Molecular Imaging and Peptide Receptor Radionuclide Therapy (PRRNT) of Neuroendocrine Tumors: Current State and Future Perspectives

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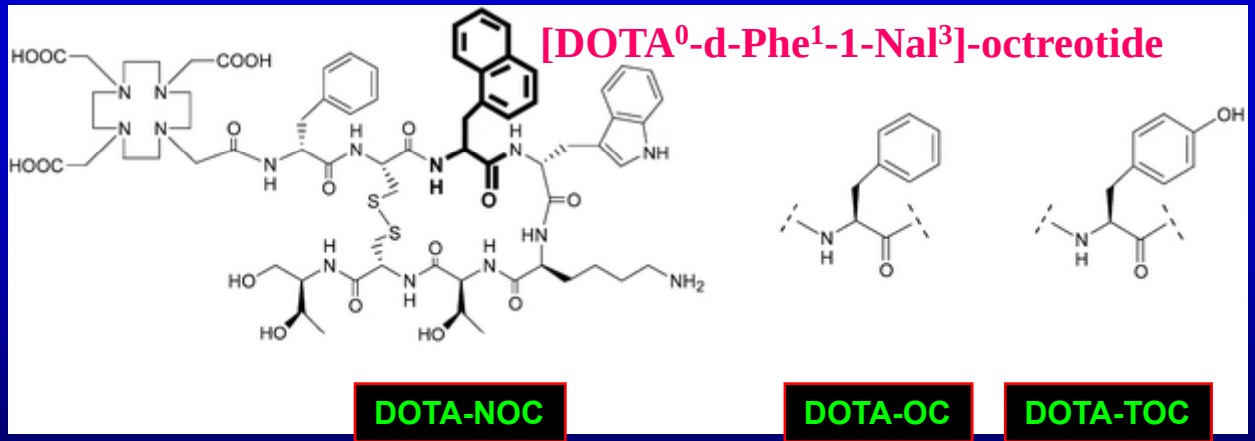


Annual Meeting of the Czech Cooperative Group for NETs (KSPNN)

PRUHONICE, April 29, 2011

Summary ^{68}Ge/Ga Generator

- Post-processing of ^{68}Ge/^{68}Ga radionuclide generators using cation exchange resin provides chemically and radiochemically pure ^{68}Ga (97±2%) within 4 min ready for on-line labelling

- Highest chemical purity guarantees for high labeling and overall product yields (e.g. ^{68}Ga-DOTA-conjugated octreotides) of 75±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}Ge/Ga generator

^{68}Ga-DOTA-TOC versus ^{111}In-DOTA-TOC and ^{99m}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

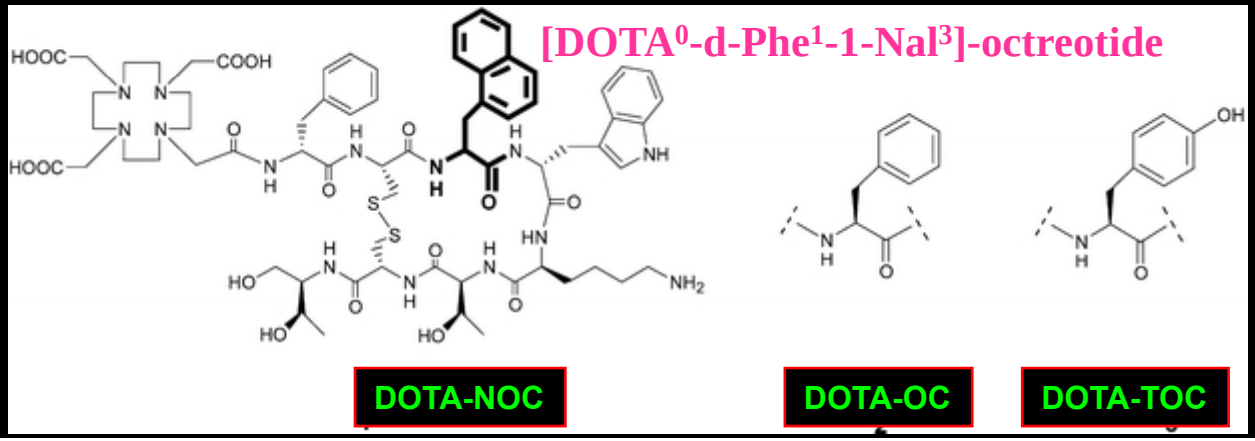
Affinity profiles (IC_{50}) for human sst 2–5 receptors

