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Clinical PET Where do we go from here?

Michael E. Casey, Ph.D.

Introduction

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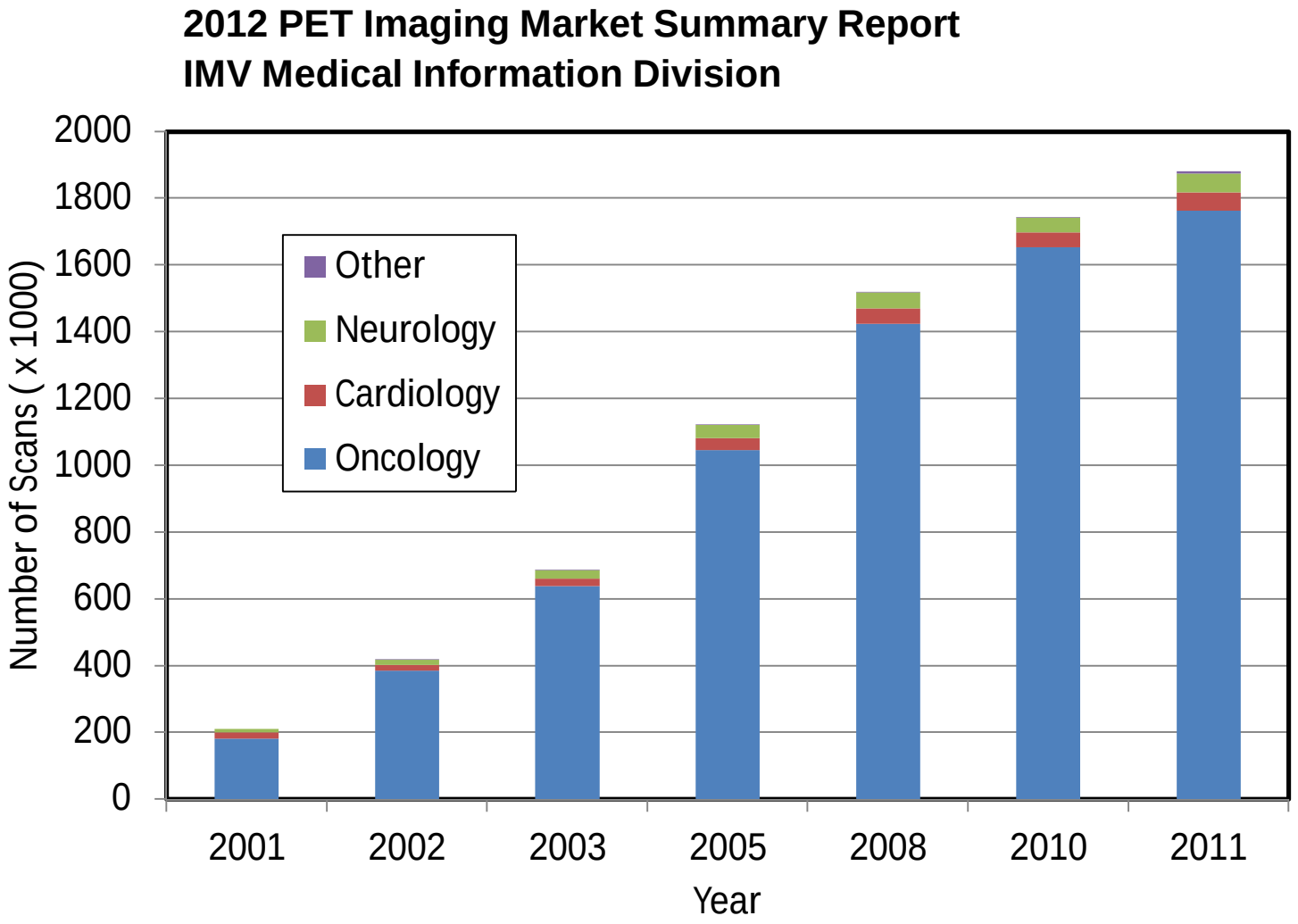
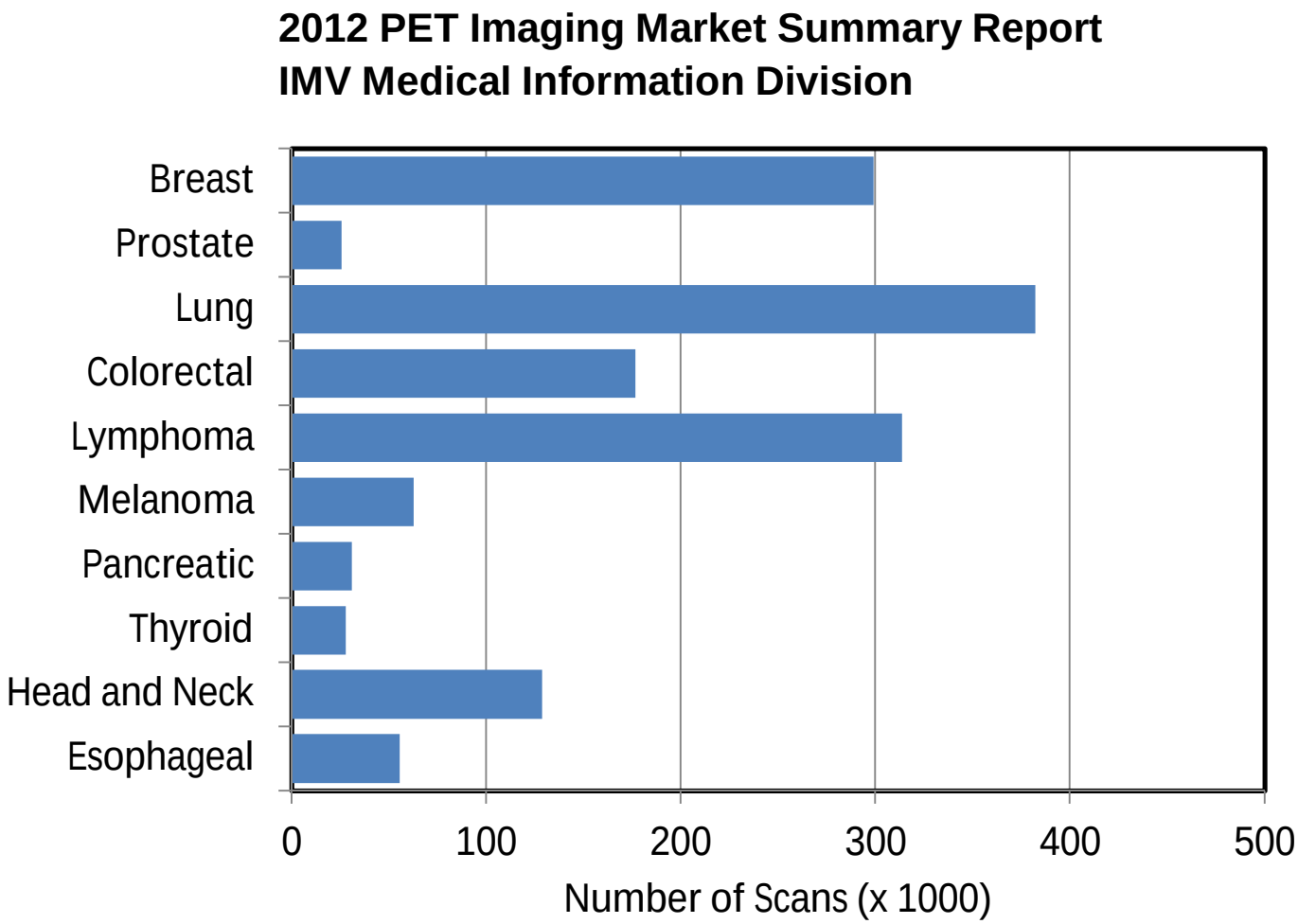
Outline

- **PET applications drive scanner development.**
- **What can be done to open up new PET applications?**
  - **Lesion detectability**
  - **Effect of increased sensitivity**
  - **Effect of spatial resolution**
  - **Effect of time resolution**
  - **Effect of motion correction**
- **New radical approaches to instrumention**
- **Potential for improved accuracy using dynamic imaging**

Introduction - Number of PET Scans by Year



Introduction - Number of Scans in the United States



Introduction - Cancer Incidence with PET Imaging Applications

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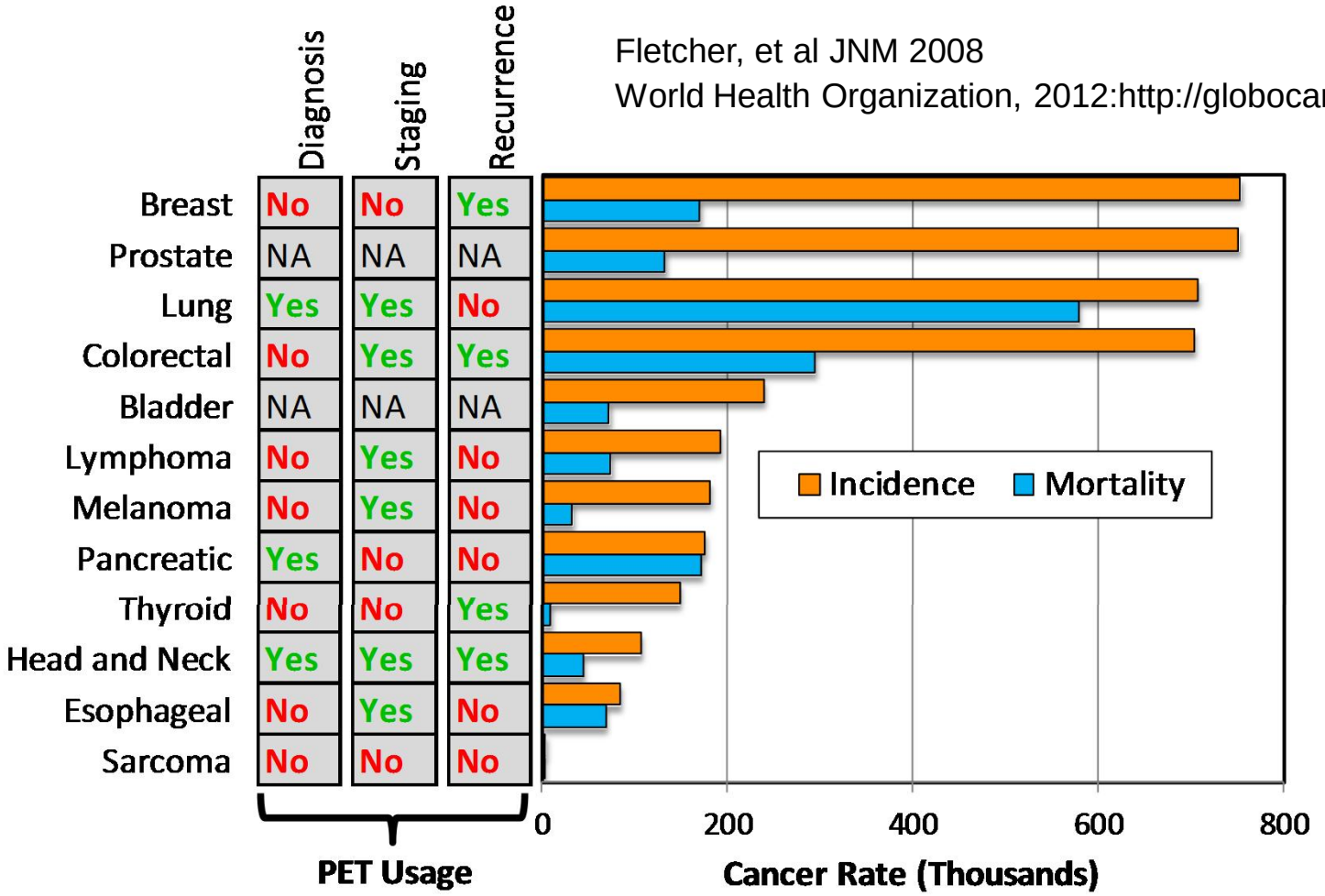
Fletcher, et al JNM 2008
World Health Organization, 2012:http://globocan.iarc.fr/factsheet.asp



Introduction

Example: Head and Neck Cancer

"With respect to nodes, the sensitivity of the imaging procedure (48%) is such that the results could not help the surgeon in deciding which level to dissect and which to spare. It is clear that the oral/head and neck oncologic surgeon should not base the need for neck surgery in clinically negative or clinically positive necks based on the result of the PET/CT scan."

Nahmias et al. PET/CT Staging in Oral/Head and Neck Cancer. J Oral Maxillofac Surg 2007.

