PET in Thyroid Cancer 2022: Focus on FDG and ^{124}I Na I

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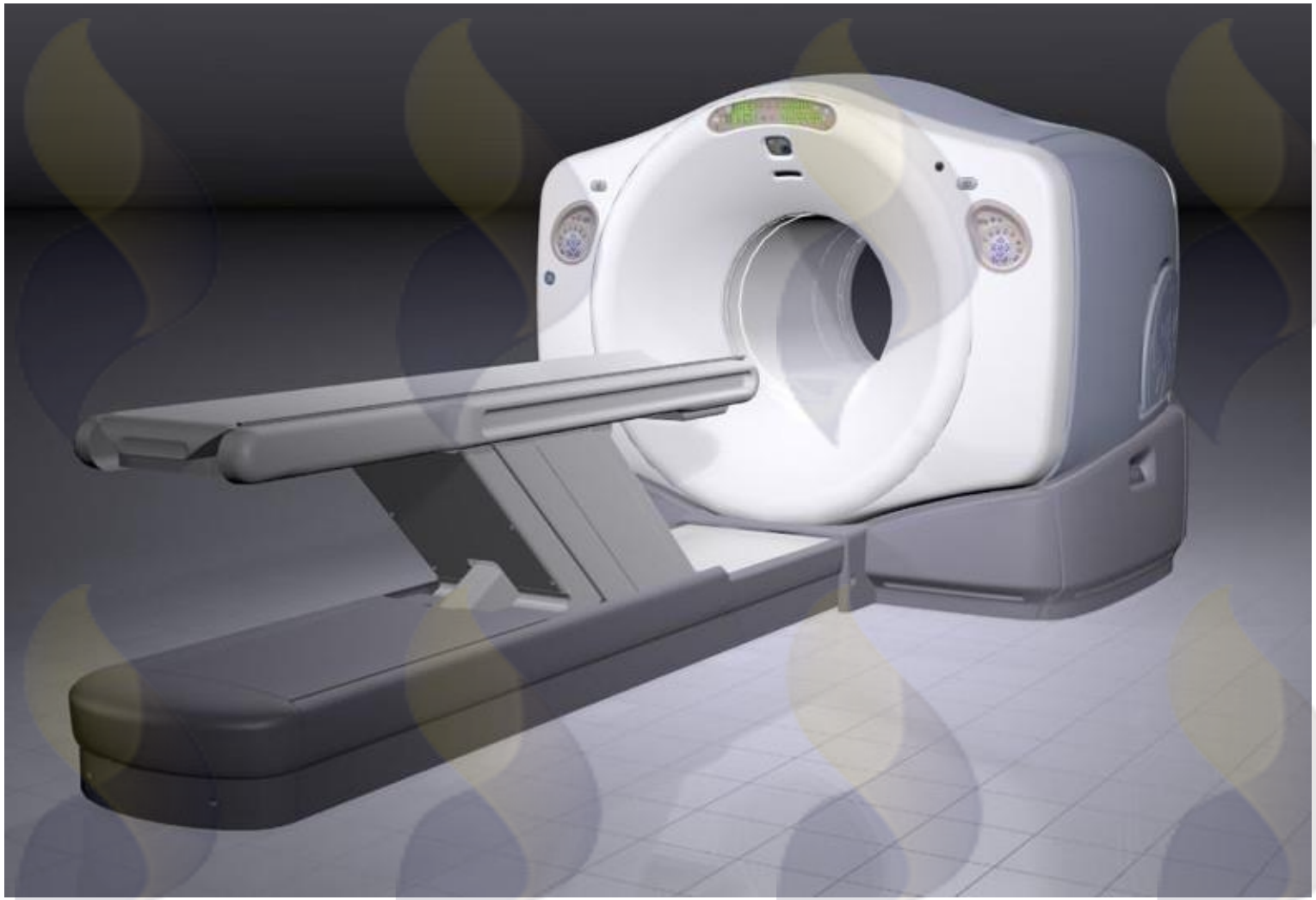
Memorial Sloan Kettering Cancer Center

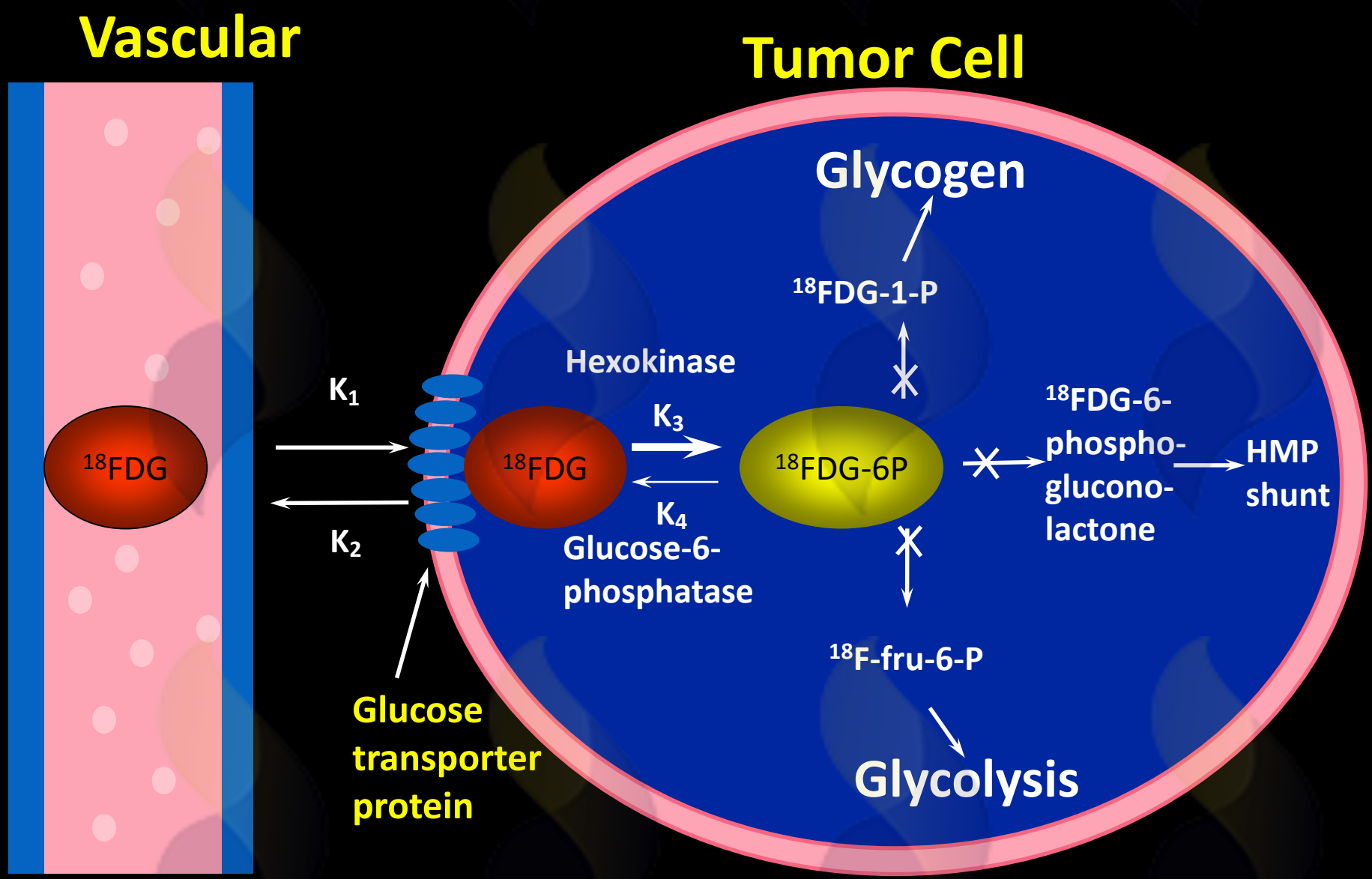
Discovery ST



Common Human Tumors and FDG PET

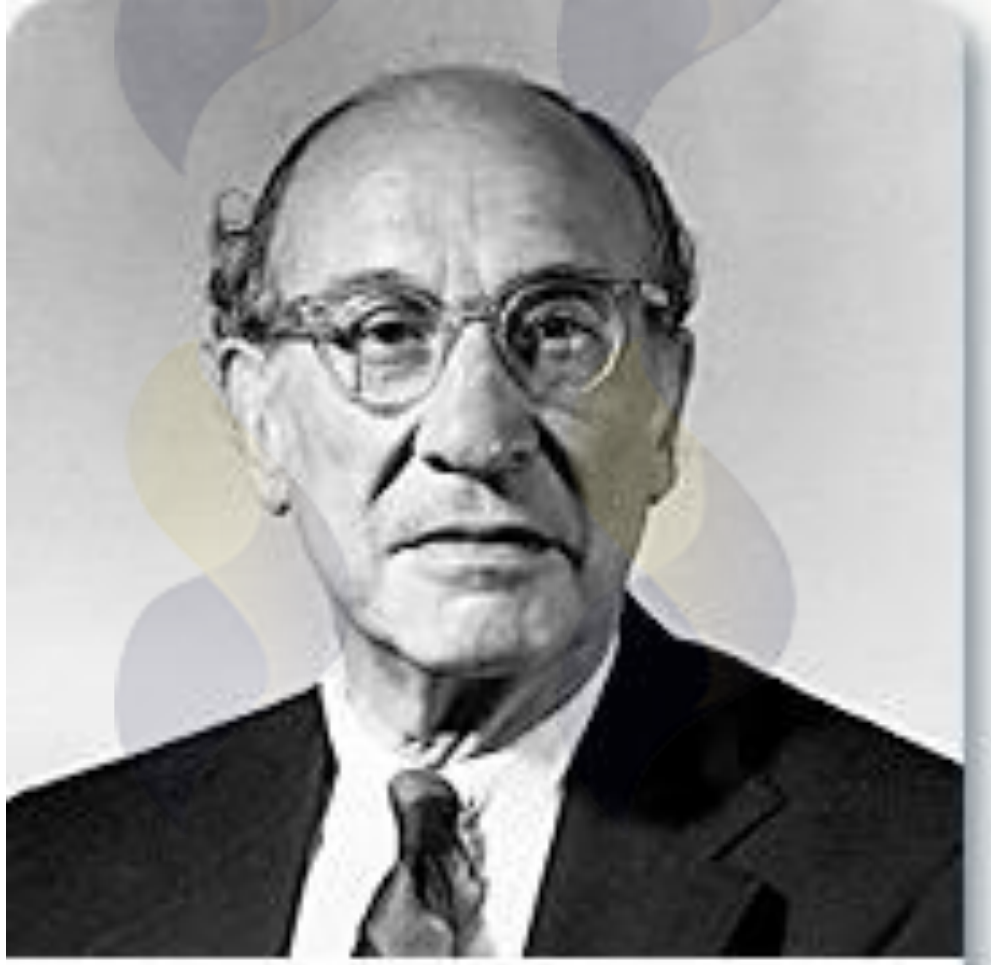
- Lymphoma
- Lung Cancer
- Breast Cancer*
- Colorectal Cancer
- ***Thyroid Cancer****
- Esophageal Cancer
- Prostate Cancer (CRPC)*
- Head and Neck Cancer

*** Tumors of Glands: FDG uptake inversely related to differentiation state**



Sokoloff validated concept of Metabolic Trapping of 2-DG and laid the groundwork for FDG application (normal brain)

Di Chiro conceptualized the application of FDG PET, recognized the value of the Warburg effect for imaging and performed the first studies in Human Tumors



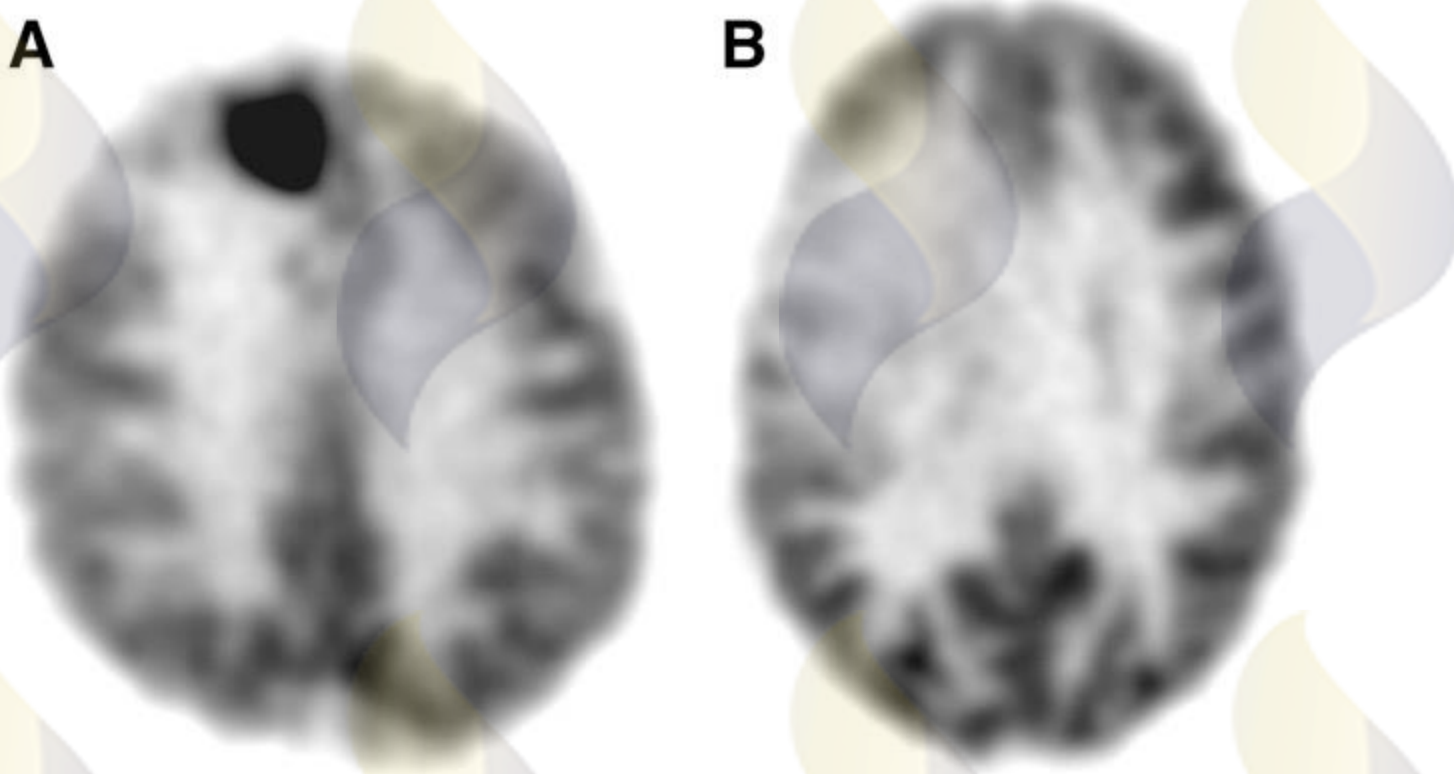
Louis Sokoloff
National Institute
of Mental Health, NIH

Lasker Award in 1981

For developing a pioneering approach (***Deoxyglucose method***) which enables scientists to visualize the simultaneous biochemical activity of an entire network of neural pathways in the brain and central nervous system.

