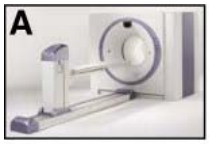
PET Imaging in the Clinic: Predictive and intermediate endpoint biomarkers

Johannes Czernin, MD
Department of Molecular and Medical Pharmacology,
David Geffen School of Medicine at UCLA

Conflict of Interest: Founder: Sofie Biosciences

PET/CT is the best modality for initial and subsequent management decisions in cancer



Biograph
6, 40, 64

Discovery
ST, STE, VCT, RX

Gemini
GXL, TF

>2000 scanners installed in the US;
>2 Mil studies in 2012
Reasonable cost ($1-3 Mil)
Established business model
Cost-effectiveness shown for many cancers
Impact on Management documented (pioneering NOPR work)
Impact on outcome shown in some cancers (MUNICON, PLUS, etc)
6500 publications under PET/CT
17545 publications under FDG
18516 publications under PET cancer
PET/CT with 10-15% higher accuracy than PET or CT alone

One stop shop frequently requires intravenous contrast

CT is indispensable for the planning of all interventions (surgery, biopsy, radiation, etc.; RECIST still standard of care)

IV contrast-enhanced FDG PET/CT is superior to contrast-enhanced CT alone and to unenhanced FDG PET/CT

i) Pfannenberg AC et al. Br J Radiol 2007;80 : 437–445 (mixed population)
ii) Pfannenberg AC et al. Eur J Nucl Med Mol Imaging 2007;34 : 36–44
iii) Tateishi U et al. Eur J Nucl Med Mol Imaging 2007; 34: 1627-1634 (colorectal cancer)

Use of IV contrast material increases lesion detectability (important in FDG negative lesions) *iv) Cantwell et al. J Comput Assist Tomogr 2008; 34: 738-744 (metastatic liver lesions)*

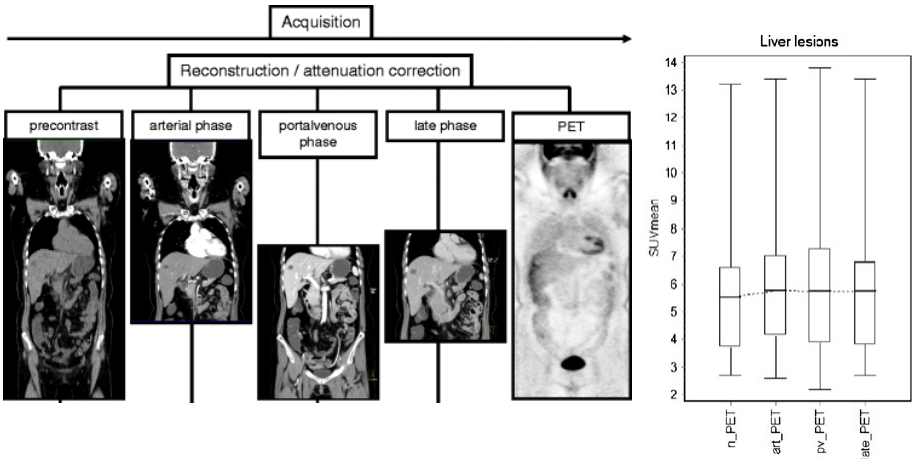
Multiphase contrast protocols are feasible

Oral contrast agents can aid in the evaluation of the GI tract

High attenuation values associated with high-density IV contrast cause attenuation-correction artifacts that are easily recognized

Multiphase contrast protocols

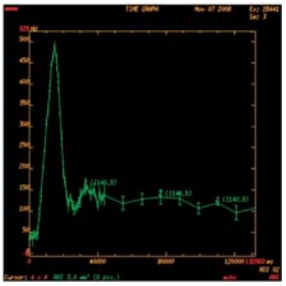
>85% of all PET/CT studies performed with iv contrast at UCLA
Multi-phase contrast in pancreas and liver



Aschoff et al; Eur J Nucl Med Mol Imaging 2012

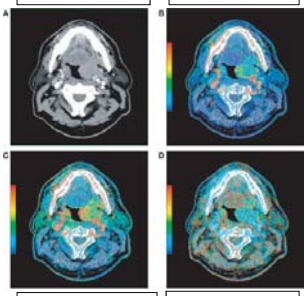
Functional parameters from CT: Quantitative Tumor Perfusion

Arterial input function



>4ml/s to obtain density-time curves (arterial input function; tumor tissue)

Conventional CT | Color map of BF

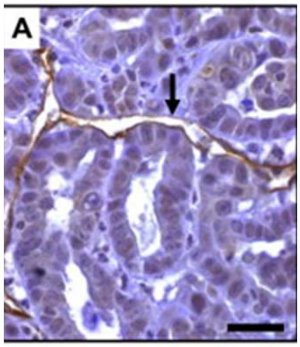


Color map of BV | Transit time

CT BF correlates with micro-vessel density and markers of angiogenesis

Petralia et al; Cancer Imaging; 2010

Efficient drug delivery?

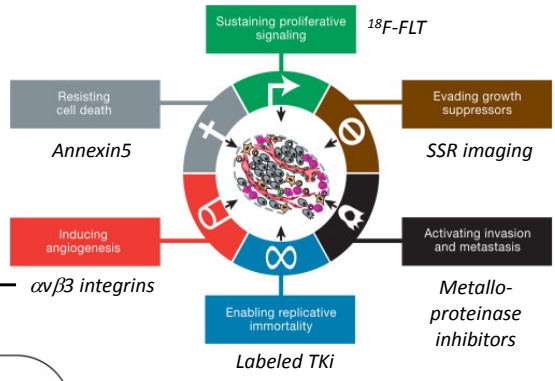


Olive et al; Nature 2009

Tissue texture correlated with hypoxia and GLUT1

Ganeshan B et al. Radiology 2013;266:326-336

The Strength of PET: Imaging the Hallmarks of Cancer; In other words, phenotyping



^{18}F-FLT

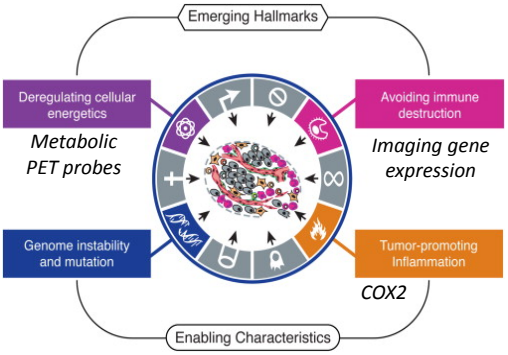
Annexin5

SSR imaging

αvβ3 integrins

Metallo-proteinase inhibitors

Labeled TKi



Metabolic PET probes

Imaging gene expression

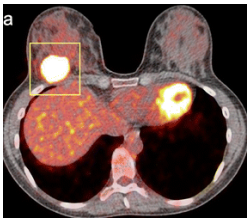
COX2

2000 PET probes and counting..

Adapted from Hanahan and Weinberg; Cell 2011

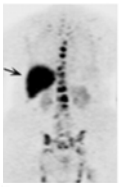
PET biomarker Definition

Koolen et al;
EJNMMI 2012



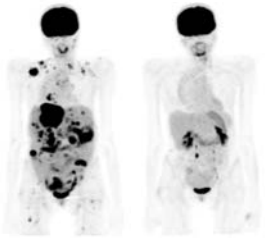
Diagnostic/Phenotypic/ Prognostic Biomarkers
Is the disease present?
What is the phenotype?
What is the prognosis?

Linden et al;
JCO 2007



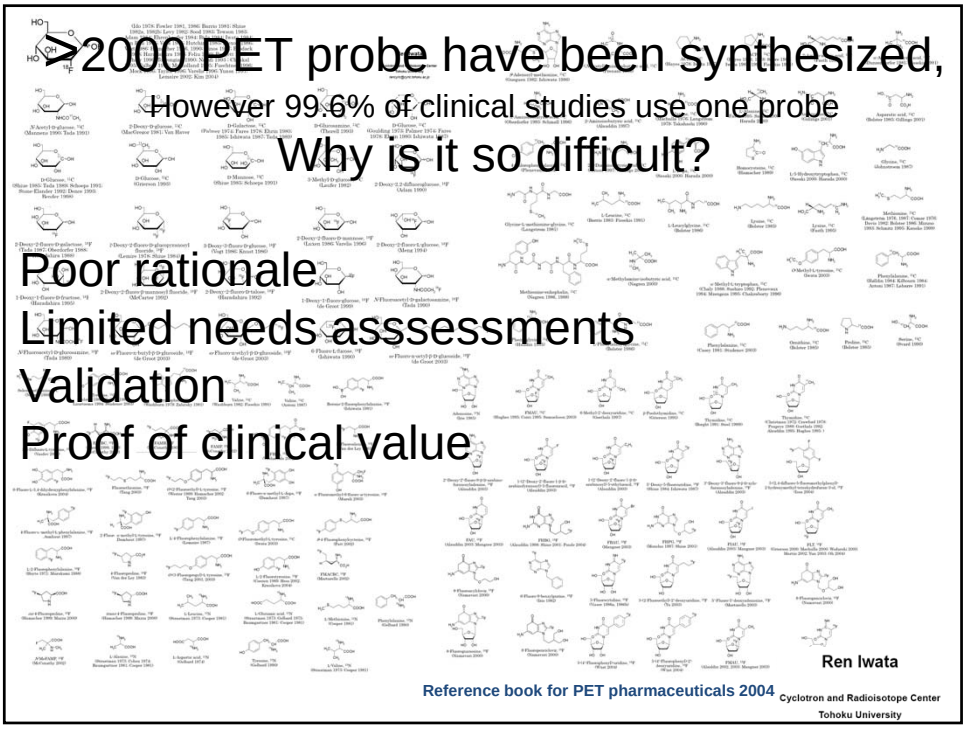
Predictive Biomarkers
Is the therapeutic target expressed?
Will the drug work?
^{68}Ga-DOTATATE; ^{18}F-FES; ^{18}F-FAC

UCLA 2013



Interm. endpoint Biomarkers
Does the drug work?
^{18}F-FDG; ^{18}F-AA; ^{18}F-FLT

PD/PK Biomarkers
How is the drug distributed?
Is the target inhibited?

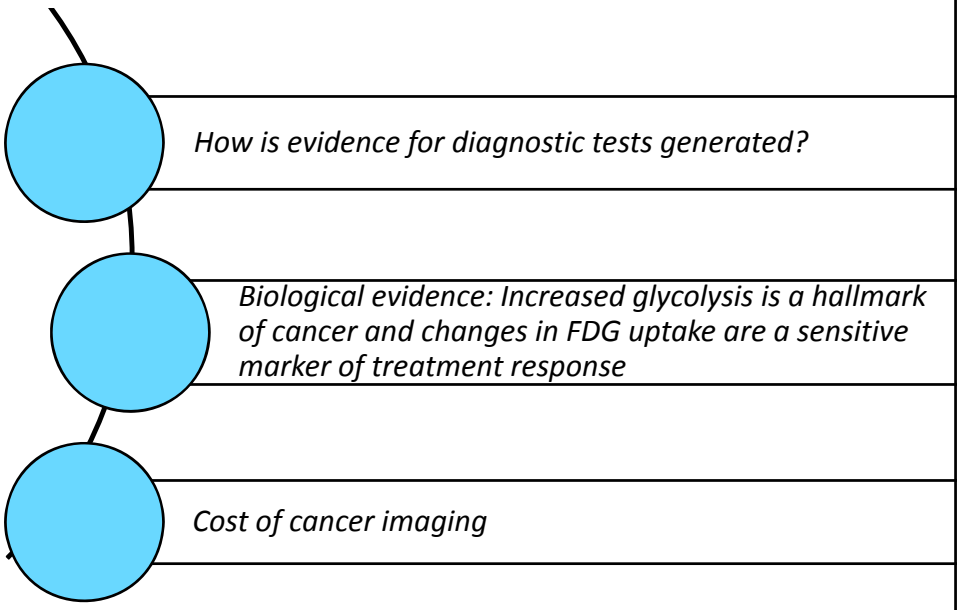


What is the required evidence for "new" imaging probes?

Feasibility	Easy to synthesize? Easy to distribute?
Assay	Does it measure what it is supposed to measure?
Accuracy	better than alternative; same, but at lower cost
Diagnostic value	How does test compare to other tests?
Therapeutic value	Does the test improve therapy?
Patient and societal value	Does the test improve patient outcome at reasonable cost (many outcome parameters should be considered)

Adapted from Jager et al; JNM 2001

Evidence Based Use of ^{18}F-FDG PET/CT



How is evidence generated?

Schueneman et al; APC club 2008: "If a test fails to improve patient-important outcomes, there is no reason to use it, whatever its accuracy."

Accuracy studies
Test 1 vs. Test 2; gold standard biopsy, imaging follow up etc.

