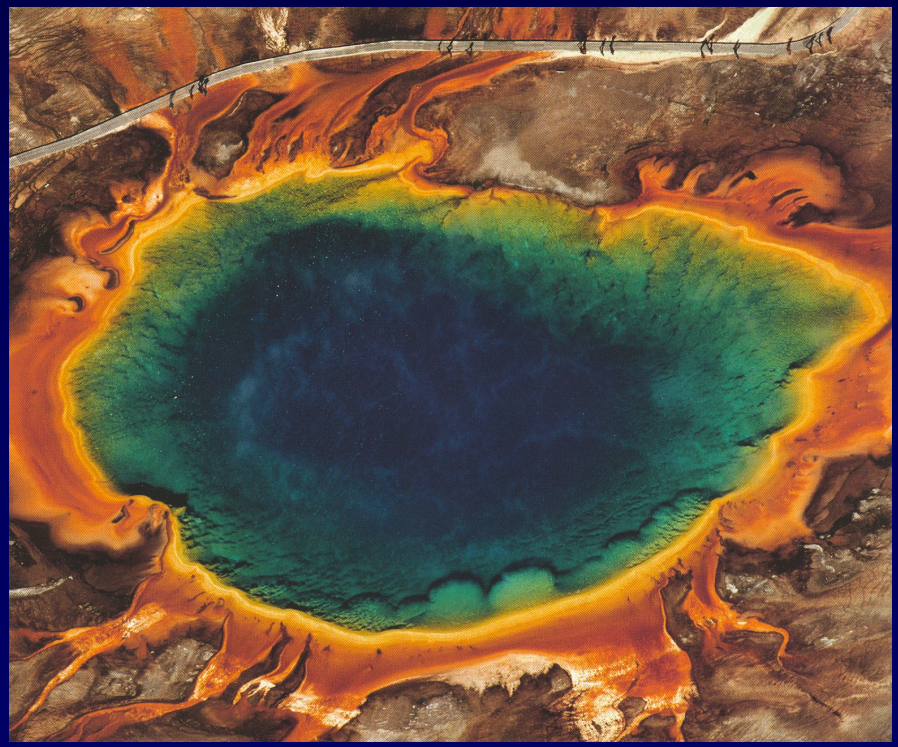
Current and Future Use of PET-CT in Breast Cancer

DBCG Thirty Years Anniversary
May 22 – 23 2008

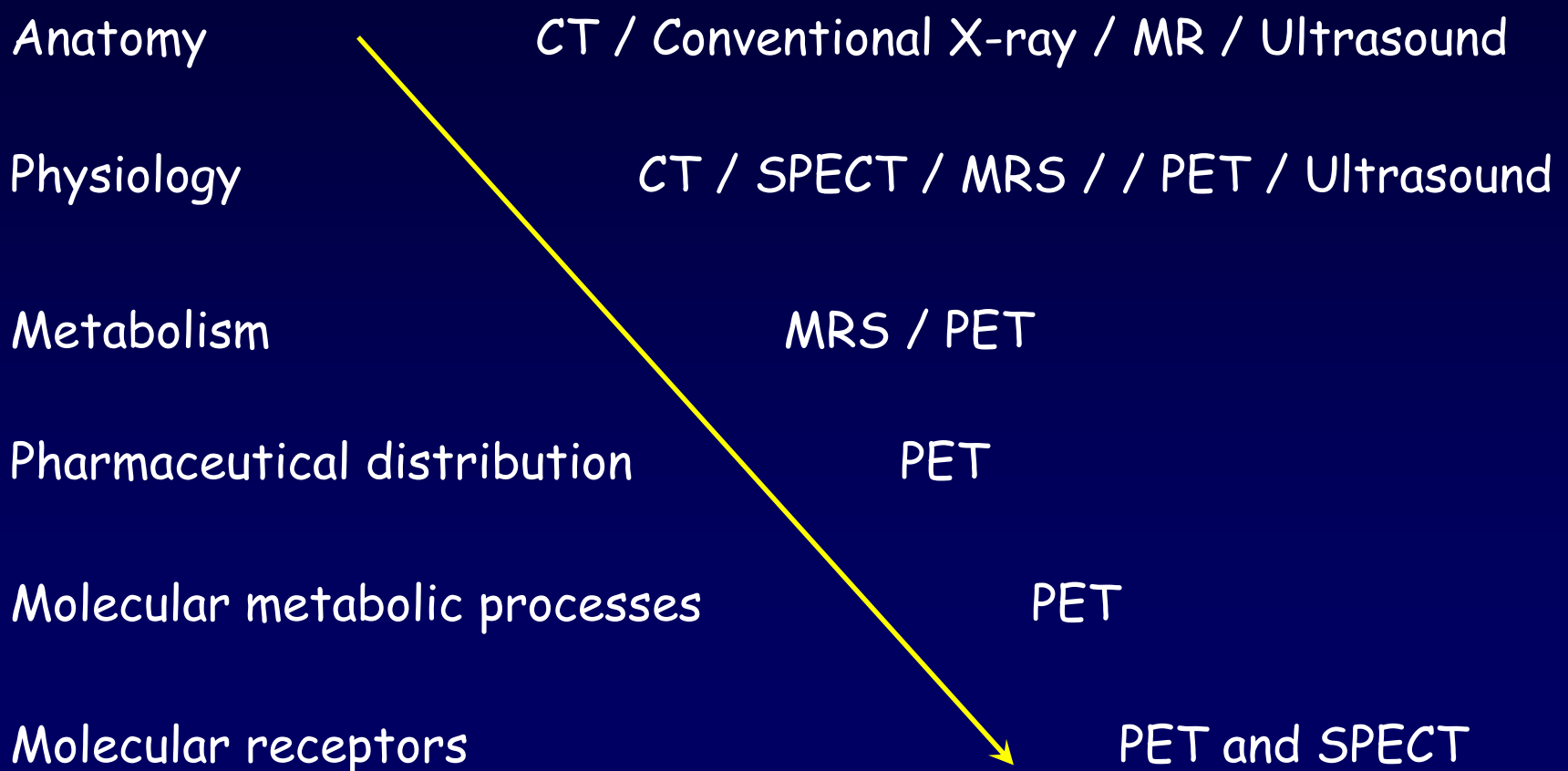
Dept. of Clinical Physiology
Hillerød Hospital

Bent Kristensen



Grand Prismatic Spring, Yellowstone National Park, USA

Diagnostic Imaging in Clinical Medicine



Some Facts about Positron Emission Tomography

- An advanced diagnostic imaging technology using radioisotopes
- Produces specific physical signals "easy" to understand (at least for physicists!) and convert to images
- The spatial resolution approaches 2-3 mm

  Scanners for animal studies: 1-2 mm
  Clinical PET-CT scanners: 5-8 mm
- Depending upon radiolabeled tracer a large number of biochemical, physiological, and pharmacological processes can be determined *in vivo* at picomolar concentrations
- The technology and tracer development are steadily advancing