Giovanni DI Chiro, M.D.
1926-1997

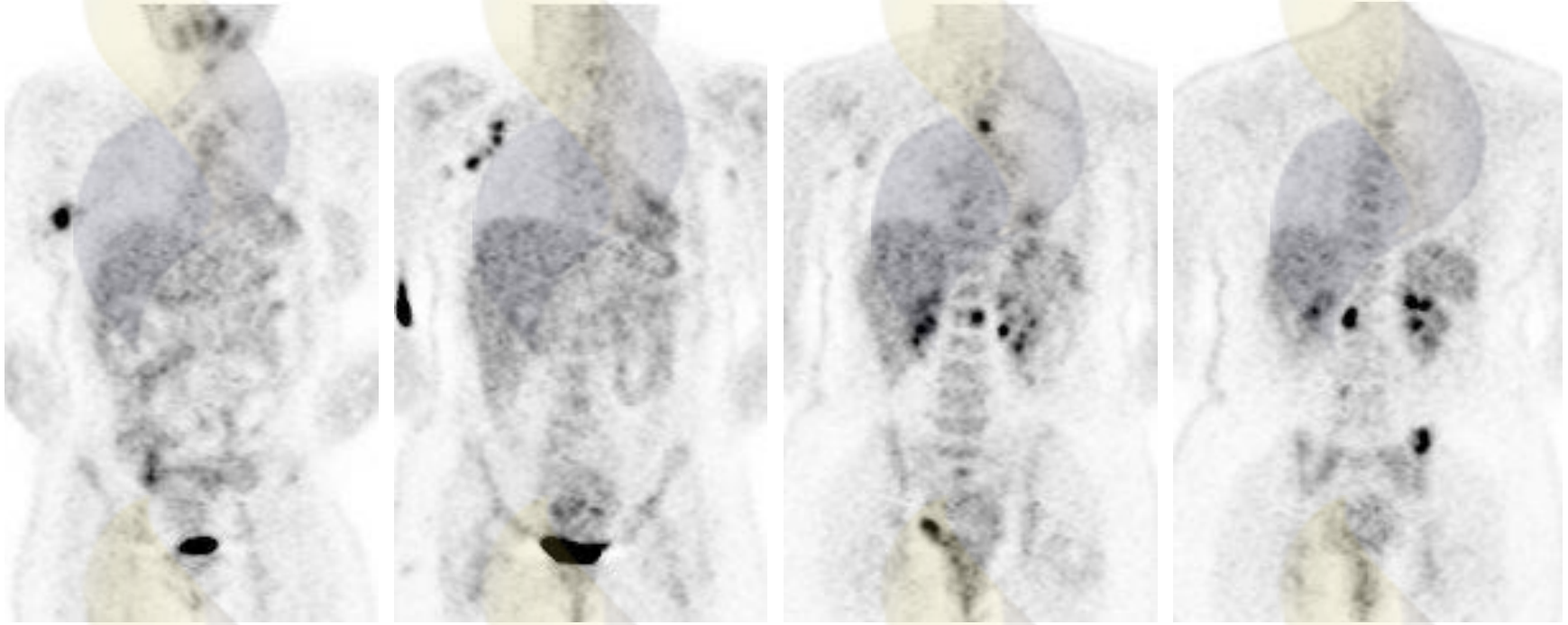
FDG PET in Brain Tumors



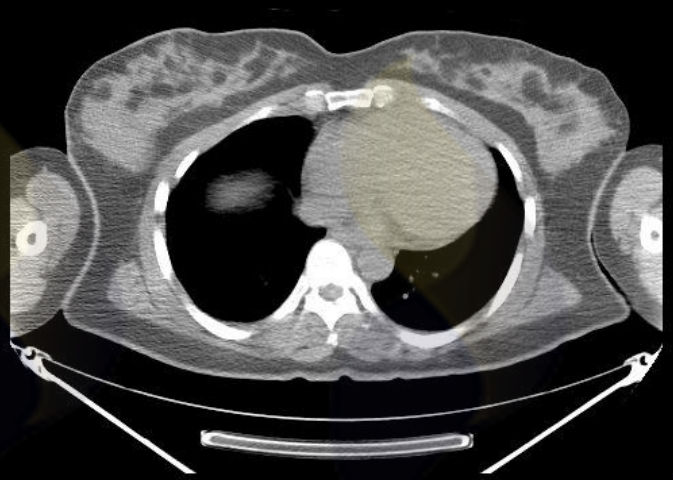
Glioblastoma Multiforme

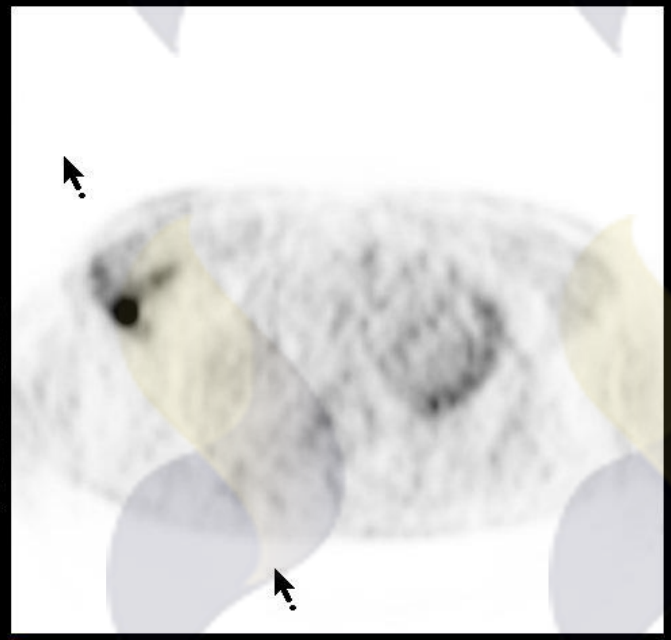
Grade II oligodendroglioma

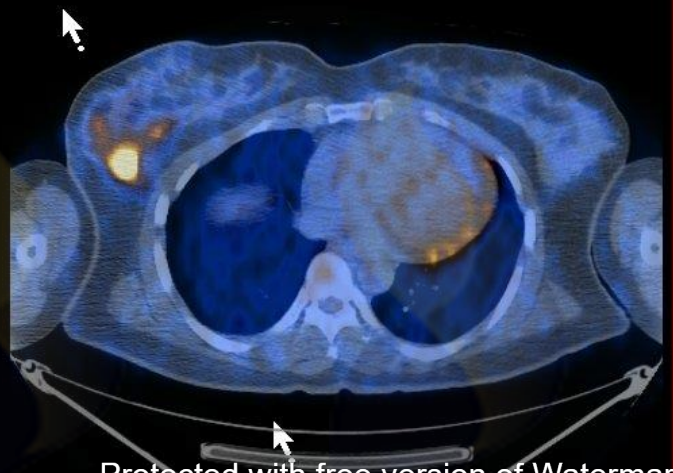
Newly Diagnosed Breast Cancer



Newly diagnosed breast cancer





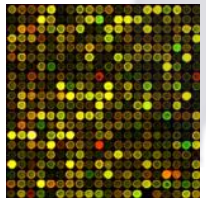


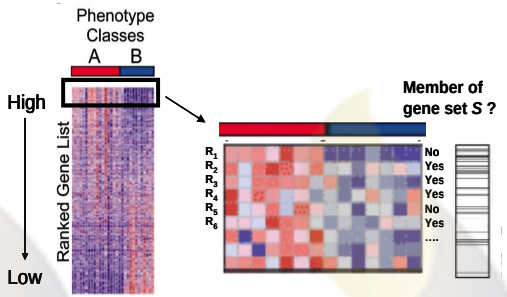
SUV

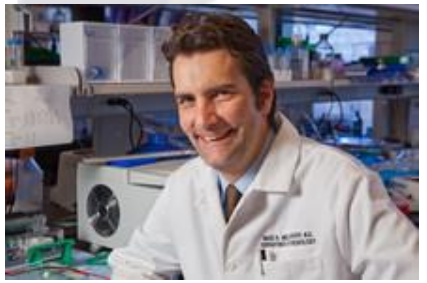
$$\frac{\text{Activity per unit volume}}{\text{Injected Activity/Body Wt*}}$$

Expe Approach

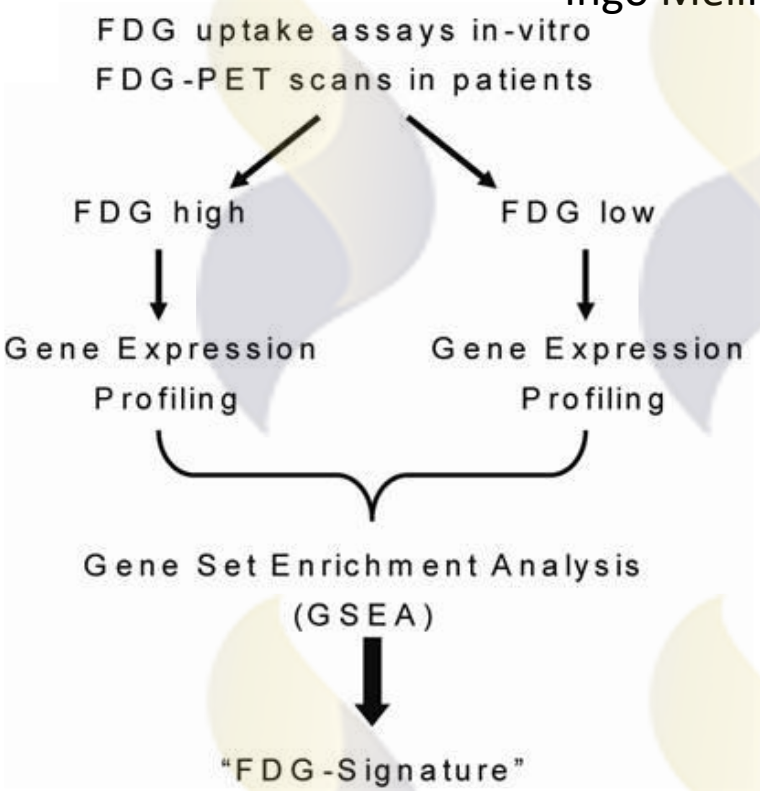
Alex Miller, Ph.D.







Ingo Mellinghoff, M.D.



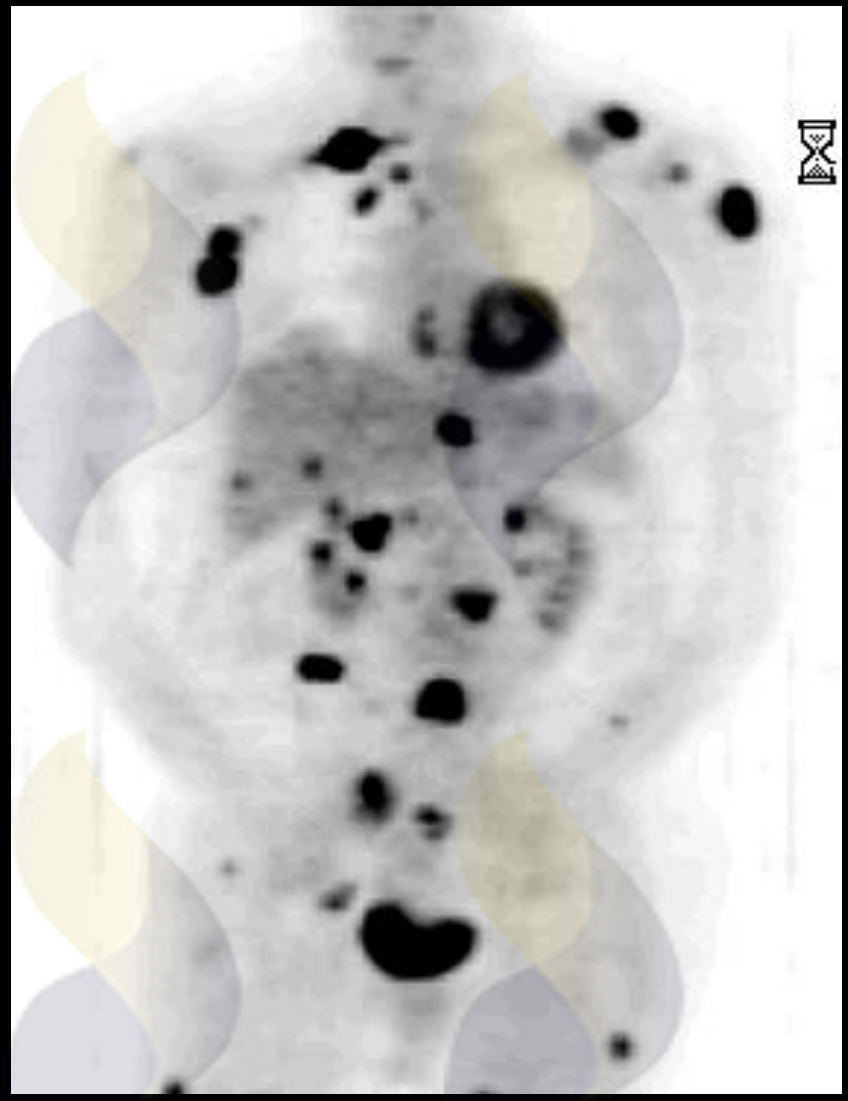
Most highly enriched metabolic pathways

METABOLIC PATHWAY ENRICHMENT ANALYSIS			
KEGG PATHWAY NAME	AVE RANK-BASED GSEA		
	NES	NOM p-val	FDR q-val
GLYCOLYSIS / GLUCONEOGENESIS - MAP00010	**3.11**	**0.00**	**0.00**
CARBON FIXATION - MAP00710	**2.17**	**0.00**	**0.03**
PENTOSE PHOSPHATE PATHWAY - MAP00030	**1.94**	**0.00**	**0.09**
AMINOACYL-TRNA BIOSYNTHESIS - MAP00970	1.88	0.00	0.10
ONE CARBON POOL BY FOLATE - MAP00670	1.88	0.02	0.08
NUCLEOTIDE SUGARS METABOLISM - MAP00520	1.86	0.01	0.08
...			