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

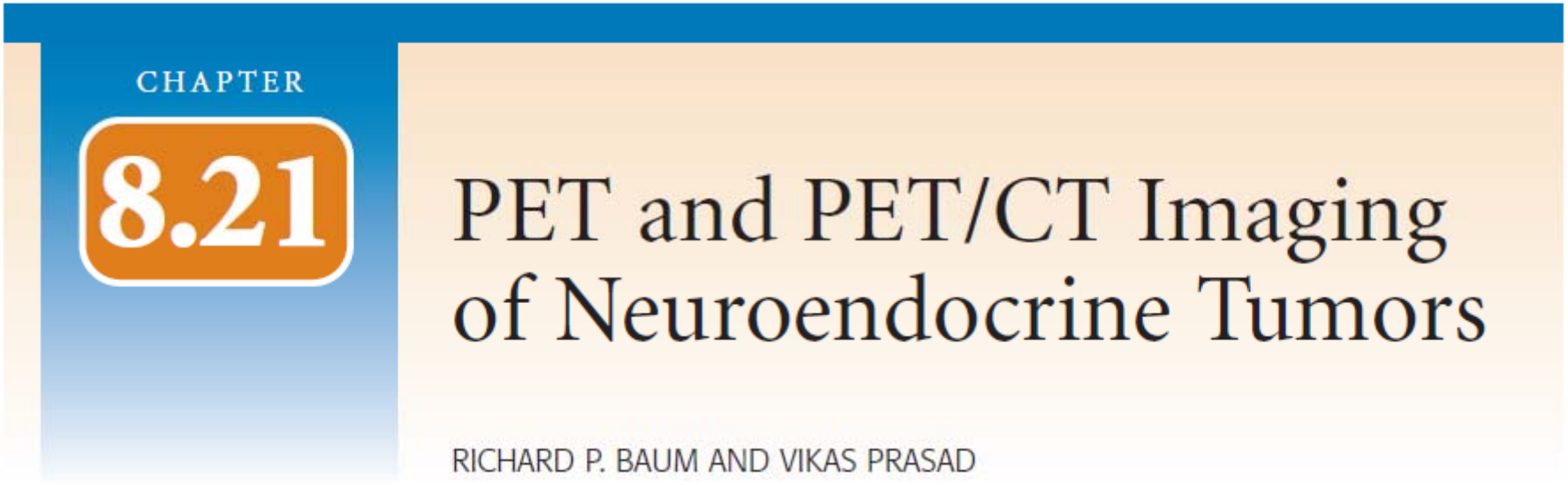
Wild D, Schmitt SJ, Ginj M, Mäcke HR, Bernard BF, Krenning E, de Jong M, Wenger S and Reubi J-C.

