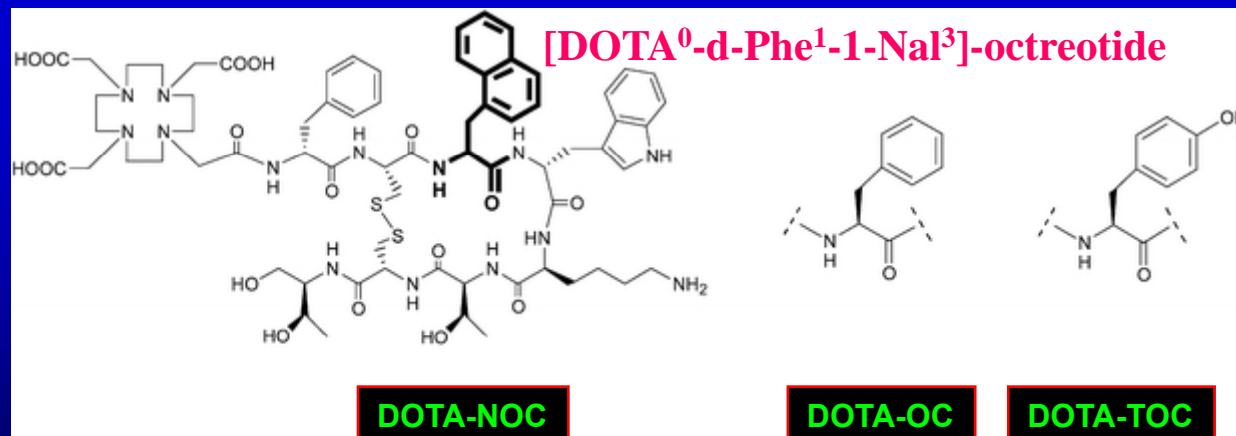


# MOLECULAR IMAGING AND PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRNT) OF NEUROENDOCRINE TUMORS: CURRENT STATE AND FUTURE PERSPECTIVES

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Annual Meeting of the Czech Cooperative Group for NETs (KSPNN)

PRUHONICE, April 29, 2011

# Summary $^{68}\text{Ge}/^{68}\text{Ga}$ Generator

- Post-processing of  $^{68}\text{Ge}/^{68}\text{Ga}$  radionuclide generators using cation exchange resin provides chemically and radiochemically pure  $^{68}\text{Ga}$  ( $97\pm 2\%$ ) **within 4 min ready for on-line labelling**
- Highest chemical purity guarantees for high labeling and overall product yields (e.g.  $^{68}\text{Ga}$ -DOTA-conjugated octreotides) of  **$75\pm 5\%$  decay corrected**
- Ready for injection – **up to 10 patients per day can be studied**  
easy handling in a nuclear medical environment  
easily to transfer to IAEA and other countries

**Significant step towards the  
routine medical use of the  $^{68}\text{Ge}/^{68}\text{Ga}$  generator**

# $^{68}\text{Ga}$ -DOTA-TOC versus $^{111}\text{In}$ -DOTA-TOC and $^{99\text{m}}\text{Tc}$ -HYNIC-TOC

*Gabriel et al. J Nucl Med 2007; 48: 508-518*

**PET**

**SPECT**

**CT**

## Results (n=84 Patients - NET)

Sensitivity	97% (69/71)	52% (37/71)	61% (41/67)
Specificity	92% (12/13)	92% (12/13)	71% (12/17)
Accuracy	96% (81/84)	58% (49/84)	63% (53/84)