PET FDG SUV and Tumor Biology: the higher the SUV, the worse the tumor grade and prognosis

- Lung Ca JCO 2004; 22:3255
- Thyroid Ca JCEM. 2006;91(2):498-505.
- Esophageal Ca JCO, 2003;21:428
- Lymphoma JCO 2005,
- Sarcoma JNM, 1988; 29:181-186.
- Glioma J Neurosurgery 1985; 62:816-822.
- Prostate: Clin Cancer Res. 2010 Dec 15: 6093-9.

Papillary Thyroid Carcinoma
FDG Uptake



PET FDG in Thyroid Cancer

- ***Robbins R et al*** Real-Time Prognosis for Metastatic Thyroid Carcinoma Based on 2-[^{18}F]Fluoro-2-Deoxy-D-Glucose-Positron Emission Tomography Scanning J Clin Endocrol Metab *JCEM.; 91(2):498-505.2006*
- ***Wang W. et al*** Prognostic Value of [18F]Fluorodeoxyglucose Positron Emission Tomographic Scanning in Patients with***J Clin Endocrinol Metab 2000 85: 1107–1113, 2000)***
- ***Wang W et al*** PET scanning with 18F-fluoro-2-deoxyglucose can localize residual differentiated thyroid cancer in patients with negative 131Iodine whole body scans. ***J Clin Endocrinol Metal. 84:2291– 2302 1999***.
- ***Wang W et al,*** Resistance of [18f]-fluorodeoxyglucose-avid metastatic thyroid cancer lesions to treatment with high-dose radioactive iodine. Thyroid. 2001 Dec;11(12):1169-75.
- ***Daniel A Pryma et al***: **Diagnostic accuracy and prognostic value of 18F-FDG PET in Hürthle cell thyroid cancer patients** J Nucl Med2006 Aug;47(8):1260-6.PMID: 16883003
- ***Ricarde-Fihlo, J et al:*** Mutational profile of Advanced Primary and Metasttic RAI refractory thyroid cancer reveals distinct Pathogenetic roles for BRAF, PIK3 CA, and AKT1 Cancer Res 2009;69(11):4885–93

FDG Uptake vs Survival

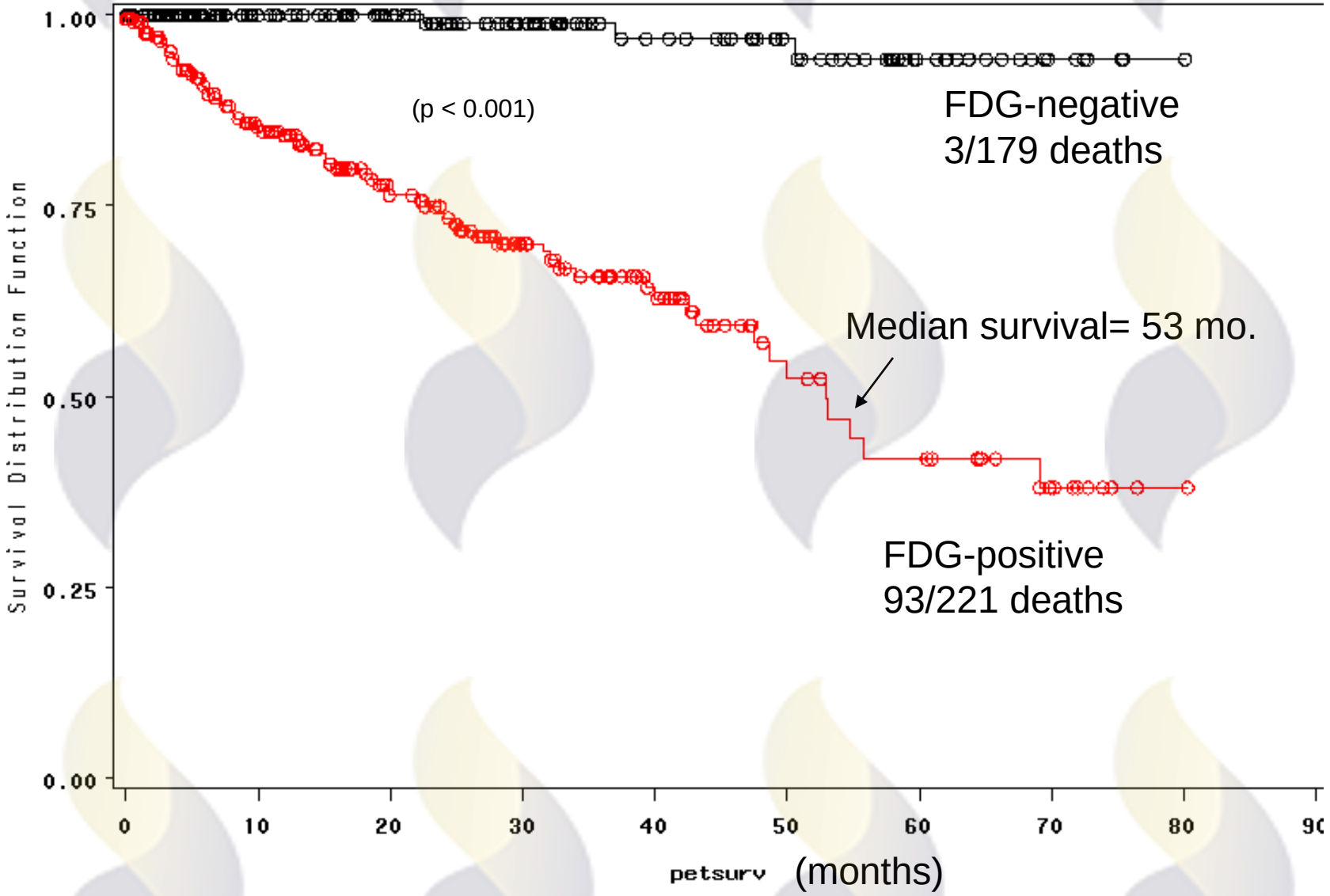
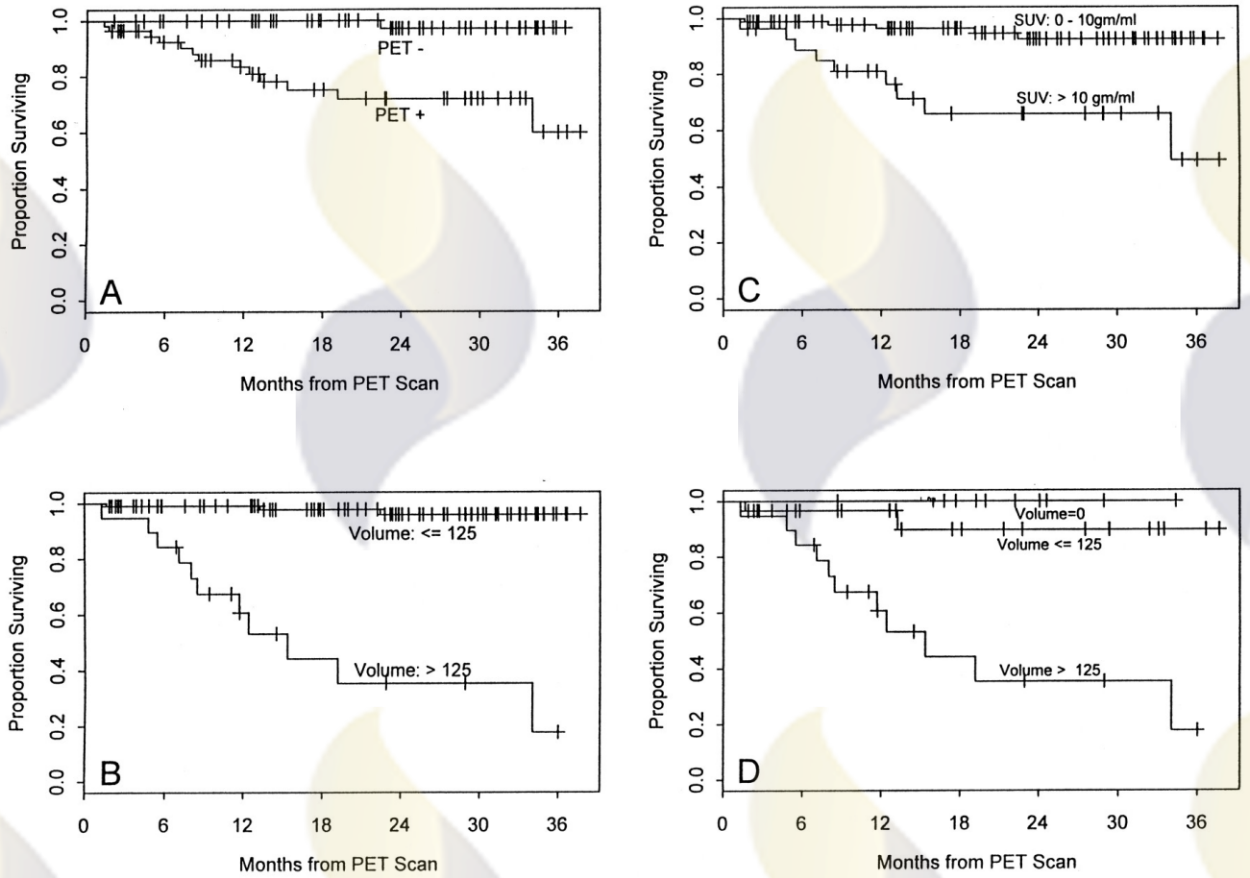
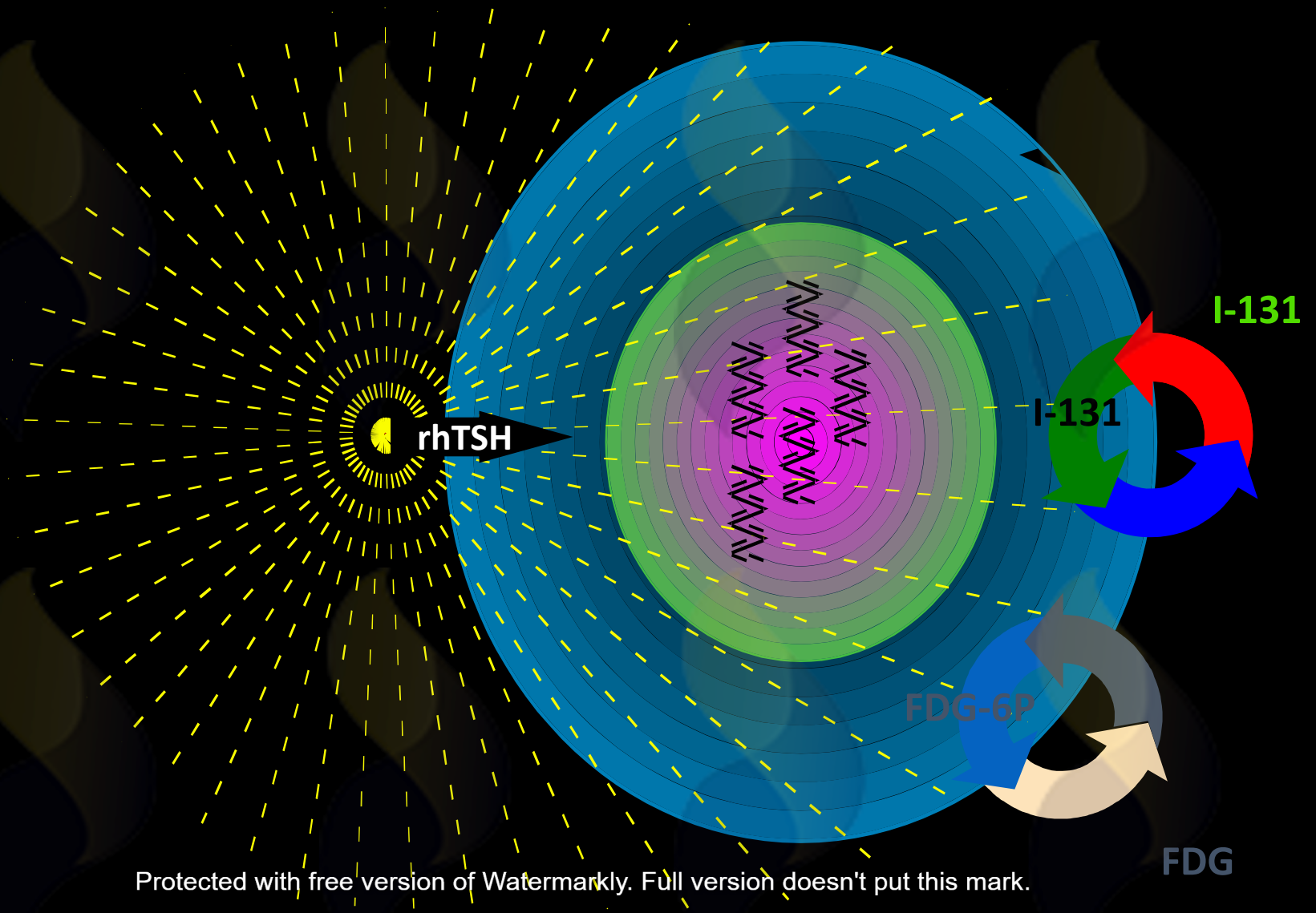


Figure 3. Kaplan-Meier plots of patient survival based on abnormal retention of FDG (A; PET +), volume of FDG-avid ...

