Recent Advances in Imaging of VHL and Other Genetically Inherited Pheochromocytomas

Karel Pacak
PRAE, NICHD, NIH, Bethesda
karel@mail.nih.gov

National Institutes of Health

Disclosure

A pending U.S. and international patent for a method to diagnose and treat pheochromocytoma and paraganglioma (PCT/US2010/056543).

Lecture outline

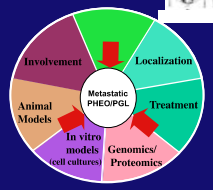
1. PHEO: Definition, important facts
2. PHEO: Moving towards functional imaging
3. PHEO: Specific tumor characteristics for imaging
4. PET/CT
5. Current functional imaging of PHEO (2008-2011)
6. Future directions in the imaging of PHEO

PHEO/PGL: Background/facts

PHEOs are chromaffin cell tumors characterized by catecholamine synthesis, storage, release, and metabolism.

Important facts

- 50% incorrectly diagnosed
- No effective treatments for metastatic tumors
- 35% hereditary (10 known genes)



Cancer 2008; 113:2020
DeGroot & Jameson, Textbook of Endocrinology 2010

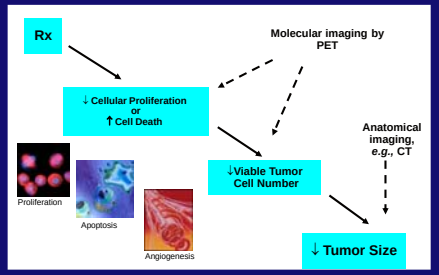
PHEO/PGL: Nomenclature

PHEO PARAGANGLIOMA (PGL)

Sympathetic Parasympathetic

Adrenal Extra-adrenal Head & Neck

Positive treatment response: Functional imaging is ahead of anatomical imaging



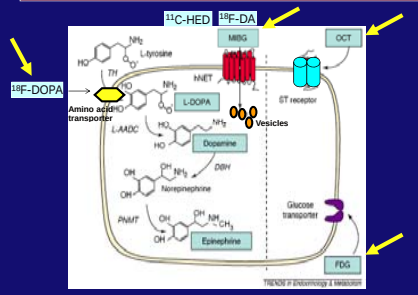
Determines prognosis, identifies/predicts treatment targets and responses

PHEOs have specific characteristics

- Take up catecholamine precursor (tyrosine)
- Synthesize, store, and release catecholamines
- Express specific receptors and transporters (norepinephrine transporter system)
- Have specific tumorigenesis pathways? (e.g. mitochondrial energy metabolism)
- Express specific genes (predict prognosis?) (e.g. carboxypeptidase E?)

Endocr. Rev. 2004; 25:568
JCI 2011; 121:880

PHEO cell-specific characteristics for functional imaging

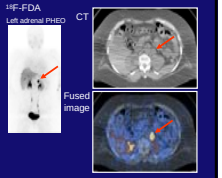


Q. J. Nucl. Med. Mol. Imaging 2008; 52:419

PET/CT as a preferred imaging modality

Dramatic improvement in tumor:

- Detection
- Localization
- Characterization



Outcome: Significant reduction (20-40%) of indeterminate or equivocal findings, scanning time & treatment planning.

Schiesser et al. Br. J. Surg.; 2010; 97:691

CURRENT FUNCTIONAL IMAGING OF PHEO (2008-2011) IS BASED ON ITS LOCALIZATION, *NOT CHARACTERIZATION*

Functional imaging of PHEO/PGL

Current imaging modalities

- ^{123}I-MIBG (being replaced as "*gold standard*")
- ^{18}F-FDG
- ^{111}In-pentetreotide (Octreoscan, SRS)

Emerging PET modalities

- ^{18}F-fluorodopamine (^{18}F-FDA)
- ^{18}F-fluorodihydroxyphenylalanine (^{18}F-FDOPA)
- ^{68}Ga-DOTATOC/DOTATATE/DOTA-Tyr^3

King et al. JCEM, 2011; 96:2799
Kroiss et al. Eur. J. Nucl. Med. Imaging 2011; 38: 865
Lussier et al. Eur. J. Nucl. Med. Mol. Imaging 2010; 37:484
Fottner et al. JCEM 2010; 95:2800
Timmers et al. JCEM 2009; 94:4757
Taieb et al. Clin. Endocrinol. 2008; 69:580
Hoegerle et al. Radiology 2002; 222:507

Current functional imaging of PHEO/PGL

During the last 4 years we further extended our initial imaging findings and implemented them in the most current imaging algorithm of PHEO/PGL.