**Combined Use of PET and CT provides the highest accuracy**



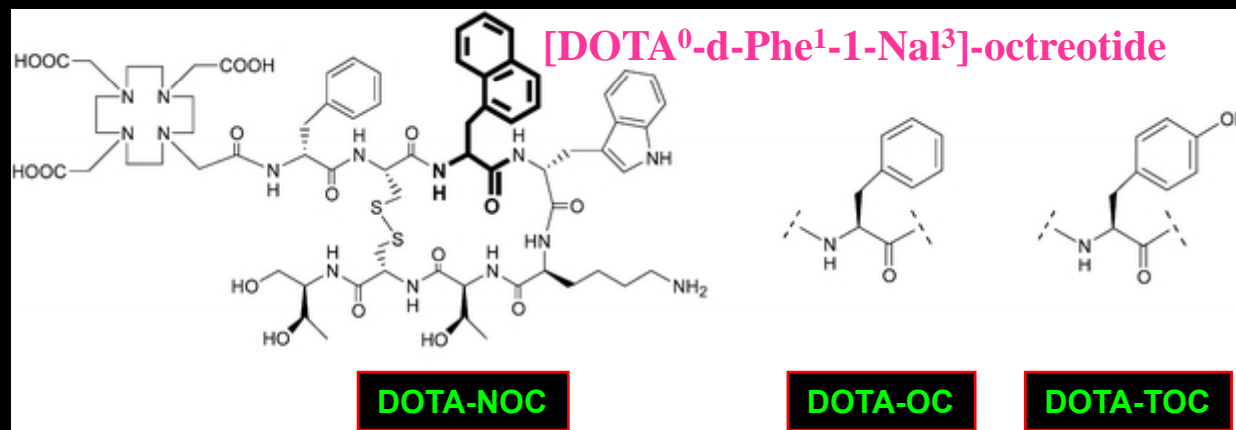
# Affinity profiles (IC<sub>50</sub>) for human sst 2–5 receptors

Compound	hsst2	hsst3	hsst4	hsst5
SS-28	2.5±0.3	5.7±0.6	4.2±0.3	3.7±0.4
In <sup>III</sup> -DOTA-NOC	2.9±0.1	8±2	227±18	11.2±3.5
Y <sup>III</sup> -DOTA-NOC	3.3±0.2	26±1.9	>1,000	10.4±1.6
Y <sup>III</sup> -DOTA-TOC	11.4±1.7	389±136	>10,000	204±92
Y <sup>III</sup> -DOTA-OC	20±2.2	27±8	>1000	58±22
Y <sup>III</sup> -DOTA-LAN	22.8±4.9	290±105	>1000	16.3±3.4

Wild D, Schmitt SJ, Ginj M, Mäcke HR, Bernard BF, Krenning E, de Jong M, Wenger S and Reubi J-C.

*Eur J Nucl Med Mol Imaging* 2003;30:1338 \*

\* **Awarded the best scientific research paper in the EJNMMI in 2003**



In Wahl R. (ed.):

Principles and Practice of PET and PET/CT.

Lippincott Williams & Wilkins, Philadelphia 2008 (p. 411-437).

CHAPTER

8.21

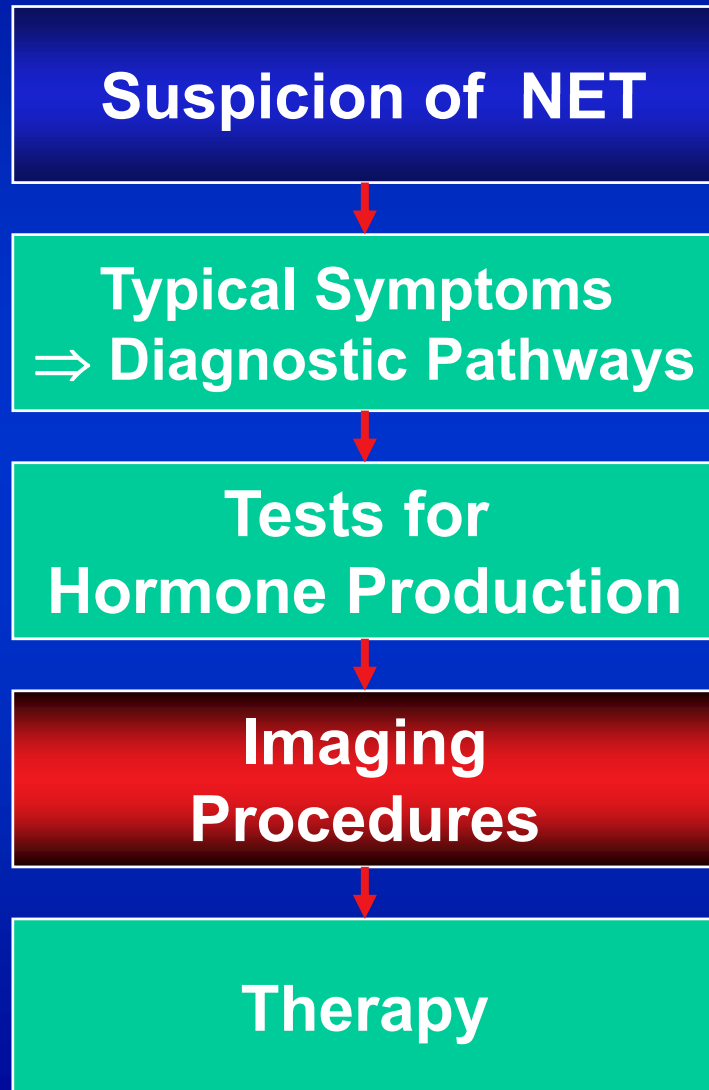
## PET and PET/CT Imaging of Neuroendocrine Tumors