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

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

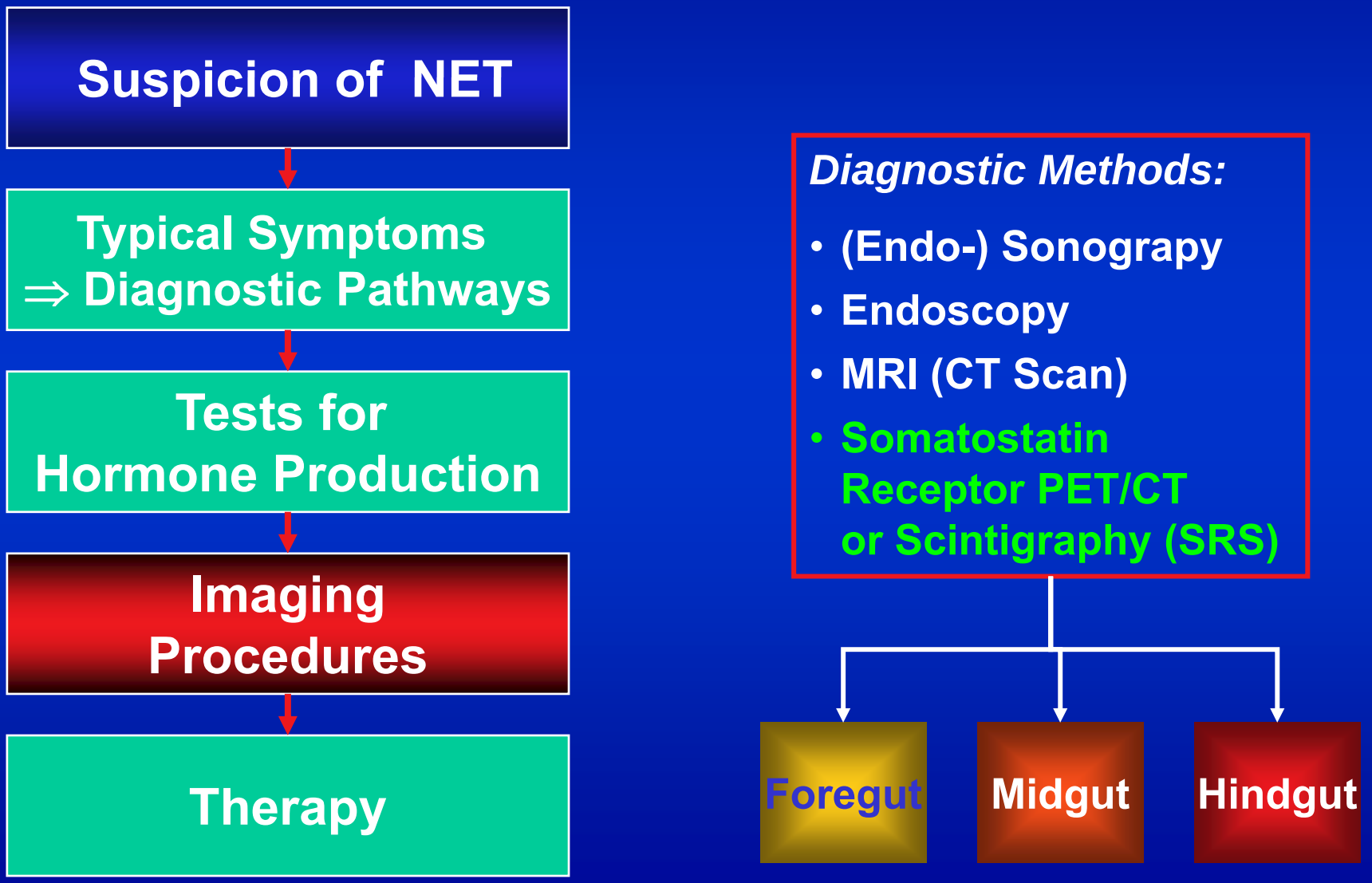


In Wahl R. (ed.):
Principles and Practice of PET and PET/CT.
Lippincott Williams & Wilkins, Philadelphia 2008 (p. 411-437).



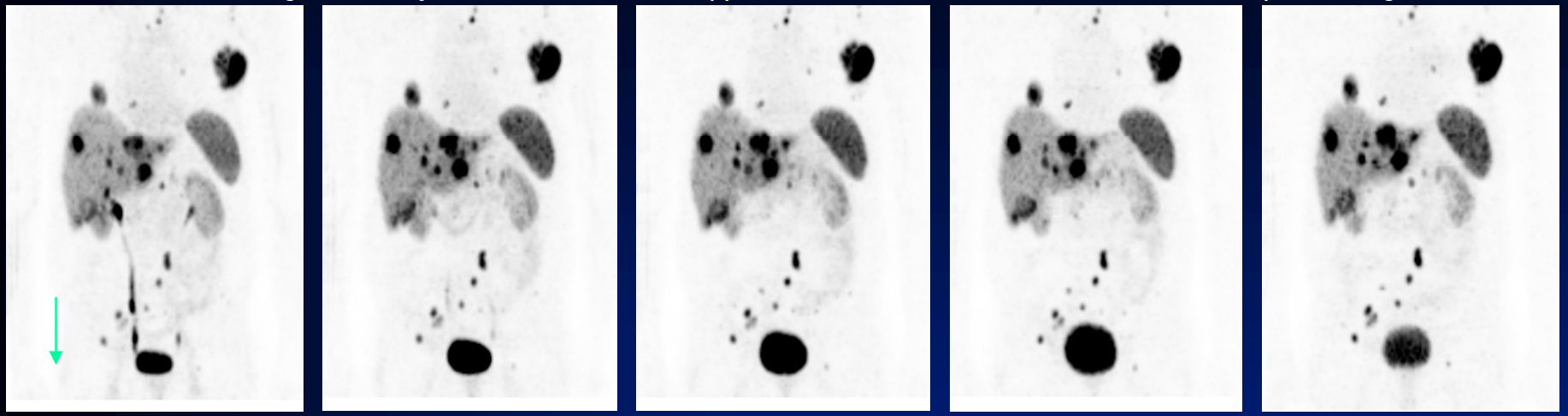
Principles and Clinical Indications

Neuroendocrine Tumors (NET)
– Diagnosis –



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}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

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-009-1205-y

ORIGINAL ARTICLE

Detection of unknown primary neuroendocrine tumours (CUP-NET) using ^{68}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}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}Ga-DOTA-NOC PET/CT is highly superior to ^{111}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.