Primary PHEO/PGL	Metastatic PHEO/PGL (per lesion)
^{18}F-FDOPA PET: 67-93%	^{18}F-FDG PET: 74%
^{123}I-MIBG scinti. (specific): 67-86%	Octreoscan: 68%
^{18}F-FDG PET: 83-93% (adrenal: 67%)	^{123}I-MIBG: 57%
Octreoscan: < 50%	^{18}F-FDOPA PET: 45%

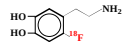
Note: ^{18}F-FDA PET only available at NIH; ^{123}I-MIBG not good for VHL PHEO

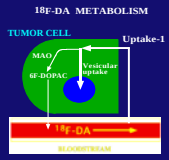
J. Nucl. Med. 2008; 49:1613
Endocr. Relat. Cancer 2008; 15:311
JCEM 2009; 94:4757
J. Nucl. Med. 2009; 50:1448
Clin. Endocrinol. 2009; 71:11

Current use of ^{18}F-FDA PET in PHEO/PGL

Currently it is accepted that in general (regardless of genetic background) ^{18}F-FDA is the best PET imaging approach for the localization of PHEO including VHL one.

[^{18}F]-6-Fluorodopamine



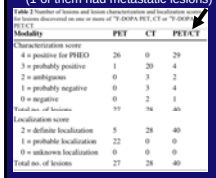


However, exceptions exist and will be discussed.

Bas et al. J. Nucl. Med. 2008; 49:1613
Timmers et al. JCEM 2009; 94:4757

Current use of ^{18}F-FDOPA PET in PHEO/PGL (1)

- 25 pts included, 18 had adrenal PHEO (1 of them had metastatic lesions)
- 25 pts with PHEO or PGL (PHEO: 12 sporadic, 2 MEN, 1 VHL, 2 NF, 2 SDHD; PGL: 7 SDHD/B) included
- Comparison to ^{123}I-MIBG
- Lesion-based study (^{18}F-FDOPA+^{123}I-MIBG)



Modality	PET	CT	PET/CT
Characterization score			
4 = positive for PHEO	26	0	29
3 = probably positive	1	20	4
2 = ambiguous	0	3	2
1 = probably negative	0	3	4
0 = negative	0	2	1
Total no. of lesions	55	74	46
Localization score			
2 = definite localization	5	28	40
1 = probable localization	22	0	0
0 = unknown localization	0	0	0
Total no. of lesions	27	28	40

Overall sensitivity ^{18}F-FDOPA PET/CT: 100%; specificity: 90%

Hyperplasia can show ^{18}F-FDOPA PET/CT positive uptake; false positive: MTC, ACC

Luster et al. Eur. J. Nucl. Med. Mol. Imaging 2010; 37:484

75% sensitivity for SDHx tumors

^{123}I-MIBG negative: -ve for VMAT1

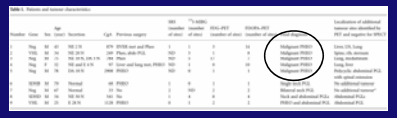
^{18}F-FDOPA is superior to ^{123}I-MIBG PET for PHEO

Fottner et al. JCEM 2010; 95:2800

Fiebrich et al. JCEM 2009; 94:3922

Current use of ^{18}F-FDOPA PET in PHEO/PGL (2)

- 11 pts with multiple or metastatic PHEO or PGL included
- Comparison to ^{18}F-FDG, ^{131}I-MIBG and Octreoscan



Suggested to combine ^{18}F-FDOPA and ^{18}F-FDG in metastatic tumors and abdominal PGL.

Taieb et al. Clin. Endocrinol. 2008; 69:580

- New data shows that ^{18}F-FDOPA is a promising imaging modality for VHL-related PHEOs

Kitano et al. Surgery 2011; 150:1122

FDG PET: Use it in metastatic PHEO

- 216 pts included in the study: 60 non-metastatic and 95 metastatic PHEOs/PGLs,
- 61: no tumor; 68 SDHB, 12 SDHD, 10 MEN2, 4 VHL, 1 NF1

Overall sensitivity

	Non-metastatic primary PPGL	Metastases	Primary head and neck PGL
FDG	72.5 (50/69)	80.4 (168/209)	69.2 (18/26)
MIBG	77.0 (48/64)	48.5 (82/169)	33.3 (7/21)
CT/MRI	95.7 (66/69)	73.2 (141/193)	

Sensitivity: SDHx vs non-SDHx metastatic

	SDHB, SDHD	Non-SDHx	p
FDG	89.8 (106/118)	61.5 (32/52)	<0.001
MIBG	41.8 (38/91)	65.9 (29/44)	0.009
CT/MRI	78.0 (85/109)	70.0 (35/50)	n.s.