Introduction

Mankoff, et. Al. "[^{18}F]Fluorodeoxyglucose Positron Emission Tomography–Computed Tomography in Breast Cancer: When… and When Not?" JOURNAL OF CLINICAL ONCOLOGY VOLUME 30 NUMBER 12 APRIL 20 2012

- "Although there have been some exceptions, the majority of recent studies and systematic reviews are in agreement with the results of the Pritchard study, and suggest a **low diagnostic yield for FDG PET/CT in patients with stage I and early stage II breast cancer**. This evidence underlies the **strong recommendation** in the current National Comprehensive Cancer Network (NCCN) consensus guidelines that systemic staging, including FDG PET/CT, is **not indicated for early-stage breast cancer** in the absence of signs or symptoms suggesting metastasis."

- "By definition and some simple mathematics, in a patient population with 5% prevalence, even an imaging test with **90% sensitivity and specificity** will yield more than **2:1 false-positive** versus true-positive findings. For a 1% prevalence, such as that seen in the Pritchard study, the ratio of false positives to true positives would be more than 10:1."

Potential Single Nodule Lung Cancer

National Comprehensive Cancer Network®

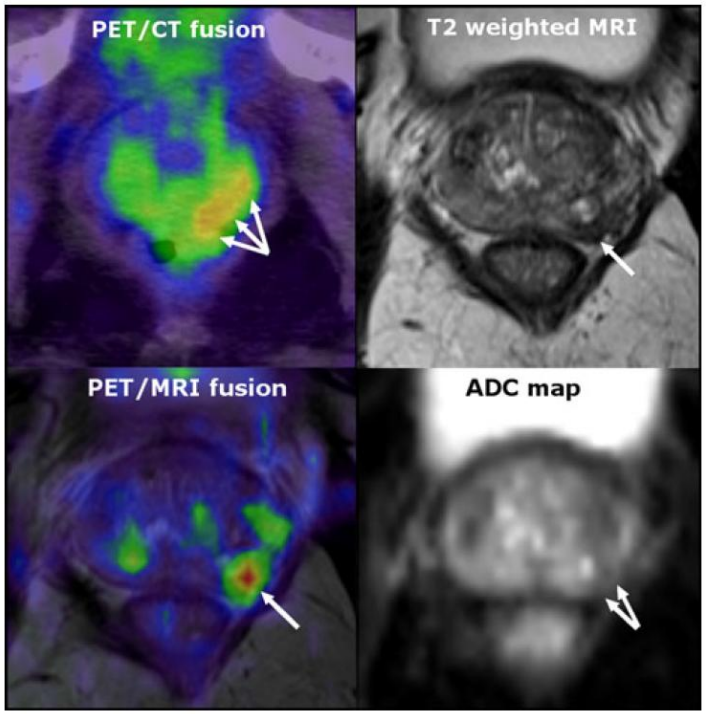
NCCN Guidelines Version 2.2014
Lung Cancer Screening

NCCN Guidelines Index
LCS Table of Contents
Discussion

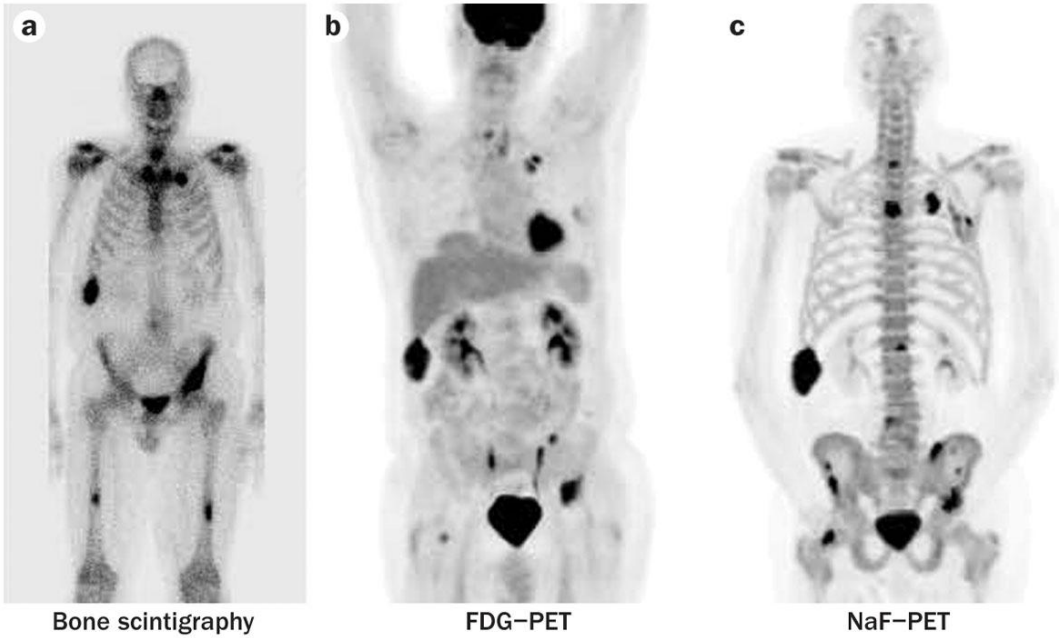
- **NCCN recommends Low Dose CT for initial screening.**
- **FDG PET/CT is recommend for evaluation of nodules 7-10 mm.**
- **With more counts and motion correction could PET/CT be useful in screening smaller nodules?**

Potential Prostate Cancer

- NCCN recently added ^{11}C-Choline and ^{18}F-NaF for investigating the cause of biochemical failure
- Potential for initial staging



Eur J Nucl Med Mol Imaging (2013) 40:1629-1630



Scher, H. I. *et al*. (2013) Validation and clinical utility of prostate cancer biomarkers *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.30

Introduction

How do we increase the clinical use of PET?

- **Oncology**
  - **Need to improve the ability to detect tumors.**
  - **We need to standardize measurements of uptake for therapy monitoring.**
- **Neurology**
  - **PET can differentiate Alzheimer from other dementia but no therapy exists.**
- **Cardiology**
  - **PET is only slightly superior to SPECT in myocardial perfusion.**
  - **Potential in imaging vulnerable plaque. Need motion correction.**
- **Other diseases**

Introduction

Given that FDG (or any tracer) is the tracer of choice, the possible knobs to turn for moving PET into new clinical areas are:

- Spatial Resolution – Make smaller crystals.
- Sensitivity (NEC) – Count longer or more scintillator.
- Time resolution – Better time resolution acts as better sensitivity.
- Motion compensation – Freezing motion improves contrast.
- Image reconstruction
    - 4D reconstruction to highlight uptake rate.
    - Standardization of recovery coefficients among scanners

What is Detectability?

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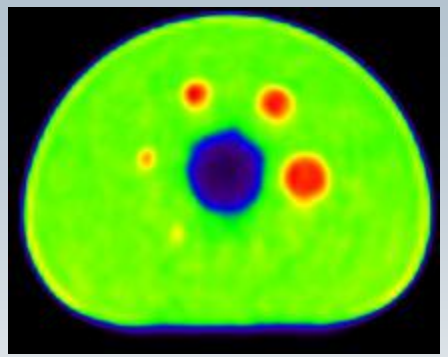
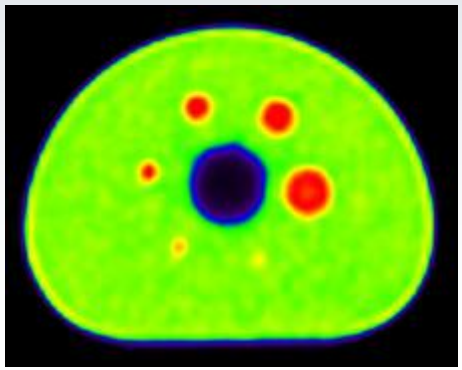
Detectability depends on the Signal to Noise ratio

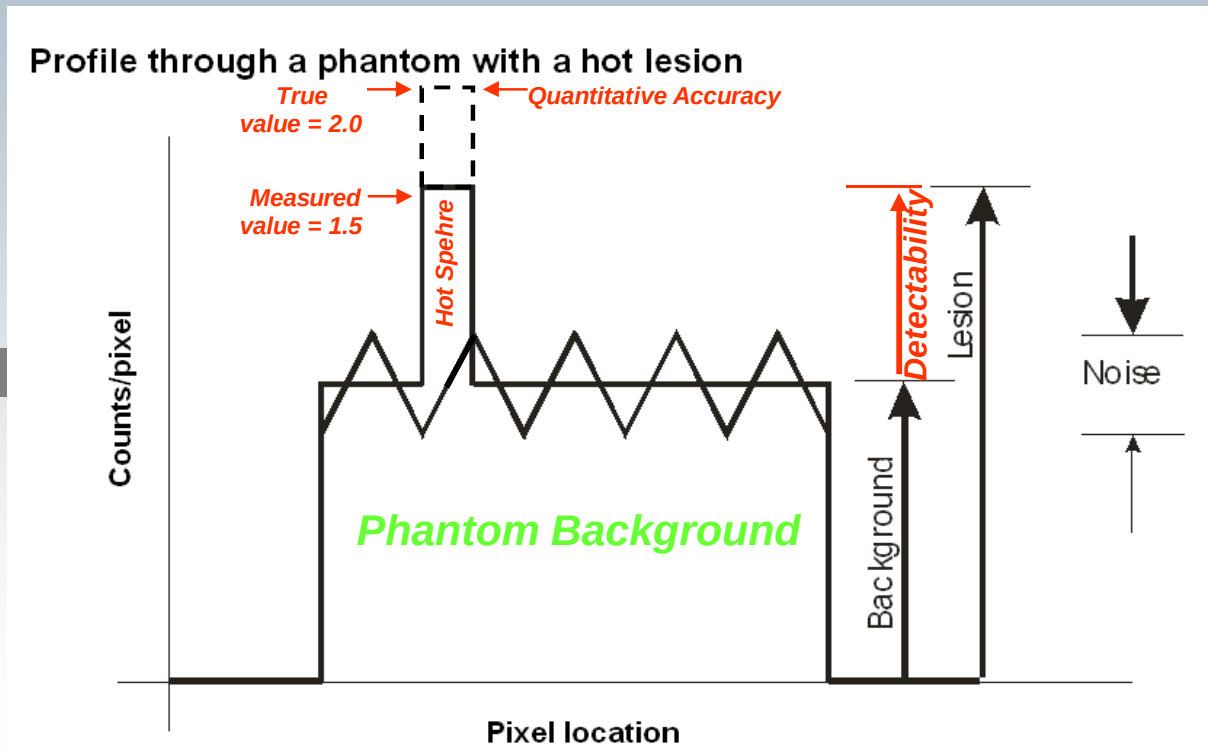
PSF Reconstruction



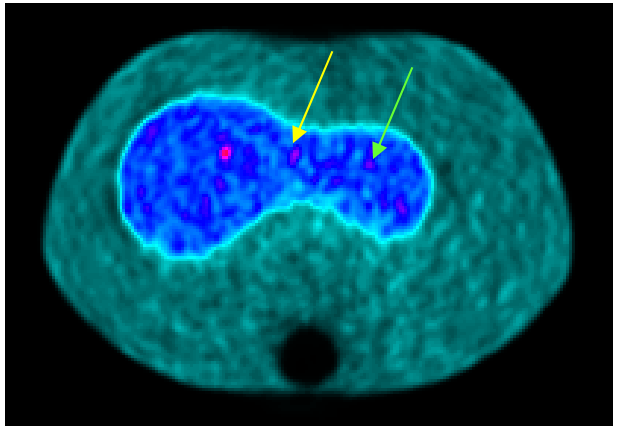
Signal to Background Ratio 2:1



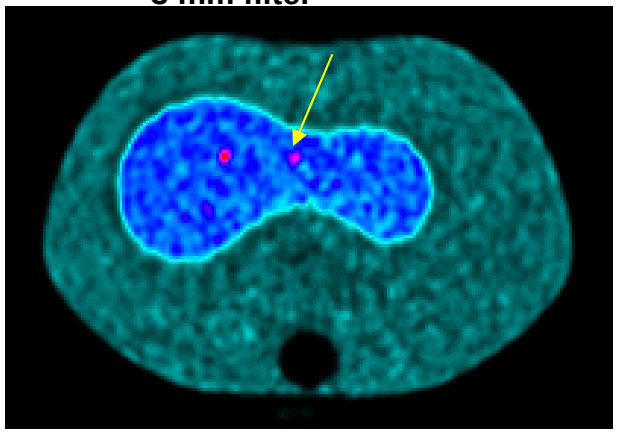
PSF plus TOF Reconstruction



What is Detectability?