Ungated RCT (^{18}F-NaF trial)
Comparison of 2 management strategies; one uses new test; the other one standard test
Outcome: OS, quality of life, PFS

Gated RCT
All pts undergo both tests; Randomization restricted to pts in whom test results would lead to different management decisions

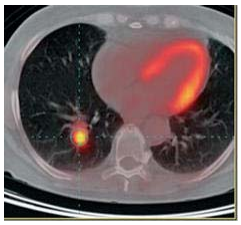
Decision modeling
Data based on literature

Management decision studies
National Oncology PET Registry (NOPR)

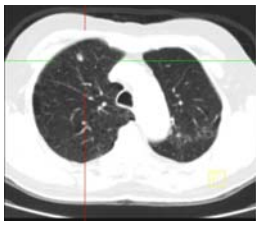
Meta-analysis, expert opinions, etc..

Test performance rated by HTA groups, regulatory agencies, etc

Question	Quality Assessment of Diagnostic Accuracy Studies (QUADAS) (14 questions)
6	**Did patients receive the same reference standard regardless of the index test result?**
7	Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)?
10	**Were index test results interpreted without knowledge of results of reference standard?**
11	Were reference standard results interpreted without knowledge of results of index test?



Reference standard: Biopsy

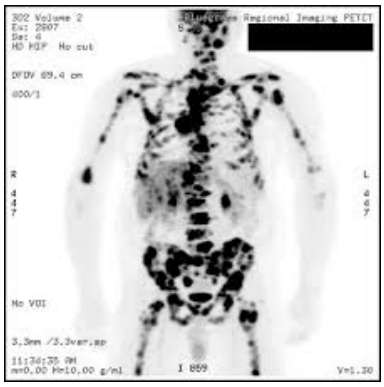


Question 6: Did patients receive same reference standard regardless of the index test result?
Sensitivity overestimated if biopsy only performed in positive scans

Question 10: Were index test results interpreted without knowledge of reference standard?
Differentiation of SPNs is biased when PET reader knows results of histopathology

These questions may NOT make sense..(see Weber et al; JNM 2011;52 Suppl 2)

Were reference standard results interpreted without knowledge of results of index test?
Histologic verification not possible unless a lesion has been identified by imaging.



Patient with widespread metastases

Were reference standard results interpreted without knowledge of results of index test?
Pathologist knows imaging findings: Thus, reference not independent of index test

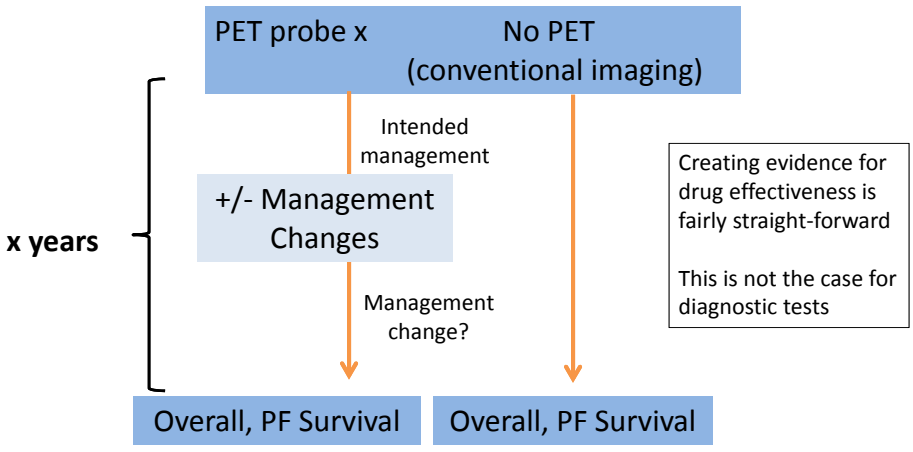
Were reference standard results interpreted without knowledge of results of index test?
Imaging used as follow up confirmation: Thus index test used as reference test

Reference standard cannot be determined when an imaging result is normal (autopsy required)

Thus, it is impossible to design a study for detection of distant metastases by an imaging modality without violating 6/14 requirements made by QUADAS.
Same true for all other imaging modalities

Study Design to determine impact on outcome in pts with Glioblastoma

Pts with suspected recurrence by MRI



Creating evidence for drug effectiveness is fairly straight-forward

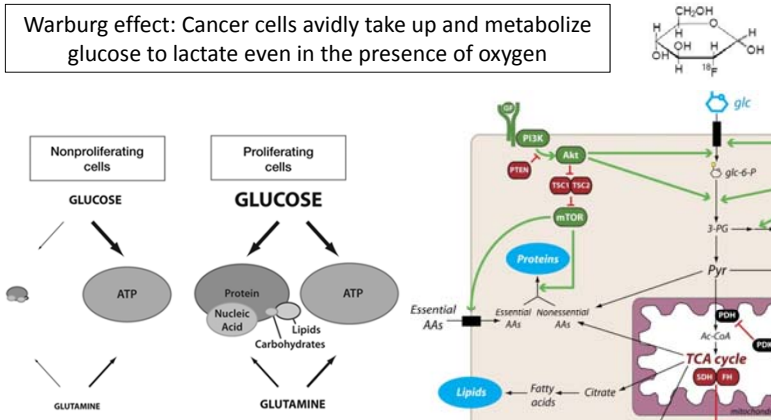
This is not the case for diagnostic tests

What if diagnostic tests are “better” than available therapeutics?

Herrmann et al; in progress

Evidence for FDG PET/CT imaging derived from Biology

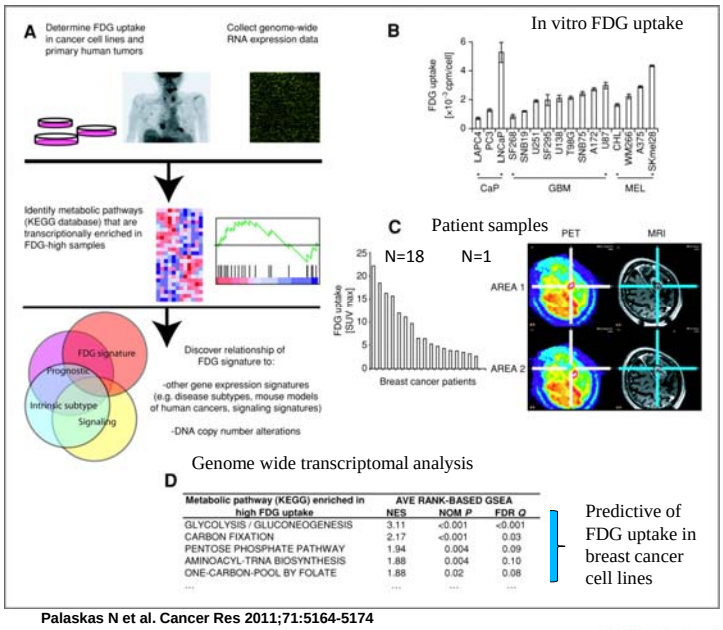
Warburg effect: Cancer cells avidly take up and metabolize glucose to lactate even in the presence of oxygen



Vander Heiden; Cold Spring Harb Symp Quant Biol 2011

DeBerardinis et al; Cell Metabolism 7, 2008; 11 - 20

Deriving an "FDG uptake" metabolic gene expression signature

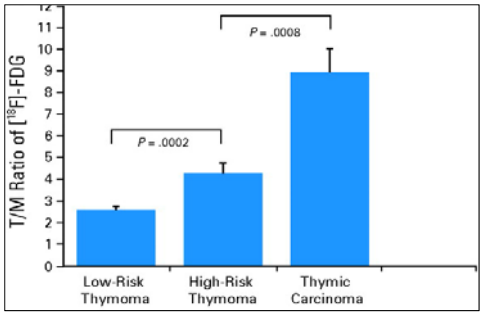


Metabolic pathway (KEGG) enriched in high FDG uptake	AVE RANK-BASED GSEA NES	NOM *p*	FDR *q*
GLYCOLYSIS / GLUCONEOGENESIS	3.11	<0.001	<0.001
CARBON FIXATION	2.17	<0.001	0.03
PENTOSE PHOSPHATE PATHWAY	1.94	0.004	0.09
AMINOACYL-TRNA BIOSYNTHESIS	1.88	0.004	0.10
ONE-CARBON-POOL BY FOLATE	1.88	0.02	0.08

Predictive of FDG uptake in breast cancer cell lines

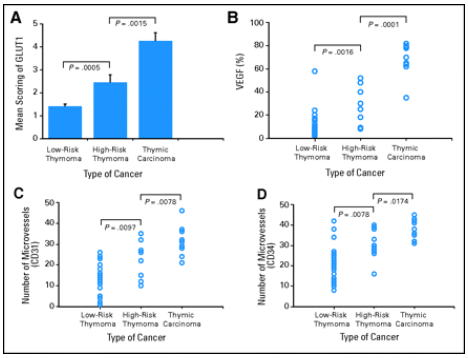
Palaskas N et al. Cancer Res 2011;71:5164-5174

American Association for Cancer Research



52 patients with thymic epithelial tumors imaged with ^{18}F-FDG

Determinants ex-vivo

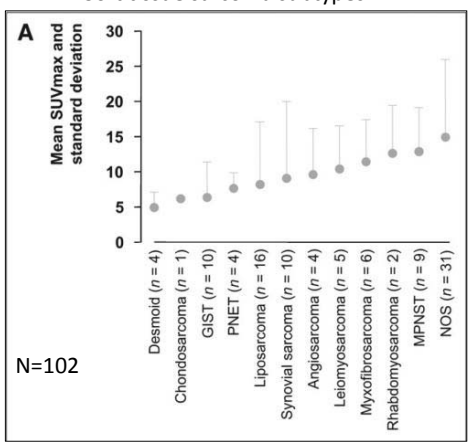


	R	P
GLUT1	0.75	.0001
GLUT3	0.27	.059
HIF-1α	0.42	.003
VEGF	0.75	.0001
CD31	0.49	.0004
CD34	0.48	.0005
p53		.002

Kaira et al; JCO 2010

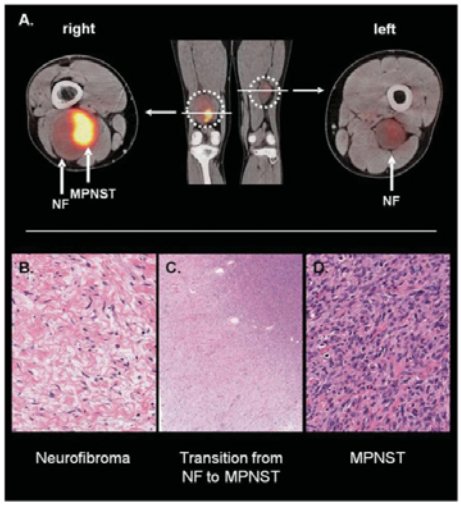
FDG-PET as a diagnostic/phenotypic biomarker in STS

Soft tissue sarcoma subtypes



N=102

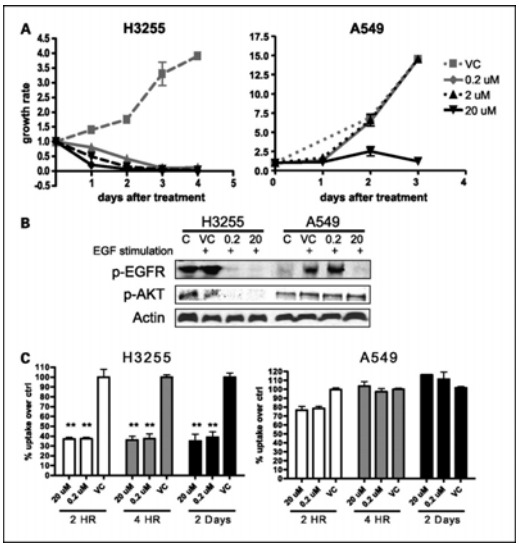
B



Benz and Herrmann et al; J Nucl Med, CCR, Cancer

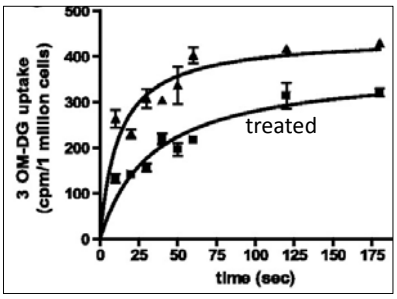
Reductions in tumor glucose use are an indicator of response to targeted therapy