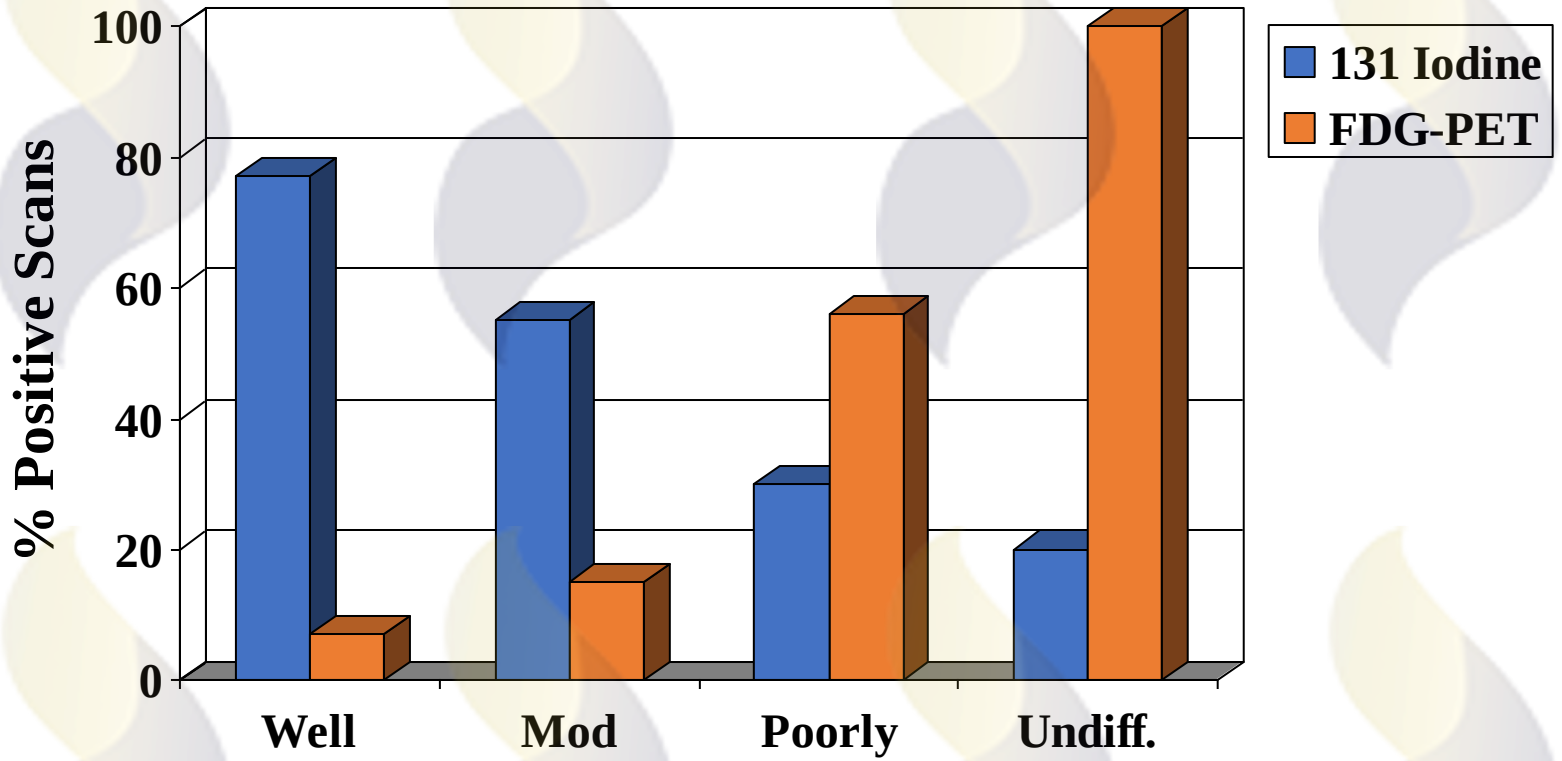


J Clin Endocrinol Metab, Volume 85, Issue 3, 1 March 2000, Pages 1107–1113, https://doi.org/10.1210/jcem.85.3.6458

Key Biology of Thyroid Cancer Cell



Effect of Tumor Differentiation on Scan Positivity



PET FDG and DTC summary findings

- FDG uptake (SUV) correlates with poor prognosis for metastatic DTC
- In regard to FDG, (TG>10: structural disease present)
  - Increasing volume of metabolically active disease is bad
  - FDG avid disease is more likely to be RAI refractory
- 131I uptake and FDG uptake are inversely correlated
- FDG can detect metastases in the absence of RAI uptake
- In advanced Hurtle cell cancer, FDG PET useful initial staging and monitoring progress and /or response
- RAIR, FDG- PET–positive metastases are enriched for BRAF mutations. If BRAF is mutated in the primary, it is likely that the metastases will harbor the defect.

FDG PET - Hurthle Cell Cancer (5% of DTC)

- Daniel A Pryma et al: **Diagnostic accuracy and prognostic value of 18F-FDG PET in Hürthle cell thyroid cancer patients** J Nucl Med2006 Aug;47(8):1260-6.PMID: 16883003
- Forty-four patients 24 positive and 20 negative ;1 false-positive and 1 false-negative study, **sensitivity of 95.8% and a specificity of 95%.**
- In 5 of 11 patients who had both positive CT and 18F-FDG PET findings, 18F-FDG PET revealed additional sites of disease.
- Prognosis: proportional ot SUV: , each increase in intensity by SUVmax unit was associated with a 6% increase in mortality ($P < 0.001$).
- The 5-y overall survival in patients with SUVmax < 10 was 92%; it declined to 64% in those with SUVmax > 10 ($P < 0.01$).
- Hürthle cell thyroid cancer should undergo 18F-FDG PET as part of their initial postoperative staging and periodically to screen for occult recurrence, particularly in patients with elevated serum thyroglobulin.

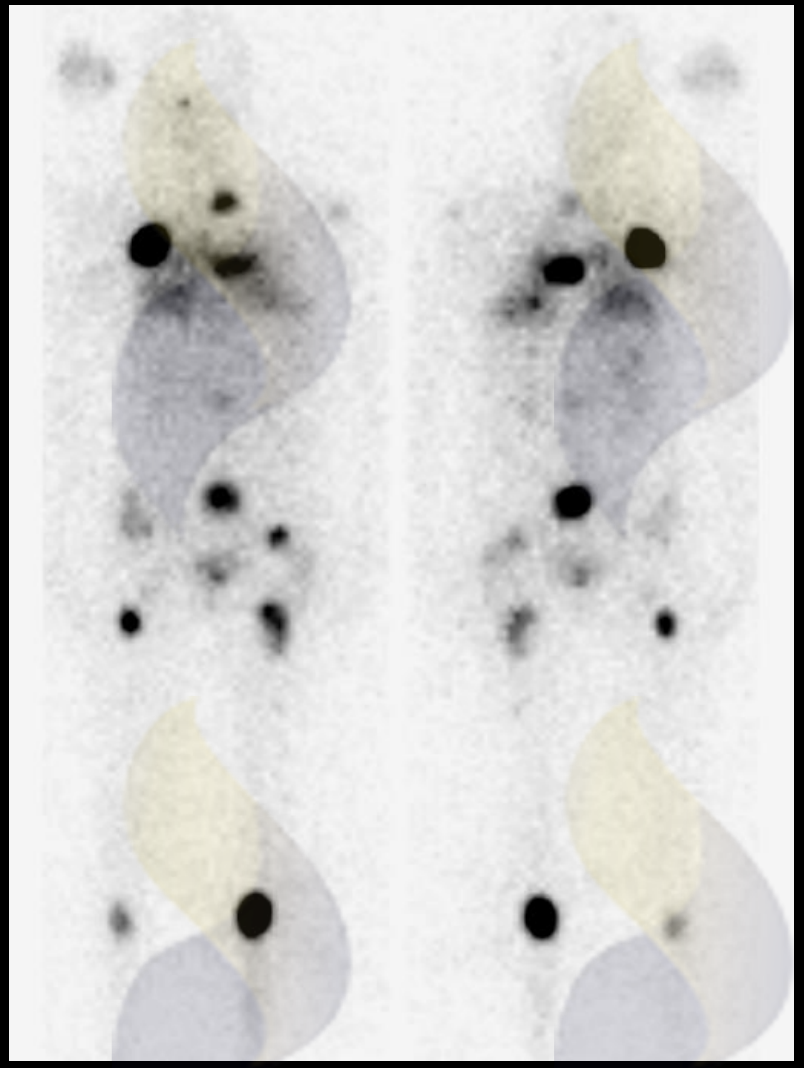
FDG PET – Role of Genetic Profile

- ***Ricarde-Fihlo, J et al**:* Mutational profile of Advanced Primary and Metasttic RAI refractory thyroid cancer reveals distinct Pathogenetic roles for BRAF, PIK3 CA, and AKT1 Cancer Res 2009;69(11):4885–93
- Patients with poorly differentiated thyroid cancers (PDTC), anaplastic thyroid cancers (ATC), and radioactive iodine- refractory (RAIR) differentiated thyroid cancers have a high mortality, particularly if positive on [18F]fluorodeoxyglucose (FDG)-positron emission tomography (PET).
- 52 primary tumors (34 PDTC and 18 ATC), and 55 RAIR, FDG- PET-positive recurrences and metastases (nodal and distant) from 42 patients.
- RAS mutations were more prevalent than BRAF (44 versus 12%; P = 0.002) in primary PDTC, whereas BRAF was more common than RAS (39 versus 13%; P = 0.04) in PET-positive metastatic PDTC.
- BRAF mutations were highly prevalent in ATC (44%) and in metastatic tumors from RAIR PTC patients (95%).
- RAIR, FDG- PET–positive metastases are enriched for BRAF mutations. If BRAF is mutated in the primary, it is likely that the metastases will harbor the defect.

Radioisotopes* of Iodine Used in Thyroid Cancer

Radionuclide	*Purpose*
• ^{131}I-Iodide	• Therapy
• ^{125}I-Iodide	• Therapy (Ablation)
• ^{124}I-Iodide	• PET Imaging
• ^{123}I-Iodine	• δ-Camera Imaging

Refractory Bone Metastases



Progression to Death
Despite > 1000 mCi ^{131}I

Unmet Need:
Better Dosimetry

The Clinical Problem: RAI-Refractory Thyroid Cancer

- Distant metastases are the most frequent cause of death for patients with differentiated thyroid cancer[1]
- Decreased RAI incorporation into metastatic sites is associated with higher mortality[2]
- New therapies for RAI-refractory thyroid cancer are desperately needed
  - Early Promise of MEK and BRAF inhibitor Drugs

Theranostic

A drug or biologic with intrinsic diagnostic and therapeutic properties

- E.g. Na $^{124}I/^{131}I$ for Dx/Rx thyroid Ca

Thyroid Cancer Treatment

Redifferentiation Therapy Imaging for ^{131}I-uptake

James Fagin

Alan Ho

Mike Tuttle

Laura Boucai

The Clinical Problem: RAI-Refractory Thyroid Cancer

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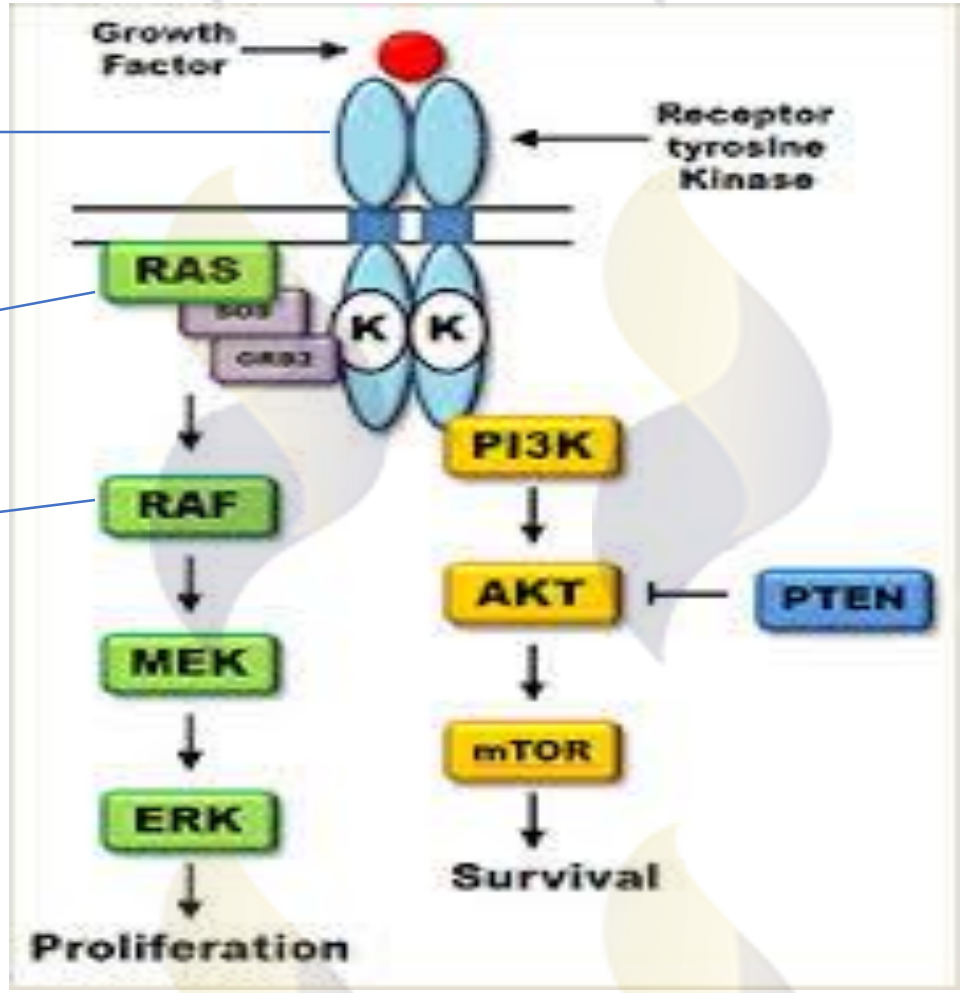
MAP Kinase Signaling and PapillaryThyroid Cancer (PTC)

RET/PTC in 3/20 patients (15%)

NRAS Q61R and *Q61K*
25% (5/20) patients

BRAF V600E 45%(9/20) patients



Driver oncogenes are known for ~95% of PTC tumors, and ~75% involve MAPK pathway

Integrated Genomic Characterization of Papillary Thyroid Carcinoma

The Cancer Genome Atlas Research Network[1]

Cell 159:676-690, 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer

Alan L. Ho, M.D., Ph.D., Ravinder K. Grewal, M.D., Rebecca Leboeuf, M.D., Eric J. Sherman, M.D., David G. Pfister, M.D., Desiree Deandreis, M.D., Keith S. Pentlow, M.Sc., Pat B. Zanzonico, Ph.D., Sofia Haque, M.D., Somali Gavane, M.D., Ronald A. Ghossein, M.D., Julio C. Ricarte-Filho, Ph.D., José M. Domínguez, M.D., Ronglai Shen, Ph.D., R. Michael Tuttle, M.D., Steve M. Larson, M.D., and James A. Fagin, M.D.