PSF OP-OSEM
4 Iterations, 336 x 336
3 mm filter



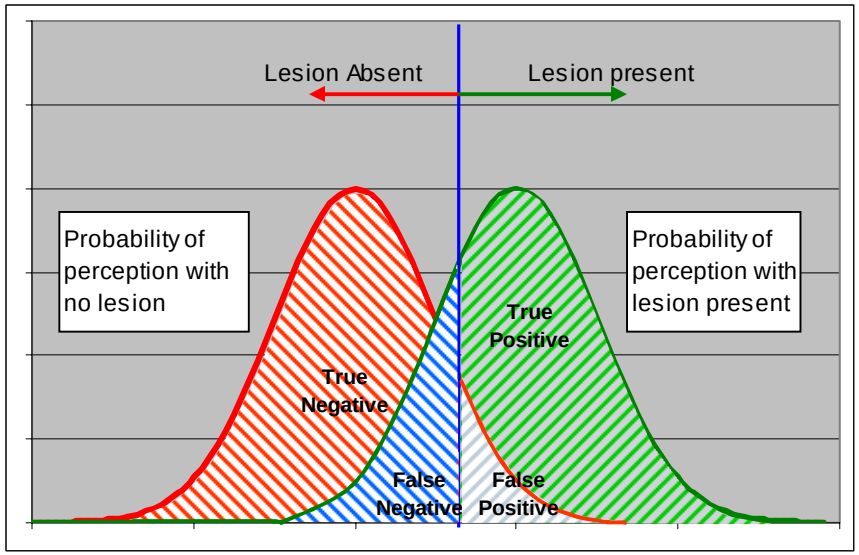
PSF TOF OP-OSEM
4 Iterations, 336 x 336
3 mm filter

Detectability is our ability to properly identify a lesion

Red distribution shows the distribution of background pixels while the green distribution shows the lesion pixels.

Noise is the width of the distribution.

Depending on the threshold applied to separate lesion from background, noise pixels can be mistaken for lesion pixels!



How to improve Detectability?

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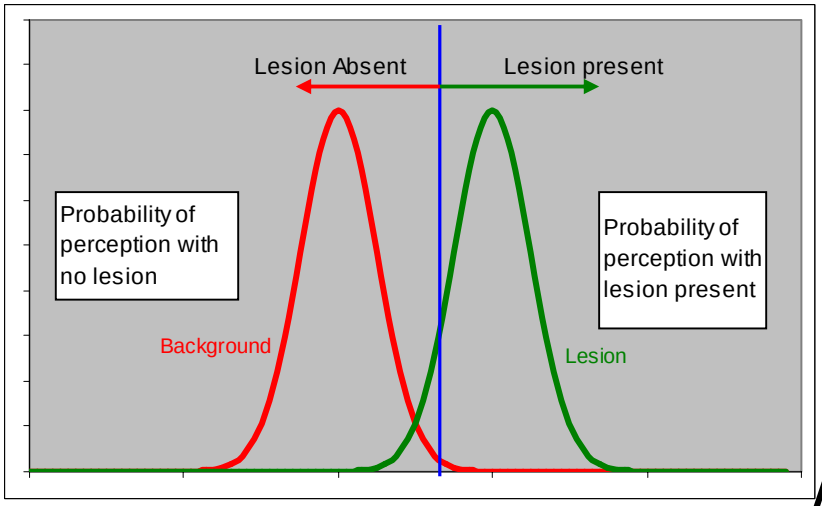
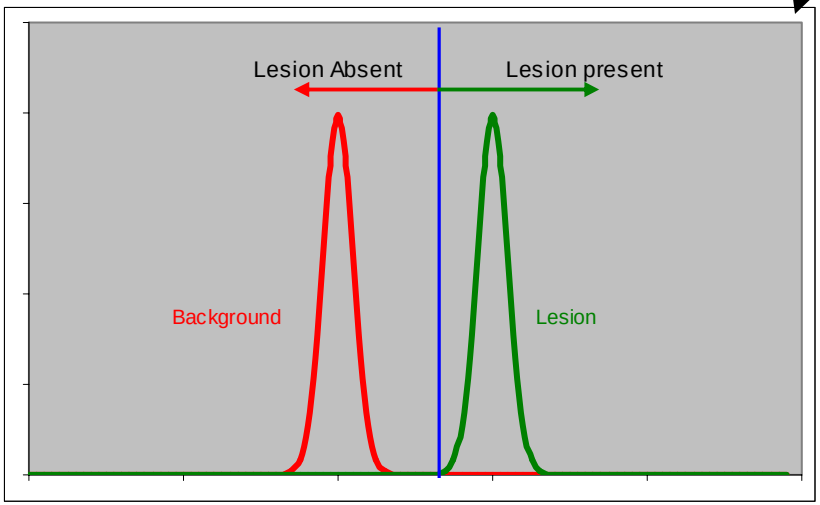
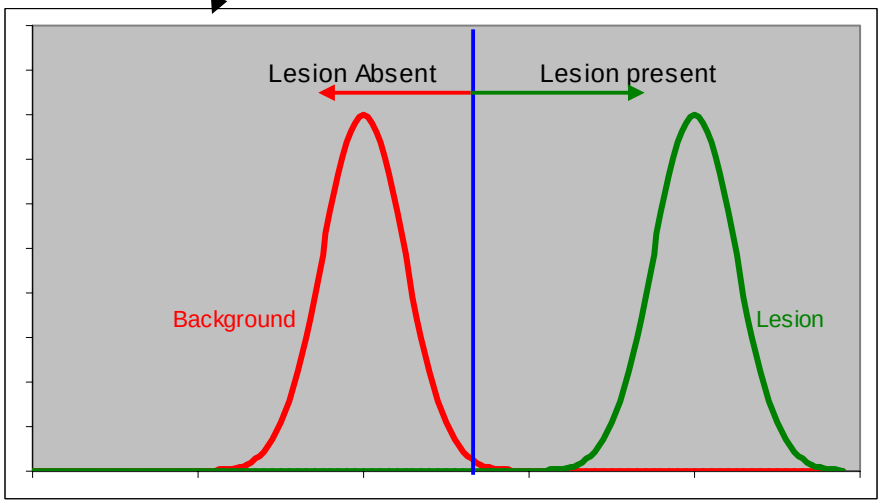


Improve the Noise:
- **Count longer**
- **Better time resolution**
- **Better sensitivity**

Improve the Contrast
- **Better tracer**
- **Better spatial resolution?**
- **Motion correction**





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Time-of-fight adds information to the data

- In conventional PET, there is no spatial information about the origin of the event along the line-of-response.
- Time-of-flight adds information about the origin.
- The information added by TOF, lowers the uncertainty of the event origin, thus improving the image noise.
- The gain from TOF was first described by Budinger and the extension to NEC by Conti.

$$NEC_{TOF} = NEC_{non\ TOF} \cdot \frac{Object\ Diameter}{\Delta t \cdot \frac{C}{2}}$$

- NEC – Noise Effective Count Rate, the effective sensitivity considering all noise sources (random and scatter coincidences).
- Δt – time resolution; C – speed of light
- **An improvement in the time resolution acts as an increase in NEC**

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Detectability Experiments

Can we simulate a realistic image and predict the sensitivity specificity of detecting a disease?

Kadrmas simulated a patient scan using anthropomorphic phantom with known lesions. This study compared reconstruction algorithms.

El Fakhri added lesions to real patient data and showed that time-of-flight reconstruction improved lesion detection.

Schaefferkoetter repeated the El Fakhri experiment with Siemens data.

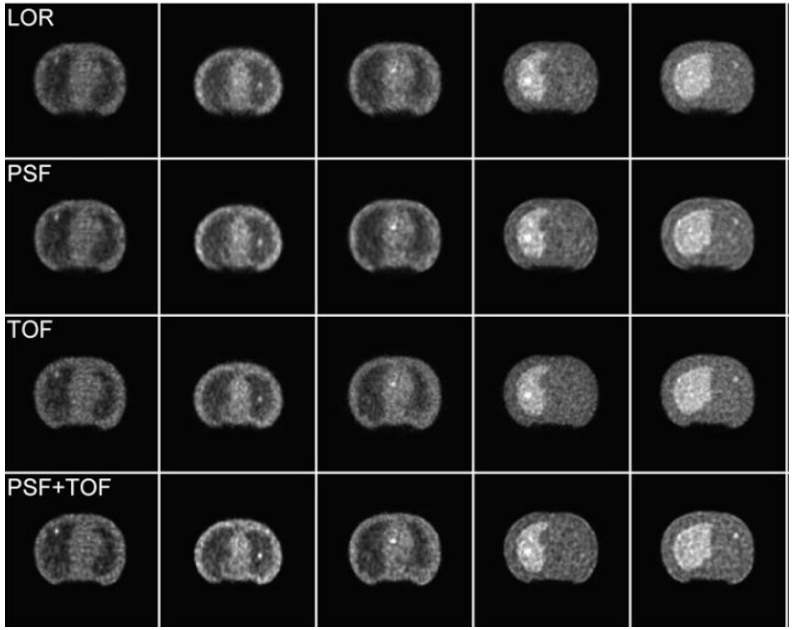
However, all three compared reconstruction algorithms but none actually explored lesion detection performance for a specific a disease.

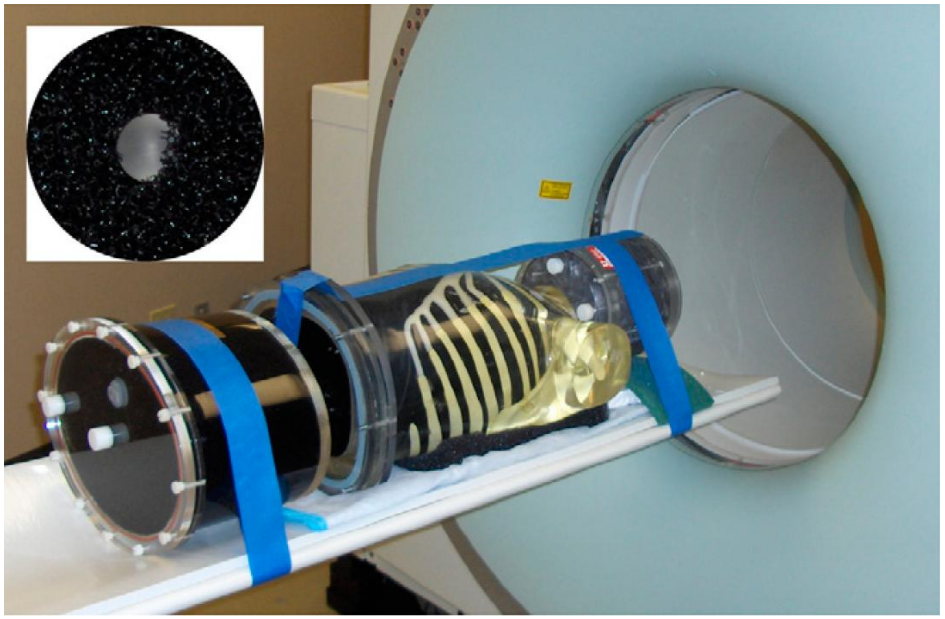
Kadrmas, Casey, Conti, Jakobi, Lois, Townsend; “Impact of Time-of-Flight on PET Tumor Detection” J Nucl Med 2009; 50:1315–1323

El Fakhri G., Surti S., Trott C.M., Scheuermann J., Karp J.S. Improvement in Lesion Detection with Whole–Body Oncologic TOF - PET. J. Nucl. Med. 2011; 52: 347-353

Schaefferkoetter; et.al. “Clinical impact of time-of-flight and point response modeling in PET reconstructions: a lesion detection Study” Phys. Med. Biol. 58 (2013) 1465–1478

Kadrmas Detectability study





- 26 Germanium spheres inserted in pseudo patient. (6, 8, 10, 12, 16 mm)
- Phantom was filled with ^{18}F and scanned at three different sphere to background concentrations
- Scanned two days with lesions and a third without lesions.

Kadrmas, Casey, Conti, Jakobi, Lois, Townsend; "Impact of Time-of-Flight on PET Tumor Detection" *J Nucl Med* 2009; 50:1315–1323

Detectability Study - Results

TABLE 1. CNPW Observer Results*

	Optimal parameters		CNPW observer results	
Algorithm	No. of iterations†	Filter SD (voxels)	P_{LOC} ± SD	A_{LROC} ± SD
LOR	6	0.5	0.588 ± 0.068	0.418 ± 0.051
PSF	8	0.1	0.706 ± 0.063	0.516 ± 0.052
TOF	6	0.5	0.804 ± 0.056	0.673 ± 0.054
PSF+TOF	8	0.1	0.882 ± 0.045	0.813 ± 0.046

*Results are for subset of images read by human observers.
†Ordinary Poisson LOR-OSEM with 7 subsets.