Production of Positron Emitters

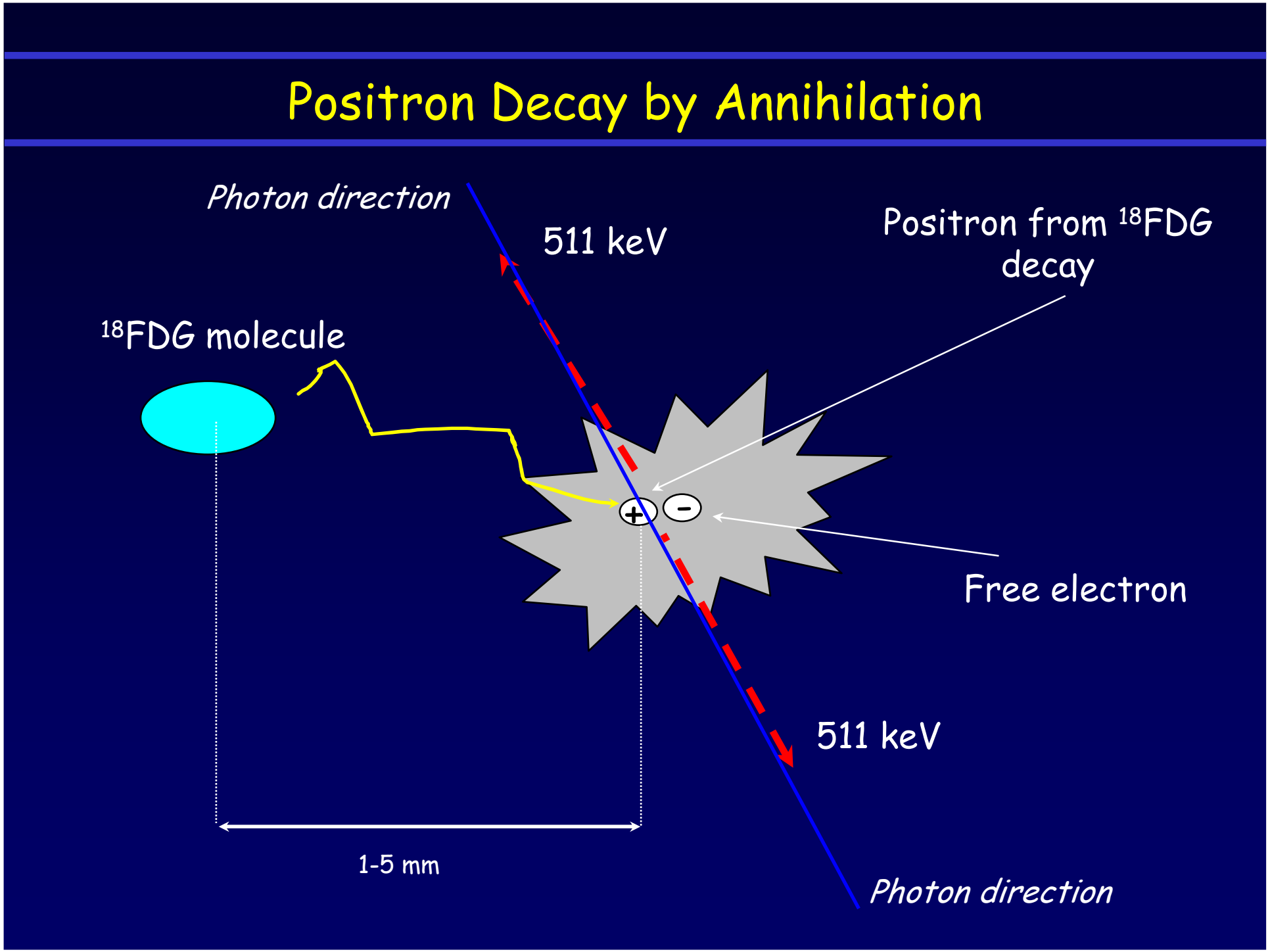
The cyclotron at Rigshospitalet

Radiochemistry and ^{18}Fluor-deoxy-glucose production

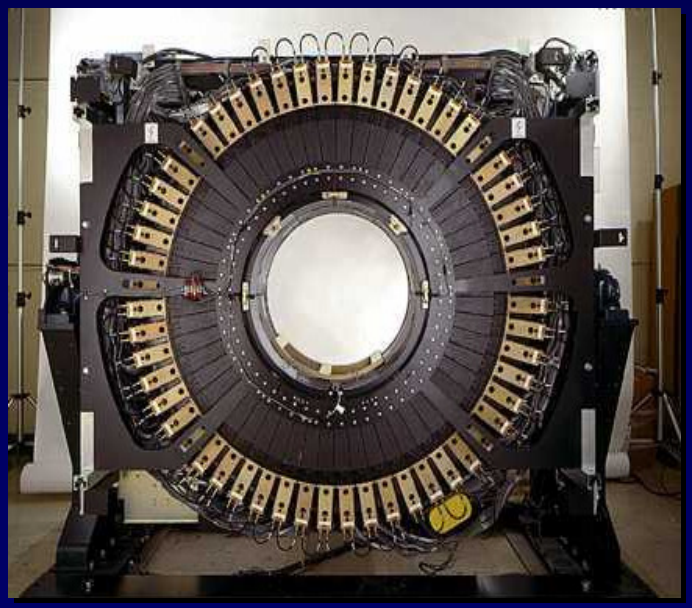
Some Positron Emitters Used in Medical Imaging

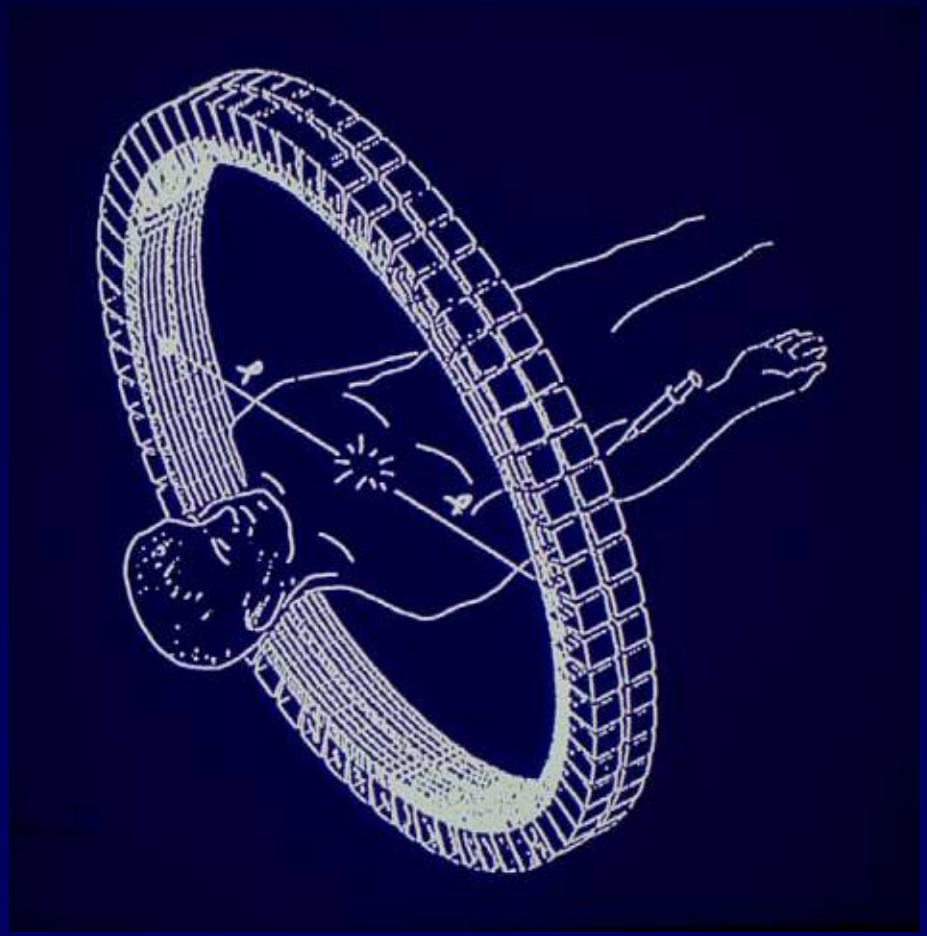
Radioisotope	Half life in minuttes
^{18}F	109.8
^{13}N	20.4
^{11}C	9.96
^{15}O	2.03