Sensitive Insensitive



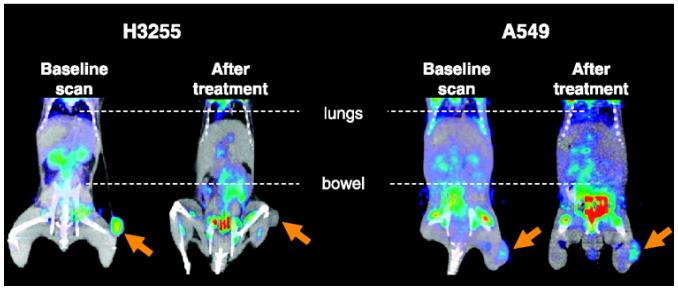
Effects on glucose transporter

vehicle

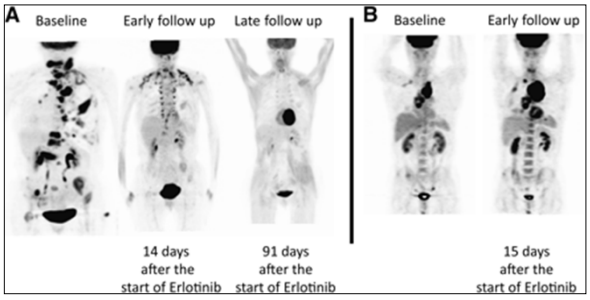


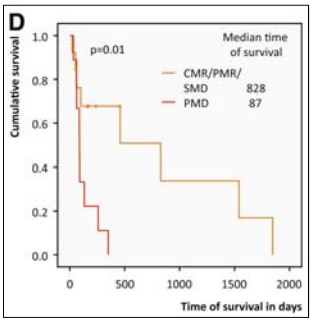
Su et al; Clin Cancer Res 2006

Translation: Changes in tumor FDG uptake after Gefitinib treatment



Su et al; Clin Cancer Res 2006

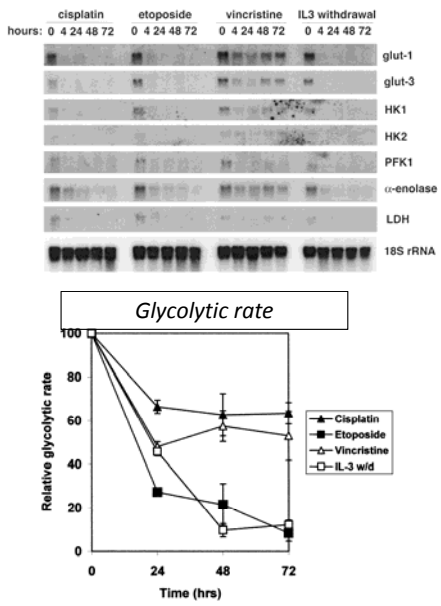


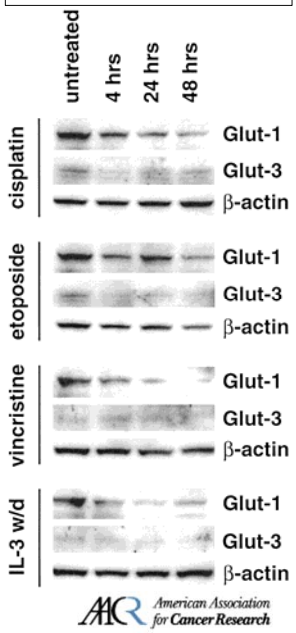


Benz et al; J Nucl Med 2011

Reductions in tumor glucose use are an indicator of response to cytotoxic therapy

Gene expression (FL5.Bcl-xl) *Protein expression*





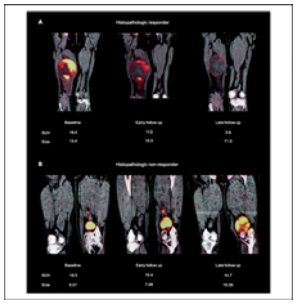
Glycolytic rate

Adapted from Zhou R et al. Cancer Res 2002;62:3515-3520

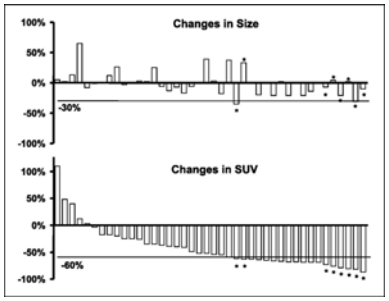
American Association for Cancer Research

Translation: Changes in tumor FDG uptake predict **histopathological response**

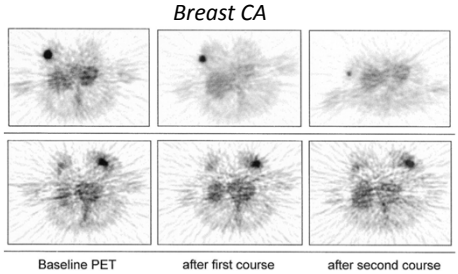
Soft tissue sarcoma



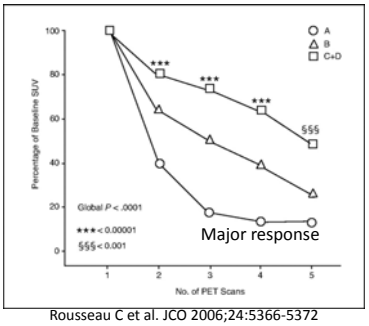
Evilevitch/Benz; Clin Cancer Res 2008, 2009



Breast CA

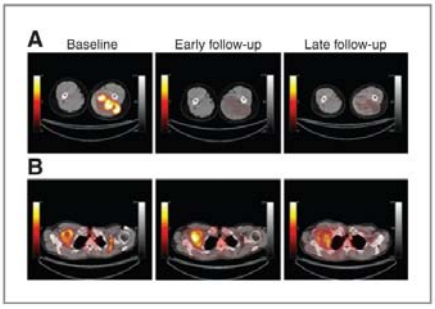


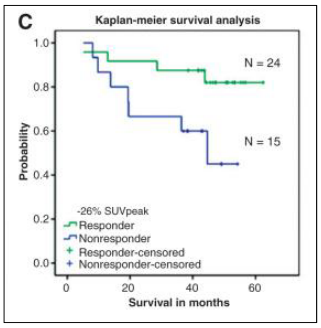
Schelling M et al. JCO 2000;18:1689-1695



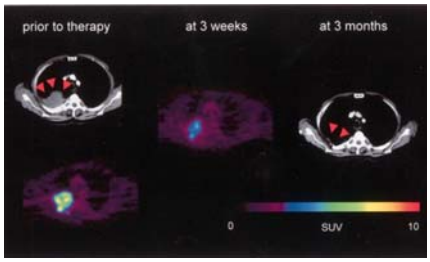
Rousseau C et al. JCO 2006;24:5366-5372

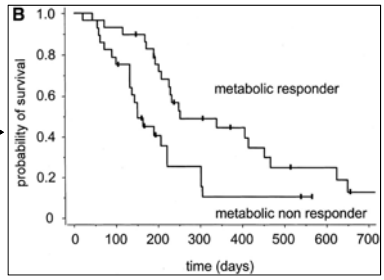
Early changes in Glucose metabolic activity predict **long term survival**





Herrmann et al; Clin Cancer Res 2012





Weber W A et al. JCO 2003

Impact on Management (NOPR)

The National Oncologic PET Registry (NOPR): Design and Analysis Plan

JNM 2007

The National Oncologic PET Registry: Expanded Medicare Coverage for PET Under Coverage with Evidence Development

ACR 2007

300 000 patients enrolled

Impact of Positron Emission Tomography/Computed Tomography and Positron Emission Tomography (PET) Alone on Expected Management of Patients With Cancer: Initial Results From the National Oncologic PET Registry

Bruce E. Hillner, Barry A. Siegel, Dawei Liu, Anthony F. Shields, Ilana F. Gareen, Lucy Hanna, Sharon Hartson Stine, and R. Edward Coleman

JCO 2008

35-50% impact on management for staging/restaging/ monitoring

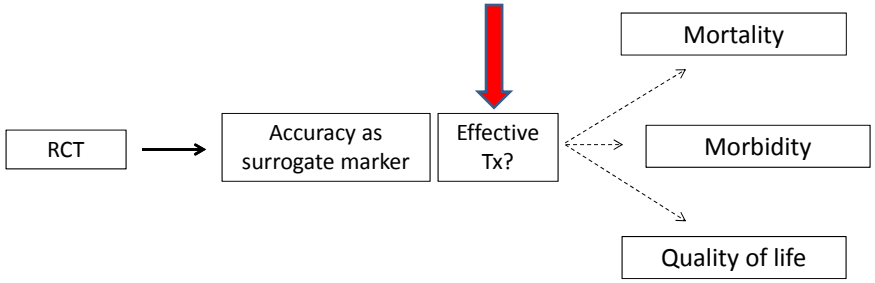
Relationship Between Cancer Type and Impact of PET and PET/CT on Intended Management: Findings of the National Oncologic PET Registry

The Impact of Positron Emission Tomography (PET) on Expected Management During Cancer Treatment

Findings of the National Oncologic PET Registry

Cancer 2009

Impact on Outcome?



Ruers 2009	JNM	Surgery for liver metastases	CT vs PET/CT	Red. # futile surgeries
Van Tinteren 2009	Lancet 2002	Presurgical staging NSCLC	PET vs convent. staging	Red. # futile surgeries
Fischer 2011	N Engl J 2011	Presurgical staging NSCLC	PET/CT vs. convent. staging	Red. # futile surgeries Mortality NS

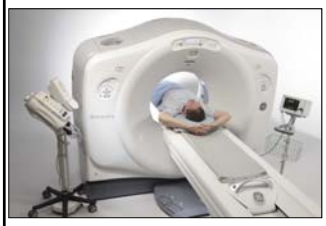
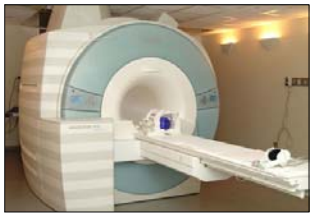
Many ongoing trials……

Because of NOPR: PET Coverage in the USA

	Initial Treatment Strategy	**Subsequent Treatment strategy**
Colorectal	Cover	Cover
Esophagus	Cover	Cover
Head & Neck	Cover	Cover
Lymphoma	Cover	Cover
NSCL	Cover	Cover
Ovary	Cover	Cover
Brain	Cover	Cover
Cervix	Cover	Cover
Small Cell Lung	Cover	Cover
STS	Cover	Cover
Pancreas	Cover	Cover
Testes	Cover	Cover
Breast	Cover w/exception*	Cover
Melanoma	Cover w/exception*	Cover
Prostate	*Non-Cover*	*Non-Cover*
Thyroid	Cover	Cover
All Other Solid	Cover	Cover
Myeloma	Cover	Cover
All oth. not listed	Cover	Cover

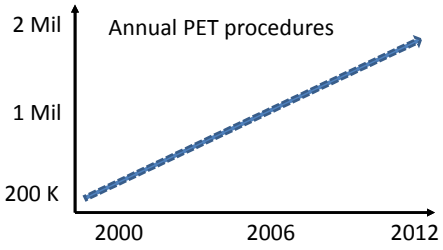
How is imaging used and how expensive is it in cancer (Medicare)

CT anatomy | *MRI: Anatomy +Function* | *PET/CT: +Molecular imaging*


Imaging costs frequently named as one of the culprits for exploding costs

Adapted from Dinan et al; JAMA 2010; 1625-1631



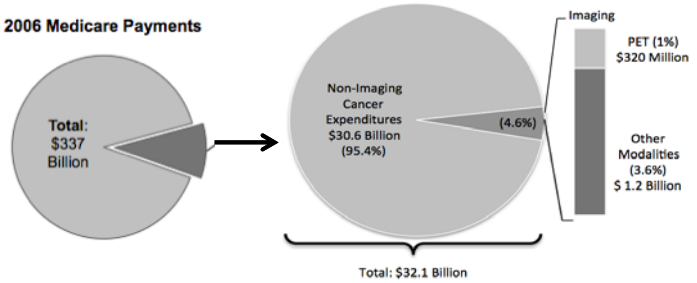
Indication	CT/MRI	CT/PET
Breast CA	3.7	11
CRC	12	16
Lung CA	5.8	5.5
NHL	7.9	5.8
Prostate CA	4	>20

What are the key cost drivers in cancer?

PET scans during first 2 years after diagnosis

Cancer type	#PET/patient	Ann. increase (%)
Breast CA	0.2	53.6
Colorectal CA	0.3	41.6
Lung CA	1.0	35.9
NHL	1.1	38.7
Prostate CA	<0.1	40.5

Adapted from Dinan et al; JAMA 2010



In-patient services, drugs, etc.
All Imaging: 4.6 %
FDG-PET/CT: 1.0-1.5%

Yang, Czernin; JNM 2011

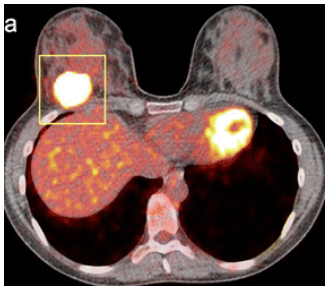
Distribution of Cancers	%
Lung cancer	29.9
Lymphoma	24.5
Breast cancer	12.4
Colorectal cancer	11.7
Head and neck cancer	8.1
Melanoma	2.7
GIST	1.0
Myeloma	1.0
Cancer of unknown primary	1.0
Esophageal cancer	1.0
Prostate cancer	0.7
Other tumors	6.0

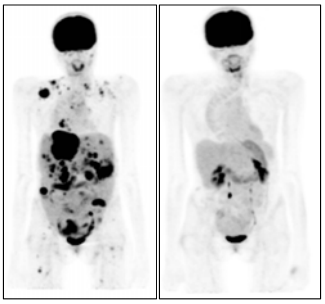
Beyer et al; J Nucl Med 2011

Indication	N	%
Diagnosis	5,516	19
Staging	6464	23
Restaging	5607	20
Suspected recurrence	5388	19
Monitoring	5,503	19
Total	22,975	

NOPR data: Hillner et al; JCO 2008

Koolen et al; EJNMMI 2012

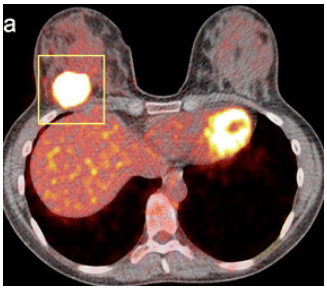




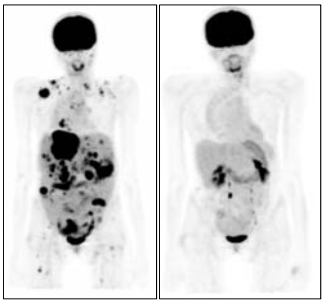
Baseline Day 21

How do we use FDG PET/CT across most cancers?