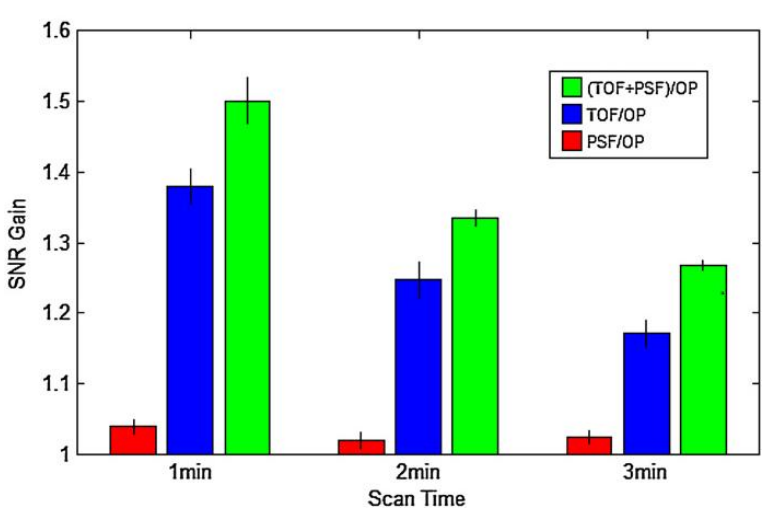
TABLE 2. Human Observer Results

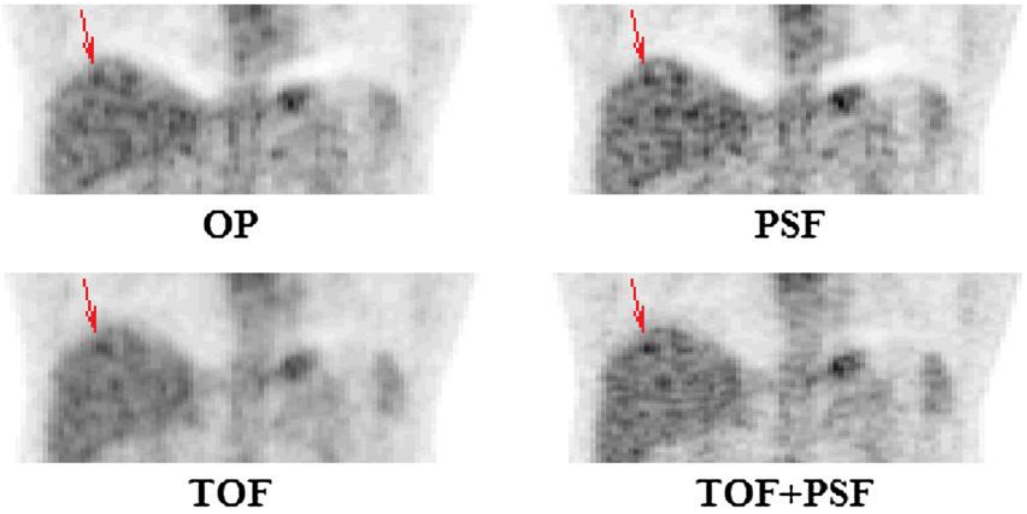
	Human observer results		Tukey all-pairs comparison (*P*)*			
Algorithm	P_{LOC} ± SD	A_{LROC} ± SD	LOR	PSF	TOF	PSF+TOF
LOR	0.549 ± 0.039	0.486 ± 0.045	N/A	0.002	0.001	<0.001
PSF	0.690 ± 0.064	0.662 ± 0.087	0.002	N/A	0.882	0.001
TOF	0.741 ± 0.043	0.691 ± 0.046	0.001	0.882	N/A	0.002
PSF+TOF	0.886 ± 0.056	0.873 ± 0.062	<0.001	0.001	0.002	N/A

*Tukey all-pairs comparison performed on A_{LROC} figure-of-merit.
N/A = not applicable.

A_{LROC} – Joint probability of choosing both the correct image and the correct location of the lesion. Larger A_{LROC} is better.

Schaefferkoetter Study





As the counting time increases (we get more counts), the differences between reconstruction methods decreases.

Schaefferkoetter; et.al. "Clinical impact of time-of-flight and point response modeling in PET reconstructions: a lesion detection Study" *Phys. Med. Biol*. 58 (2013) 1465–1478

Detectability can be improved through increasing acquisition time or sensitivity

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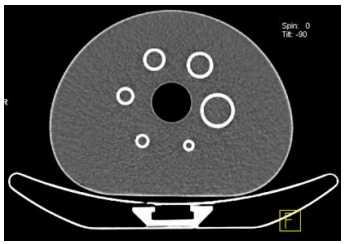
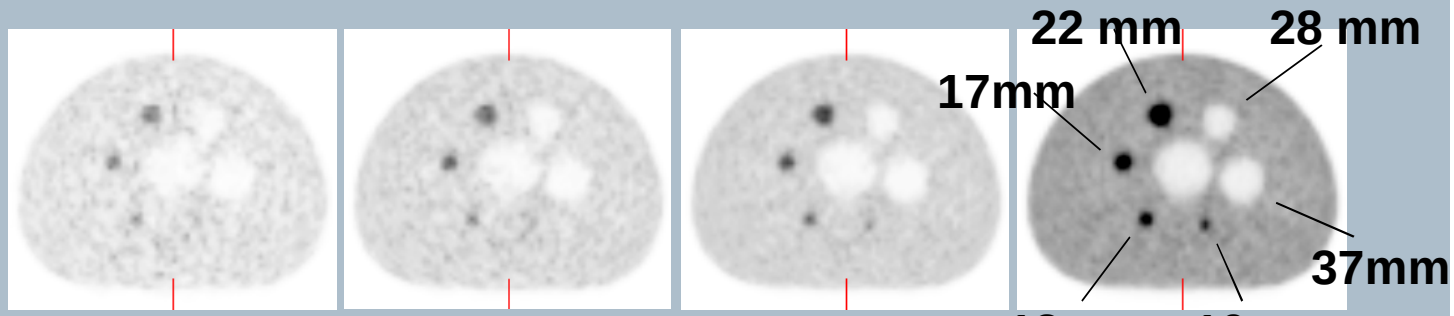


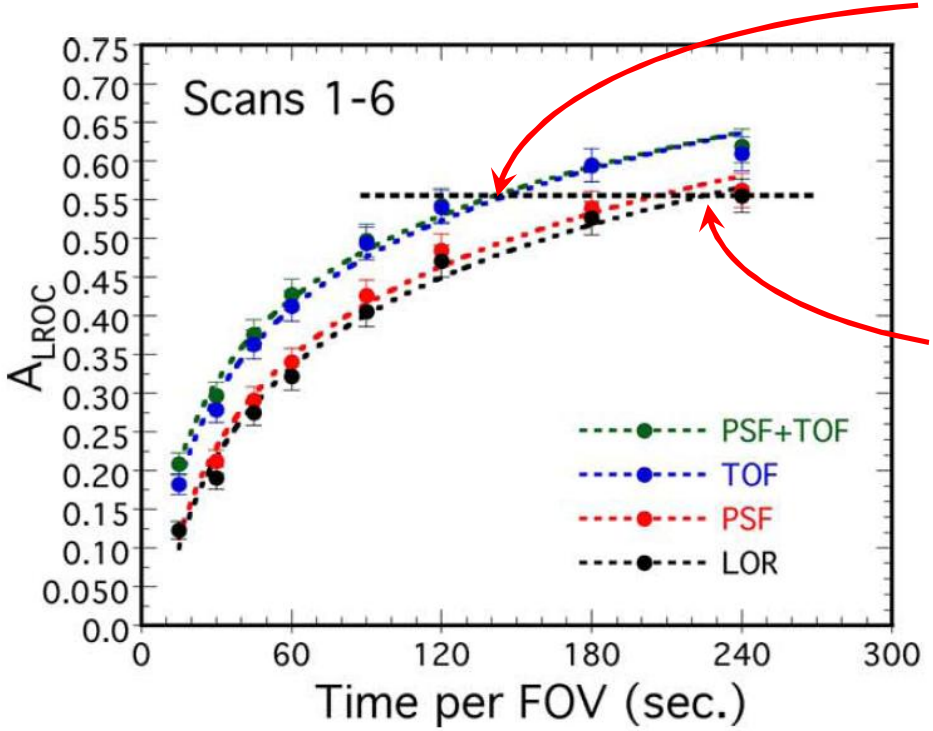
CT Image



10 mCi, 1h P.I. Standard 3D OSEM Clinical Reconstruction parameters 3i21s

Kadrmas' Detectability Study

Adding TOF information to the reconstruction has the same effect as increasing the scan time.



TOF images exhibited the same detectability (ALROC ≈ 0.55) at 140 seconds as non-TOF at 240 seconds

Kadrmas, et. al; "Effect of Scan Time on Oncologic Lesion Detection in Whole-Body PET" *IEEE Trans. Nucl. Sci.* VOL. 59, NO. 5, 2012

Signal to noise in patient scan

Signal is lesion minus background. Noise is pixel to pixel standard deviation within an ROI in the liver. SNR typically peaks after a few iterations.

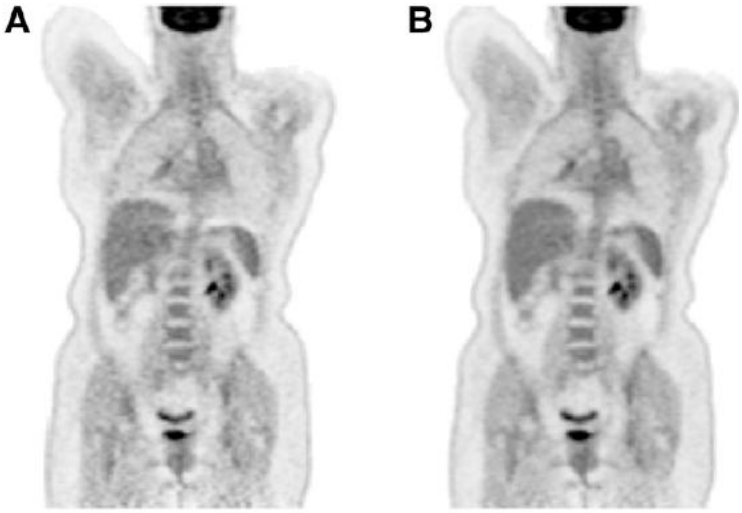
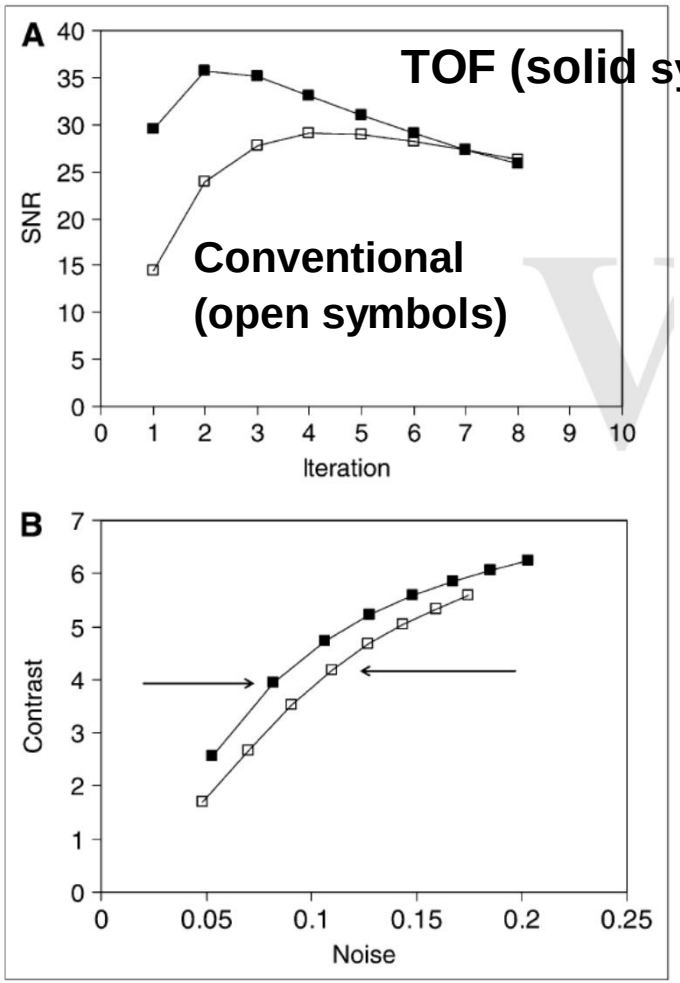


FIGURE 6. A 79-kg patient (BMI 34.2) with lung cancer reconstructed (A) without TOF information and (B) with TOF. Note the almost complete disappearance of the photopenic artifact above the liver and the spleen in B.