Sensitivity: Soft tissue vs bone metastases

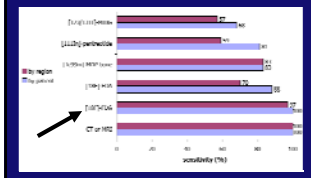
	Soft tissue	Bone	p
FDG	74.7(109/146)	93.7 (59/63)	0.002
MIBG	43.2 (51/118)	59.6 (31/52)	0.036
CT/MRI	70.8 (97/137)	78.6 (44/56)	n.s

Specificity: PHEO/PGL ruled out ^{18}F-FDG PET: 95% CT/MRI: 90% ^{123}I-MIBG SPECT: 77%

JNCI, under revision

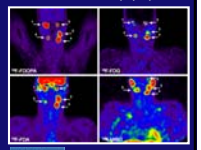
Two new imaging exceptions

SDHB-related metastatic PHEO/PGL



Timmers et al. JCO 2007; 25:2262
Taieb et al. J. Nucl. Med. 2009; 50:711

Head and neck PGLs (HNPGLs): ^{18}F-FDOPA: 100% (9 pts)



King et al. JCEM 2010; 95:481
King et al. JCEM 2011; in press

^{18}F-FDOPA superior to Octreoscan or ^{18}F-FDG for HNPGLs

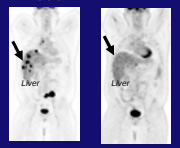
Chanier et al. Clin. Endocrinol. 2011; 74:21
Taieb et al. Clin. Endocrinol. 2008; 69:580

^{18}F-FDG PET: Monitor therapeutic responses

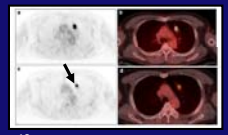
^{18}F-FDG PET:
"Marks" more aggressive PHEOs/PGLs
"Selects" tumors more likely to respond to chemotherapy

^{18}F-FDG

Before *After*



He et al. Endocrine, 2009; 36:189

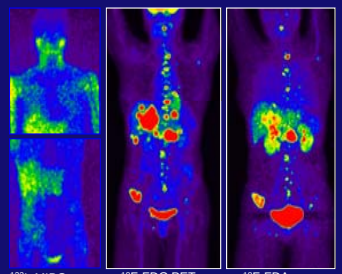


^{18}F-FDG PET:
To monitor responses to ^{131}I-MIBG therapy using SUV

Nakazawa et al. Eur. J. Nucl. Med. Mol. Imaging 2011; in press

^{123}I-MIBG scintigraphy: If negative think about SDHB

- 21 pts included in the study (12 with metastatic disease)
- 11 out of 21 pts (52%) had an SDHB gene mutation; 7 out of 11 (63%) had metastatic tumors

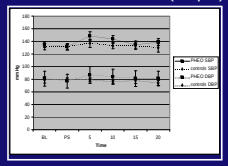


^{123}I- MIBG ^{18}F-FDG PET ^{18}F-FDA

Endocr. Relat. Cancer, in press

PHEO: No harm to the patient if contrast CT used

CT non-ionic contrast (22 pts)



Baid et al. Ann. Intern. Med. 2009; 150:27

Current PET imaging algorithm for PHEO

Head/neck SDHx-related PGLs → ^{18}F-FDOPA PET

Adrenal PHEO → ^{18}F-FDA/DOPA PET

Metastatic PHEO/PGL → ^{18}F-FDA PET

Metastatic SDHB-related PHEO/PGL → ^{18}F-FDG PET

More studies are needed to address the role of ^{18}F-FDOPA in non-SDHx (VHL) HNPGLs and metastatic tumors (VHL); also which imaging modality should be used for TMEM127- and MAX-related PHEO/PGL.