Koolen et al; EJNMMI 2012



UCLA 2013



Baseline Day 21

Initial treatment strategy

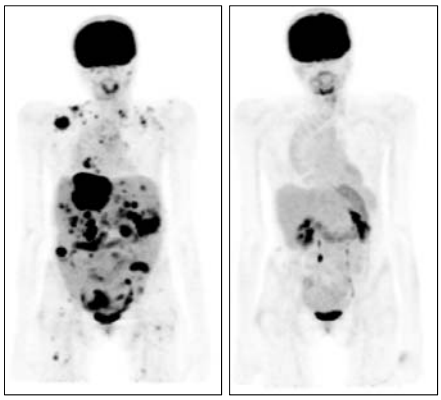
Diagnostic/Phenotypic/ Prognostic Biomarker
Diagnosis, Staging

Subsequent treatment strategy

Intermediate endpoint Biomarker
Treatment Monitoring

Conclusion

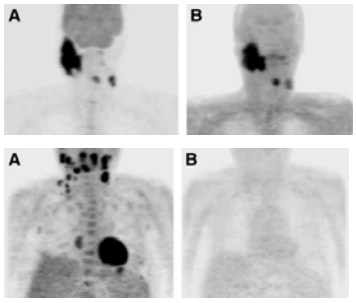
- FDG PET imaging has a strong and translatable underpinning in tumor biology
- Evidence based approaches never applied to MRI or CT (does this mean that these techniques are not useful?)
- Randomized trials difficult to conduct (no financial support, no stakeholders)
- Nevertheless, impact on management and outcome demonstrated



The fundamental role of increased glucose metabolism is well established
Do we really need to show the usefulness of PET for each cancer/each indication?

Can we image substrate utilization in cancer and what could we learn?

FDG *Synergistic* FET



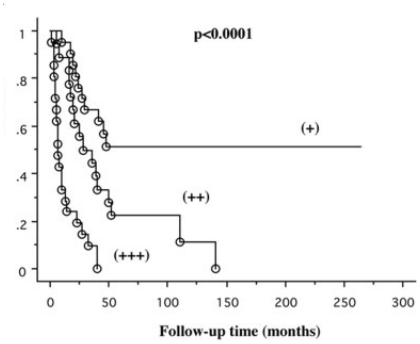
Glycolysis dominant
Pauleit et al; JNM 2005

FDG

CMET

Amino acid dominant
Hsieh et al; Ann Nucl Med 2008

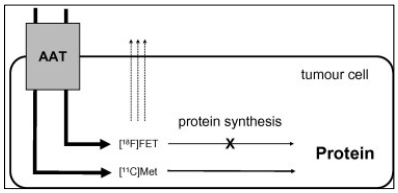
LAT1 expression and survival in lung CA



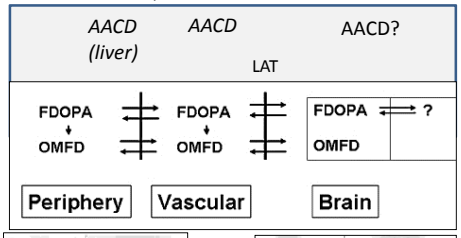
+,++,+++: degree of staining for LAT1; n=60

Nawashiro et al; Int J Cancer 2006

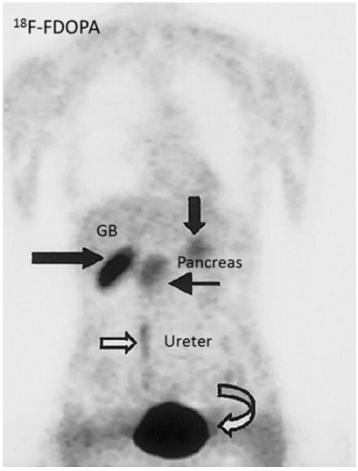
Imaging AA Transport and Metabolism : Diagnostic and prognostic information

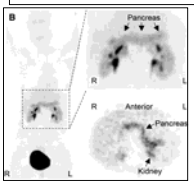


Schiepers et al; J Nucl Med 2007

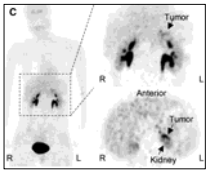


Biodistribution





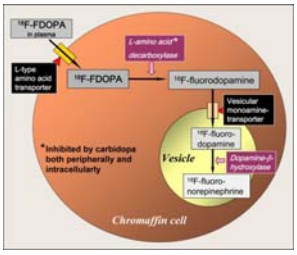
- Carbidopa



+ Carbidopa

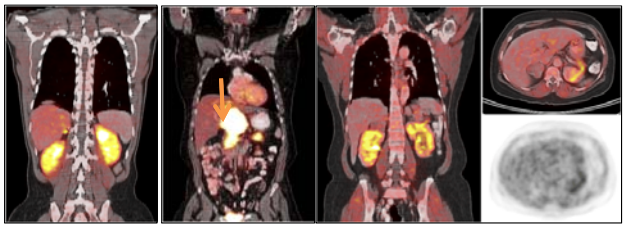
Timmers et al; JNM 2007

Why [18F]-FDOPA?



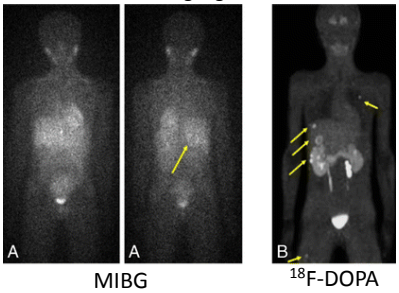
Pheochromocytoma

Adenoma



Imani et al; J Nucl Med 2009

Paraganglioma



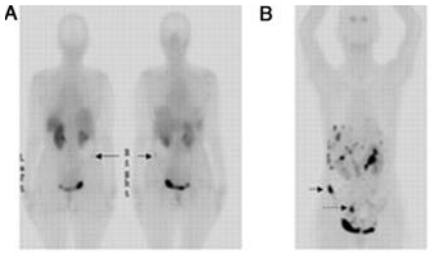
MIBG

18F-DOPA

	18F-DOPA	MIBG	p
Primary	8/12 (66%)	4/12 (33%)	0.2
Soft tissue rec./metastases	38/45 (84%)	14/45 (31%)	<0.001
Bone/bone marrow	95/99 (96%)	70/99 (71%)	<0.001

Piccardo et al Eur J Nuc Med Mol Imaging 2011

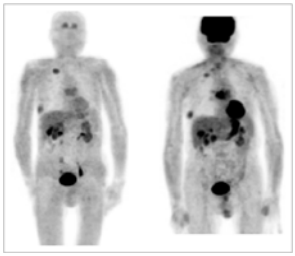
Carcinoid



^{111}In-Octreotide ^{18}F-FDOPA

Montravers; J Clin Endocr. Metab 2009

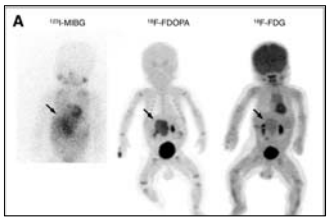
Med.thyroid CA



^{18}F-FDOPA ^{18}F-FDG

Verbeek; JNM 2012

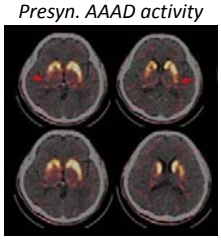
Neuroblastoma



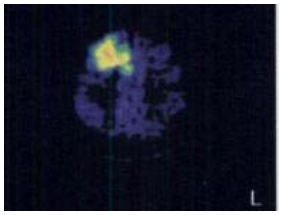
FDOPA vs AADC expr.: p<0.0001

Lu; JNM 2013

Presyn. AAAD activity



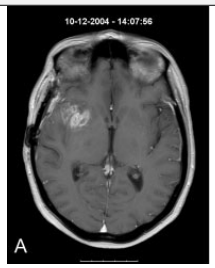
Brain tumor imaging



Management of primary brain tumors

Symptoms: headaches, seizures, syncope, vomiting, changes in mental status

Initial Diagnosis



Consider clinical trials at all stages, especially up front, adjuvant, and at relapse

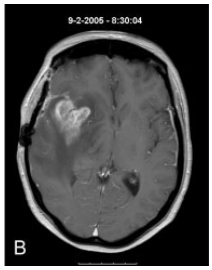
Multidisciplinary approach is necessary

- Neurosurgery
- Neuro-oncology
- Radiation therapy
- *Maximal resection when possible*
- RTX + CTX

Adjuvant CTX for anaplastic glioma and glioblastoma

PET?

MRI (ceT1)



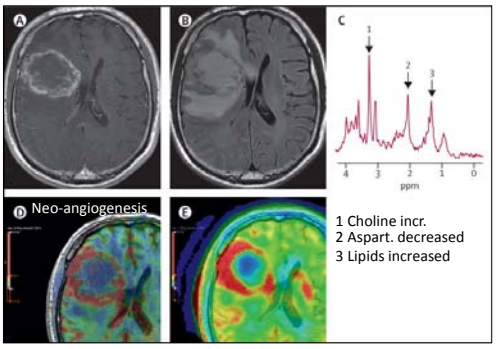
Progressive disease

- **Consider clinical trials**
- Consider surgical resection at relapse
- Salvage chemotherapy using cytotoxics/cytostatics
- Consider Stereotactic Radiotherapy

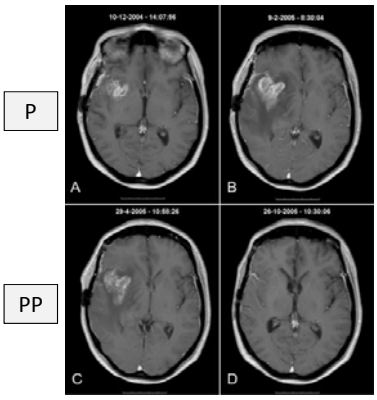
PET?

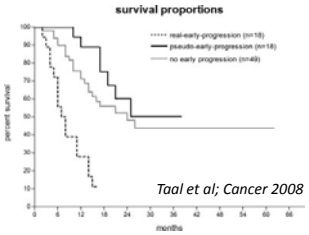
(Median survival: 12 m; no treatment 7-9 m)

Strengths an limitations of MRI



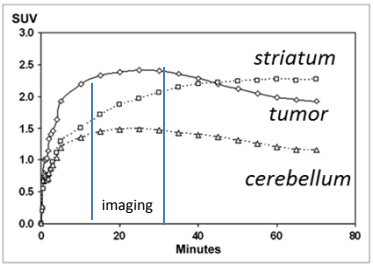
Adapted from Ricard et al; Lancet 2012





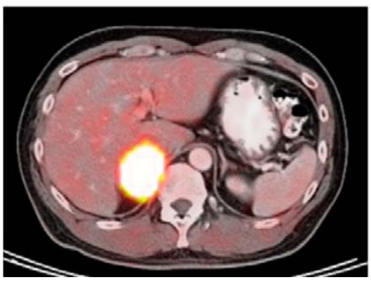
Taal et al; Cancer 2008

^{18}F-FDOPA imaging protocol (ca. 130 pts/year)



Brain imaging
- 200 mg of Carbidopa 1 h prior to tracer injection

- ^{18}F-FDOPA: 5-10 mCi
10 min uptake period
20 min scan

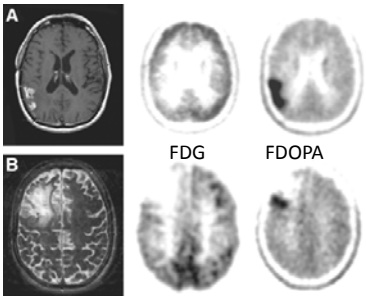


Whole body imaging
200 mg of Carbidopa 1 h prior to tracer injection

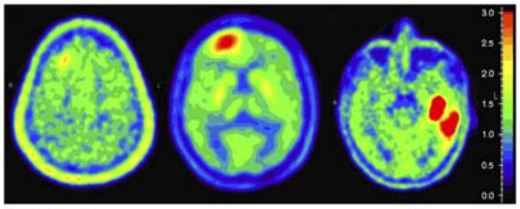
- ^{18}F-FDOPA: 5-10 mCi
45 min uptake period
2-5 min/bed position
-CT with/without iv and oral contrast