Lois et. al. "An Assessment of the Impact of Incorporating Time-of-Flight Information into Clinical PET/CT Imaging" *J Nucl Med; 2010; 51:237-245*

SNR as a function of BMI

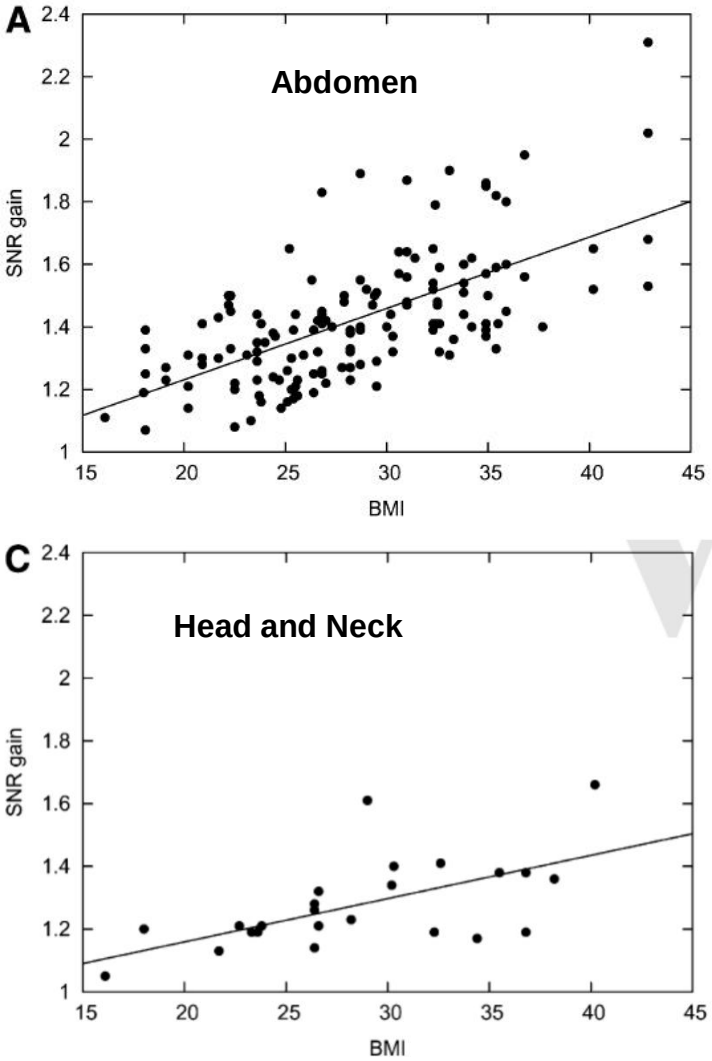


FIGURE 4. Measured SNR gain factor vs. BMI, for small lesions (<2 cm) located in different parts of the body for a group of 100 patients: (A) 144 lesions located in the abdomen, (B) 67 lesions located in the lungs, and (C) 30 lesions located in the head and neck.

Spatial Resolution

Moses et. al. proposed an empirical relationship for the reconstructed resolution given by the formula:

$$FWHM = 1.25\sqrt{\left[\left(\frac{d}{2}\right)^2 + (0.022 * D)^2 + s^2 + u^2\right]}$$

Where:

d - is the size of the crystal

D - is the diameter of the system in cm

s - is the source size (1 mm for NEMA)

u - is the identification uncertainty which includes both inter-crystal scatter and block decoding.

W. W. Moses and S. E. Derenzo, "Empirical observation for spatial resolution degradation in positron emission tomographs using block detectors," J. Nucl. Med., vol. 33, no. 5, p. 101P, 1993

Reduced Resolution

We know all the physics in Moses' formula except the uncertainty, u.

Rearrange the formula to remove the effect of ring diameter and source size. The resulting "Reduced Resolution" should be only a function of crystal size.

$$Reduced\ Resolution = 1.25 \cdot \sqrt{\left(\frac{Resolution}{1.25}\right)^2 - (D \cdot 0.022)^2 - s^2}$$

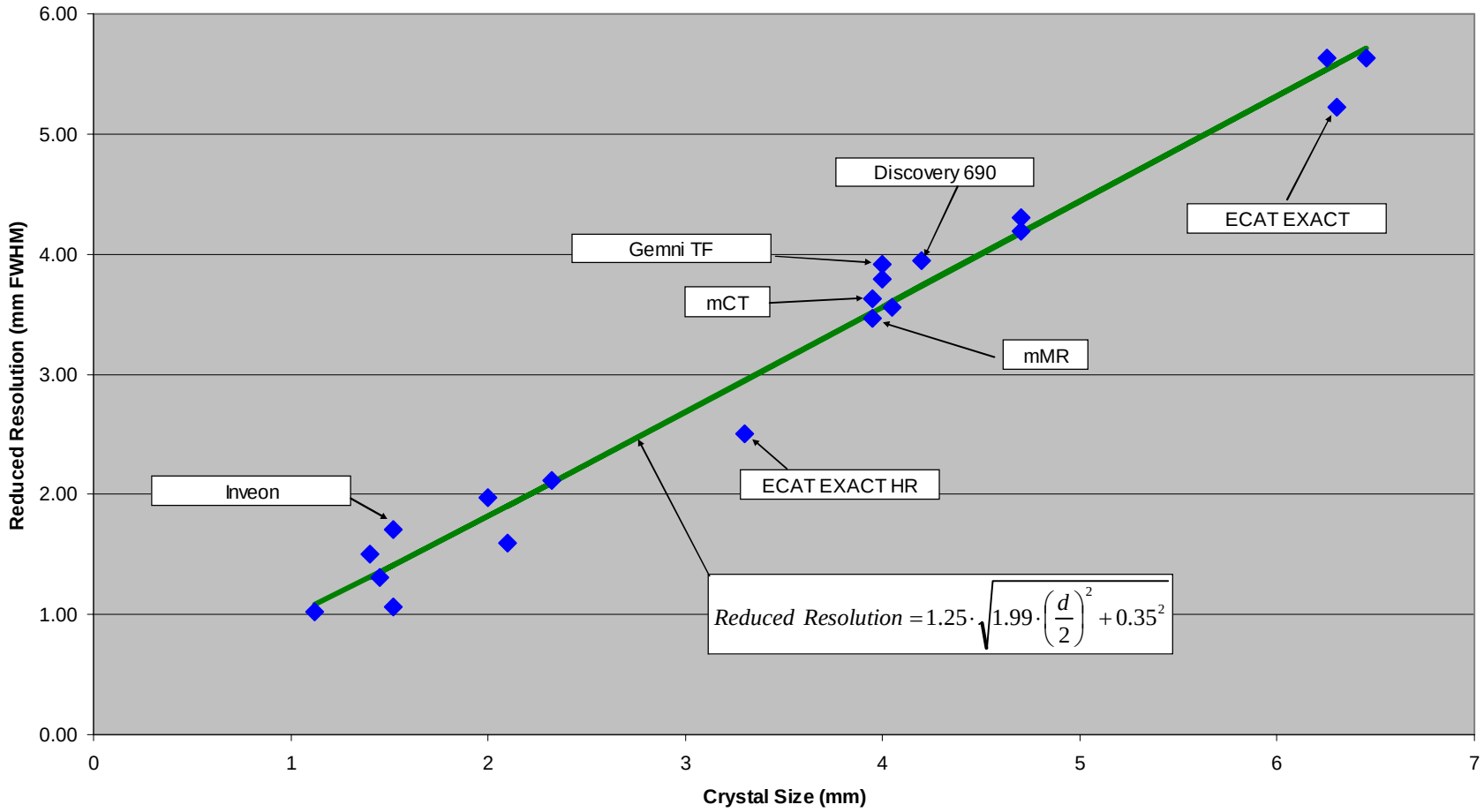
For clinical, the NEMA source (s) is 1mm ^{18}F

For pre-clinical, the NEMA source (s) is 0.3 mm ^{22}Na

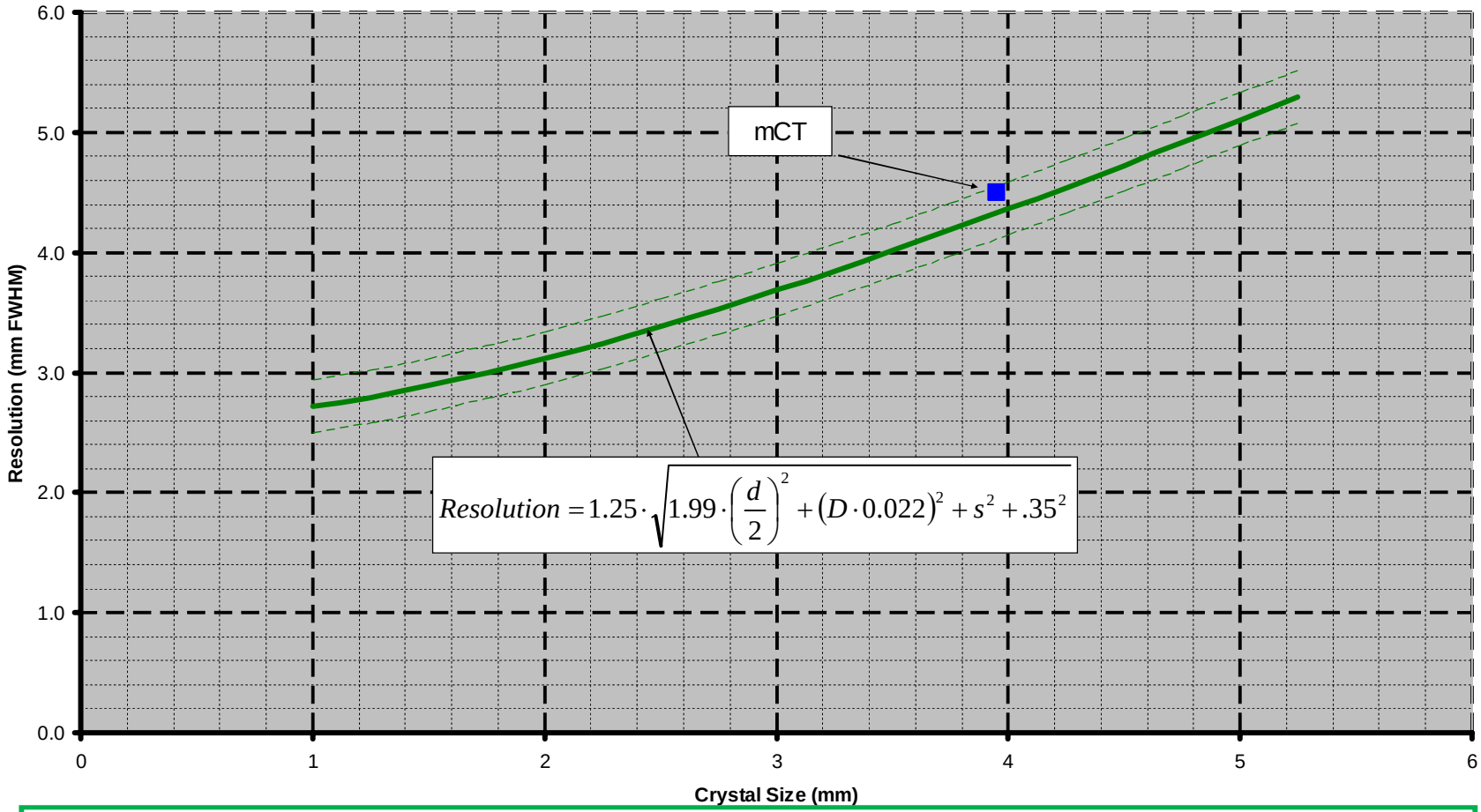
Literature search for measured spatial resolution