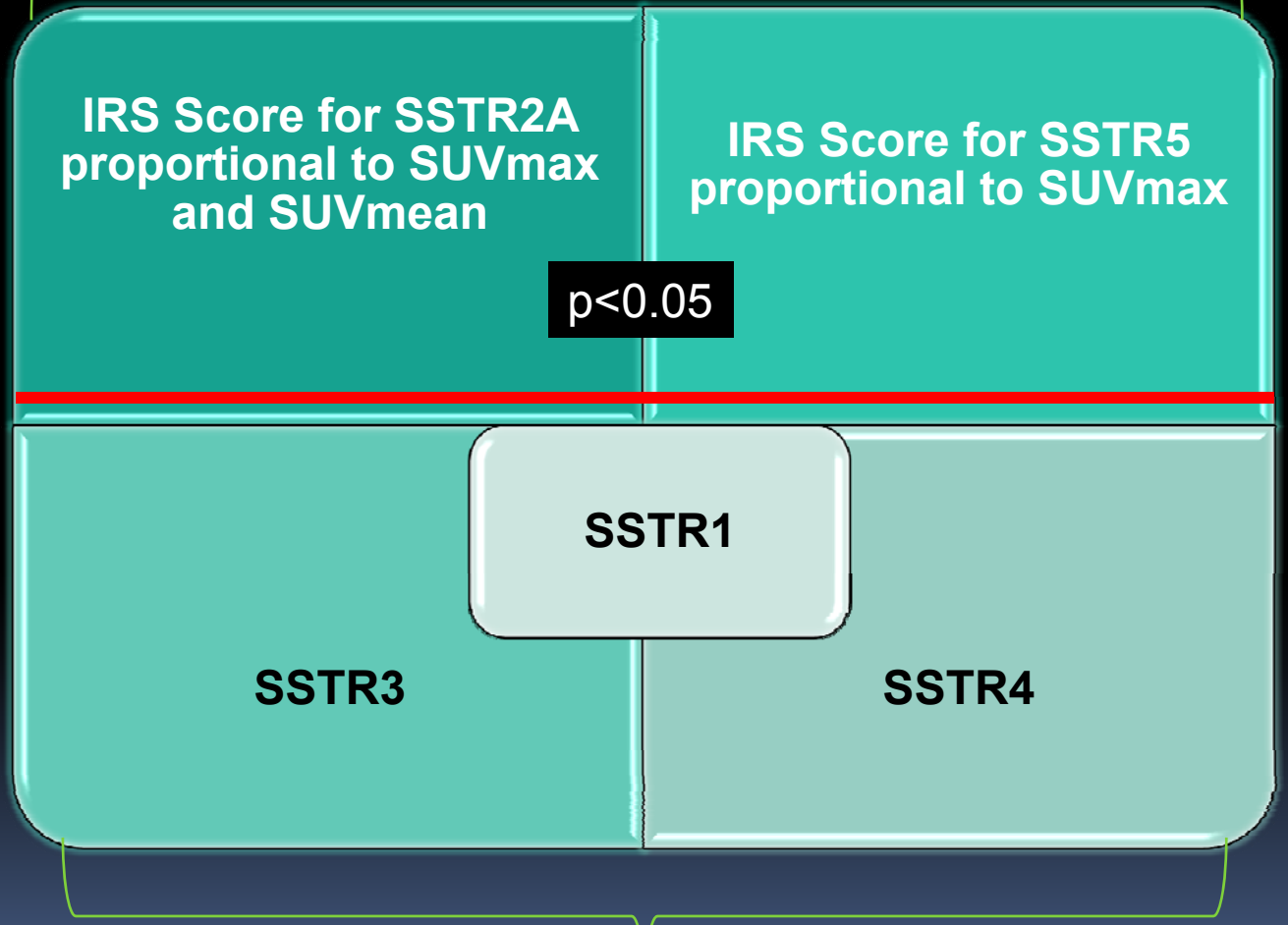
V. Prasad, R.P. Baum

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

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

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

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



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		
WHO 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
RECIST J N CI 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