Positron Decay by Annihilation



The Dedicated Whole Body PET-CT scanner



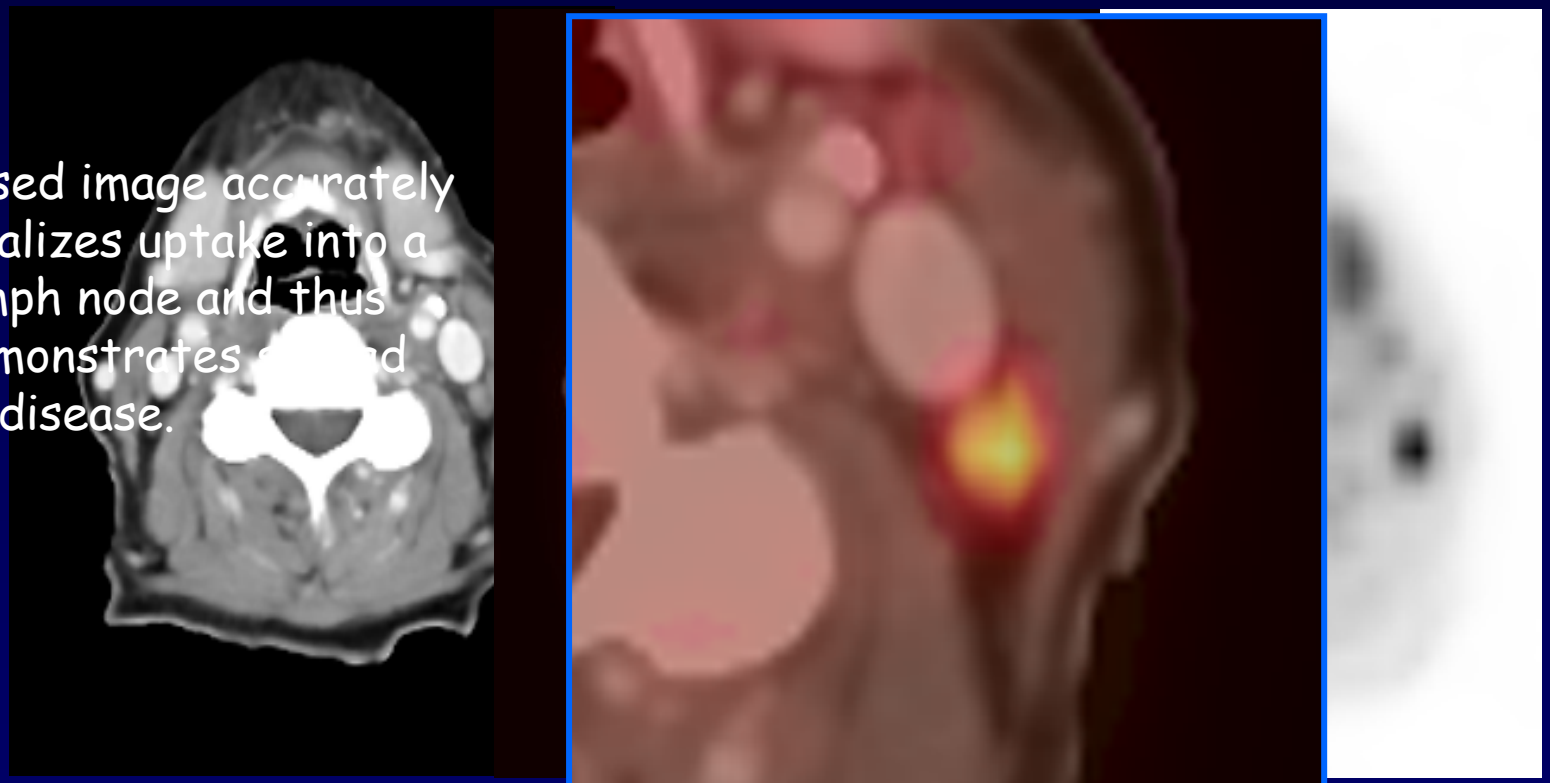


Discovery LS Plus PET-CT

Why Combine Morphology + Function?

- to image different aspects of disease
- to identify tracer uptake
- to simplify the image interpretation
- to give added value to CT and PET

Fused image accurately localizes uptake into a lymph node and thus demonstrates spread of disease.



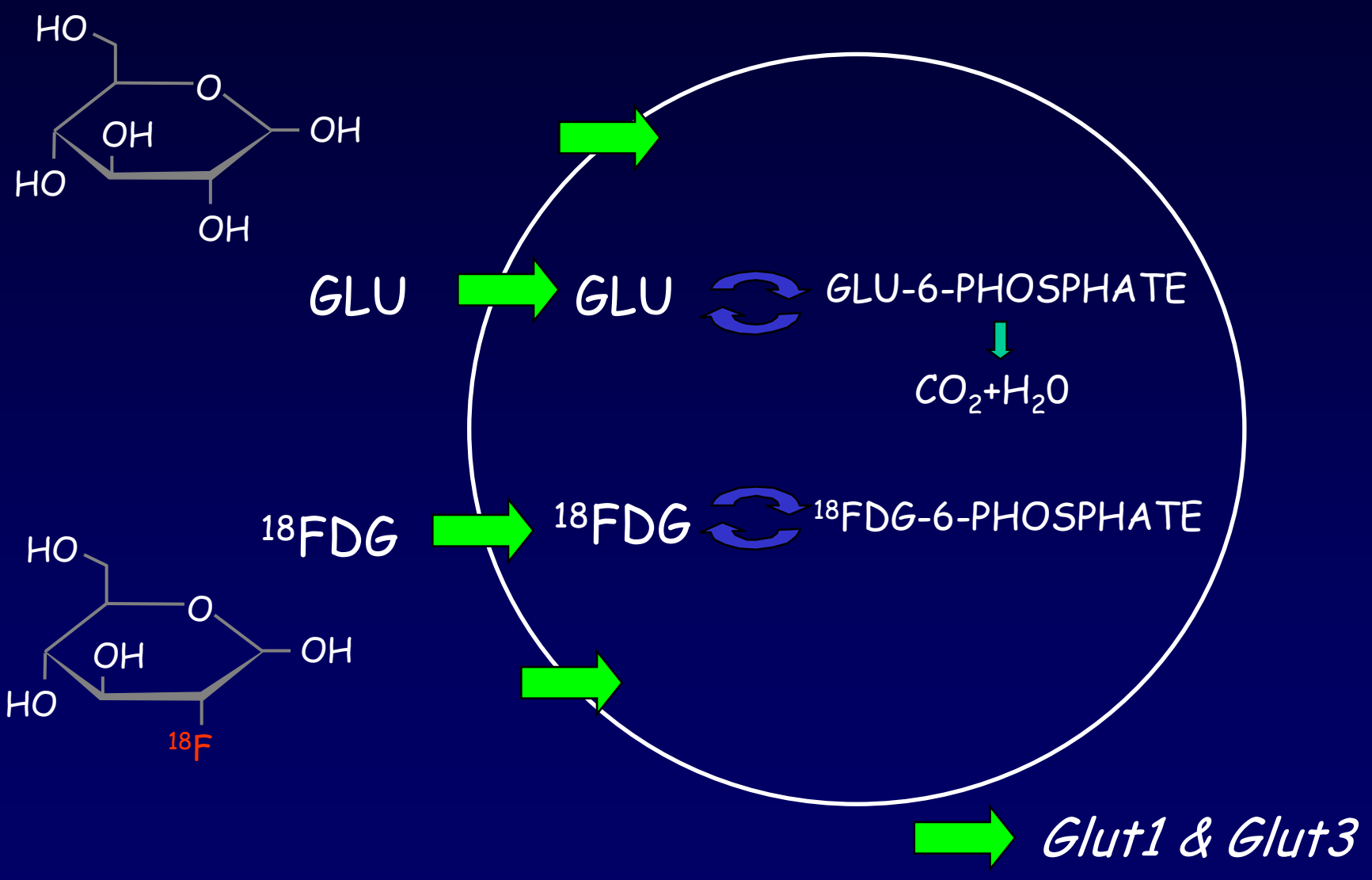
CT (anatomy) PET-CT fusion PET (function)