Scanner	Transaxial Crystal	Axial Crystal	Ring Diameter	Material	Resolution	Reference
Discovery ST	6.3	6.3	88.6	BGO	**5.9**	De Ponti et al.: "D-600 performance for the NEMA NU 2-2007 parameters" Med. Phys. 38 „2…, February 2011
Discovery STE	4.7	6.3	88.6	BGO	**5.1**	
Discovery 600	4.7	6.3	80.1	BGO	**4.9**	
Discovery 690	4.2	6.3	81.0	LYSO	**4.7**	Bettinardi et al.: Physical performance of the new hybrid PET=CT Discovery-690; Medical Physics, Vol. 38, No. 10, October 2011
Gemni TF	4.0	4.0	90.3	LYSO	**4.8**	Surti et al."PERFORMANCE OF LYSO TOF PET/CT";THE JOURNAL OF NUCLEAR MEDICINE • Vol. 48 • No. 3 • March 2007
Ingenuity TF	4.0	4.0	90.3	LYSO	**4.7**	Zaidi;Design and performance evaluation of a whole-body Ingenuity TF PET–MRI system;Phys. Med. Biol. 56 (2011) 3091–3106
ECAT HR+	4.05	4.39	82.4	BGO	**4.4**	HERZOG et al.: NEMA NU2-2001 GUIDED PERFORMANCE EVALUATION OF FOUR SIEMENS ECAT PET SCANNERS; IEEE TRANSACTIONS ON NUCLEAR SCIENCE, VOL. 51, NO. 5, OCTOBER 2004
ECAT EXACT	6.25	6.75	82.4	BGO	**6.2**	
ECAT ACCEL	6.45	6.45	82.4	LSO	**6.2**	
ECAT HR	3.3	6.3	82.2	BGO	**3.6**	Wienhard et al. "The ECAT EXACT HR: Performance of a new high resolution positron scanner" Journal of Computer Assisted Tomography (1994) Bd.18, Nr.1, S.110-118
HRRT	2.1	2.1	46.9	LSO	**2.4**	Wienhard et al. "The ECAT HRRT: Performance and First Clinical Application of the New High Resolution Research Tomograph" IEEE TRANSACTIONS ON NUCLEAR SCIENCE, VOL. 49, NO. 1, FEBRUARY 2002
mCT	3.95	3.95	85.6	LSO	**4.5**	Siemens Internal
mMR	3.95	3.95	65.6	LSO	**4.1**	
NanoPET/CT	1.12	1.12	18.1	LYSO	**1.2**	Szanda et al. "National Electrical Manufacturers Association NU-4 Performance Evaluation of the PET Component of the NanoPET/CT Preclinical PET/CT Scanner" J Nucl Med 2011; 52:1741–1747
Inveon	1.52	1.52	16.1	LSO	**1.8**	Bao et al, "Performance Evaluation of the Inveon Dedicated PET Preclinical Tomograph Based on the NEMA NU-4 Standards", J Nucl Med March 2009 vol. 50 no. 3 401-408
Vista	1.45	1.45	11.8	LYSO/GSO	**1.4**	Wang et al. "Performance Evaluation of the GE Healthcare eXplore VISTA Dual-Ring Small-Animal PET Scanner",J Nucl Med November 2006 vol. 47 no. 11 1891-1900
rPET-1	1.4	1.4	14.0	MLS	**1.6**	Canadas et al. "NEMA NU 4-2008 Performance Measurements of Two Commercial Small-Animal PET Scanners: ClearPET and rPET-1", IEEE TRANSACTIONS ON NUCLEAR SCIENCE, VOL. 58, NO. 1, FEBRUARY 2011
ClearPET	2	2	22.0	LYSO/LuYAP	**2.1**	
X-PET	2.32	2.32	16.5	BGO	**2.2**	Prasad et al. "Performance Evaluation of the FLEX Triumph X-PET Scanner Using the National Electrical Manufacturers Association NU-4 Standards",J Nucl Med October 1, 2010 vol. 51 no. 10 1608-1615
Focus120	1.52	1.52	15.0	LSO	**1.2**	Kim et al, "Performance Measurement of the microPET Focus 120 Scanner", J Nucl Med September 2007 vol. 48 no. 9 1527-1535

Reduced Resolution

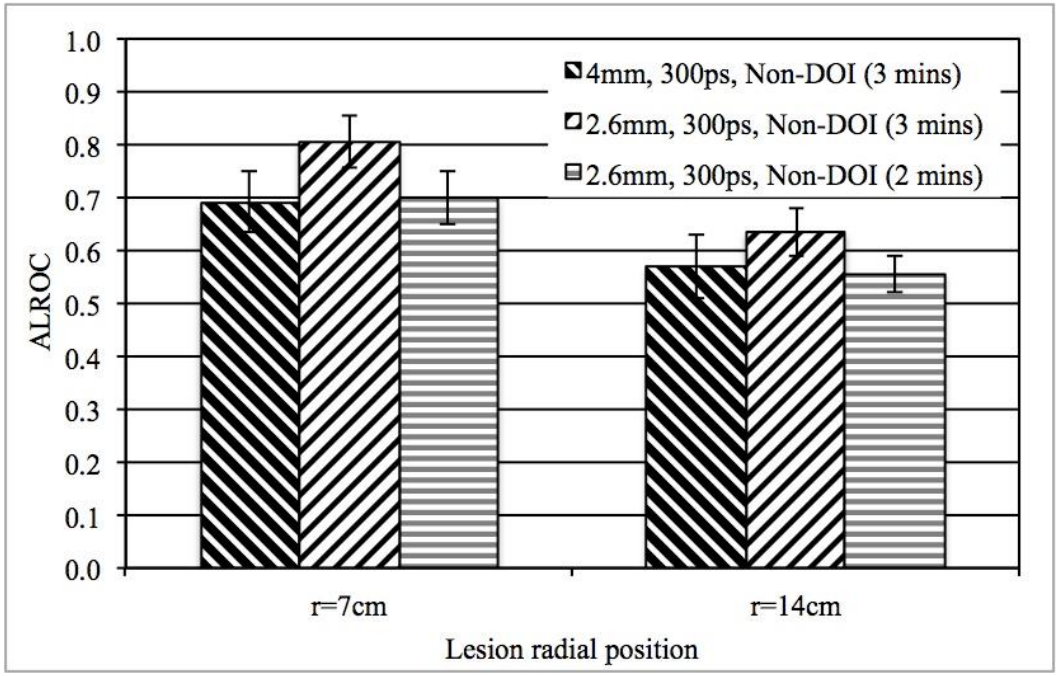


Predicted Resolution for 85 cm diameter scanner



Due to the positron momentum, smaller crystals produce less gain in resolution at clinical detector ring diameters.

Resolution and/or Sensitivity?



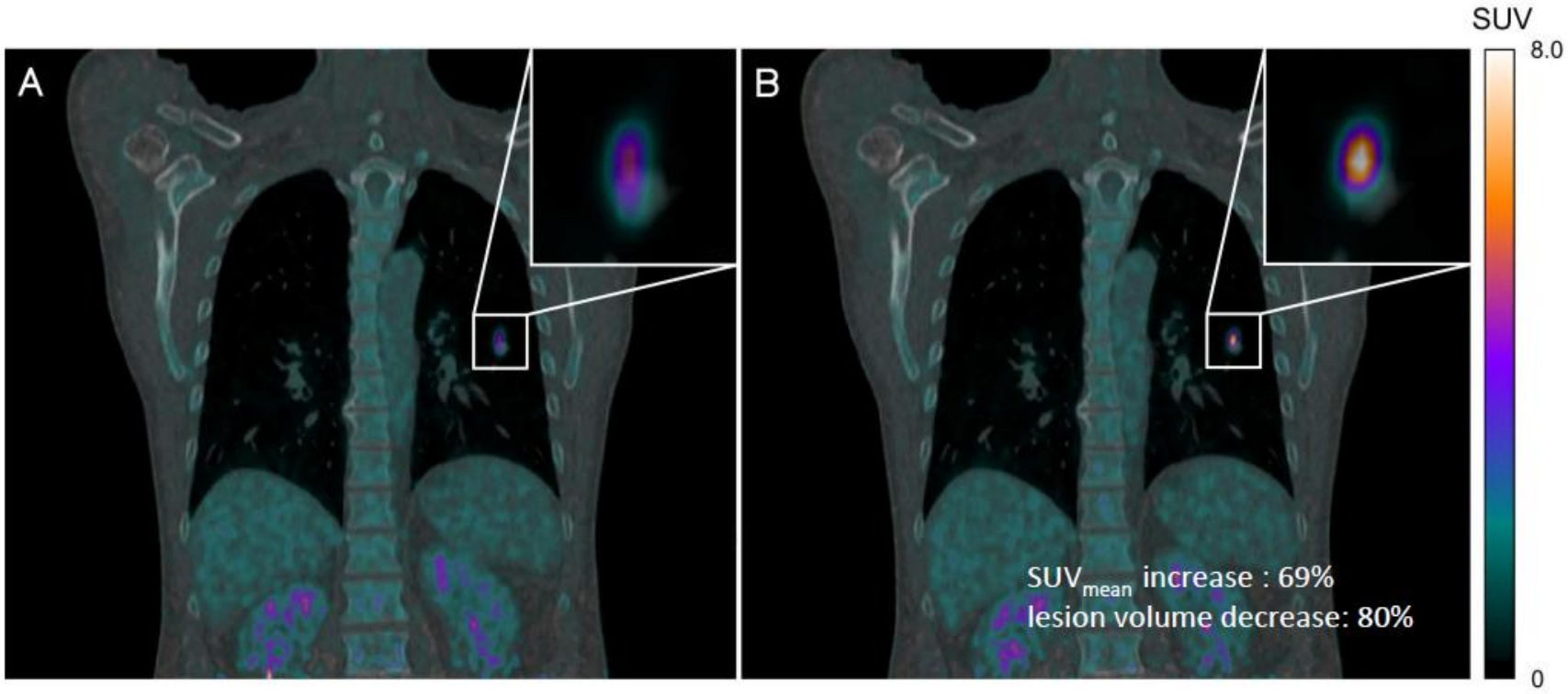
- **35 cm diameter phantom with 16 5 mm diameter spherical lesions at 6:1 uptake compared to background.**
- **A 2.6 mm crystal with 120 second acquisition produced the same detectability as 4 mm crystal with a 180 second acquisition**

Spatial resolution can provide a modest gain.
Much more gain is possible by increasing sensitivity (counting time).

Surti,S; Shore,A; Karp, J; "Design Study of a Whole-Body PET Scanner With Improved Spatial and Timing Resolution;" ***IEEE Trans Nucl Sci***

Motion Freeze improves SUV

Patient with a non-small cell lung cancer lesion



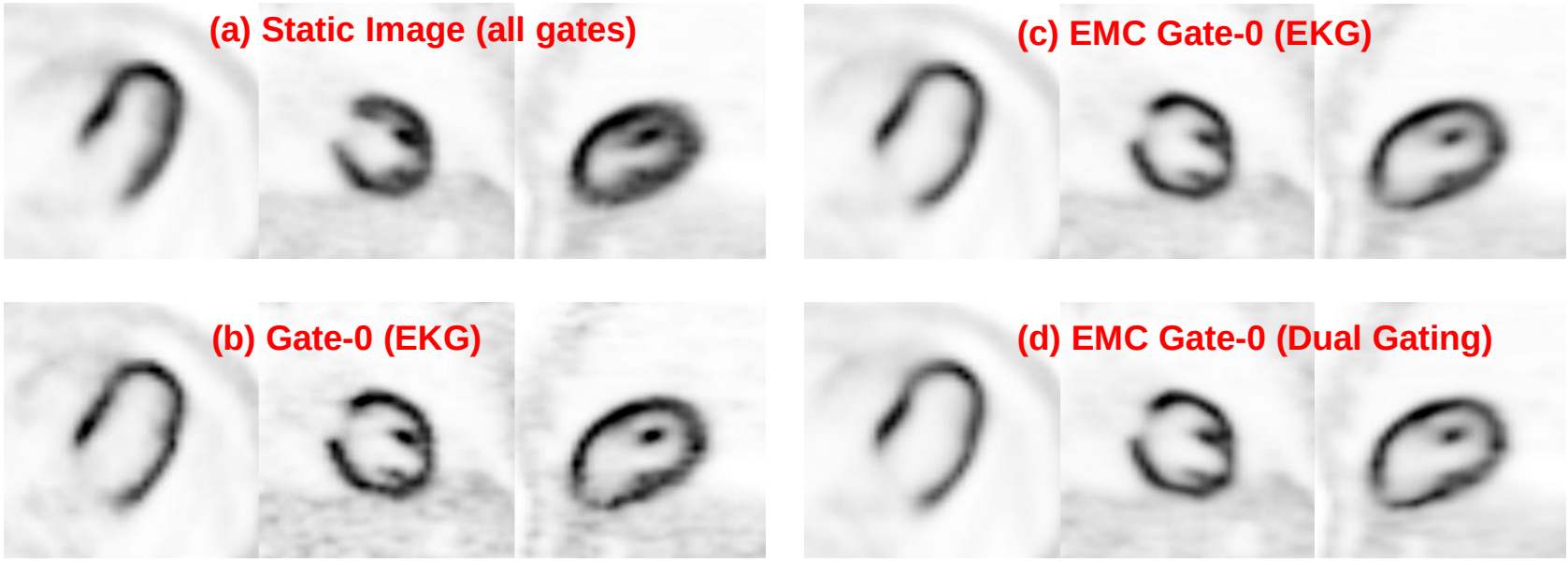
Non-gated, 126 s acquisition time

Optimal respiratory gated,
35% duty cycle (~ 126 s)

Department of Radiology and Nuclear Medicine
University of Twente

Elastic respiratory and cardiac motion

Dual gating of the heart has the potential of allowing the imaging of Atherosclerotic plaque.



Hong, et al “Elastic Motion Correction for Cardiac PET Studies” IEEE Medical Imaging Conference, Seoul Korea, 2013

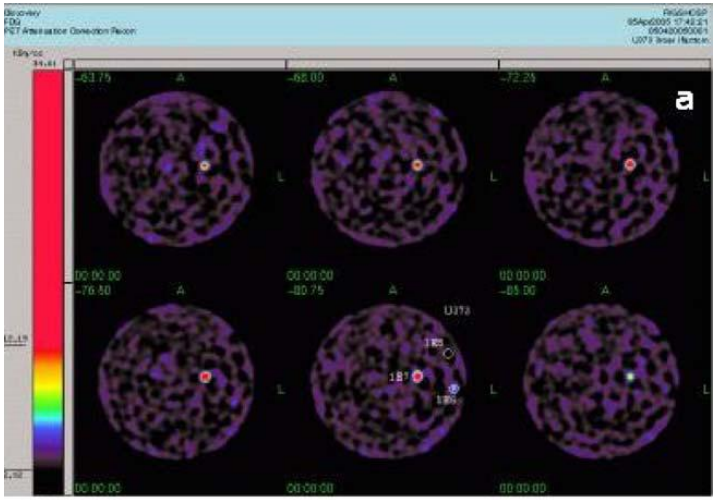
Limits of Detectability

Fischer incubated cells (SCLC, glioblastoma) in FDG and then scanned in a cylinder containing 4.1 MBq/cc in the background. The tube with 10^7 cells is visible. (Scanned with GE Discovery)

The Fischer experiment concludes that the limit of detection is ~10^7.