Diagnostic accuracy of ^{18}F-FDOPA

Recurrent



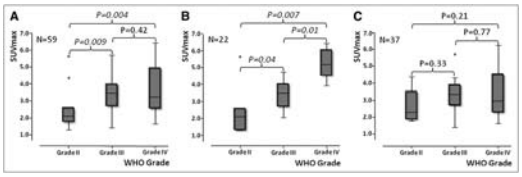
^{18}F-FDOPA uptake and tumor grade



WHO grade:	II	III	IV
Histology:	oligodendroglioma	oligoastrocytoma	glioblastoma
Ki-67:	1%	25%	40%
SUVmax:	2.39	3.49	6.42

Ratio	% Sens	% Spec	% PPV	% NPV
T/S > 1.0	96	100	100	88
T/S > 0.75	100	86	96	100
T/N > 1.3	96	86	96	86
T/W > 1.6	96	86	96	86

FDOPA detects LG and HG tumors
FDG positive in HG tumors



All *New* *Recurrent*

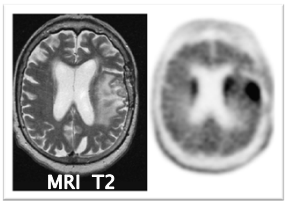
Chen et al; JNM 2006, Fueger et al; JNM 2010

Impact of ^{18}F-DOPA PET on managing patients with brain tumors

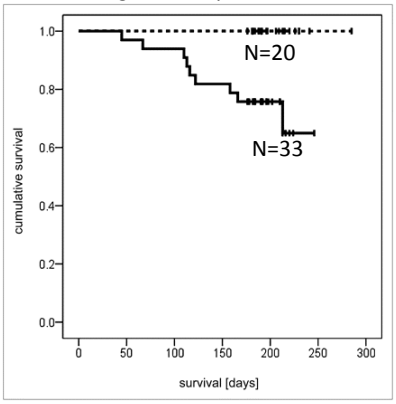
Tumor grade (n=58)	N	%
WHO I	0	0
WHO II	15	26
HG — WHO III	15	26
HG — WHO IV	21	36
Unknown	7	12

Management changes in 24/58 patients

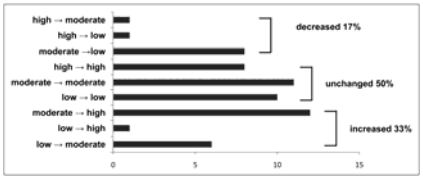
W/W	→ Chemo	6/24 pts (25%)
Chemo	→ W/W	4/24 pts (17%)
Chemo	→ Surgery	2/24 pts (8%)
R+C	→ C	2/24 pts (8%)
W/W	→ R/C	2/24 pts (8%)



Prognostic implications



Level of suspicion



Walter et al; J Nucl Med 2012

[^{18}F]-AA transport imaging (^{11}CMET, ^{18}F-FET, ^{18}F-FDOPA) for brain tumor imaging

Feasibility	yes
Accuracy	yes
Diagnostic value	yes; pseudo-progression vs progression
Prognostic value	yes
Therapeutic value	Impact on Management: Yes Does it result in better treatment?
Patient and societal value	Does it result in improved survival and/or quality of life, at acceptable cost/reduces costs at same outcome?

Prospective randomized trial under way for ^{18}F-FDOPA

Study Design to determine impact on outcome in pts with cancer

(UCLA, Kaiser Permanente, UC Irvine, University of Wuerzburg)

"positive MRI"

Randomization

AA PET | No AA PET (conventional imaging)

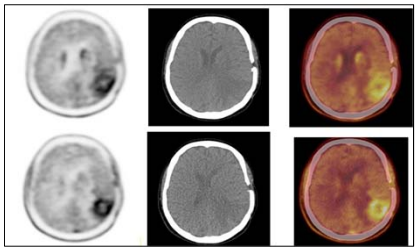
Intended Management

+/- Management Changes

Management change implemented?

OS, PFS | OS, PFS

FDOPA

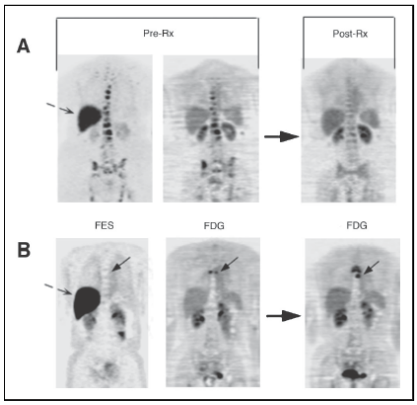


FET

Herrmann et al; in progress

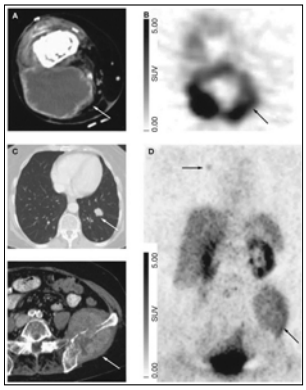
Predictive Biomarkers: Is the *therapeutic* target expressed?

[^{18}F]-FES



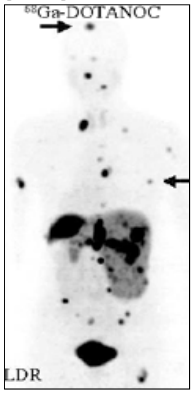
Linden 2006

[^{18}F]RGD-Peptides



Beer; 2005

[^{68}Ga]DOTATOC

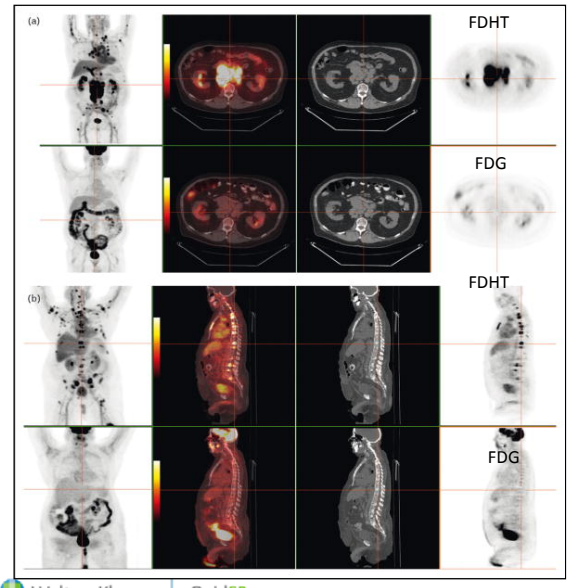


Wild , Mäcke 2005

There are many PET probes for bone imaging

Probe	T/2 (min)	Target	Process	Applications
^{18}F-NaF	***110***	***Hydroxyapatite***	***Bone formation***	***Osteoblastic***
^{18}F-FDG	***110***	***Glut1,3; hexokinase***	***Glycolysis***	***Osteolytic***
^{11}C-Choline	20	Choline kinase	lipid synthesis	Prostate
^{18}F-Choline	110	Choline kinase	lipid synthesis	Prostate
^{11}C-Acetate	20	FAS	Lipid synthesis	Prostate
^{11}C-Meth	20	L-AAT	AA metabolism	Myeloma
^{18}F-DOPA	110	L-AAT	AA metabolism	NET
^{68}Ga-SSR	68	SSR 2,5	SSR expression	NET
^{18}F-Estradiol	110	ER	Receptors	Breast
^{18}F-FDHT	110	AR	Receptors	Prostate
^{124}Iodine	4.2 days	Na-I-symporter	Iodine metab.	Thyroid
^{68}Ga-PSMA	68	PSMA	Receptor exp	AI
^{89}Zr-mAB	78h	PSMA	Receptor exp	AI
^{89}Zr-mAB	78h	PSA	Receptor exp	AD
^{18}F-FACBC	110	LAT?	AA Transport	Recurrence

Androgen and Estrogen Receptor Imaging: Predictive biomarkers in bone metastatic imaging?



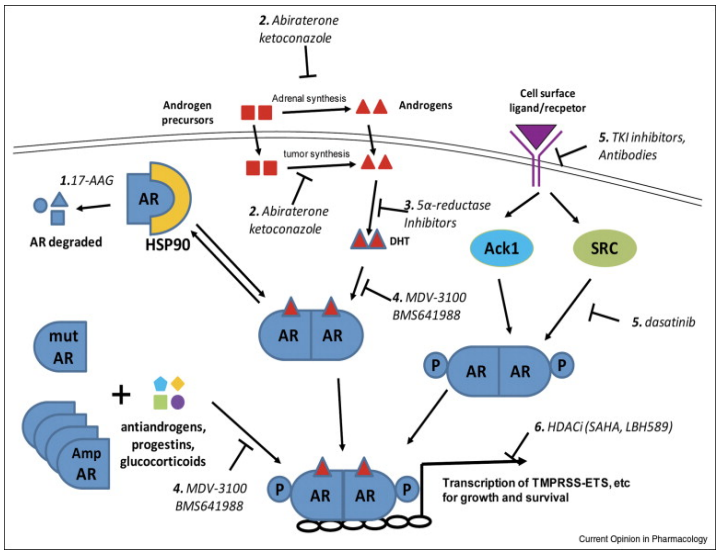
Discordant FDHT and FDG

Does hormone receptor expression predict response to hormone treatment? Thus far no published evidence..

Adapted from Molecular imaging of prostate cancer.
Fox, Josef; Schoder, Heiko; Larson, Steven

Current Opinion in Urology. 22(4):320-327, July 2012.
DOI: 10.1097/MOU.0b013e32835483d5

Numerous therapeutic approaches: Schematic representation of therapeutic targets of the AR pathway

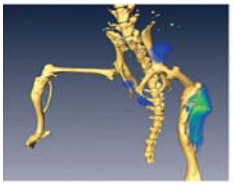


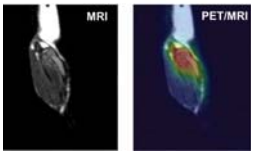
Schematic representation of therapeutic targets of the AR pathway.

Current Opinion in Pharmacology Volume 8, Issue 4 2008 440 - 448
Yu Chen , Charles L Sawyers , Howard I Scher

Imaging targets in prostate cancer

PSA (human kallikrein 3)
Serine protease
Released into perivascular space; AR signaling dependent gene
Specific for prostate CA

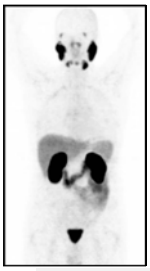


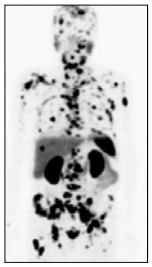


^{89}*Zr-5A10*
*AB R*ecognizes PSA prior to EC protein binding (Ulmert et al; 2012)

PSMA (glycoprotein)
Cell migration
Nutrient uptake
Receptor function
Not specific for PrCA

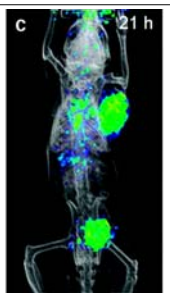
AB → EC: ^{68}Ga urea based peptidomimetcis (HBED-CC)
37 pts. Afshar-Oromeih ; Eur J Nucl Med 2013; Eder et al 2012





Intracellular
^{89}*Zr-7E11 (mAB)*
Treatment responses?
Ruggiero A; JNM 2011

PSCA (cell surface glycoprotein) overexpressed in localized prostate cancers; correlates with Gleason score, pathologic stage, AI.

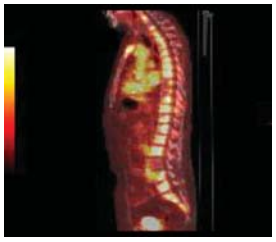


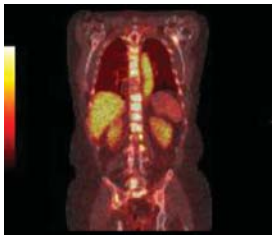
Leyton J; Clin Cancer Res 2008

How should we use these?

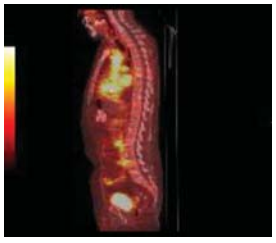
PD of MDV3100 (pure AR antagonist) measured with FDHT

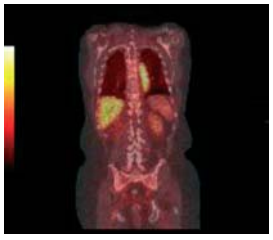
Baseline





4 weeks of MDV3100





Scher et al; Lancet 2010

Summary: Probes for diagnosing and phenotyping of bone metastases

Diagnosis

^{99}Tc MDP
^{18}F-NaF
^{18}F-FDG , ^{11}C/^{18}F-choline
^{18}F-FACBC
MRI
CT
PSA, PSMA, PSCA ligands

Phenotyping

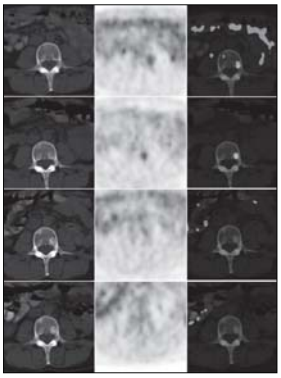
PSMA
PSA
PSCA
^{18}F-FDG
^{18}F-FACBC
^{11}C/^{18}F-choline
Hormone receptors

Predictive biomarkers?