FUTURE DIRECTIONS IN PHEO IMAGING ARE IN ITS CHARACTERIZATION

PET detects unique tumor characteristics

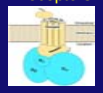
Advantage of PET scanning: measures tumor processes in vivo

Glucose & energy metabolism

Mitochondrial dysfunction

DNA & protein synthesis

Receptors



Angiogenesis

Cell proliferation

Apoptosis

Assessment of molecular processes specific to various PHEOs using multimodality imaging

AIM: To further characterize PHEO/PGL-specific molecular processes in vivo using state-of-the art Siemens mCT Biograph (PET/CT)

^{18}F-Fluorothymidine:

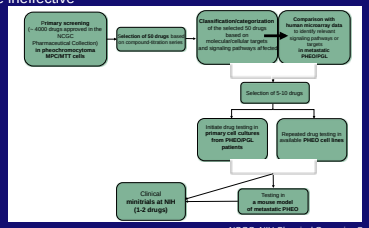
To assess cell proliferation; initially 12 pts to be studied. We hypothesize that SDHB tumors have a higher proliferation rate compared to other PHEOs/PGLs. Also to evaluate eligibility for treatment and monitor treatment responses and predict prognosis.

^{18}F-Fluoromisonidazole: To assess cellular hypoxia; to assess e.g. specific target-based chemotherapeutics: HIFα as a promising target?

Lehmann et al. PNAS 2009; 106:14004
Pichler et al. J. Nucl. Med. 2010; 51:333

Drug-repositioning screening

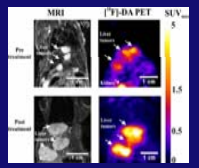
AIM: To identify new therapies for metastatic PHEO/PGL and to accelerate their use in a clinical setting since current therapies are ineffective



NCGC: NIH Chemical Genomics Center

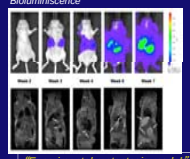
Animal model of metastatic PHEO to test new therapeutic approaches

Long-standing experience with CT, MRI, and PET scanning in an animal model of metastatic PHEO and recently, we have introduced a bioluminiscence method for metastatic PHEO.



Methods 2010; 50:20
Nucl. Med. Biol. 2011; in press

Bioluminiscence



"Experimental metastasis model"

Cancer Lett; 2012; 316:46

APPLICATION: To monitor tumor growth and regression in vivo; harvested tumor tissue further analyzed (gene expression profiling).

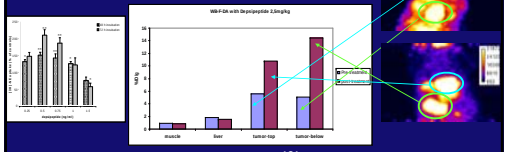
Increased expression of NET by depsipeptide

Failure of ^{131}I-MIBG therapy is often due to low expression of NET on PHEO cell membrane.

AIM: Increase expression of NET on PHEO cells.

USE: Depsipeptide: histone deacetylase inhibitor.

WB scan 60 minutes after administration of ^{18}F-DA



APPLICATION: Pretreatment before ^{131}I-MIBG therapy?

Endocr. Relat. Cancer 2011; 18:143

Future trends in PHEO imaging

- Development of *new radiopharmaceuticals* to assess:

1. Tumor-specific treatment options: specific targets on tumor cell membrane, vessels and stroma
   - IGFR, VEGFR2
   - HIFalpha
2. Pharmacodynamics: monitor drug transport & responses

Future trends in PHEO imaging

- Application of *PET/MRI scanning*

(head and neck PGLs; liver lesions, s/p radiofrequency ablation, cardiac PGLs)

We have to move from sensitivity/specificity to TUMOR CHARACTERIZATION, treatment planning & prognosis.

Acknowledgement

Deep thanks to all the members of my laboratory for their dedication, long working hours, and heart to help those who suffer.

NIH/NICHD/NCI/NINDS/CIT/NHGR
A. DeCherney
C. Stratakis
T. Fojo
M. Merino

Nurses and members of CC PheoPara Alliance

RADIOLOGY
A. Ling

NUCLEAR MEDICINE/PET
C. Chen
J. Reynolds
P. Herscovitch
C. Millo
M. Whatley

SURGERY and VHL group
W. M. Linehan
G. Bratslavsky
E. Kebebew

Outside co-investigators (G. Eisenhofer, A. Tischler, J. Carrasquillo and many others)

"Patients are our passion and we are their hope"