RICHARD P. BAUM AND VIKAS PRASAD

**Principles and  
Clinical Indications**

# Neuroendocrine Tumors (NET)

## – Diagnosis –



### *Diagnostic Methods:*

- (Endo-) Sonography
- Endoscopy
- MRI (CT Scan)
- **Somatostatin Receptor PET/CT or Scintigraphy (SRS)**

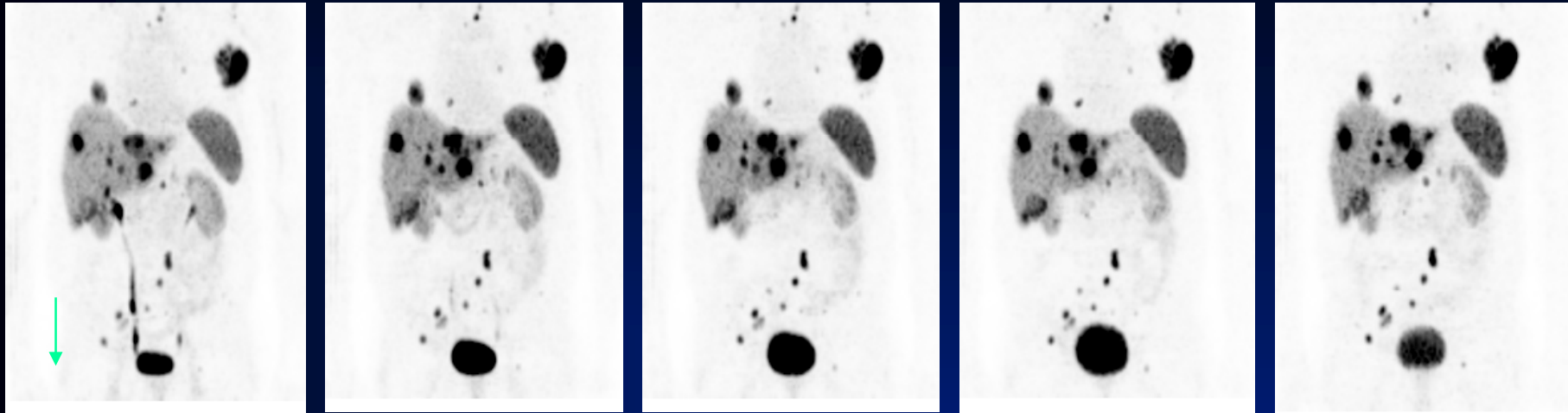
Foregut

Midgut

Hindgut

# Ga-68 SMS Receptor PET – Imaging Technique

Images courtesy Heiner Bihl/Gabriele Pöpperl Klinik für Nuklearmedizin •Katharinen-Hospital, Stuttgart



0:20 p.i.

0:40 p.i.