Initial treatment strategy

Therapy

Hormonal Tx
EBR
Alpharadin
Biphosphonates
Small molecule inhibitors
Chemotherapy



Intermediate endpoint biomarkers

^{18}F-FDG
^{11}C/^{18}F-choline
IC PSMA?

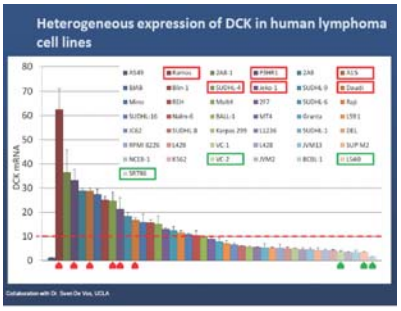
Subsequent strategy

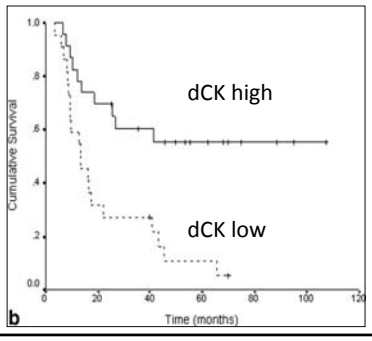
Predictive PET biomarker for nucleoside analog prodrugs

Rationale

- NA prodrugs require deoxycitidine kinase (dCK) for their activation (gemcitabine, clofarabine, decitabine, etc)
- dCK overexpressed to various degrees in many cancers
- Response rates are low

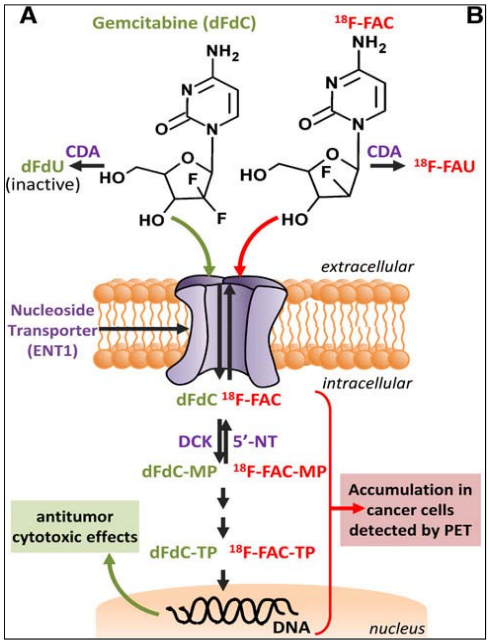
- Differential screening for pyrimidine NAs targeting dCK
- High binding affinity (low nm) in vitro





Marechal et al; Cancer 2010

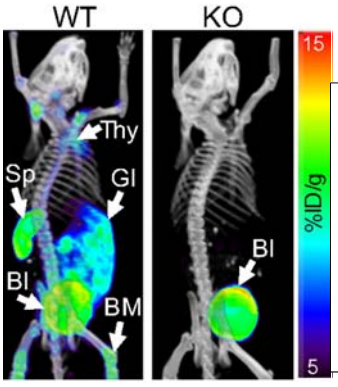
Who will respond?



Laing et al PNAS 2009

Probe Specificity and treatment response predictions

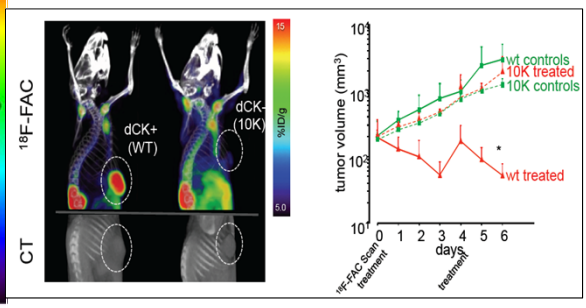
Sensitivity Specificity



Toy et al; Proc Natl Acad Sci 2010
Campbell et. al. J Nucl Med. 2010

Response to gemcitabine

L1210, L1210K



Lee et al; J Nucl Med 2011

Clinical translation of predictive biomarkers

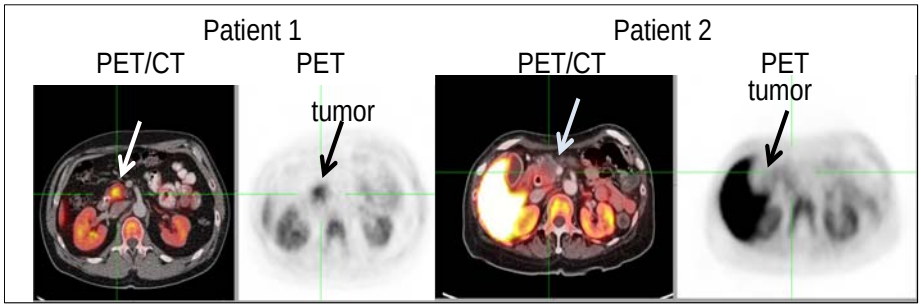
30 resectable patients imaged with ^{18}F-FAC PET/CT

↓

Excised tumor examined for dCK activity and expression

↓

Correlation between dCK activity/expression and ^{18}F-FAC uptake



Czernin et al; 2013; unpublished data

What is the point? What does it mean for patients?

Translational Study 1

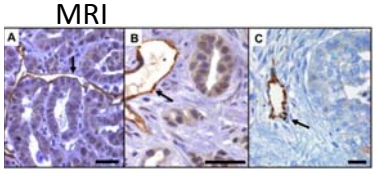
Resectable cancer

^{18}F-FAC PET

Surgery

Tumor fragment

MRI



Olive et al; Nature 2009

Histology **dCK** **Xenografts**

Translational Study 2

Non-resectable cancer

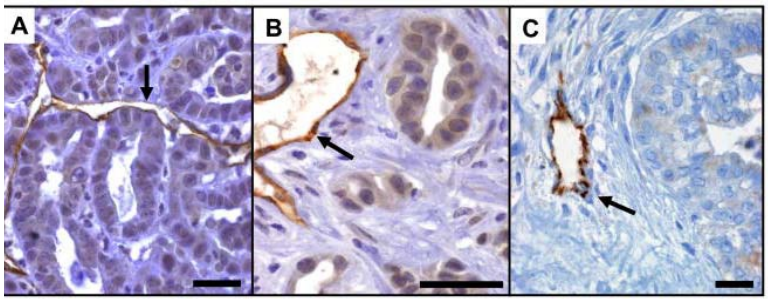
^{18}F-FAC PET

Gemcitabine

Clinical Course

Overall Survival **Progression FS**

Problems in study design



Sampling problems
- Small tissue fragments

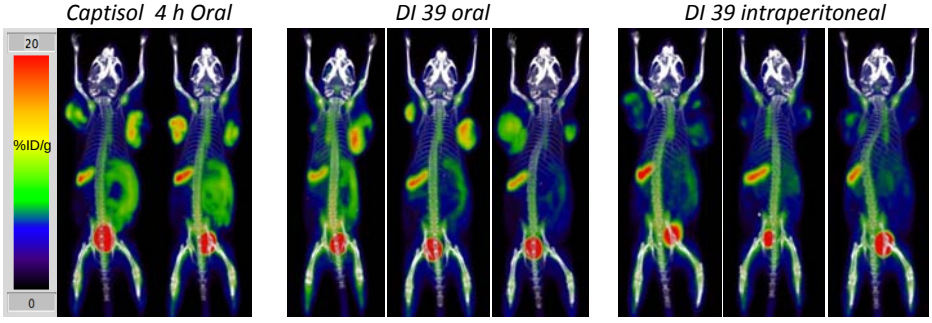
Probe delivery
- Low tumor perfusion but high dCK activity
- High tumor perfusion but low dCK activity

Tumor stroma

^{18}F-FAC as Pharmakodynamic Marker of dCK inhibitors

Dose: 50mg/kg

Captisol 4 h Oral | *DI 39 oral* | *DI 39 intraperitoneal*

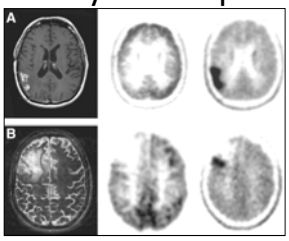


At 50mg/kg the intraperitoneal administration is superior to oral administration

Radu group at UCLA

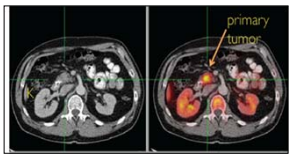
Summary: A rich portfolio of PET biomarkers

Koolen et al; EJNMMI 2012



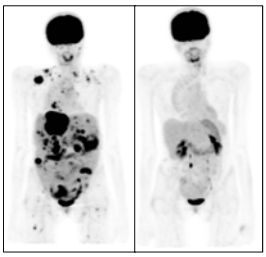
Diagnostic/Phenotypic/ Prognostic Biomarkers
Is the disease present?
^{18}F-FDG; AA, ^{18}F-FLT; etc, choline, ect

UCLA 2013



Predictive Biomarkers
Is the therapeutic target expressed?
Will the drug work?
^{68}Ga-DOTATATE; ^{18}F-FES; ^{18}F-FAC

UCLA 2013



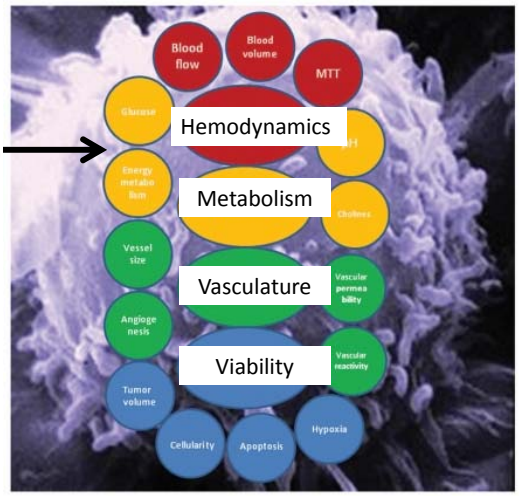
Intermediate endpoint Biomarkers Does the drug work?
^{18}F-FDG; ^{18}F-AA; ^{18}F-FLT

A few words about MRI: Capabilities have dramatically expanded

These arguments have been made for PET/MRI

- No Radiation
- Molecular capabilities (Research)
- True simultaneous acquisition
- Better for selected indications
  - Brain
  - Prostate
  - Head/Neck
  - Pancreas
  - Liver

But is there a good reason for marrying PET with MRI?



Kauppinen/Peet; Cancer Biol Ther. 2011

Argument #1 for PET/MRI

CT carries a significant radiation risk

Brenner DJ and Hall EJ; N Engl J Med 2007
Radiation doses of as high as 25 mSv might increase cancer risk

Brenner DJ et al; Radiology 2011:
Greatly reduced relevance for patients with limited life expectancy

D. J. Shah et al; British Journal of Radiology 2012 "Risks of medical imaging at effective doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent"
"Predictions of hypothetical cancer incidence and deaths in patient populations exposed to such low doses are highly speculative and should be discouraged"

Women of child bearing age
Pediatric population

Do magnetic fields have a mutagenic effect (Ames test)?
From Schreiber et al; J. Magn. Reson. Imaging 2001;14:779–788.