Courtesy of David Townsend, Ph.D.
University of Tennessee Medical Center

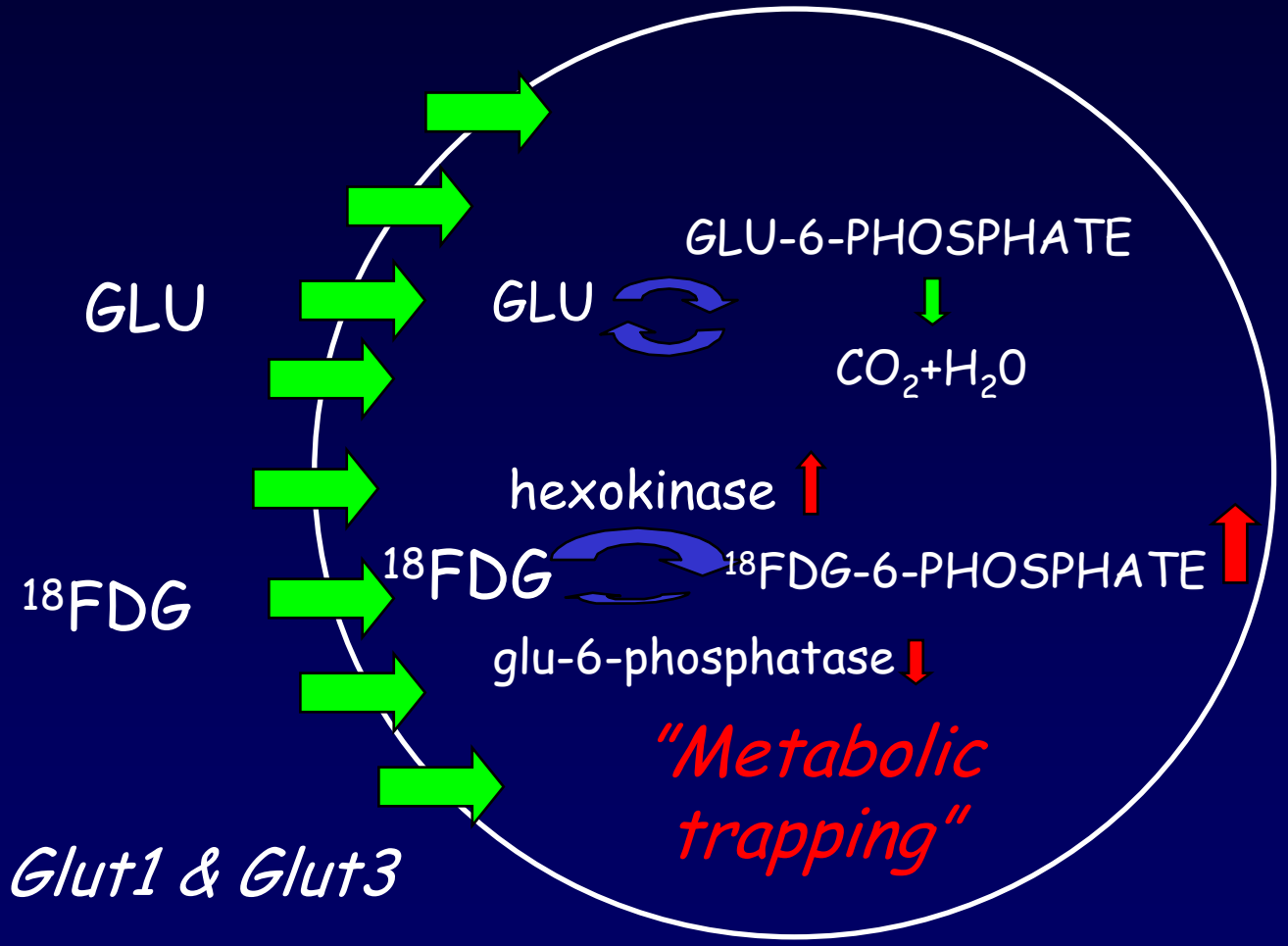
Tracers Tested in Human Breast Cancer Imaging

^{18}F-deoxyglucose (^{18}FDG)	Glucose metabolism
$H_2^{15}O$	Blood flow
^{18}F-Fluoromisonidazole	Tissue hypoxia
^{18}F-fluoro-oestradiol (^{18}FES)	Oestrogen receptor expression
^{11}C-Methionine	Amino acid transport and metabolism
^{18}F-Thymidine/^{11}C-Thymidine	Cellular proliferation
^{18}F-Fluoride	Bone formation

Glucose and ^{18}FDG Transportation into Normal Cells



Glucose and ^{18}FDG Transportation into Cancer Cells



Use of PET in Primary Breast Cancer

PET and Primary Tumour Diagnosis 1/2

TNM	Size (cm)	Number	Sensitivity (%)
pTis		12	42
pT1	< 2.0	44	68
pT1a	< 0.5	4	25
pT1b	> 0.5 – 1.0	8	25
pT1c	> 1.0 – 2.0	32	84
pT2	> 2.0 – 5.0	62	92
	> 2.0 – 3.0	33	94
	> 3.0 – 4.0	15	87
	> 4.0 – 5.0	14	93
pT3	> 5.0	14	100

Avril. J Clin Oncol 2000; 18: 3495

PET and Primary Tumour Diagnosis 2/2

- Sensitivity varies in the range of 84% to 93%

  Overall specificity is relatively high (85-100%). False positives do occur in some benign inflammatory conditions and fibroadenoma

- Major factors explaining the varying ^{18}FDG uptake are:

  1) Differences in tumour size

  2) Histopathology (infiltrating ductal adenocarcinoma has higher levels of ^{18}FDG uptake than lobular adenocarcinoma)

  3) Tumour growth pattern (nodular vs. diffuse)

  4) Differences in proliferation (monoclonal antibody MIB-1)

Avril. J Nucl Med 2001; 42: 9

PET and Axillary Lymph Node Staging 1/2

Studies using axillary lymph node dissection as reference

Study	No. of Patients	Sensitivity (%)	Specificity (%)	Positive Predictive value (%)	Negative Predictive value (%)	Prevalence (%)
Smith. Ann Surg 1998, 228: 220	50	88	97	95	92	42
Greco. J Natl Cancer Inst 2001; 93: 630	167	94	86	84	95	43
Schirmeister. Eur J Nucl Med 2001; 28: 351	85	79	92	82	79	40
Yutani. J Comput Assist Tomogr 2000; 24: 274	38	50	100	100	73	42
Adler. Radiology 1997; 203: 323	50	95	66	63	95	38
Van der Hoeven. Ann Surg 2002;236: 619	23	57	100	100	60	61
Lovrics. Breast Cancer Res Treat 2002; 76: S129	74	46	98	86	89	-
Wahl. J Clin Oncol 2004; 22: 277	360	61	80	62	99	-

PET and Axillary Lymph Node Staging 2/2

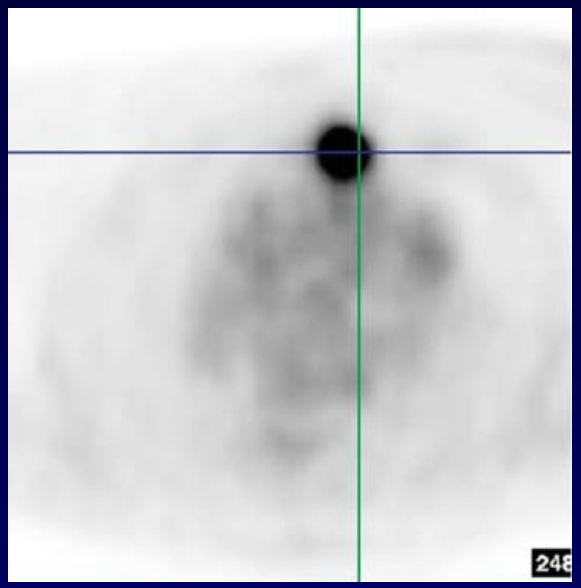
Diagnostic accuracy of ^{18}FDG-PET vs.
Sentinel Lymph Node Biopsy (SLNB) in 236 patients

Measure	^{18}FDG-PET	SLNB
Sensitivity (%)	37	96
Specificity (%)	96	100
Positive predictive value (%)	88	100
Negative predictive value (%)	66	97
Overall accuracy (%)	70	98

