fine et al reported that capecitabine (CAP), the prodrug of 5-FU, and temozolomide (TEM) were synergistic in inducing apoptosis in BON neuroendocrine tumor (NET) cell lines.

• A Phase II trial selected 28 patients with metastatic well-moderately differentiated NET (ki-67 ≤20%) who had shown progression only on 60mg Sandostatin LAR (if octreotide scan positive) and were treated with:
  - CAP 1,500mg/m²/day (PO divided BID, maximum 2,500 mg/day) on d1-14, and TEM 150-200mg/m²/day on d10-14, with the next two weeks off, in a 28 day cycle.
    - Overall RR was 43% (11% CR) and SD rate was 54%, with clinical benefit in 97%. ORR was 41% in carcinoid tumors.
    - Ongoing mPFS is >20mo for all subtypes with 18/28 (64%) having progressed and ongoing mOS of >25.3mo. (The ongoing PFS in pancreatic NETs (>18.2 mo) was 150% greater than reported with everolimus and sunitinib)

http://meetinglibrary.asco.org/content/122616-143
Genetics of PCC/PGL – Role of SDH

- Different predisposition genes are known (NF1, RET, VHL, SDHD, SDHC, SDHB, SDHA, SDHAF2, TMEM127, MAX, FH). In >40% of the cases, PCC/PGL are due to a germline mutation, and in >20% of the cases to a somatic mutation in one of these genes.

- Germ-line mutations in the mitochondrial complex II genes, SDHD at chromosome 11q23, SDHB at chromosome 1p36, and SDHC at chromosome 1q21-23, is reported to cause hereditary paraganglioma.

Many tumor cells, in contrast to normal cells, have been shown to require the amino acid glutamine to produce energy for growth and survival. To exploit the dependence of tumors on glutamine, CB-839, a potent and selective inhibitor of the first enzyme in glutamine utilization, glutaminase, is being tested in a Phase 1 study in patients with solid tumors.

G) SDH-deficient non-GIST tumors
Treatment with sunitinib for patients with progressive metastatic pheochromocytomas and sympathetic paragangliomas

- Eight patients treated with sunitinib experienced clinical benefit:
  - PR: 3/17
  - SD: 5/17 (four with predominant skeletal metastases that showed a 30% or greater reduction in FGD uptake)
  - Of 14 patients who had hypertension, six became normotensive and two discontinued antihypertensives.
  - One patient treated with sunitinib and rapamycin experienced a durable benefit beyond 36 months.
  - Most patients who experienced a clinical benefit were carriers of SDHB mutations.

Cabozantinib for Malignant Pheochromocytoma

Cabozantinib (INN) (development code name XL184; marketed under the trade name Cometriq) is a small molecule inhibitor of the tyrosine kinases c-Met and VEGFR2, and has been shown to reduce tumor growth, metastasis, and angiogenesis.

Cabozantinib was approved by the U.S. FDA in November 2012 for the treatment of medullary thyroid cancer, and undergoing evaluation for approval in kidney cancer.

Currently under study for PC/PG.
IMMUNOTHERAPY: Unleashing your immune system
PD-1 and PD-L1: Immune checkpoint inhibitors
Oncolytic Virus Clinical Trial for Neuroendocrine Tumor Patients Begins at Uppsala University, Sweden

April 6, 2016

It is with great excitement that we share the announcement of the start of the AdVince clinical trial for neuroendocrine cancer patients at Uppsala University in Sweden – the oncolytic virus is on its way to the first patient in the trial!!

From freezer to patient, the AdVince oncolytic virus is on its way!
Figure. Recruitment of Effector Adaptive Immune Response Against the Tumor After Exposure to PVSRIPO.

http://www.cancernetwork.com/sites/default/files/figures_diagrams/1603DejardinsFig.png
Viruses are genetically engineered to selectively kill tumor cells and induce a potent and adequate anti-tumor immune response, even in drug-resistant cancer stem cells.

In order to target metastatic sites, researchers are evaluating various cell types as carriers to deliver oncolytic virus at the tumor site.

In particular, we are evaluating macrophages as virus carriers. Major efforts are underway in neuroendocrine cancer, primarily working with oncolytic adenovirus but also Semliki Forest virus and Vaccinia virus.

Evolution of Systemic Therapies for NETs

- **1907**: First description of carcinoid
- **1980**: Synthesis of octreotide
- **1985**: Approval of octreotide for carcinoid syndrome
- **1990**: Approval of octreotide + interferon for carcinoid syndrome
- **1995**: Approval of lanreotide for carcinoid syndrome
- **2000**: Octreotide inhibits tumor growth
- **2010**: Pasireotide in trials for carcinoid syndrome
- **2011**: Lanreotide inhibits tumor growth
- **2013**: Approval of everolimus for pNET

**pNET** = pancreatic neuroendocrine tumor

**Chemotherapy**

- **Approval of streptozocin + 5-fluorouracil (US)**

**PRRT**

- **Approval of sunitinib for pNET**

**Temozolomide**
A Karpathakis et al. NET: cracking the epigenetic code

**Epigenetics**
- 1940s Waddingtons Epigenetic Landscape
- 1960s DNA methylation
- 1960-70s Histone modifications
- 1983 Global hypomethylation
- 1989 Tumour suppressor promoter hypermethylation
- 1990s Bisulphite treatment
- 2001 ‘Histone code’ hypothesis
- 2001 microRNAs in cancer
- 2003 Human Epigenome Project
- 2005 Azacitidine FDA approval
- 2006 Vorinostat FDA approval
- 2008 High throughput methylation sequencing analyses
- 2010 Roadmap Epigenomics project

**Neuroendocrine tumours**
- 1907 ‘Karzinoid’
- 1950s Serotonin as marker
- 1978 Somatostatin for symptom control
- 1980 Streptozocin chemotherapy
- 1982 Octreotide
- 1983 Interferon
- 1986 Chormogranin A as marker
- 1989 Somatostatin receptor scintigraphy
- 1999 Peptide receptor radionuclide therapy
- 2002 Novel somatostatin analogue Pasireotide
- 2009 Somatostatin analogues prolong PFS
- 2011 Sunitinib and Everolimus FDA approved
- 2011 ATRX/DAXX/MEN1 mutations and ALT in pancreatic NETs

**IMMUNOTHERAPY**

**TARGETED THERAPIES**

*Source: Penn Medicine, Abramson Cancer Center*
THANK YOU