1:00 p.i.

1:20 p.i.


1:40 p.i.

**Injected activity:** 1.5 MBq/kg (100-150 MBq, 3-4 mCi). 20 mg Lasix iv

**Start of acquisition:** 60-90 min p.i. (30-180 min)

**Acquisition parameters:** 2 min. per bed position

**Effective radiation dose:** 3 mSv for 150 MBq  $^{68}\text{Ga}$ -DOTATOC (+CT)  
(Octreoscan® 12 mSv)

**Imaging characteristics:** fast kinetics, fast renal clearance, high quality images with very low background  high tumor uptake allows detection of very small lesions (3 to 5 mm) already 30 to 60 min. p.i.

**Image analysis:** visual and quantitative (SUV) evaluation

# Staging of NET

## by Receptor-PET/CT

- **Whole-body diagnosis („one-stop shop“)**
- **Detection of unknown primary tumors (CUP)**
- **Evaluation of receptor status before PRRT  
or octreotide therapy**

## Detection of unknown primary neuroendocrine tumours (CUP-NET) using $^{68}\text{Ga}$ -DOTA-NOC receptor PET/CT

Vikas Prasad • Valentina Ambrosini •  
Merten Hommann • Dieter Hoersch • Stefano Fanti •  
Richard P. Baum

*Results* In 35 of 59 patients (59%),  $^{68}\text{Ga}$ -DOTA-NOC PET/CT localised the site of the primary: ileum/jejunum (14),

Received: 30 November 2008 / Accepted: 12 June 2009

*Conclusion* Our data indicate that  $^{68}\text{Ga}$ -DOTA-NOC PET/CT is highly superior to  $^{111}\text{In}$ -OctreoScan (39% detection rate for CUP according to the literature) and can play a major role in the management of patients with CUP-NET.

# Indication

## Re-staging, Follow-up

e.g. in patients with rising tumor markers  
(chromogranin, serotonin, calcitonin, glucagon)  
for detection of recurrence

# Indication

## Patient evaluation before PRRT

**Receptor density** – determined by  
**receptor PET/CT:**

semiquantitative measurement by

***SUV (Standardized Uptake Values)***

**Biodistribution of the Ga-68 labeled somatostatin analog DOTA-NOC in patients with neuroendocrine tumors: characterization of uptake in normal organs and tumor lesions.**

*V. Prasad, R.P. Baum*

*Q J Nucl Med Mol Imaging 2010; 54:61-67*

# **Ga-68 DOTA-NOC receptor PET/CT: SUV of primary tumors and metastases**

<b>SUV in primary tumors and metastases (n = 1,400 studies)</b>	<b>Mean</b>	<b>Range</b>
<b>Primary tumors</b>	<b>19.2</b>	<b>8.2 – 109</b>
<b>Liver mets</b>	<b>20.9</b>	<b>3.3 - 105</b>
<b>Lymph node mets</b>	<b>9.5</b>	<b>4.2 – 152</b>
<b>Bone mets</b>	<b>13.6</b>	<b>3.0 – 20.4</b>
<b>Brain mets</b>	<b>12.3</b>	<b>4.6 – 17.2</b>
<b>Lung mets</b>	<b>2.3</b>	<b>1.6 – 5.6</b>
<b>Abdominal mets</b>	<b>14.8</b>	<b>5.8 – 34.1</b>

**Somatostatin receptor imaging using Ga-68 DOTA-NOC PET/CT gives accurate estimation of the receptor density.**

**IRS Score for SSTR2A  
proportional to SUVmax  
and SUVmean**

**IRS Score for SSTR5  
proportional to SUVmax**

**$p < 0.05$**

**SSTR1**

**SSTR3**

**SSTR4**

**No significant correlation between the IRS score for SSTR1, SSTR3 and SSTR4 with the semiquantitative parameters  $p > 0.05$**

# Evaluation of therapy response

**Problems of using WHO  
or RECIST criteria:**

- 1 or 2-dimensions only
- what is the amount of vital tumor?