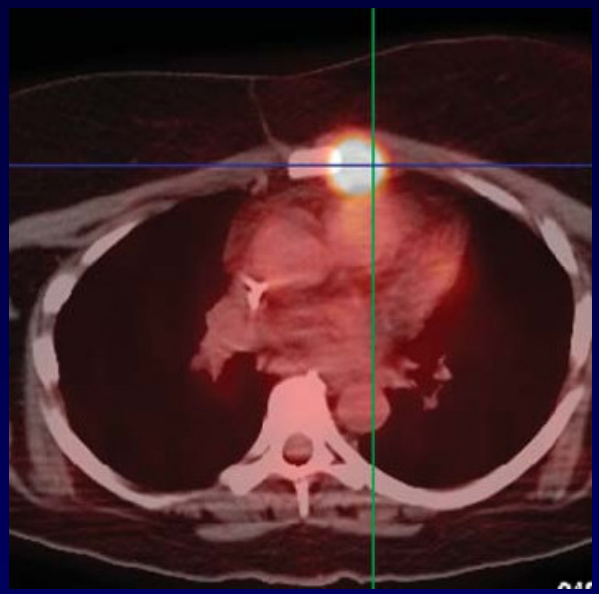
Veronesi. Ann Oncol 2007; 18: 473

Mediastinal Lymph Node Staging in Breast Cancer

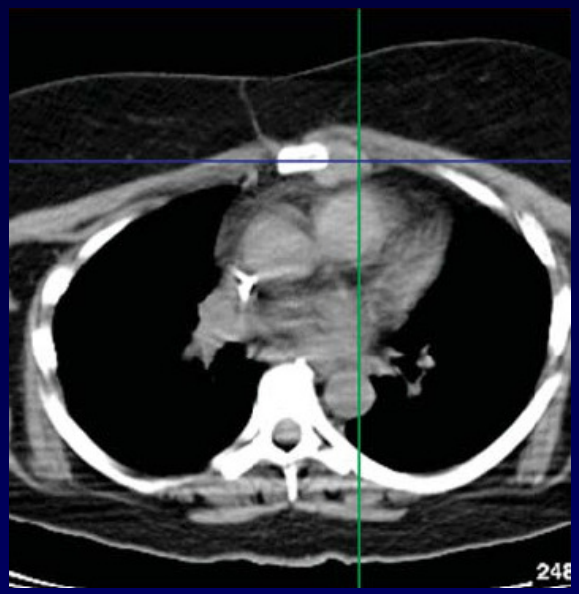
^{18}FDG-PET



PET-CT fusion



CT

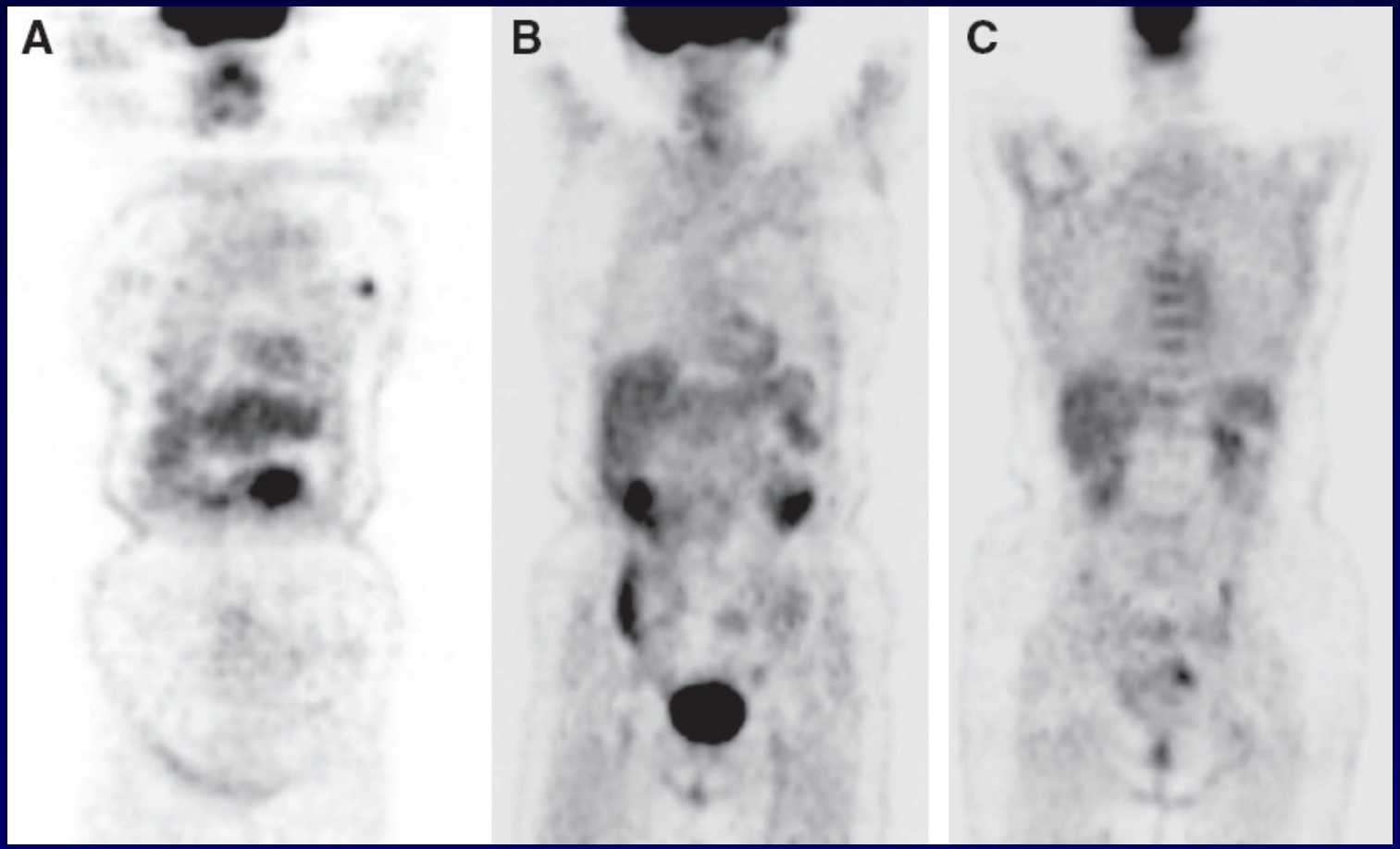


^{18}FDG-PET-CT is superior to CT alone in detection of metastatic mediastinal lymph nodes. Future use?

Eubank. J Clin Oncol 2001; 19: 3516

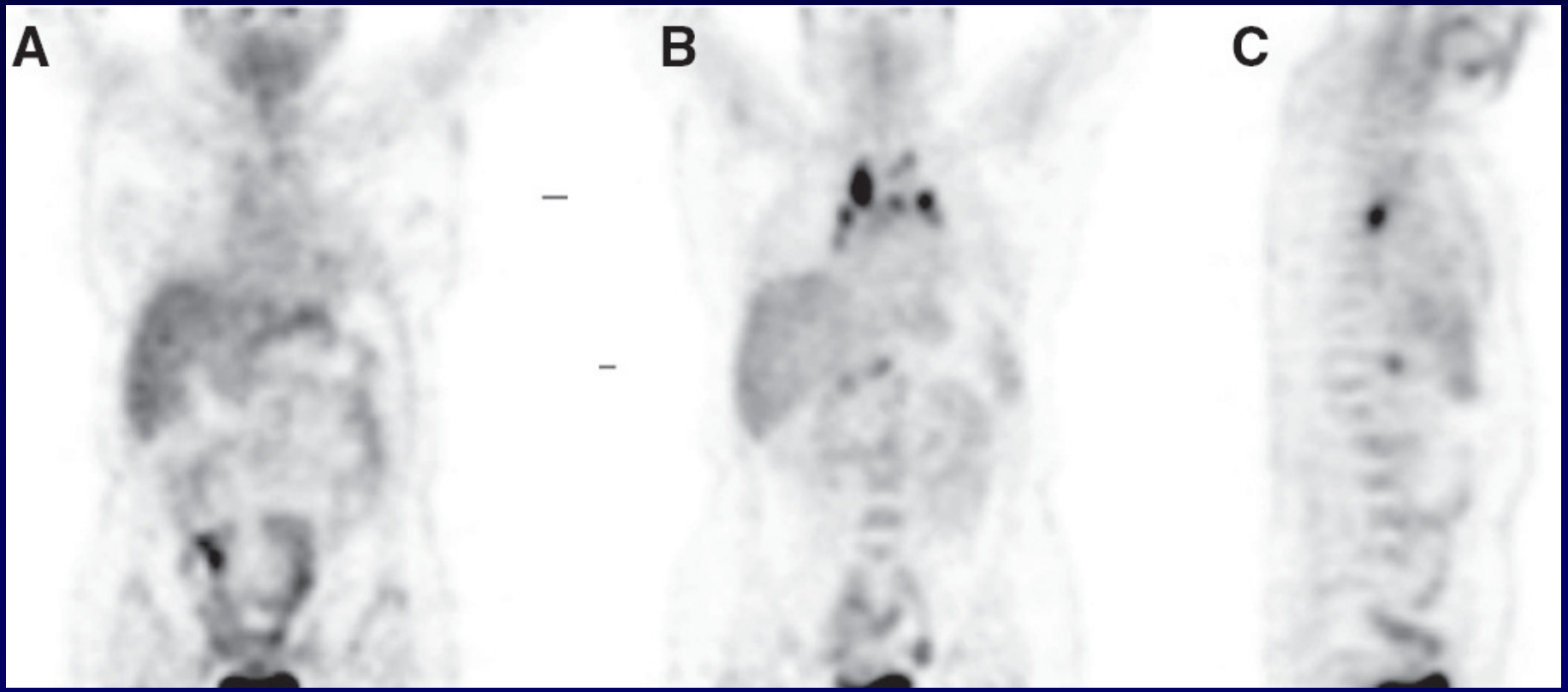
Preoperative Staging with PET 1/3

^{18}FDG uptake in left primary tumour, but not in axillary lymph node with micrometastatic deposit