Increase in hypoxanthine-guanine phosphoribosyl transferase gene mutations
Increase in DNA strand breaks in rat brain cells
Increase in revertants in co-exposed *Salmonella typhimurium* TA 100
Increase in micronuclei in human lymphocytes (only in presence of the parallel static magnetic field)
Increase in the number of sister chromatid exchanges at 400 mT, but neither at 5 mT nor at 50 mT
Increase in hypoxanthine-guanine phosphoribosyl transferase gene mutations in co-exposed Chinese hamster ovary cells
Increase in hypoxanthine-guanine phosphoribosyl transferase gene mutations in p53 deficient human osteosarkoma cells

DNA repair mechanisms are powerful

Argument #2 for clinical PET/MRI: MRI is "better" than CT for some indications

In pancreatic cancer (Shrikhande et al; HPB 2012)
Choice between CT or MRI/MRCP is often determined by the availability of the modality and by the technical expertise; CT and MRI equally accurate

CT and MRI are underreporting vascular invasion in pancreatic cancer. MRA does not add information on vascular staging when compared with CT and MRI. *(Zhang et al; Pancreatology 2012)*
MRI and CT similarly accurate for characterizing cystic lesions *(Lee et al; Clin. Radiology 2011; Visser et al; AJR 2007)*

Liver metastases
Niekel et al; meta-analysis;
Radiology 2010

Modality*	Mean Sensitivity (%)†	Mean Specificity (%)†
CT ($n = 9$)	83.6 (66.9, 92.8)	94.9 (92.9, 96.3)
MR imaging ($n = 6$)	88.2 (64.8, 96.8)	92.5 (89.5, 94.6)
FDG PET ($n = 6$)	94.1 (91.6, 95.9)	95.7 (92.7, 97.6)
FDG PET/CT ($n = 3$)	96.5 (94.2, 97.9)	97.2 (92.8, 99.0)

CT, MRI, PET and US with comparable performance in metastatic H/N cancer
Meta analysis : Liao et al; BMC Cancer 2012
Meta analysis: de Brondt et al; Eur J Radiol 2007

Same for recurrent nasopharyngeal CA
Meta-analysis: Liu et al; Radioth.and Oncology 2007

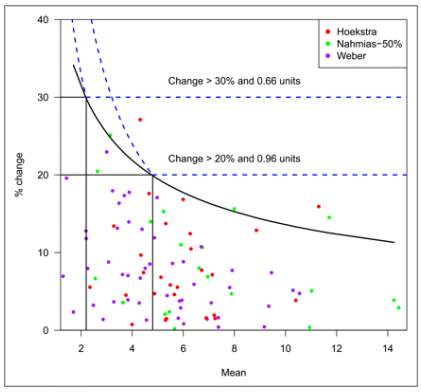
And even in prostate cancer LN staging……
CT Sens: 42%; MRI Sens: 39%
Meta-analysis: Hoevels et al; Clinical Radiology 2008

Using LN specific contrast MRI superior to CT; Mulicenter trial; Heesakkers et al; Lancet Oncology 2008

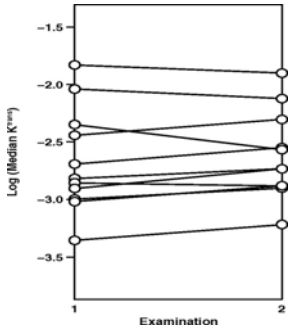
Argument #3 for PET/MRI
Simultaneous measurements of molecular processes are important

^{18}F FDG tumor uptake is reproducible
De Langen et al; JNM 2012

Study interval 1-4 days



Reproducibility of MRI Perfusion measurements (baseline vs 2-7 days later)
Ng et al; AJR 2010

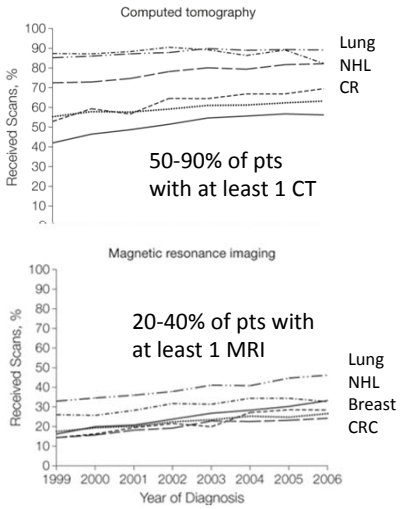


The rate of reproducibility of DCE-MRI parameters is in the range of 10%–20%

Highly unlikely that gene expression, transcription and translation changes within minutes. Why then would we need integrated systems?

The business of PET/MRI; Trends in cancer imaging in the US (CMS data)

CT and MRI utilization 2006-2008



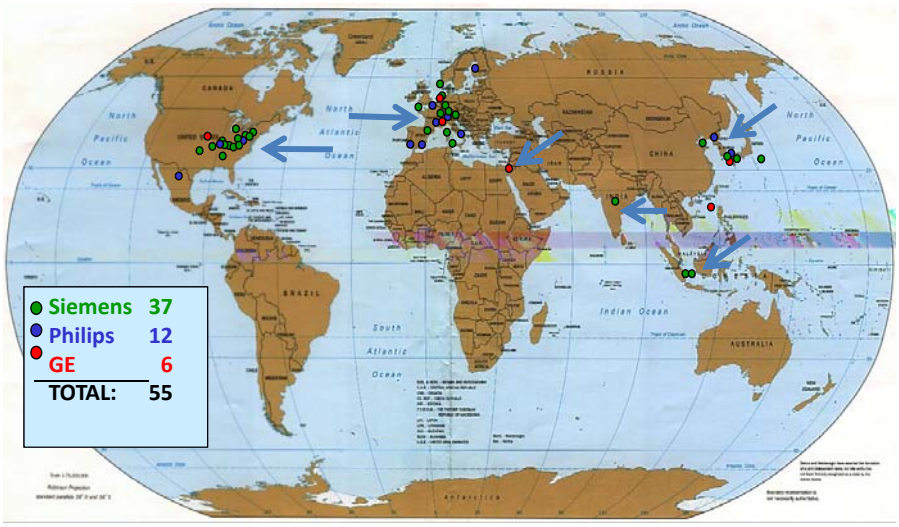
CT and MRI/pt within 2 y of diagnosis

Indication	CT/MRI
Breast CA	3.7
CRC	12
Lung CA	5.5
NHL	7.9
Prostate CA	4

Adapted from Dinan et al; JAMA 2010; 1625-1631

Thus, CT is the dominating modality in cancer: Cost, operation, value

PET/MR: Worldwide distribution up to Q1 2013



Almost all systems in academia or public health care

Courtesy of David Townsend

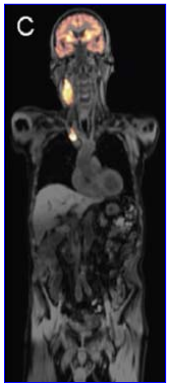
Interesting sales numbers

Adapted from David Townsend

PET/CT 2002 – 2004: 360 *Units shipped in US*
A technical *evolution* and a clinical *revolution*

PET/MRI 2010 – 2012: 14 *Units shipped in US*
A technical *revolution: But is there a real need?*

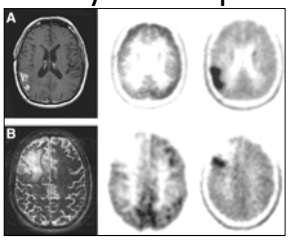
	PET/CT (Mil $)	PET/MRI (Mil $)
Equipment	0.9 - 3	5+
Build out	1	2.5 (at UCLA)
Service contract/y	0.25	0.5
Throughput	12-15 pts/d	6-8 pts/day
Reimbursement	$1250	$1250?



Great research tool: tumor perfusion; phenotyping of tumors using "molecular" MRI (predictive markers); improved diagnostic accuracy of PET/MRI over PET/CT?
But do I really need an integrated system to do this?

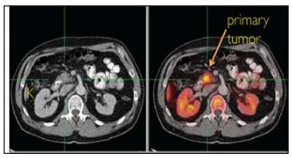
Summary: A rich portfolio of PET biomarkers

Koolen et al; EJNMMI 2012



Diagnostic/Phenotypic/ Prognostic Biomarkers
^{18}F-FDG; AA, ^{18}F-FLT; etc, choline, ect

UCLA 2013



Predictive Biomarkers
Is the therapeutic target expressed?
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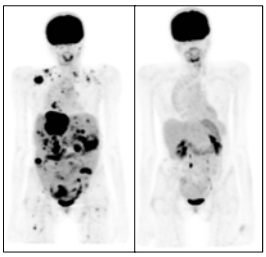
UCLA 2013



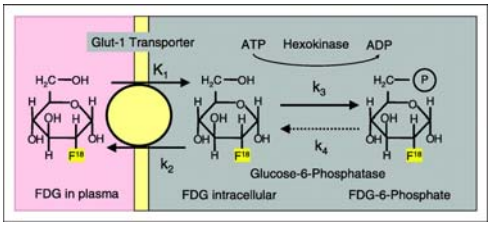
Intermediate endpoint Biomarkers Does the drug work?
^{18}F-FDG; ^{18}F-AA; ^{18}F-FLT

A randomized trial to determine the value of 18F-NaF bone imaging in patients with prostate CA

If you design a good study you must be willing to accept the results….!!!!

The 3 most frequently used bone imaging probes

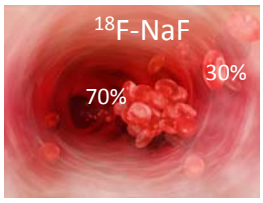
Tumor Metabolism



Kelloff G J et al. Clin Cancer Res 2005;11:2785-2808

Bone Metabolism

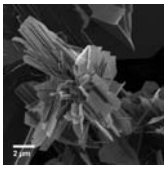
Rapid renal clearance



ECF

(100%)

OH



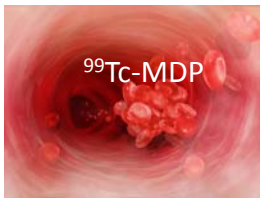
Hydroxyapatite

↓

Fluoroapatite

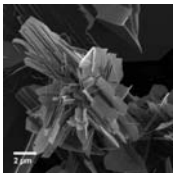
Accumulation depends on area of exposed bone surface

Slow renal clearance



(60%)

Chemisorption



2/3 Hydroxyapatite
1/3 Calcium phosphate

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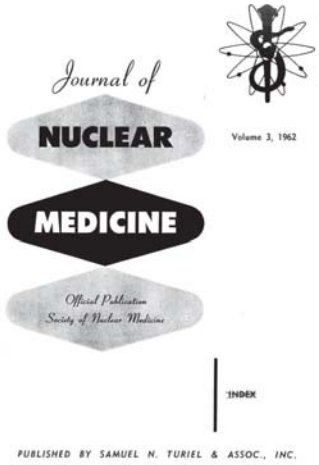
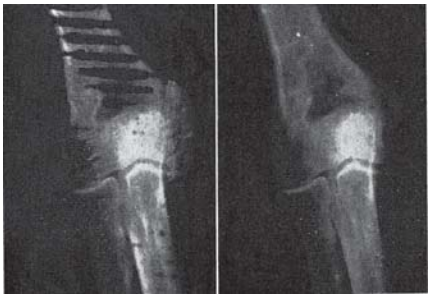
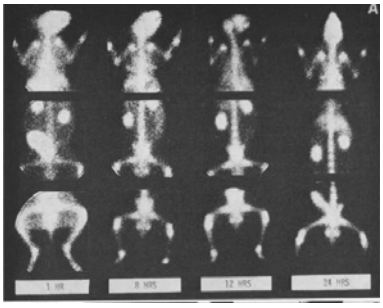
^{18}F-NaF standard method for bone scintigraphy in 1960s (Blau 1962)



Renewed interest due to PET and PET/CT and ^{99}MO/^{99}Tc generator shortage

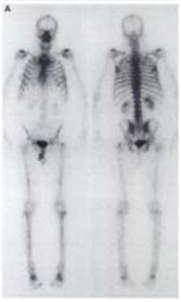


^{99}Tc diphosphonates; Subramanian et al; Radiology 1971



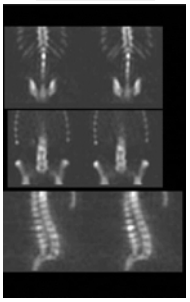
Incremental improvements

^{99}Tc MDP Planar



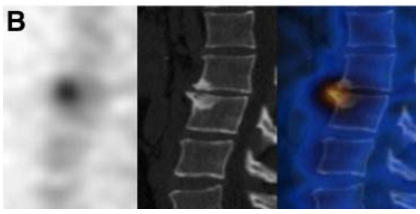
Good sensitivity
Limited specificity

SPECT



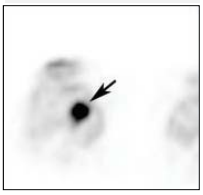
Improved sensitivity
Improved specificity

SPECT/CT



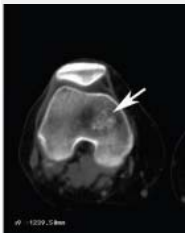
Even better Sens/Spec

^{18}F-NaF PET

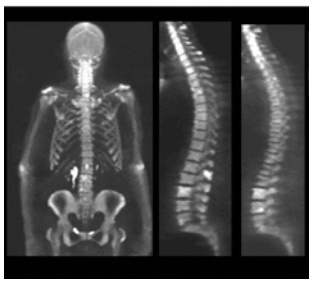


Very high sensitivity
Limited specificity

^{18}F-NaF PET/CT



^{18}F-NaF PET/CT



Highest sensitivity
Very good specificity (spine/ribs)

^{18}F-NaF PET/CT is superior to ^{18}F-NaF PET and appears to be superior to ^{99}Tc MDP