# Morphologic Response Criteria

	Response		SD	PD
	CR	PR		
<b>WHO</b> Cancer 1981;47 207-14	complete disappearance of all disease manifestations in two observations at an interval of at least 4 weeks	≥ 50 % decrease in tumor size	↑ or ↓ in tumor size of < 25 %	> 25 % increase in tumor lesions and/or appearance of new foci of tumor

**Neither WHO nor RECIST criteria address tumor response with biological and metabolic markers.**

<b>RECIST</b> J N C I 2000;92 205-16	disappearance of all tumor lesions	decrease in the sum of longest diameter of tumor lesion	neither PR nor PD	at least 20 % increase in sum of the longest diameter of tumor lesion
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# *Monitoring Response to Therapy*

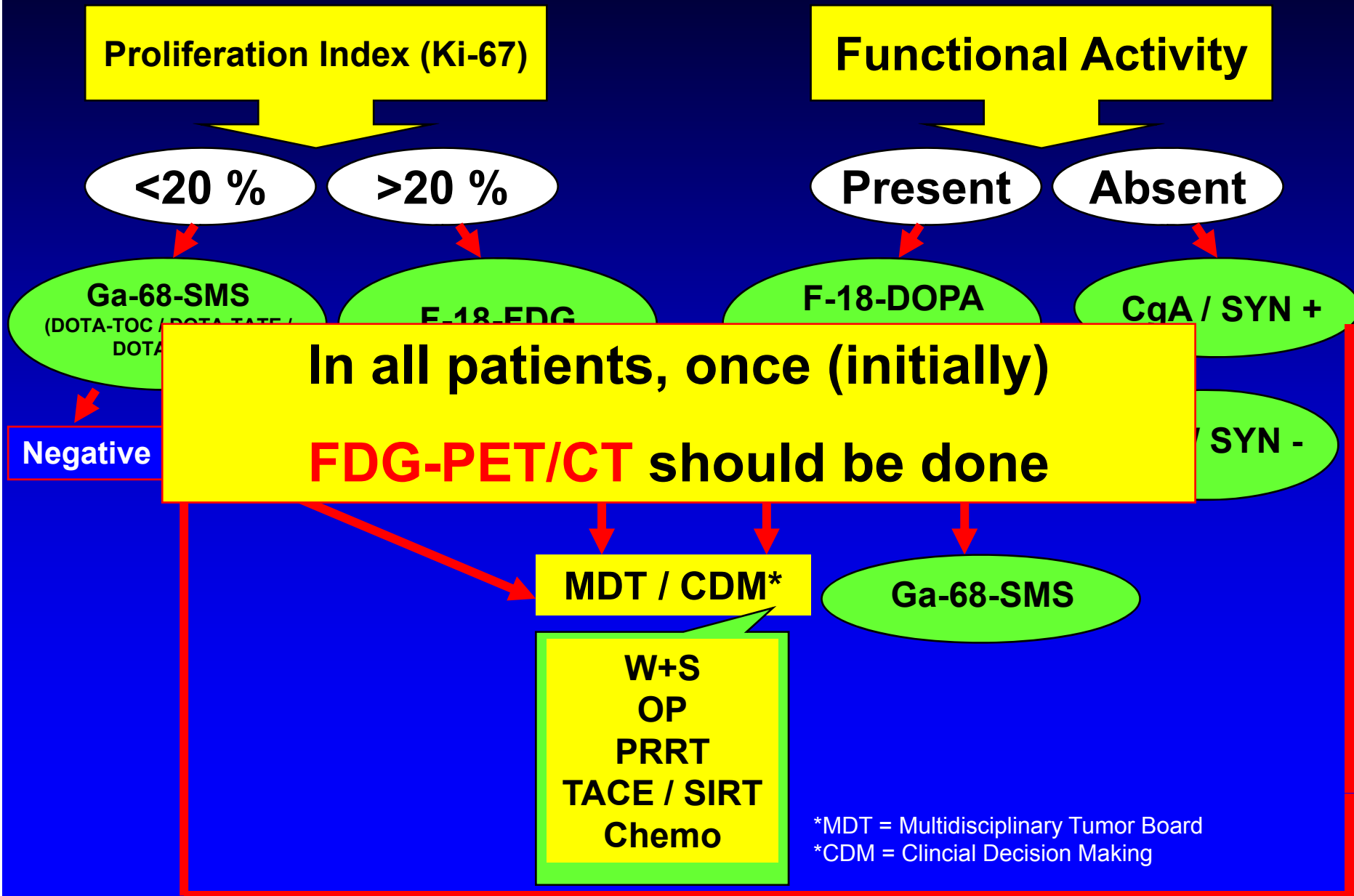
DESIST RECIPT

USE PERCIST

MOLECULAR RESPONSE

PRECEDES MORPHOLOGY !

# PET/CT in NET: Diagnostic Algorithm - Staging/CUP



# PET/CT in NET: Diagnostic Algorithm - Restaging

## Therapy Response

## Follow-Up

What is the clinical question to be answered? Status of patient (KPS, ECOG)

Repeat most relevant  
diagnostic modality

Use most relevant  
diagnostic modality

PET/CT, MRI, 4-phase CT

PET/CT (SMS, FDG, DOPA

Decision on further  
therapeutic strategy

In addition when needed

- Endoscopy
- EUS
- Ultrasound
- Fluoride PET/CT
- ...

Depending on the clinical question,  
primarily a whole-body diagnostic approach should be chosen.

# Conclusion

*Baum et al. Recent Res Cancer Res. 170:225-42 (2008)*

Receptor PET/CT using Ga-68-labeled somatostatin analogues enables the molecular imaging of neuroendocrine tumors and their metastases with **very high diagnostic sensitivity and specificity** (n=4,788 Ga-68 PET/CT studies as of August 30, 2010)