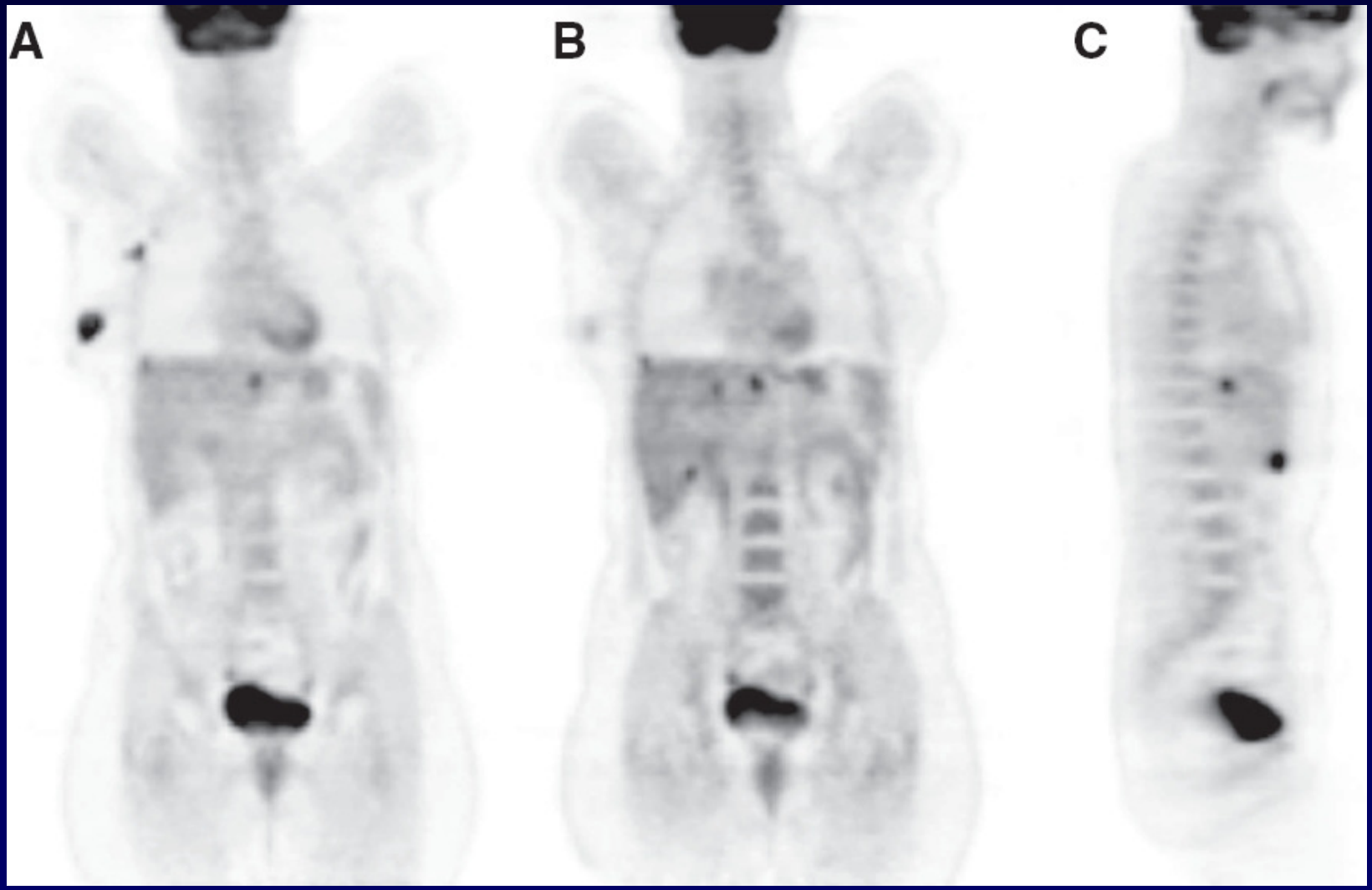
Preoperative Staging with PET 2/3

No ^{18}FDG uptake in left primary breast tumour, but uptake in mediastinal, hilar, and para-aortic lymph nodes which turned out to contain sarcoidosis



Preoperative Staging with PET 3/3

^{18}FDG uptake in right primary tumour, axillary lymph node, and liver metastases



Current Use of PET-CT in Breast Cancer

- No place in primary tumour diagnosis or lymph node staging at the moment
- Identification of metastatic disease at initial diagnosis in selected patients, e. g.
  - Equivocal findings on conventional imaging
  - Abnormal biochemistry
  - Stage III tumour
- In case of verified or suspected recurrence, e. g.
  - Before aggressive therapy
  - Disease response after therapy
  - Disease extent

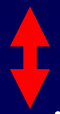
Eubank WB et al. Impact of FDG PET on defining the extent of disease and on the treatment of patients with recurrent or metastatic breast cancer. AJR 2004; 183: 479-86

Isasi CR et al. A meta-analysis of FDG-PET for the evaluation of breast cancer recurrence and metastases. Breast Cancer Res Treat 2005; 90: 105-12

What Will the Future with PET-CT Bring?

Future Use of PET-CT in Breast Cancer

- Dedicated PET-CT Mammography
- Better tailoring of old and new treatments (surgery, endocrine therapy, chemotherapy, radiotherapy)
- Monitoring of treatment with quantitative measures



- Prognostication

Mankoff DA. J Mammary Gland Biol Neoplasia 2006; 11: 125-36

Assessment of Tumour Glucose Use with ^{18}FDG PET

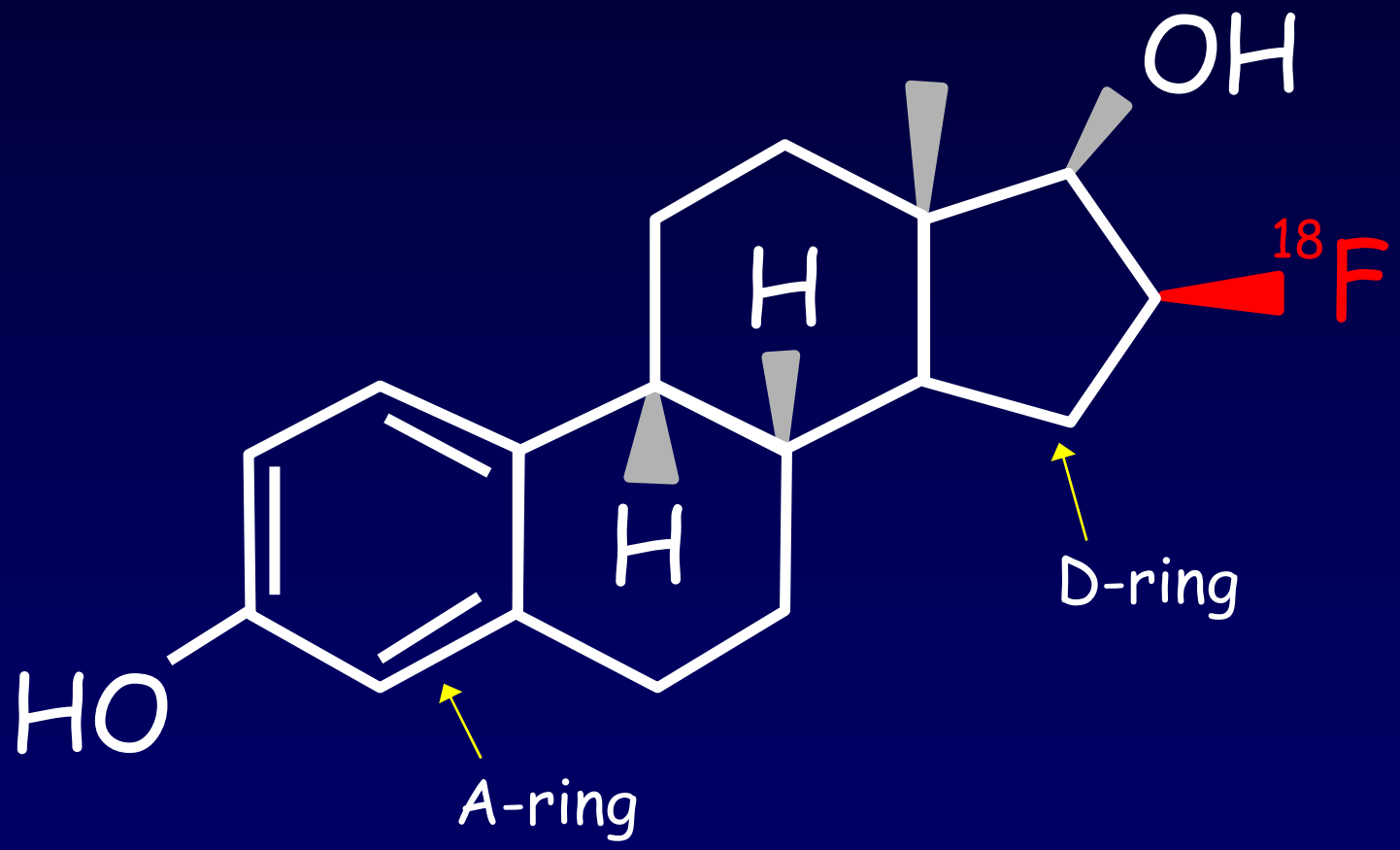
- Standard Uptake Values (SUV) are used

- $$SUV = \frac{\text{Activity Concentration}}{\frac{\text{Injected Dose } ^{18}\text{FDG}}{\text{Body Weight}}}$$