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

Monitoring Response to Therapy

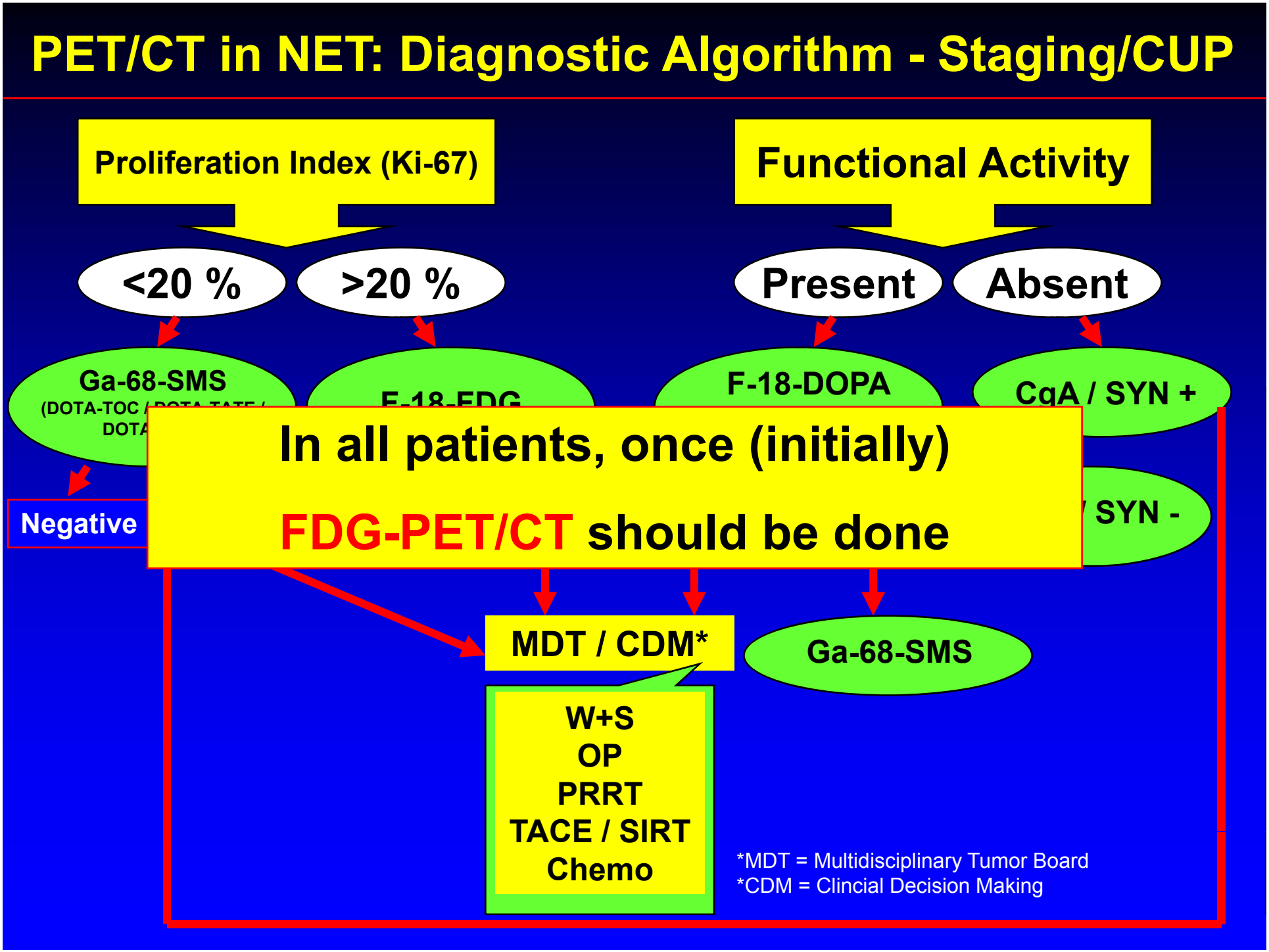
D E S I S T R E C I S T

U S E P E R C I S T

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 approch 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

- [^{68}Ga-DOTA,Tyr^{3}]octreotide (DOTA-TOC)
- [^{68}Ga-DOTA,1-Nal]octreotide (DOTA-NOC)*
- [^{68}Ga-DOTA]-TATE*
- [^{68}Ga-DOTA]-Lanreotide
- [^{68}Ga-DOTA]-Bombesin / AMBA* and DEMOBESIN*
- [^{68}Ga-DOTA]-D-Glu-Gastrin*
- [^{68}Ga-DOTA]-F(ab')$_2$-herceptin
- ^{68}Ga-Citrate
- ^{68}Ga-DOTA-Tyrosin*
- ^{68}Ga-DOTA-HSA Microspheres*
- ^{68}Ga-NOTA-RGD (angiogenesis)*
- ^{68}Ga-BPAMP (osteoblastic metastases)*
- ^{68}Ga-DOTA-α-MSH (melanoma)*
- ^{68}Ga-DOTA-SHAL (lymphoma)*
- …and many more to come!

**first use in Bad Berka*

Future Directions

Fourth generation peptides

Antagonists of radiolabeled peptides may be superior to agonists

Pansomatostatins: targeting a broader subtype and tumor spectrum

Multireceptor targeting