N Engl J Med 2013; 368:623-632. February 14, 2013

Primary Objective

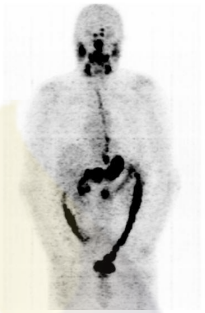
To determine whether RAI incorporation increases in RAI-refractory thyroid cancer metastases after 4 weeks of treatment with a MAPK pathway inhibitor.

Selumetinib (AZD6244 Hyd-Sulfate, ARRY-142886)

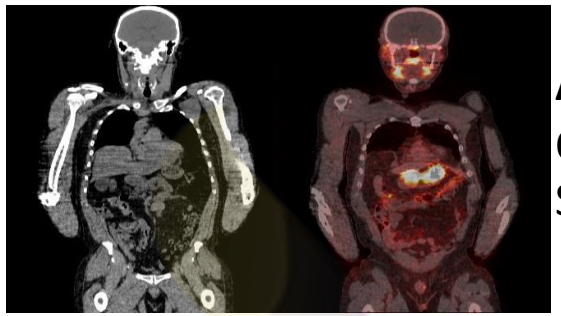
Highly selective, allosteric inhibitor of MEK 1/2

Inhibits MEK1 *in vitro* with an IC_{50} of 14.1 +/- 0.79 nM[1]

[1] *Yeh TC, Clin Cancer Res 13: 1576-1583, 2007.*



PET images



CT images Ffused images

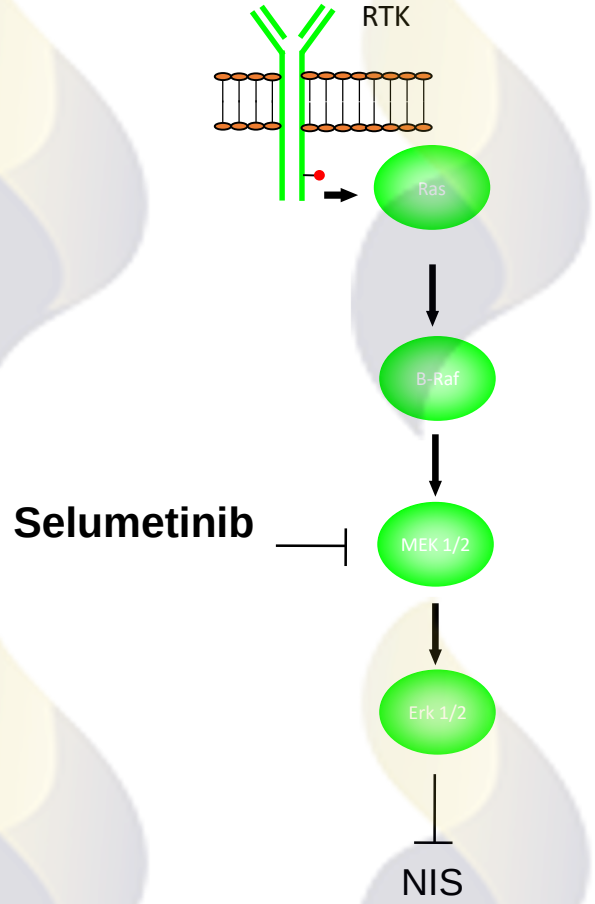
Normal Biodistribution of ^{124}I

^{124}I –Positron Emission Tomography (PET)/CT

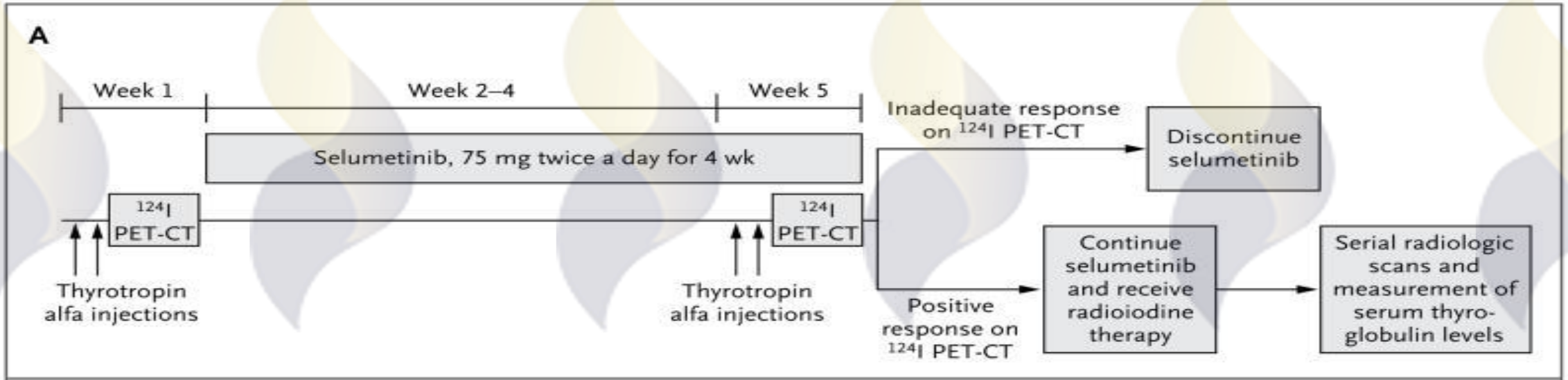
Advantages of ^{124}I –PET

Quantitative, allows lesional dosimetry

Structural correlates for iodine incorporation



Restoring Radiodine Uptake in Thyroid Cancer
Ho et al: N Engl J Med. 2013 Feb 14; 368(7): 623–632.



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Tumor Genotype	Patients with Increased Iodine Uptake in a Lesion after Selumetinib	Patients Who Received Radioiodine
	no./total no. of patients	
BRAF	4/9	1/9
NRAS	5/5	5/5
RET/PTC	2/3	1/3
Wild-type	1/3	1/3
Total	12/20	8/20

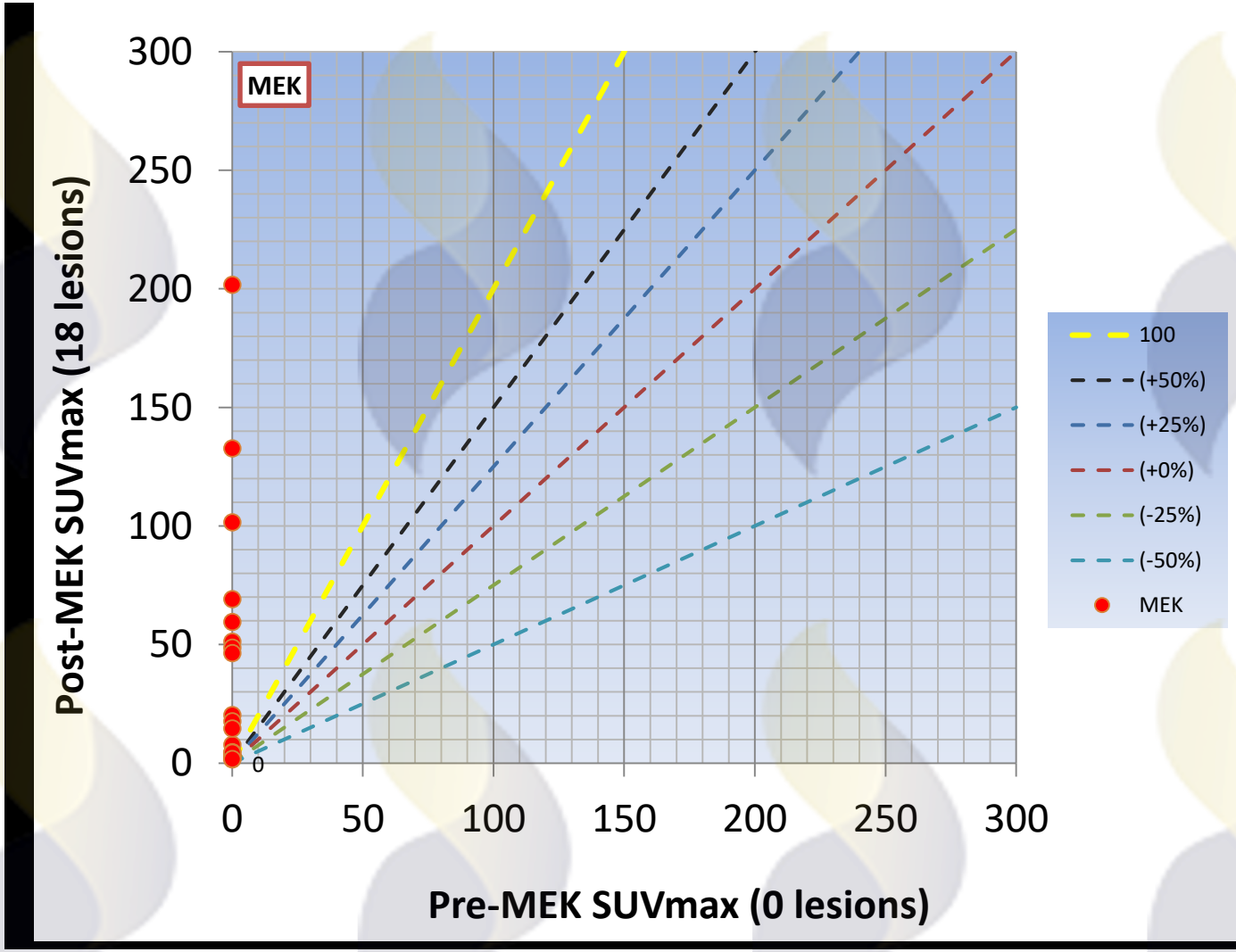
^{124}I PET: Selumetinib induces iodine incorporation in a BRAF MUT patient

Baseline

Post-Selumetinib

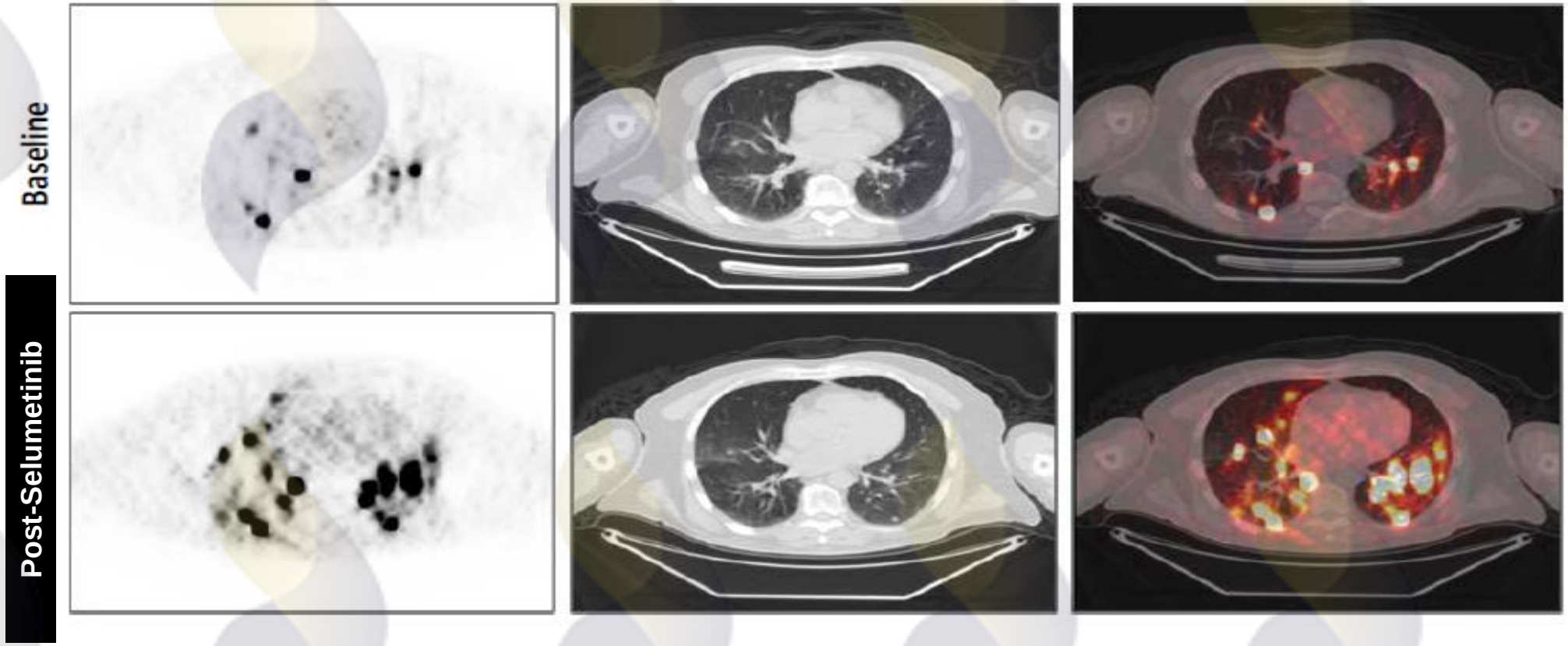
Ravinder Grewal

^{124}I PET Lesional Analysis: Selumetinib induces iodine incorporation in nearly all metastases