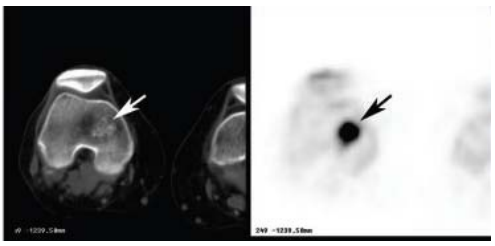
	^{18}F-NaF PET		^{18}F-NaF PET/CT	
	Sens (%)	**Spec (%)**	**Sens (%)**	**Spec (%)**
All	72	72	85*	*97**
Spine	50	86	84*	*100**
Thoracic cage	76	40	94	*87**
Pelvic bones	83	67	86	89
Skull	80	30	60	100
Long bones	100	25	100	100

*$p<0.05$

44 pts with Breast, Prostate, Lung, Colon, Ovary, Myeloma, Lymphoma, …

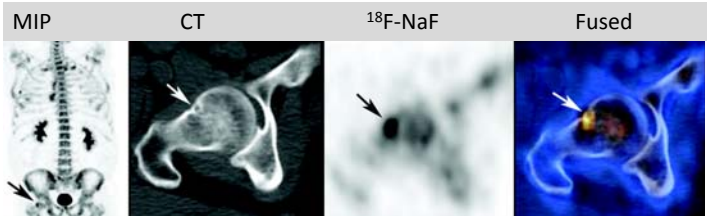
Patients	**Sens (%)**	**Spec (%)**
PET	88	56
PET/CT	100*	**88***

Even-Sapir et al; J Nucl Med 2004



Enchondroma

PET vs PET/CT: Reasons for false positives on ^{18}F-NaF scans



Sub-chondral bone cyst in prostate CA

Location	Finding
Vertebral column	Degenerative disk disease, osteophytes, facet joint disease, Schmorl's node, fracture
Thoracic cage	Radionecrosis, fracture, arthritic changes at the acromioclavicular and sternoclavicular joints, postop. changes
Pelvic bones	Avulsion injury, insufficiency fracture, Paget's disease, arthritic changes, postoperative changes
Skull and facial bones	Sinusitis, mastoiditis, osteoma
Long bones	Enchondroma, subchondral cyst, trochanteric bursitis, tendonitis, stress fracture

Einat Even-Sapir et al; J Nucl Med 2004

Where are we going? Strategy for ^{18}F-NaF Approval

CMS NCD February 26, 2010

^{18}F-NaF-PET should be covered only under an approved coverage with evidence development (CED) study

At that time no qualifying clinical study that would enable this coverage

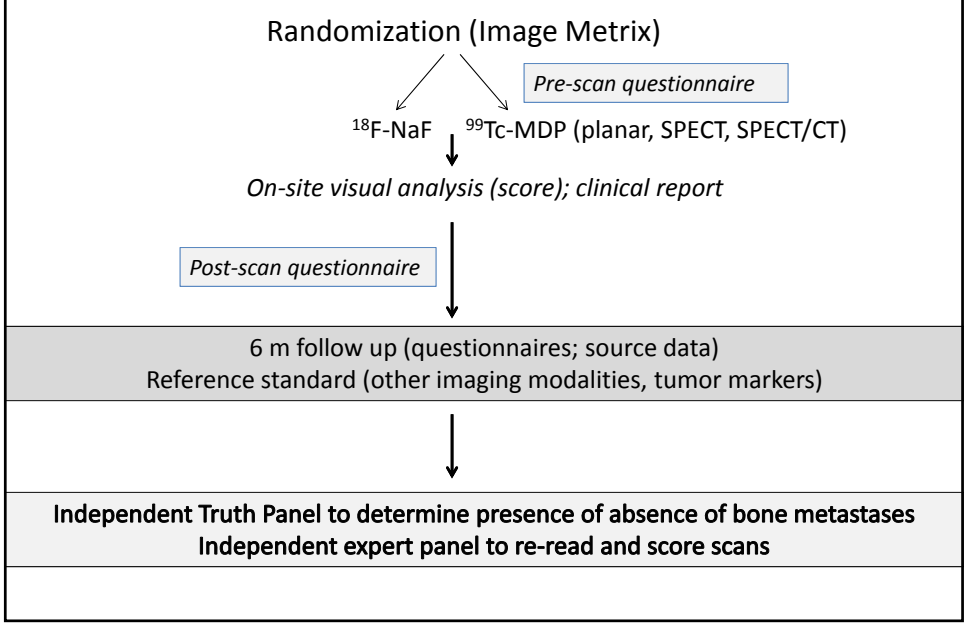
Now there is, once again NOPR!

	^{18}F-FDG NOPR	**^{18}F-NaF NOPR**
PET scans registered	157,453	*8,475*
PET scans consented/eligible	116, 953	*6,417*
# facilities (minimum 1 scan)	1,693	*633*

But, NOPR alone no longer sufficient..

NOPR data Courtesy Barry Siegel 2012

^{18}F-NaF PET/CT versus ^{99}mTc-MDP for Detecting Bone Metastases:
A Randomized International Multi-center Trial (19 sites in US, Switzerland, Australia, Austria)
Currently 530 pts enrolled



Surprising Preliminary Results

Bone Mets	^{18}F-NaF PET/CT	^{99m}Tc-MDP	Combined
Pos	18/155 (11.6%)	23/167 (13.8%)	41/322 (12.7%)
Neg	137/155 (88.4%)	144/167 (86.2%)	281/322 (87.3%)
Total	155	167	322

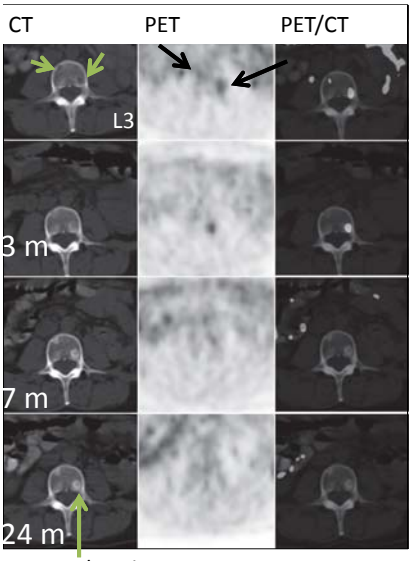
	^{18}F-NaF PET/CT	^{99m}Tc-MDP
1	0.8687	0.9272
2	0.9267	0.9450
3	0.9645	0.9566

^{18}F-NaF does not appear to be superior…..

^{18}F-FDG can be used for monitoring of breast CA bone metastases

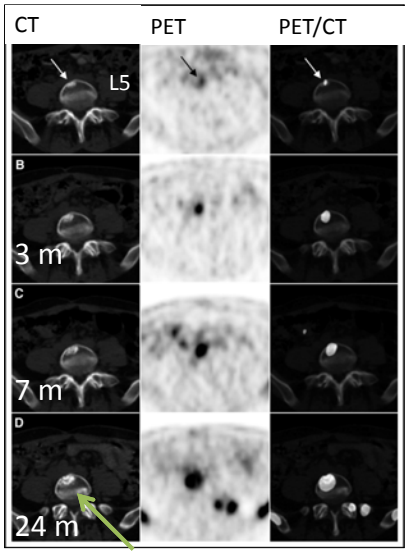
Du eta l; J Clin Oncol 2007:3440-3447

Osteolytic met responding



more sclerotic

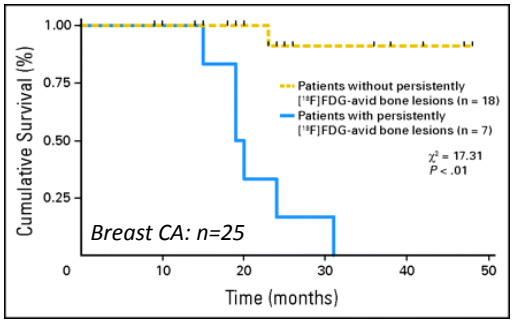
Osteoblastic met non-responding



larger

*Change in morphology and ^{18}F-FDG uptake **following treatment***

Initially Osteolytic (77)		Osteoblastic (41)		Mixed (11)	
Treatment		Treatment		Treatment	
81% FDG - and Sclerotic	*19% FDG +* Osteolytic	*52% FDG -* Sclerotic	*48% FDG +* Size ↑	*45% FDG -* Sclerotic	*55% FDG +* het.
All negative at late fu		All negative at late fu		All negative at late fu	

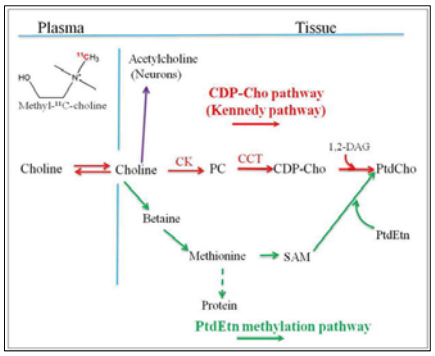


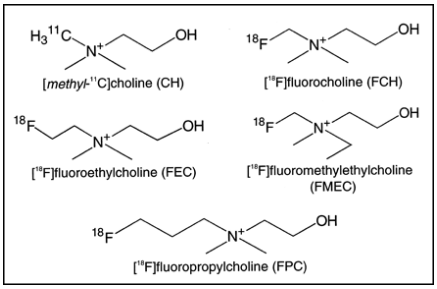
Du …Ell P; 2007; J Clin Oncol

FDG PET provides
- Phenotypic information
- Prognostic information (see prostate CA)
- Response assessments

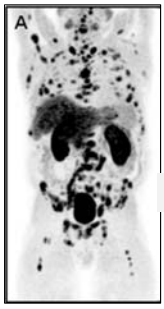
Morris et al; Clin Cancer Research 2005 (anti-microtubule CTX)

Probes, Metabolism, Images





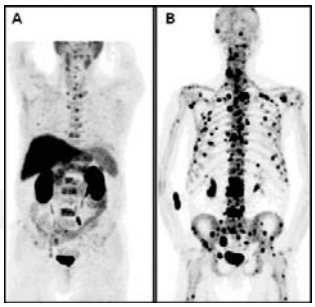
DeGrado et al; J Nucl Med 2001



But what do we learn?

Choline PET

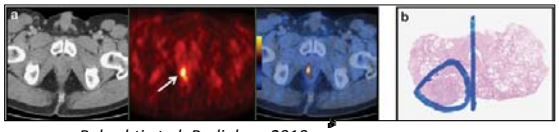
Choline PET



NaF PET

Beheshti et al; Seminars in Nuclear Medicine 2009

Potential applications of Choline analogs in Prostate cancer



Beheshti et al; Radiology 2010

Initial Diagnosis

Gleason score 7; PSA: 7.8 ng/ml

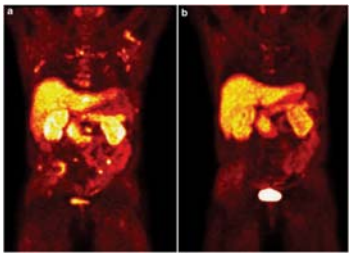
Detection of recurrence (^{18}F-choline)

Literature data	*N*	*PSA range/ or mean*	*Key findings*
Cimitan *et al.*	100	1	Higher Sens when PSA (>2–5 ng/ml)
Husarik *et al.*	68	0.36–100†	Lower Sens when PSA (<2–5 ng/ ml)
Beheshti *et al.*	21	56±64*	*Heavily sclerotic bone metastases may be ^{18}F-FCH-neg.*
Panebianco *et al.*	84	2	^{18}F-NaF/CT-negative bone marrow mets may be ^{18}F-FCH pos.
Casamassima *et al.*	71	0.2–2†	^{18}F-FCH more spec. than ^{18}F-fluoride

Bauman et al; Prostate Cancer and Prostatic Diseases 2012

Most likely more aggressive phenotype (higher PSA levels, higher PSA velocity); probably useful for identifying site of recurrence

Treatment Monitoring



Before and after 3 m of taxol

Beheshti et al; Eur J Nucl Med Mol Imag 2008

The utility of PET is expanding and the emphasis is shifting: Lets focus on phenotyping and predictive biomarkers

1990s: ^{18}F-FDG and others as diagnostic/prognostic biomarkers (more work to be done; see ^{18}F-NaF)

2000s: ^{18}F-FDG and others as intermediate endpoint biomarkers (more work to be done; standardization; reimbursement)

2010s: - Predictive biomarkers (^{18}F-FES;^{18}F-DHTS, etc)
- PET in drug development (PK and PD)
- Theranostics

Advanced PET/CT: Understand biology of disease
Use imaging probes to determine whether the therapeutic target is present and whether the target is inhibited by the drug (PD)

Future of PET/CT

- *Diverse portfolio of PET probes for research and clinic*
  - Diagnostic
  - Phenotypic
  - Prognostic
  - Predictive
  - Intermediate endpoint
- Drug development (PK and PD markers)
- Theranostics (precise organ dosimetry can be studied)

Together with CT: Most powerful current diagnostic tool in oncology
Role of PET/MRI to be determined (no doubt about research applications)

Challenges
- Standardization
- 2000 PET probes (do they make sense?)
- Close cross disciplinary collaborations (Biologists, radio-chem, chemistry, mol. imaging, radiologists, oncologists, material scientists, etc.)
- High regulatory bar (management, outcome, costs, reimbursement)