- It is necessary to follow a strict protocol to avoid serious errors:

Paravenous injection; residual activity in syringe:	↓ SUV
No decay correction of injected activity:	↓ SUV
Variable time between injection and imaging:	↑ SUV with longer time
Incorrect cross-calibration of scanner and dose calibrator:	↓↑ SUV

^{18}F-16α-17β-Fluoro-Oestradiol (^{18}FES)



^{18}FES & ^{18}FDG PET in Metastatic Breast Cancer 1/3

- 47 patients with oestrogen receptor positive primary tumours
- Predominantly bone metastases and soft tissue metastases (3 with visceral metastases only)
- Treated with aromatase inhibitors (68% received prior tamoxifen)
- Response evaluated blindly (CT, bone scan, MRI, PET, tumour markers, and symptoms of pain)
- 11 patients had an objective response. Quantitative, but not qualitative ^{18}FES uptake was significantly associated with response
- None of 10 patients with HER2 overexpressing tumours responded

Linden. J Clin Oncol 2006; 24: 2793

^{18}FES & ^{18}FDG PET in Metastatic Breast Cancer 2/3

Qualitative ^{18}FES-PET results vs. response

Uptake	Response	Stable Disease	Progressive Disease	Total
FES+	11	16	14	41
FES-	0	2	4	6
Total	11 (23%)	18	18	47

Dichotomized quantative ^{18}FES-PET results vs. response

Result	Responding	No Response (stable and progressive disease)	P value
SUV > 1.5	11 (23%)	21	0.01
SUV $\leq$ 1.5	0	15	
Flux > 0.2	10	14	0.005
Flux $\leq$ 0.2	0	14	