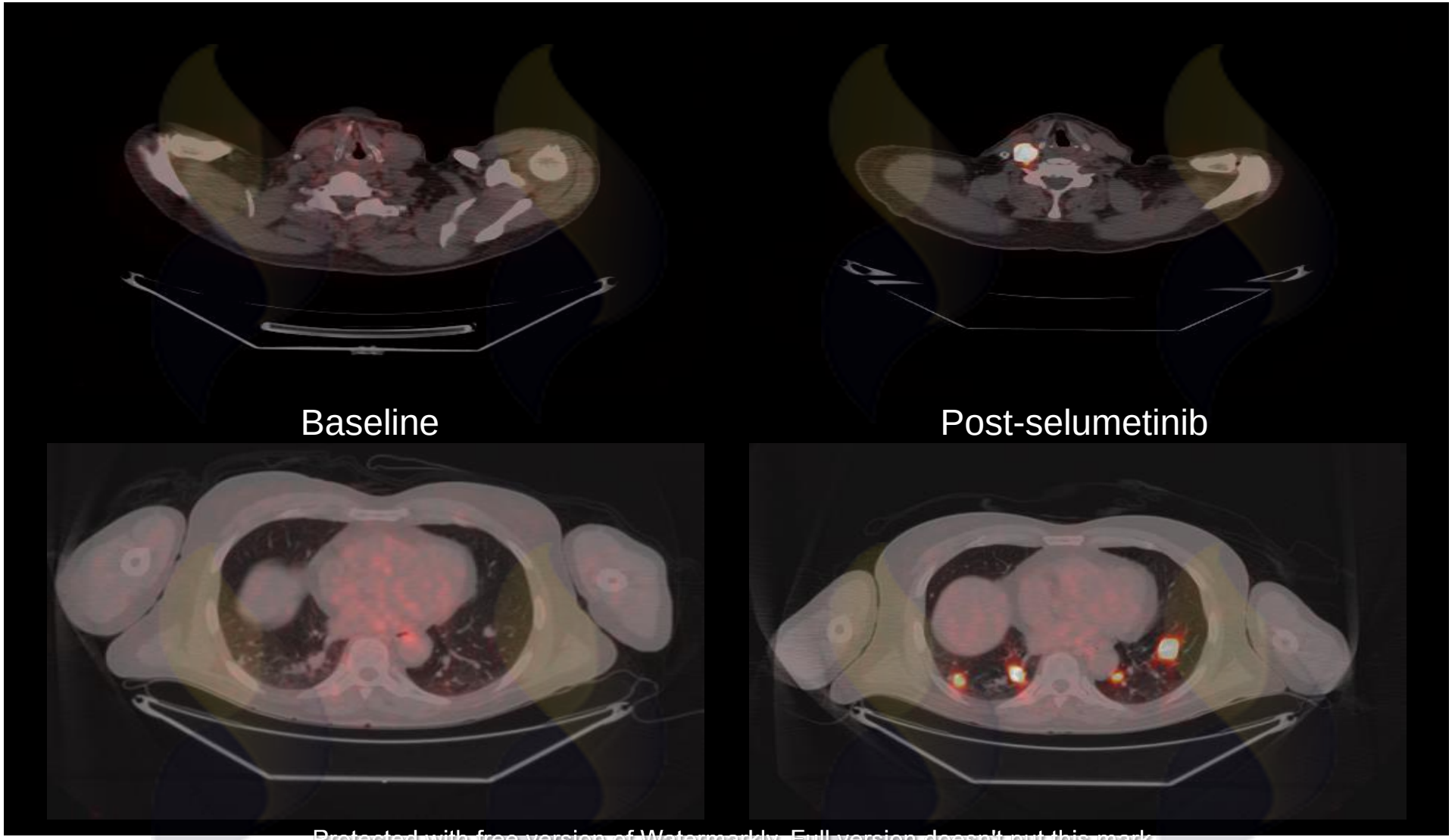


Desiree D'Andreis and Ravinder Grewal

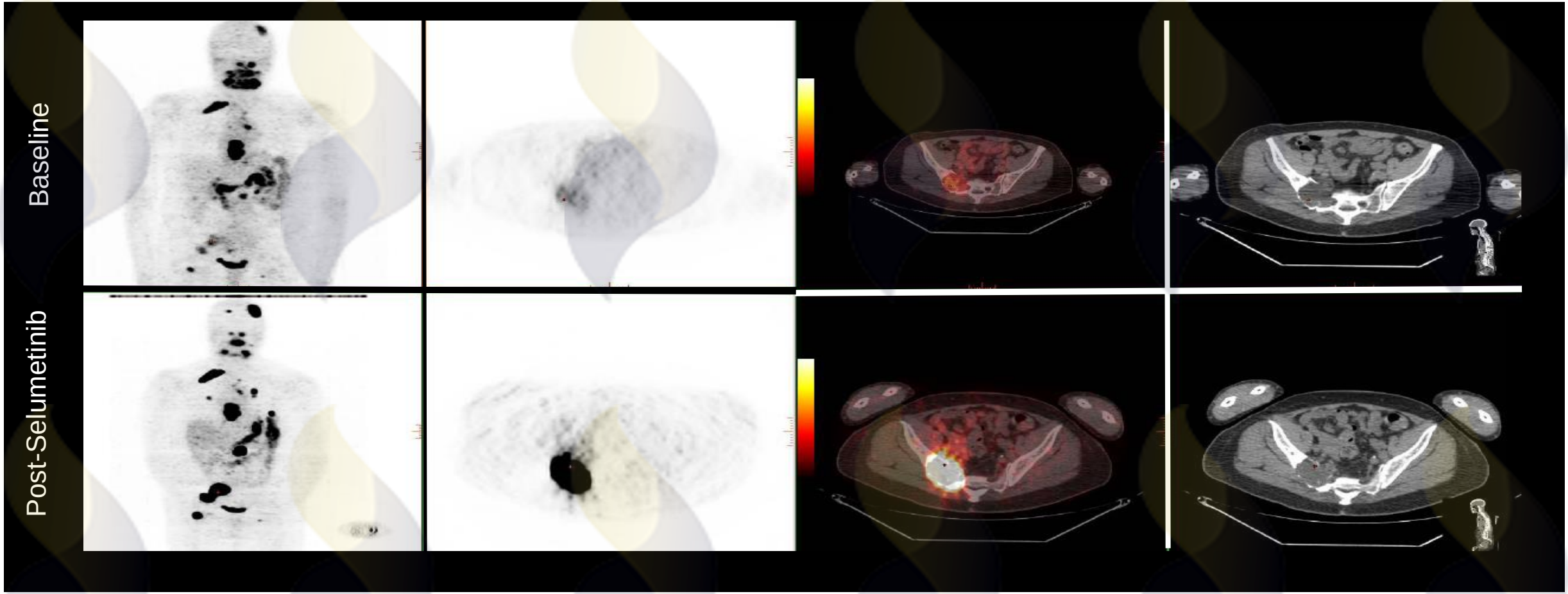
Selumetinib increases iodine incorporation in an *NRAS* MUT patient with ^{124}I negative and positive lesions



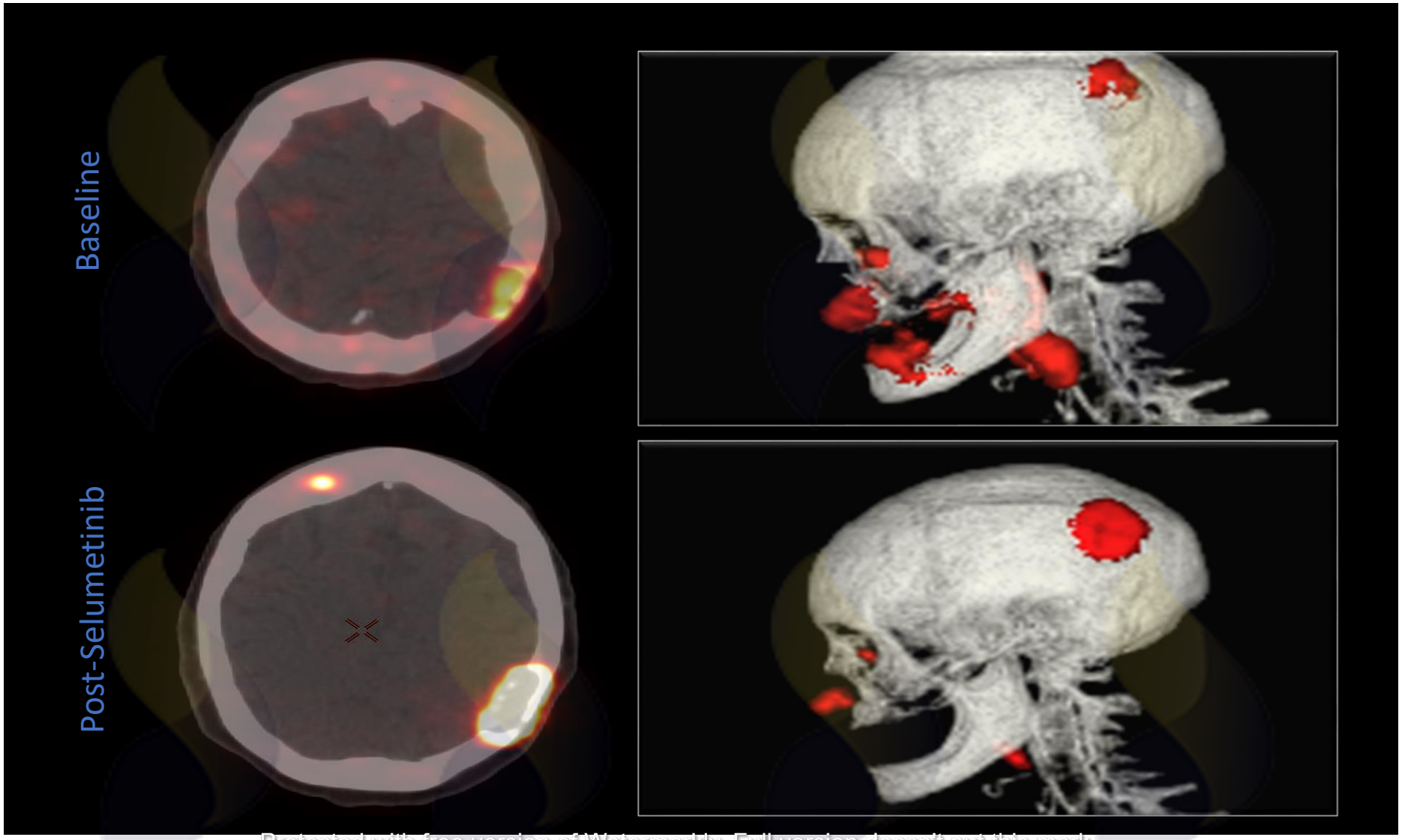
^{124}I PET/CT: Fused Axial Images (*BRAF* MUT patient)



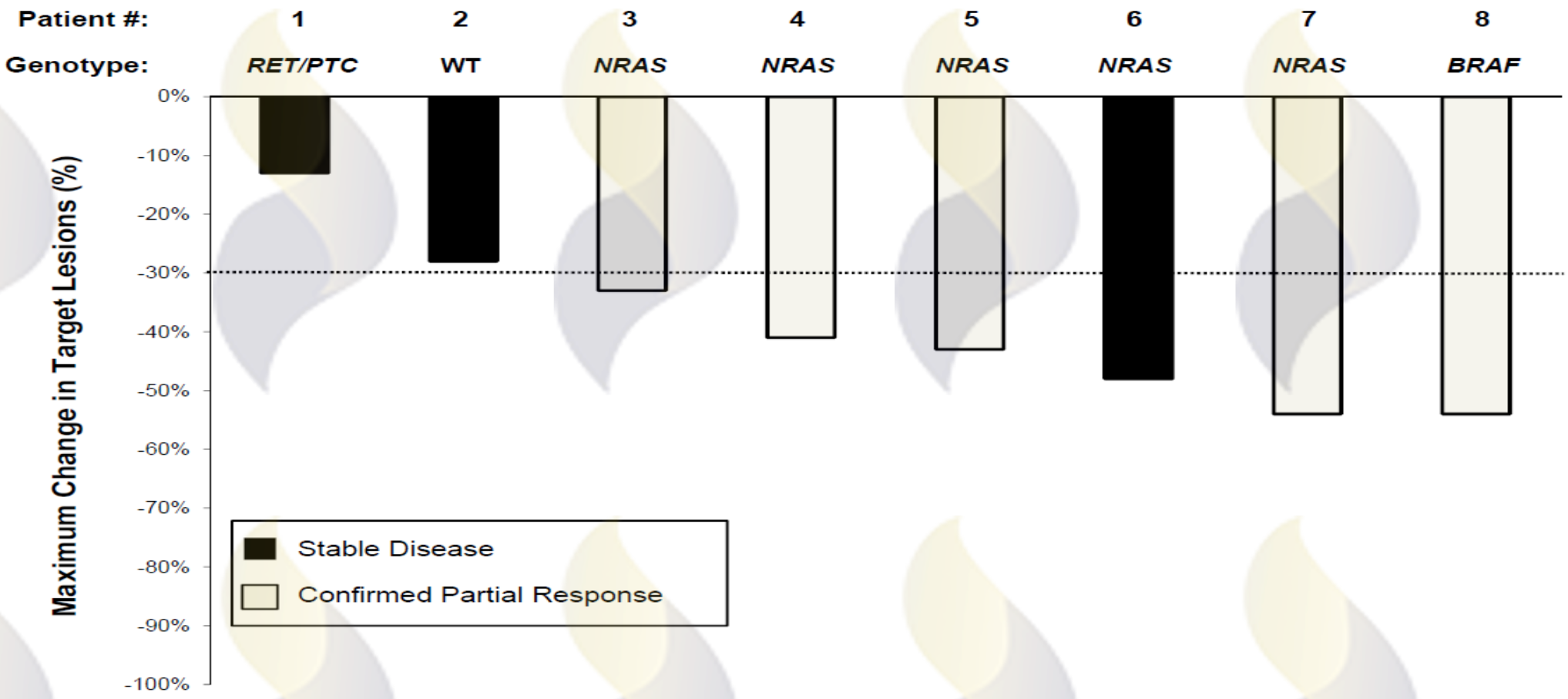
^{124}I PET: selumetinib increases iodine incorporation in bone metastases (*NRAS* MUT patient)