## Advantages of Ga-68 SMS PET/CT: *The Bad Berka Experience*

- Quantitative, **reproducible data** (SUV) which can be used for selecting patients for PRRT and evaluation of therapy response
- **Fast protocol** (60-90 min.), patient friendly, low radiation burden (10-12 mSv)
- Flexibility, **daily use**, lower (!) cost than Octreotide scintigraphy
- A new **gold standard** for *in vivo* SMS receptor imaging

**Future perspectives:** new peptides (e.g. for lung, breast, and prostate cancer), general nuclear medicine applications (e.g. lung perfusion PET/CT for detection of PE, myocardial, bone, kidney, liver imaging, infection and many more).

# Ga-68 Labeled Tracers in Clinical Use

- [<sup>68</sup>Ga-DOTA,Tyr<sup>3</sup>]octreotide (DOTA-TOC)
  - [<sup>68</sup>Ga-DOTA,1-Nal]octreotide (DOTA-NOC)\*
  - [<sup>68</sup>Ga-DOTA]-TATE\*
  - [<sup>68</sup>Ga-DOTA]-Lanreotide
  - [<sup>68</sup>Ga-DOTA]-Bombesin / AMBA\* and DEMOBESIN\*
  - [<sup>68</sup>Ga-DOTA]-D-Glu-Gastrin\*
  - [<sup>68</sup>Ga-DOTA]-F(ab')<sub>2</sub>-herceptin
  - <sup>68</sup>Ga-Citrate
  - <sup>68</sup>Ga-DOTA-Tyrosin\*
  - <sup>68</sup>Ga-DOTA-HSA Microspheres\*
  - <sup>68</sup>Ga-NOTA-RGD (angiogenesis)\*
  - <sup>68</sup>Ga-BPAMP (osteoblastic metastases)\*
  - <sup>68</sup>Ga-DOTA-α-MSH (melanoma)\*
  - <sup>68</sup>Ga-DOTA-SHAL (lymphoma)\*
  - ...and many more to come!
- \*first use in Bad Berka*

# FUTURE DIRECTIONS

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Fourth generation peptides

Antagonists of radiolabeled peptides may be superior to agonists

Pansomatostatins: targeting a broader subtype and tumor spectrum

Multireceptor targeting