Linden. J Clin Oncol 2006; 24: 2793

^{18}FES & ^{18}FDG PET in Metastatic Breast Cancer 3/3

Pretreatment scans

Posttreatment scan

Patient 1: ER+ metastases

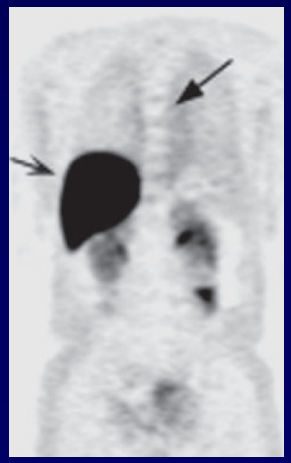
Response at 3 months

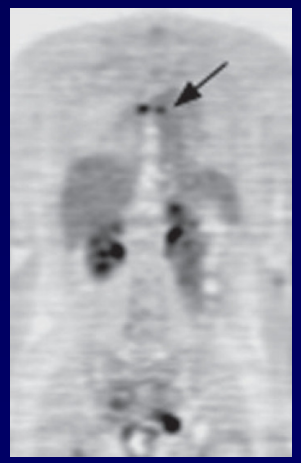
^{18}FES

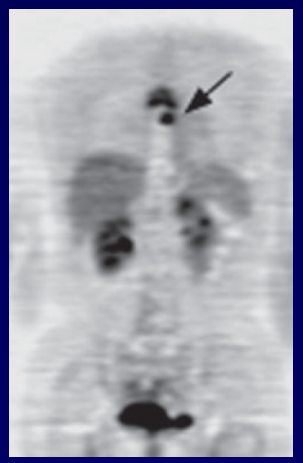
^{18}FDG

^{18}FDG

Patient 2: ER- metastases





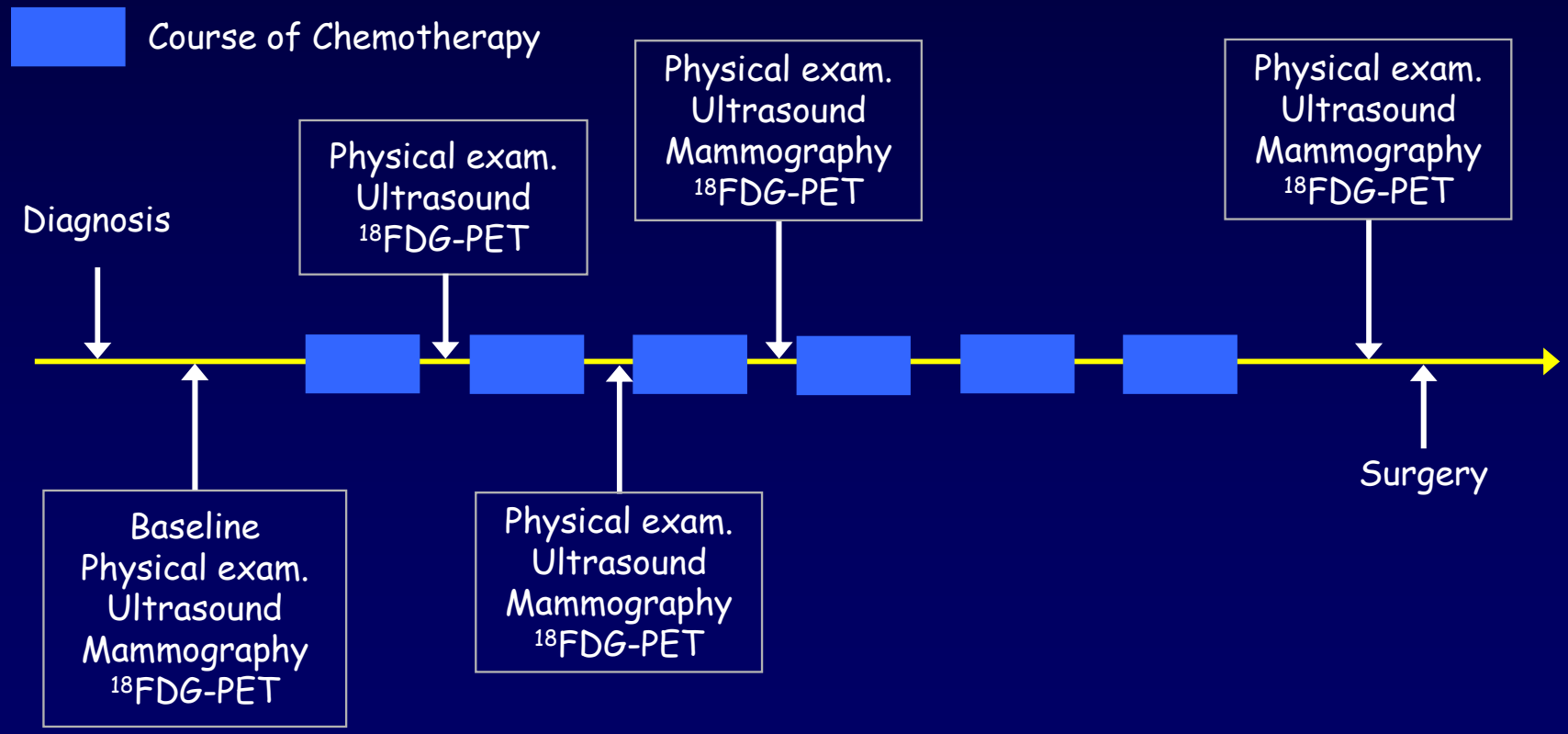


Progressive disease at 6 months

Linden. J Clin Oncol 2006; 24: 2793

Monitoring Response with ^{18}FDG-PET by Neoadjuvant Chemoterapy 1/2

A prospective study with 64 stage II and III breast cancer patients



Rousseau. J Clin Oncol 2006; 24: 5366

Monitoring Response with ^{18}FDG-PET by Neoadjuvant Chemoterapy 2/2

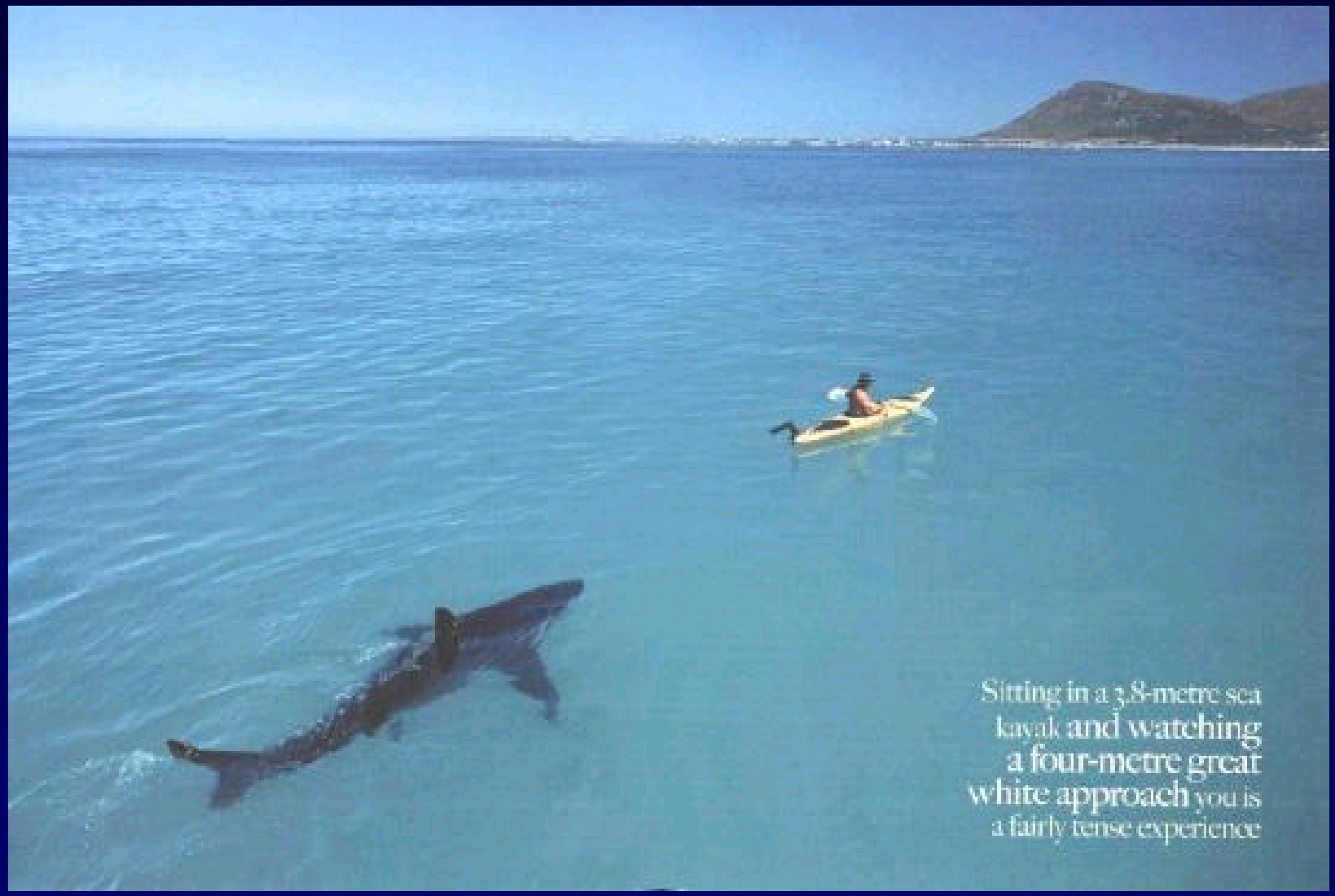
- After surgery gross residual disease was found in 28 patients and minimal residual disease in 36 patients (~ responders)
- SUV decreased to background levels in 34/36 (94%) of responders
- Using 60% of SUV at baseline as cutoff value data showed:

	Course of chemotherapy		
	1	2	3
Sensitivity	61%	89%	88%
Specificity	96%	95%	73%
Neg. predictive value	68%	85%	83%

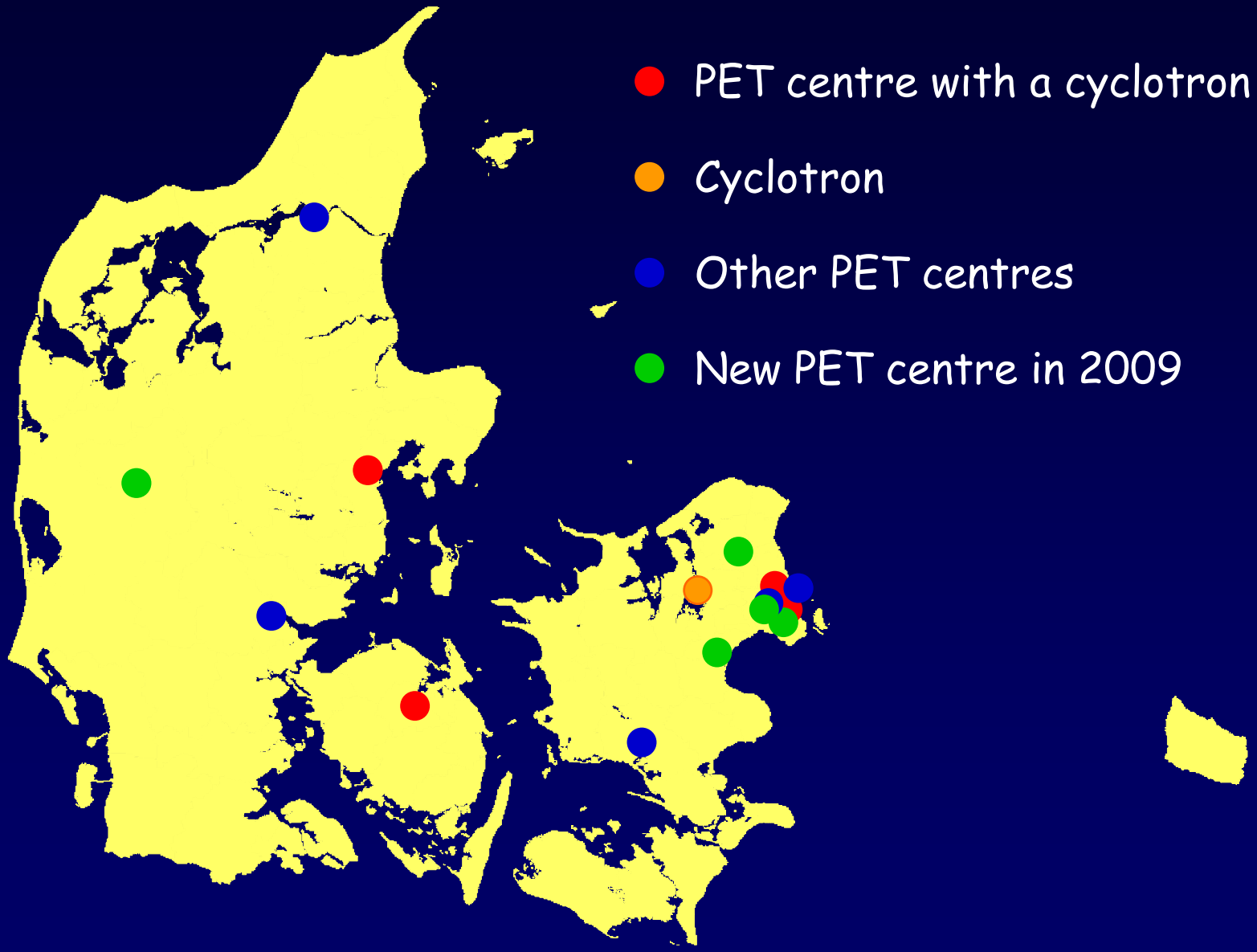
The same parameters with: ultrasound: 64%, 43%, and 55%
Mammography: 31%, 56%, and 45%
after 6 courses of chemotherapy

Rousseau. J Clin Oncol 2006; 24: 5366

With PET You Never Know. Something very Big and Exciting May Suddenly Appear!



The Near Future: PET-CT Scanners in Denmark 2009



Thank you for your attention!