^{124}I PET: selumetinib increases iodine incorporation in bone metastases (*NRAS* MUT patient)



Responses for RAI-Treated Patients



Ho, A.L. et. al., NEJM, 368:623-632, 2013

Summary

- Selumetinib enhances iodine incorporation in patients with RAI refractory thyroid cancer and reverses RAI resistance
- Selumetinib effects upon iodine incorporation are dependent upon tumor genotype.
- All 8 patients treated benefited from Selumetinib induction of RAI, with 6/8 PR and 8/8 TG drop
- Ho et al: N Engl J Med. 2013 Feb 14;368(7):623-32. doi: 10.1056/NEJMoa1209288

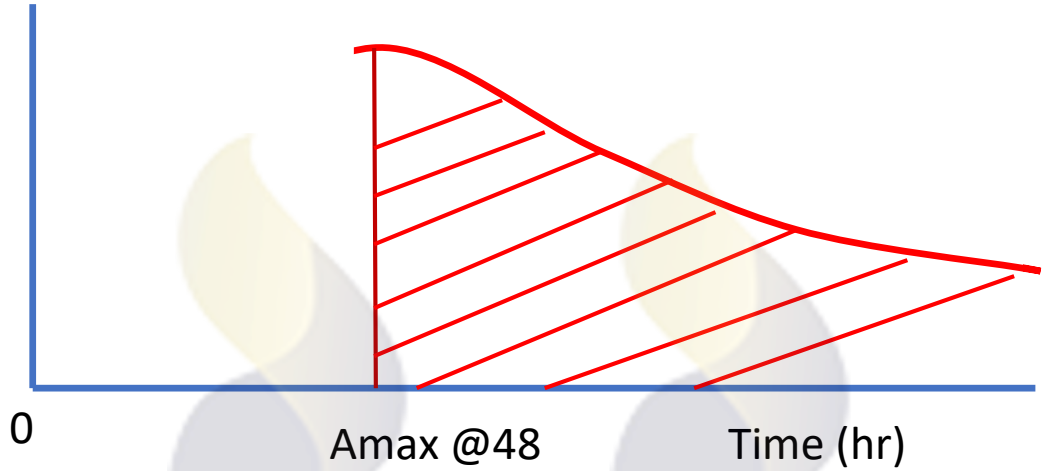
^{124}I for lesion specific dosimetry in thyroid cancer

*Selecting for >2000 cGy lesion dose improved response rate for ^{131}I Rx

Ho A et al: N Engl J Med. 2013 Feb 14;368(7):623-32

Screen: Simplified dose model

The simplified model relies on the PET information from a single 48hr PET scan.



$$\text{Dose (cGy)} = \int A_{max} \exp\frac{-(0.693 * t)}{m \quad \tau_e} \Delta\phi$$

where τ_e = 48hr which is an average effective half-life in each lesion and $\Delta\phi$ = 0.405 g.cGy/ µCi.hr which is the equilibrium dose constant.

It can be shown that SUV > 20 would get > 2000 cGy*, per lesion for an administered dose of 250 mCi, the usual maximum outpatient treatment dose

*Maxon Threshold for response

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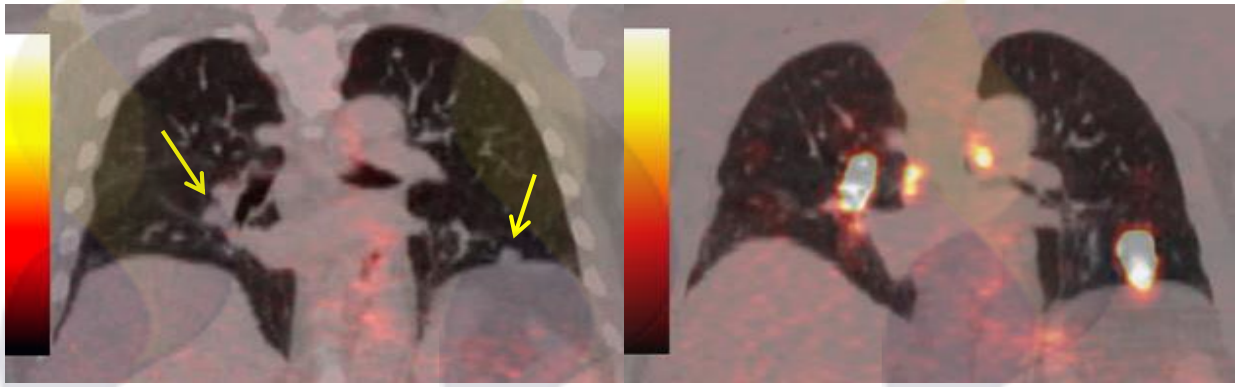
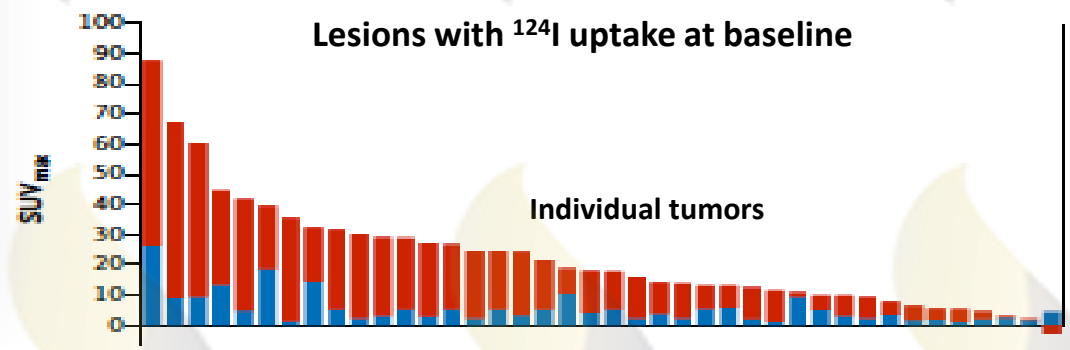
Ho AL, et al Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N Engl J Med. 2013 Feb 14;368(7):623-32

MEK inhibition restores radioactive iodine uptake



^{124}I PET/CT Baseline

^{124}I PET/CT After Selumetinib



- *RET, BRAF, RAS* mutant thyroid cancer → ↑MAPK signaling → RAI refractory
- MEK inhibition restores iodine uptake
- ^{124}I effective for ^{131}I dosimetry
- Selumetinib increased ^{124}I uptake in 12/20 pts (4/9 B*RAF*, 5/5 *NRAS* mutant)
- 8/12 pts reached ^{131}I dosimetry level
- Phase III trial planned

Essential Cores

Radiochemistry and Molecular Imaging Probes
Pathology
Biostatistics

Collaborators

Fagin (CBEP, CR)

Larson (IMRAS, CR)

Ho (CR)

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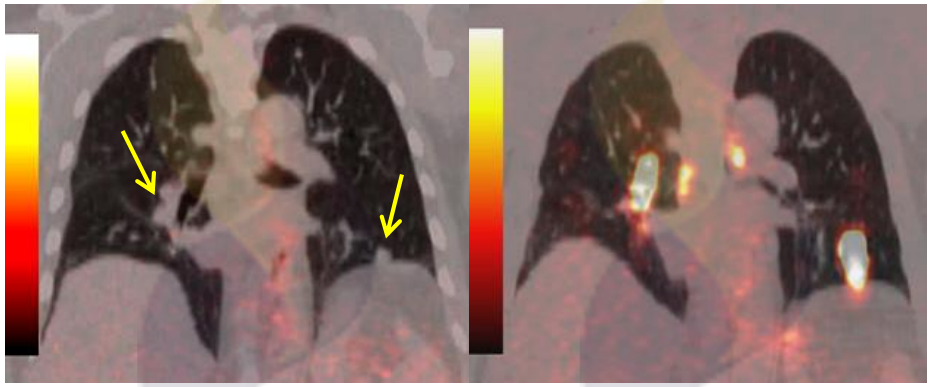
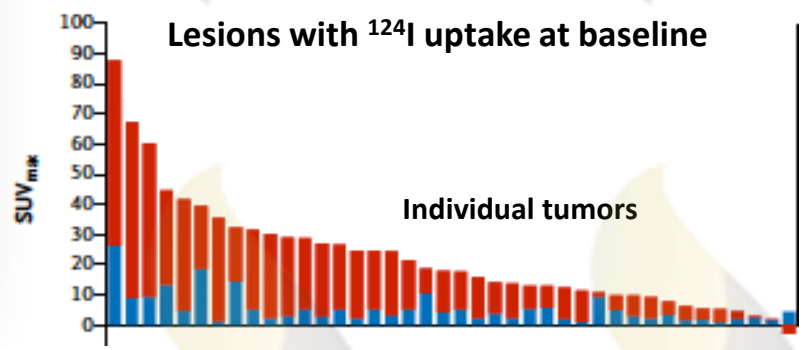
Ho AL, et al Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N Engl J Med. 2013 Feb 14;368(7):623-32

MEK inhibition restores radioactive iodine uptake



^{124}I PET/CT Baseline

^{124}I PET/CT After Selumetinib



- *RET, BRAF, RAS* mutant thyroid cancer → ↑MAPK signaling → RAI refractory
- MEK inhibition restores iodine uptake
- ^{124}I effective for ^{131}I dosimetry
- Selumetinib increased ^{124}I uptake in 12/20 pts (4/9 *RAF*, 5/5 *NRAS* mutant)
- 8/12 pts reached ^{131}I dosimetry level
- Phase III trial planned

Essential Cores

Radiochemistry and Molecular Imaging Probes
Pathology
Biostatistics

Collaborators

Fagin (CBEP, CR)

Larson (IMBAS, CR)

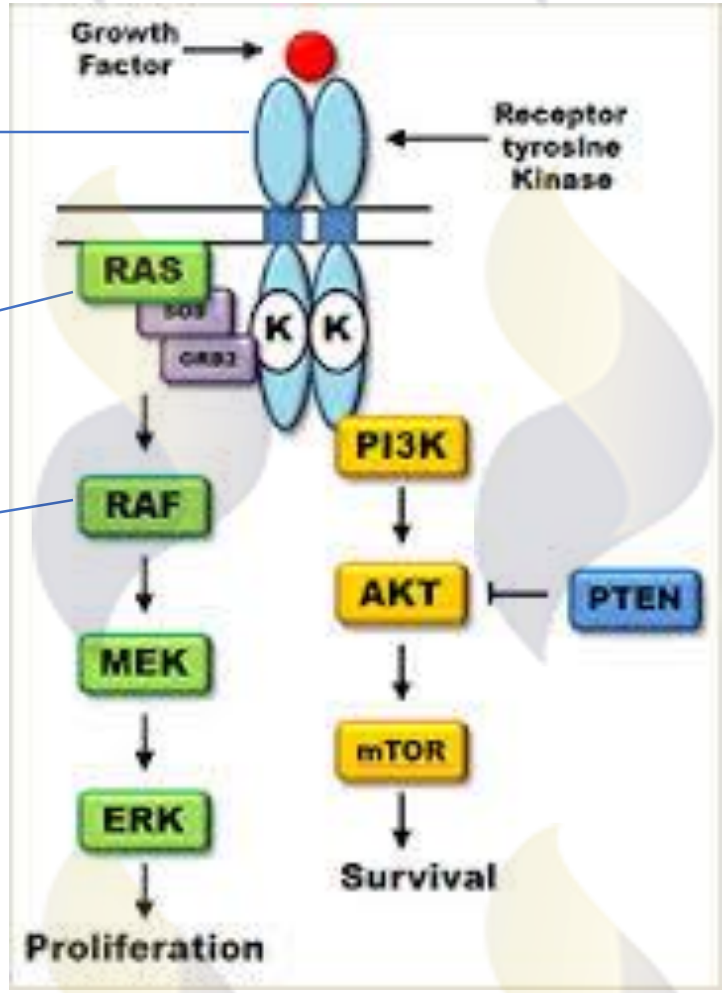
Ho (CR)

MAP Kinase Signaling and PapillaryThyroid Cancer (PTC)

RET/PTC in 3/20 patients (15%)