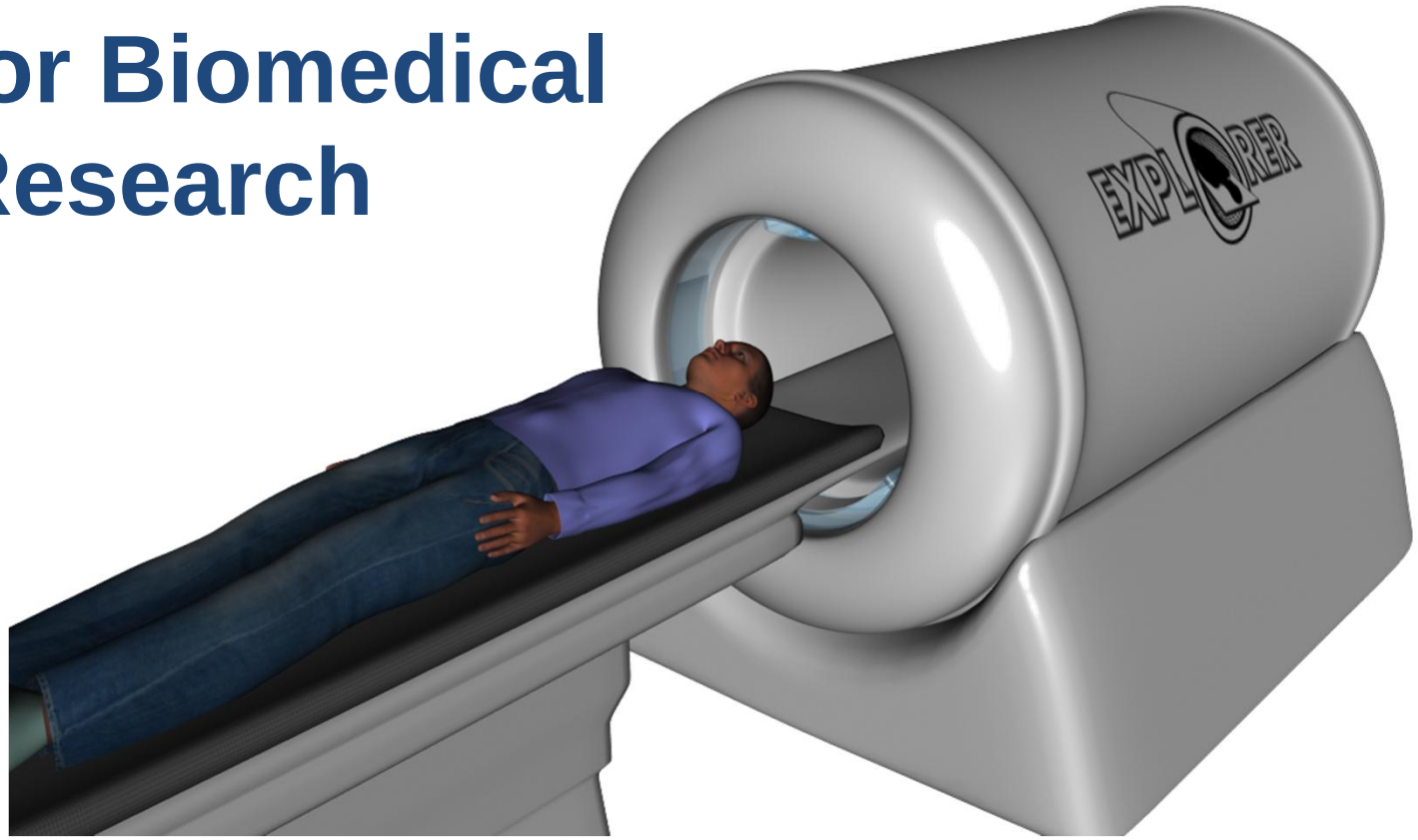
10^6 cells make a tumor of approximately 1 mm diameter.

A 5 mm lesion is approximately 25 x 10^6 cells or 2.5 times larger than the Fischer experiment with the detection of 10^7 cells.



Fischer; "How few cancer cells can be detected by positron emission tomography? A frequent question addressed by an in vitro study" Eur J Nucl Med Mol Imaging (2006) 33:697–702

EXPLORER: A Total-Body PET Scanner for Biomedical Research



EXPLORER.ucdavis.edu

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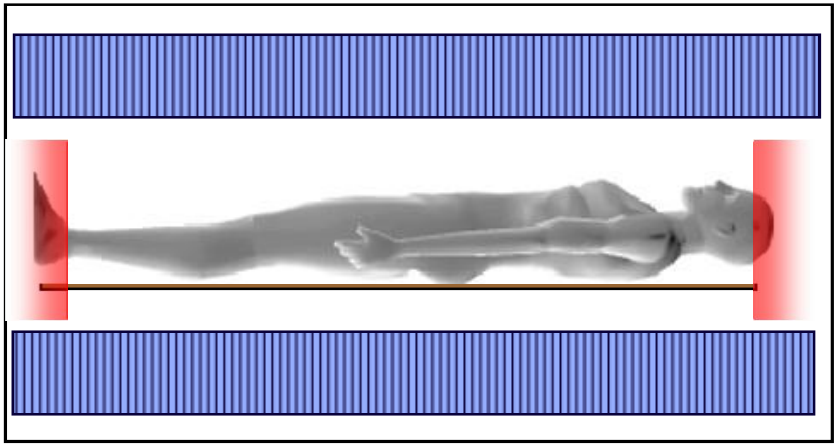
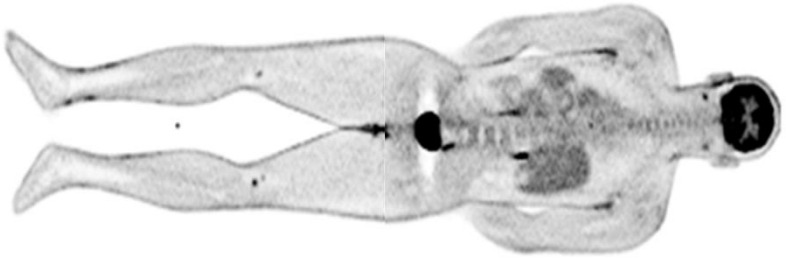
Penn

Total-Body PET: Maximizing Sensitivity

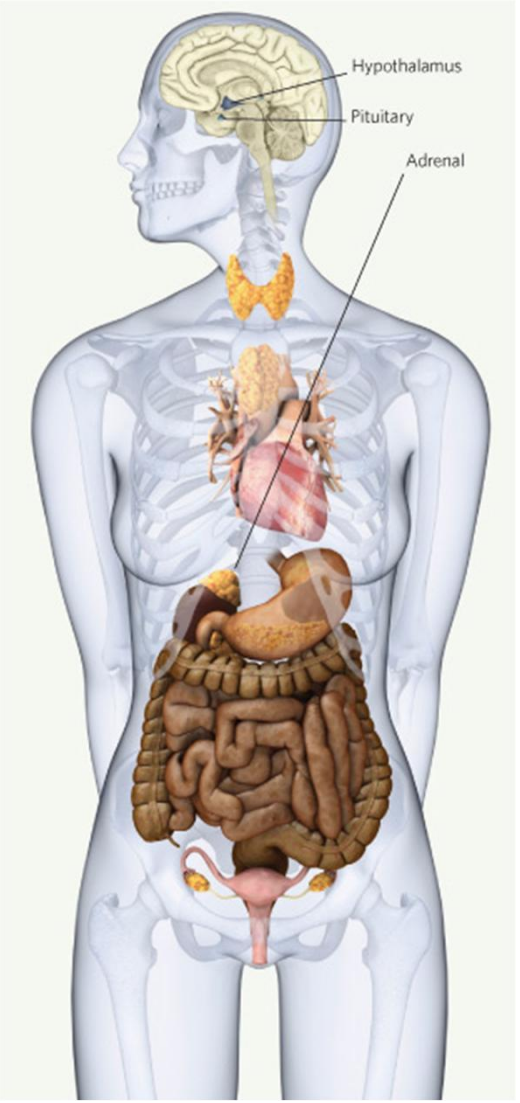
- x40 gain NEC for total-body imaging!
- x4-5 gain in NEC for single organ imaging
- Whole-body kinetics
  - All tissues/organs simultaneously
  - Better temporal resolution





Applications

- **Systemic disease and therapies:**
  - Cancer: Ultra-staging and micrometastasis
  - Inflammation
  - Infection
  - Cellular therapy and trafficking
  - Mind-body interactions
- **Total body pharmacokinetics**
  - Drug development
  - Toxicology
  - Biomarker discovery
- **Low dose opens up new populations:**
  - Expanded use in pediatrics
  - Use in chronic disease
  - Studies of normal biology



VP-PET Insert Prototype Integrated in a PET/CT

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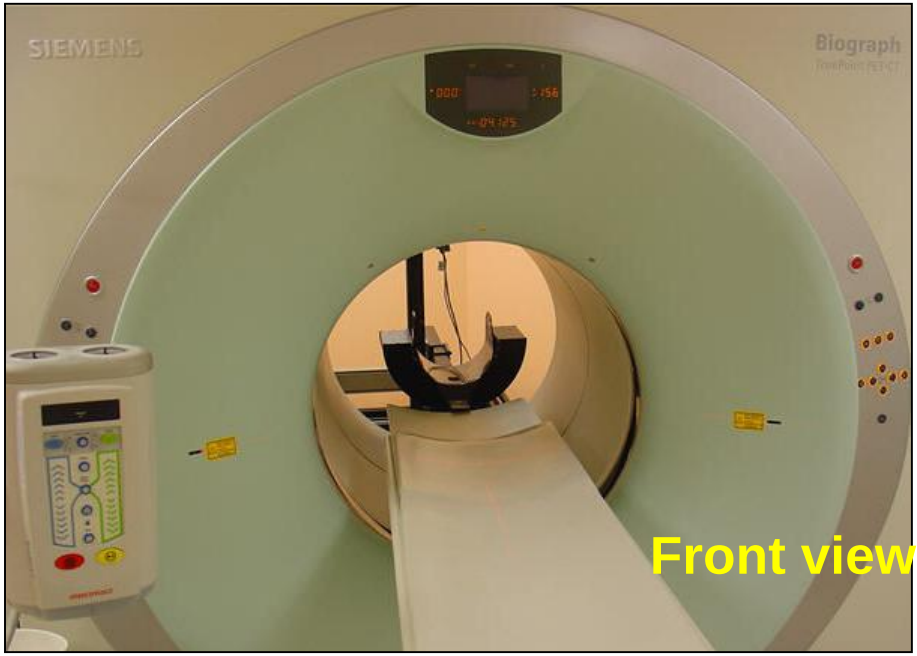
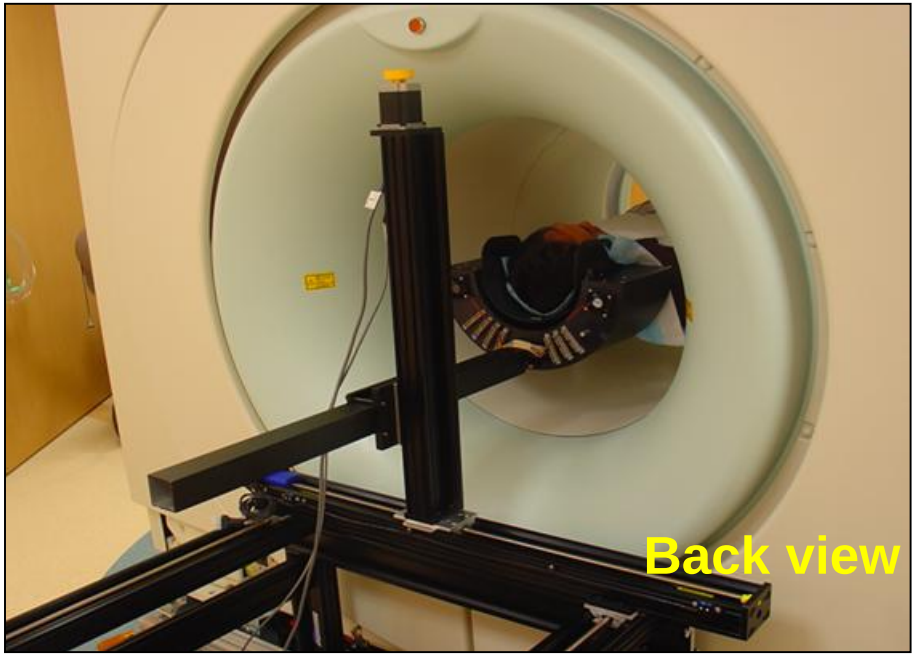




Siemens Biograph 40 PET/CT : 4 detector rings, 13x13 LSO/block, 4x4x20 mm^3 crystal
Prototype VP-PET insert: 28 modules in 2 half-rings, 13x13 LSO/block, 2x2x5 mm^3 crystal
Positioning: concentric to the scanner rings, supported by a 3D linear stage
Imaging FOV: reduced from ~21 cm to 16 cm axially (central 7 cm has higher resolution)

Washington
WASHINGTON UNIVERSITY IN ST LOUIS
MIR Mallinckrodt Institute of Radiology

Courtesy of Prof. Yuan-Chuan Tai

4D Reconstruction of K_i images

Whole body dynamic imaging of K_i has the potential to improve quantitation compared to SUV.

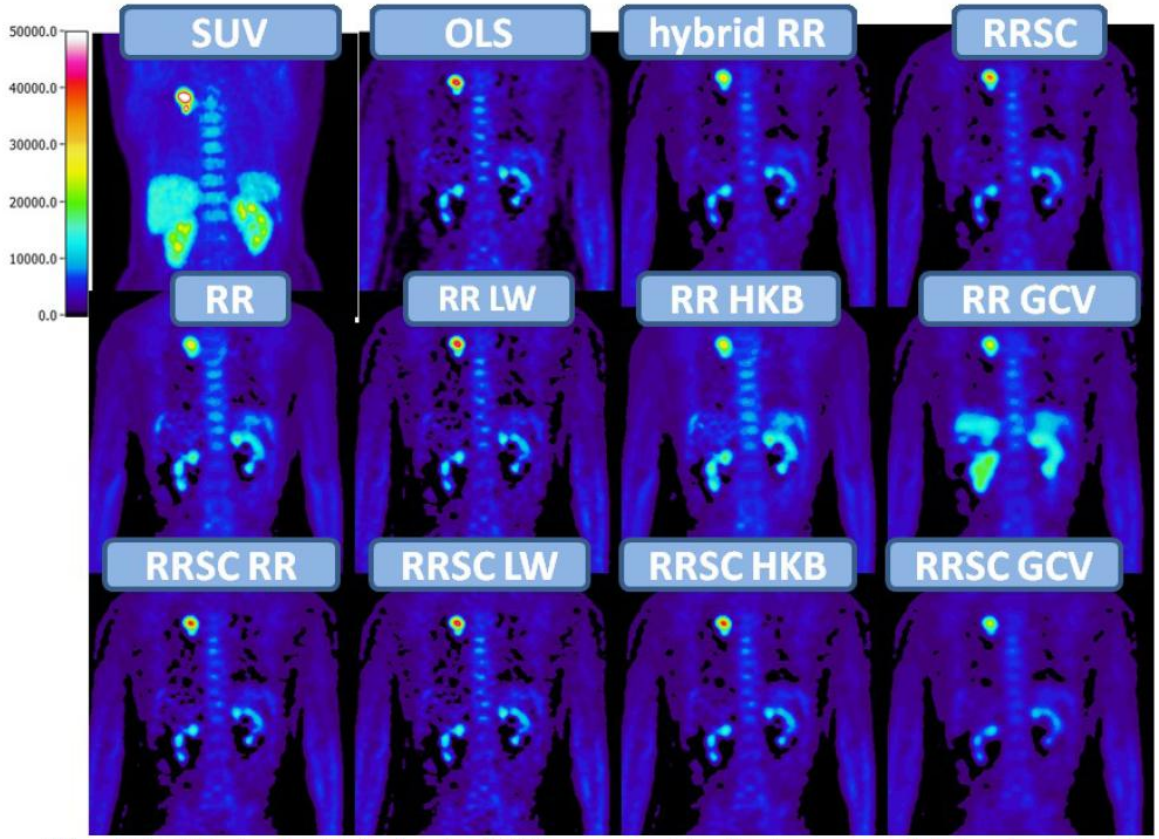


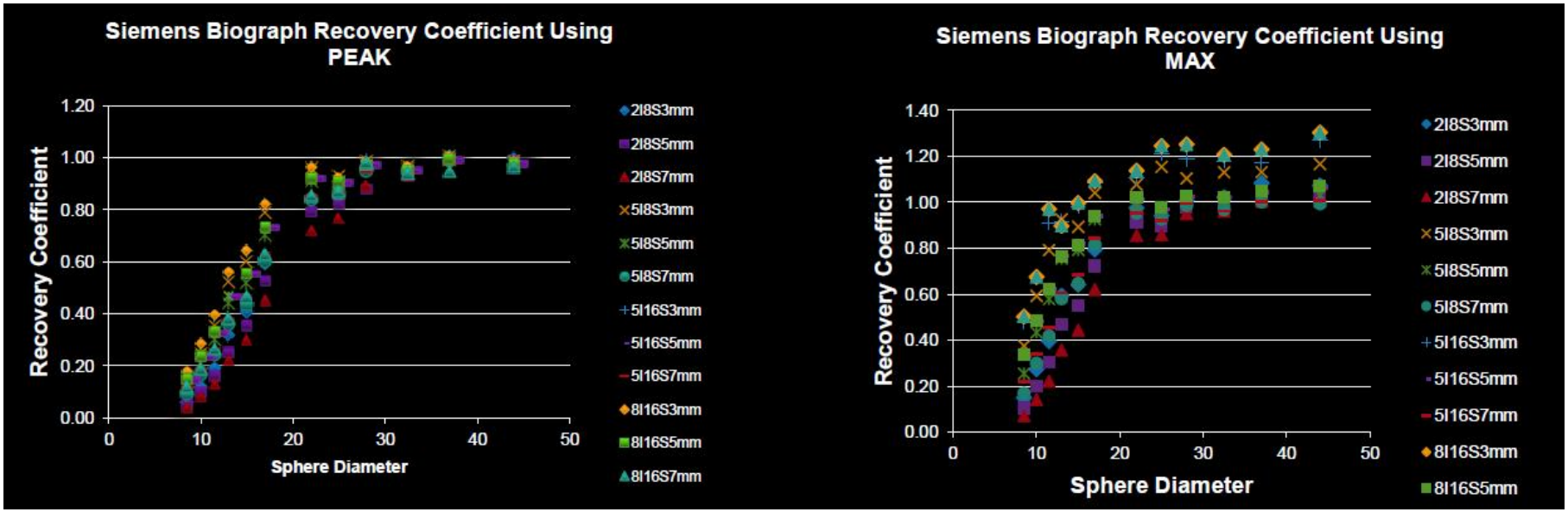
Fig. 10. Clinical whole body PET parametric K_i images, obtained with GE Discovery RX scanner, compared against SUV image

Karakatsanis, N; et al; "Enhanced Whole-body PET Parametric Imaging Using Hybrid Regression and Thresholding Driven by Kinetic Correlations" *IEEE Medical Imaging Conference*, 2012

Reconstruction Harmonization

Harmonized PET Reconstructions for Cancer Clinical Trials

Sunderland JJ [1], Kinahan PE [2], Karp JS [3], Boellaard R [4], Byrd D [2], Scheuermann J [3], Panetta J [3], Sensoy L [1], Casey MW [5], Stearns CW [6], Shao L [7], Clarke BN [8]
University of Iowa [1], University of Washington [2], University of Pennsylvania [3], VU University, Netherlands [4], Siemens Molecular Imaging [5], GE Healthcare [6], Philips Healthcare [7], Society of Nuclear Medicine and Molecular Imaging Clinical Trials Network [8]



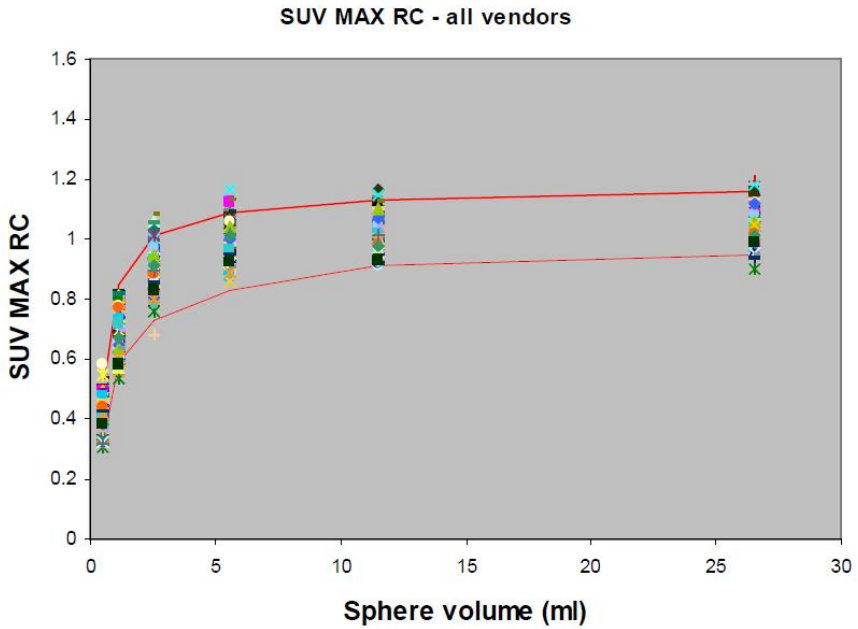
SUV_{PEAK} Specifies the maximum value from a 1 cm diameter sphere convolved with the image. SUV_{MAX} simply picks the maximum pixel from the image using the user specified filter.

Harmonization can be achieved by selecting the an appropriate filter to match the reconstruction.

Reconstruction Standardization

FDG PET and PET/CT: EANM Procedure Guidelines for Tumour PET Imaging: version 1.0

Eur.J.Nucl.Med.Mol.Imag. 2010



Radiation Treatment planning with PET

In the US, PET usage increased from 38% in 2006 to 86% in 2012

- **Target volume selection – Identify metastatic involvement.**
- **Target volume involvement – GTV may be changed with respect to CT.**
- **Determining the presence of hypoxia - Dose escalation.**
- **Treatment monitoring**

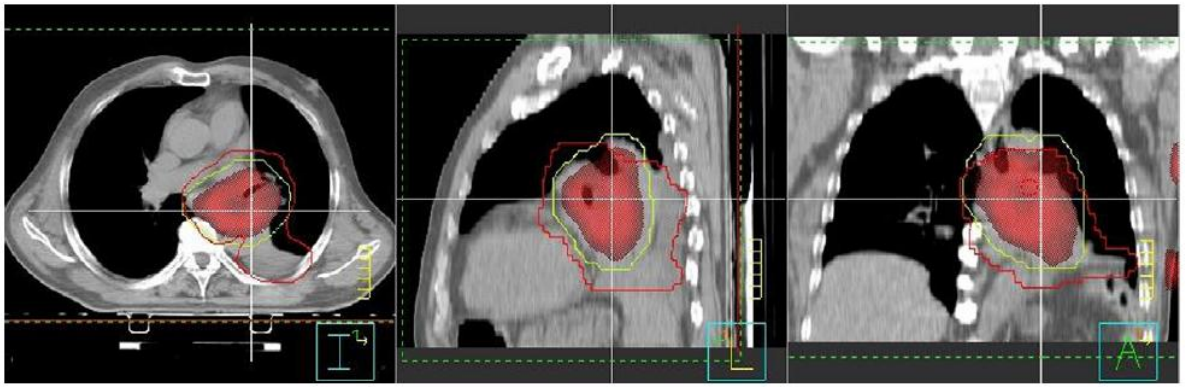


Fig. 2. Radiotherapy planning using CT and PET derived 3D information: the yellow line shows the GTV as derived form PET plus an 8 mm expansion; the red line represents the CT-derived GTV + 8 mm expansion. Please note: (a) the general shrinkage of the GTV using PET and (b) the missing part of the GTV using CT (red line) in the sagittal view (image in the middle) as compared to the PET-derived GTV (yellow line) still containing tumor. Yellow line, GTV (derived from FDG-PET) + 8 mm expansion. Red line, GTV (derived from CT) + 8 mm expansion.

D. De Ruysscher, C.-M. Kirsch / Radiotherapy and Oncology 96 (2010) 335–338

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Conclusions

For PET to move into new clinical applications, we need carefully examine the limitations by correlating histopathological evidence with the imaging.

Improvements in lesion detectability can be achieved through improvements in sensitivity, time resolution and spatial resolution.

We need to explore radical changes rather than incremental improvements.

We need to go beyond conventional static imaging.

Motion correction offers the potential to improve the contrast of lesions in the lung and potentially enable atherosclerosis.

Harmonization of reconstruction (recovery) can allow the pooling of multi-site data for greater statistical power.

PET more changes the management of radiation treatment planning.

Thank you!

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