NRAS Q61R and *Q61K* *25% (5/20) patients*

BRAF V600E
45%(9/20) patients



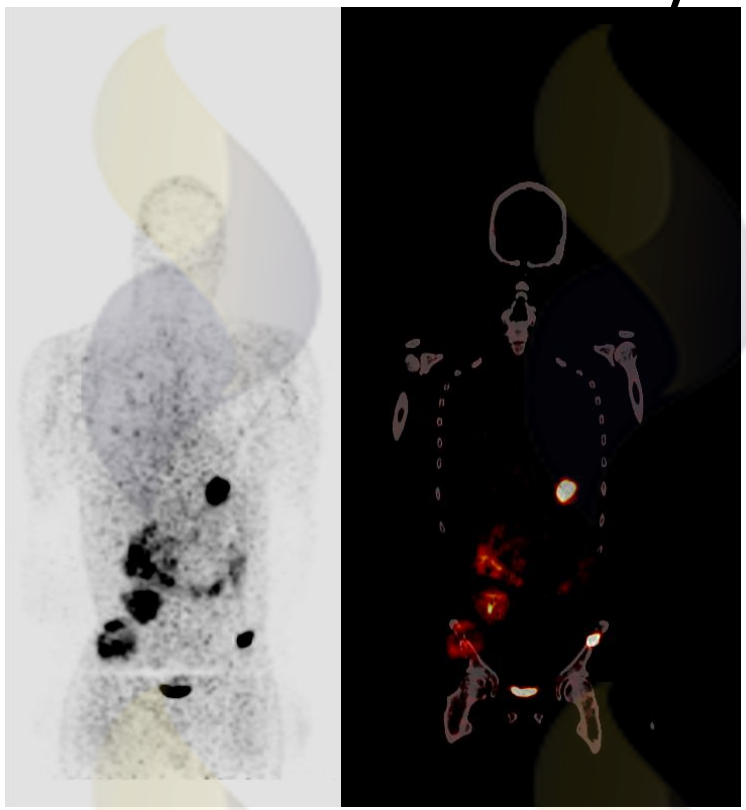
Driver oncogenes are known for ~95% of PTC tumors, and ~75% involve MAPK pathway

Integrated Genomic Characterization of Papillary Thyroid Carcinoma

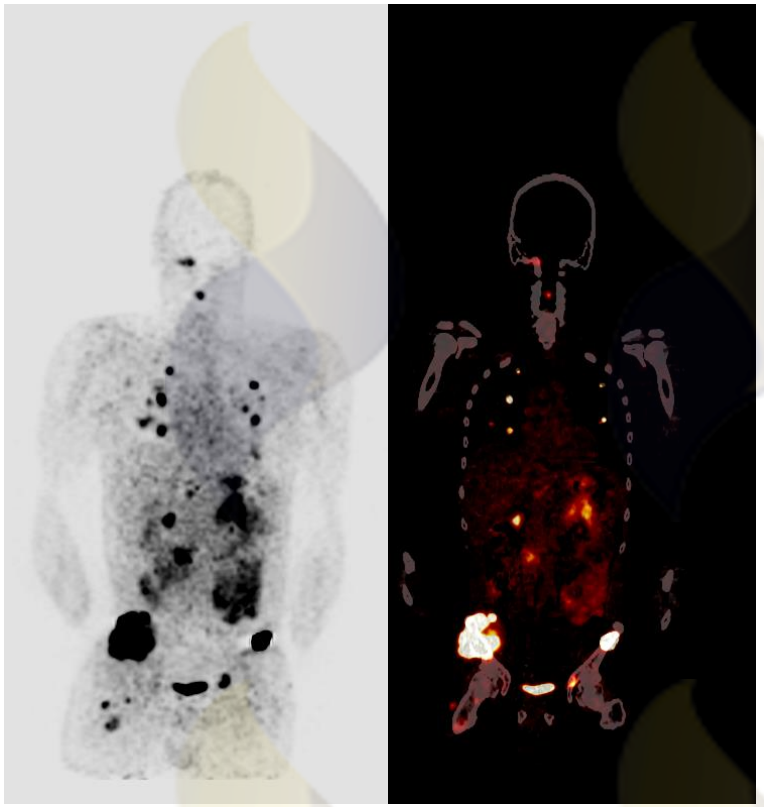
The Cancer Genome Atlas Research Network[1]

Cell 159:676-690, 2014

Ras Mutant Trametanib (GSK MEK inhibitor)

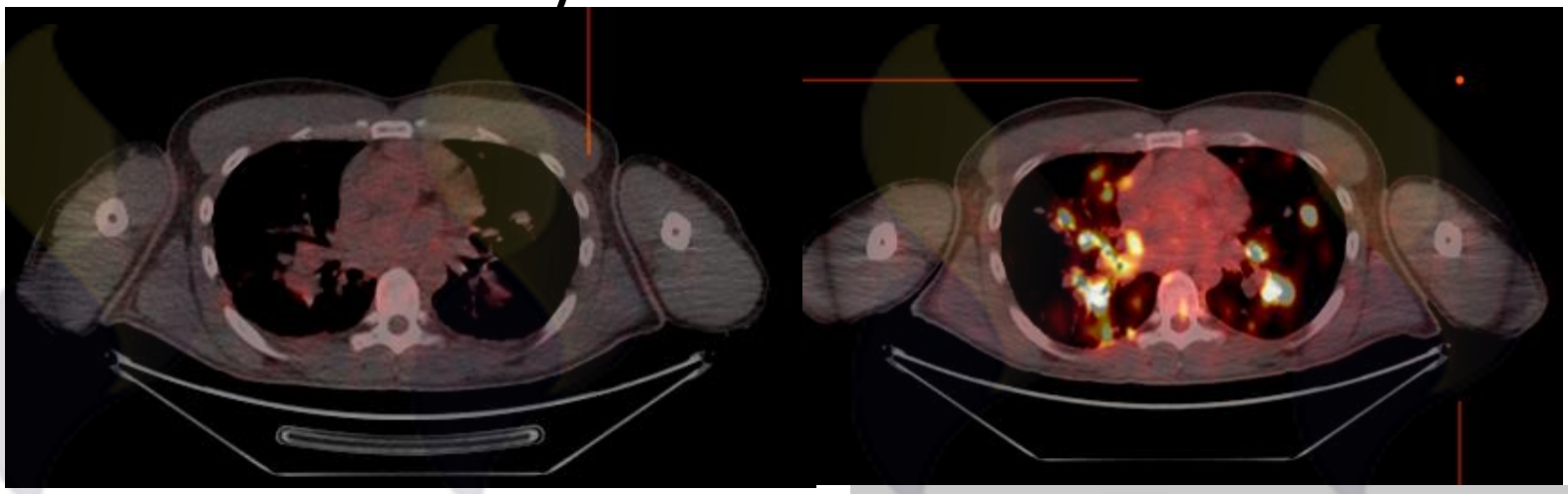


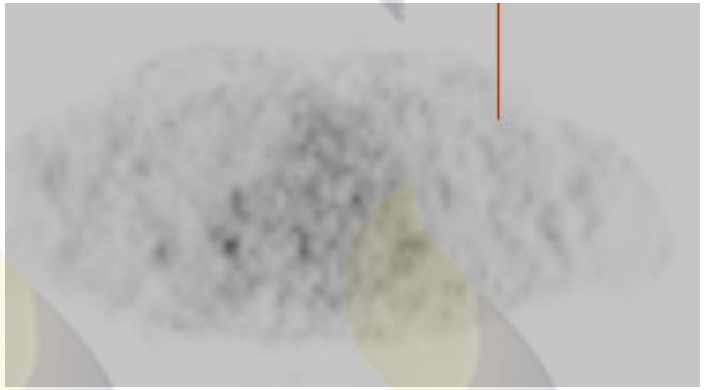
Before

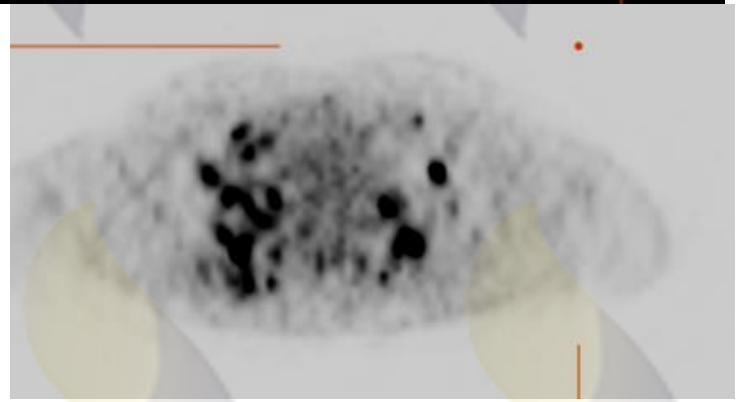


After

Ras Mutant Trametanib (GSK MEK inhibitor)



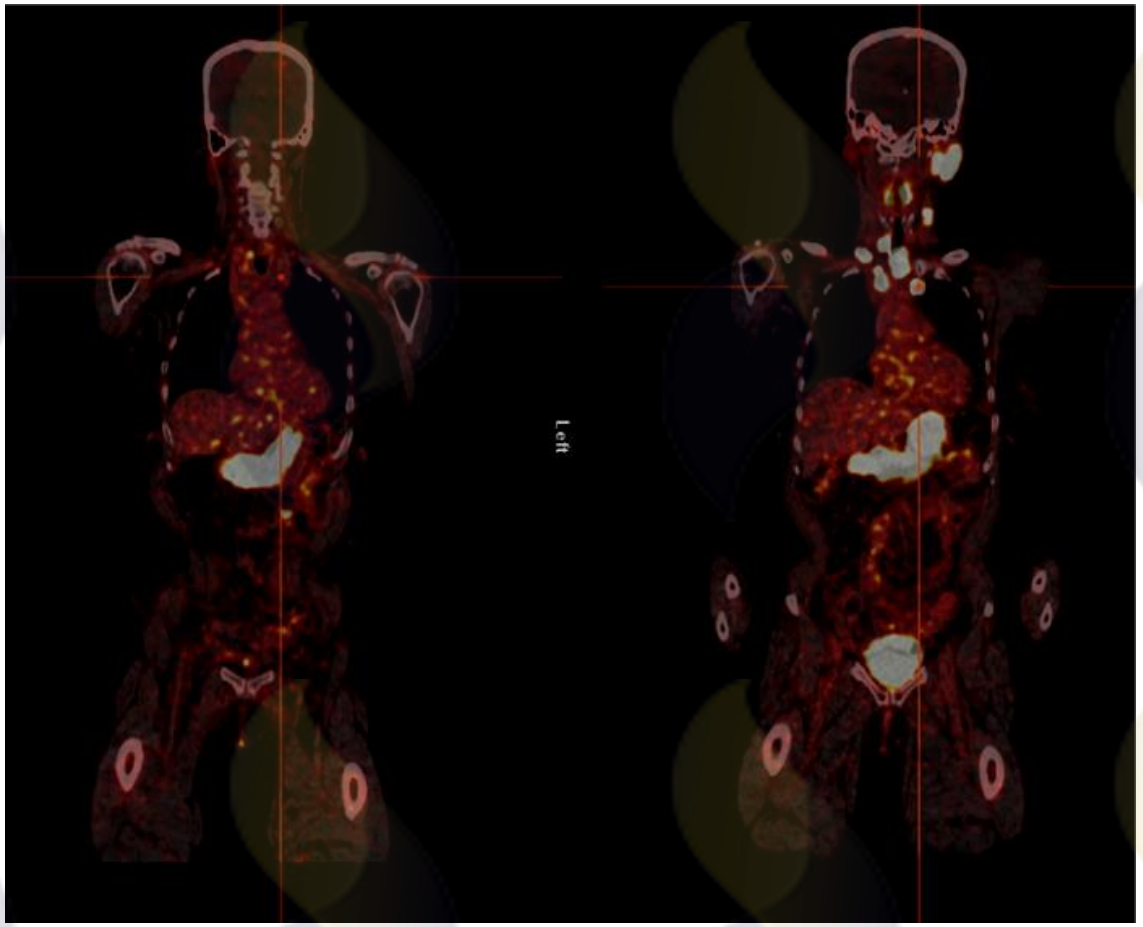




Before

After

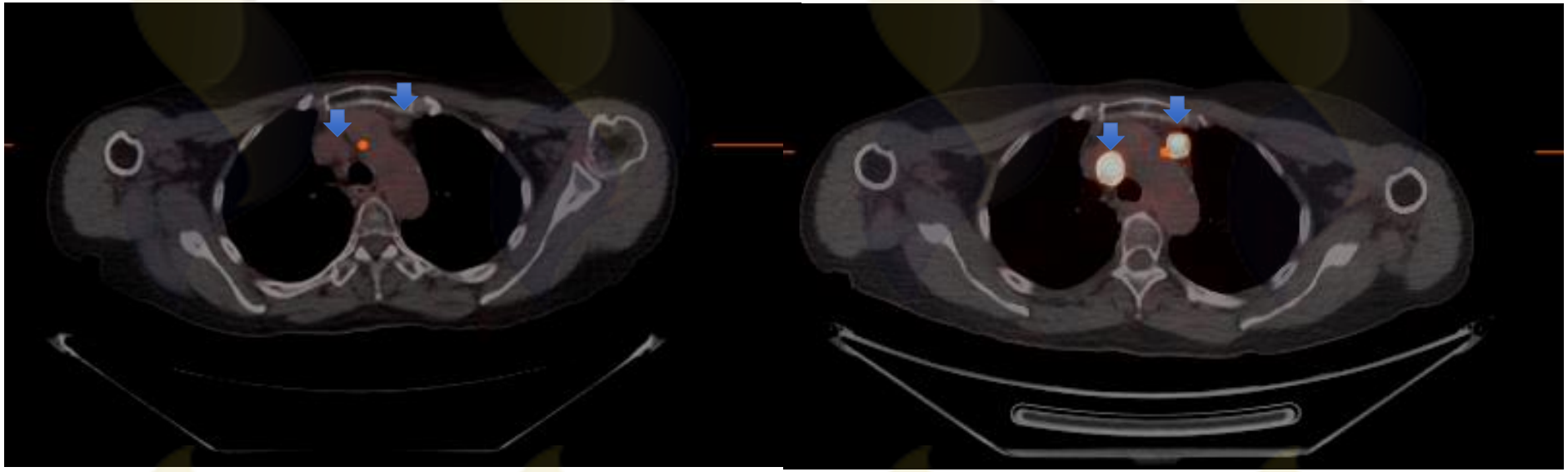
BRAF inhibitor
(Genentech Vemurafanib)



Before

After

BRAF inhibitor
(Genentech Vemurafanib)



Before

After

PET/CT in Clinical Practice: Thyroid Cancer

- PET CT FDG is a marker of de-differentiation and poor prognosis, but is useful for staging advanced disease and monitoring treatment response
- PET CT $Na^{124}I$ is a promising theranostic in advanced DTC as an aid to staging , monitoring RAI uptake reinduction therapy re-induction therapy.
  - 48 HOUR single time point >2000 cGy predicts for likely RECIST response