Imaging as a predictor of therapeutic response

Daniel A. Pryma, MD
Gerd Muehllehner Professor of Radiology
Perelman School of Medicine at the University of Pennsylvania

Perelman School of Medicine
University of Pennsylvania

1

Acknowledgement

- David Mankoff, MD, PhD

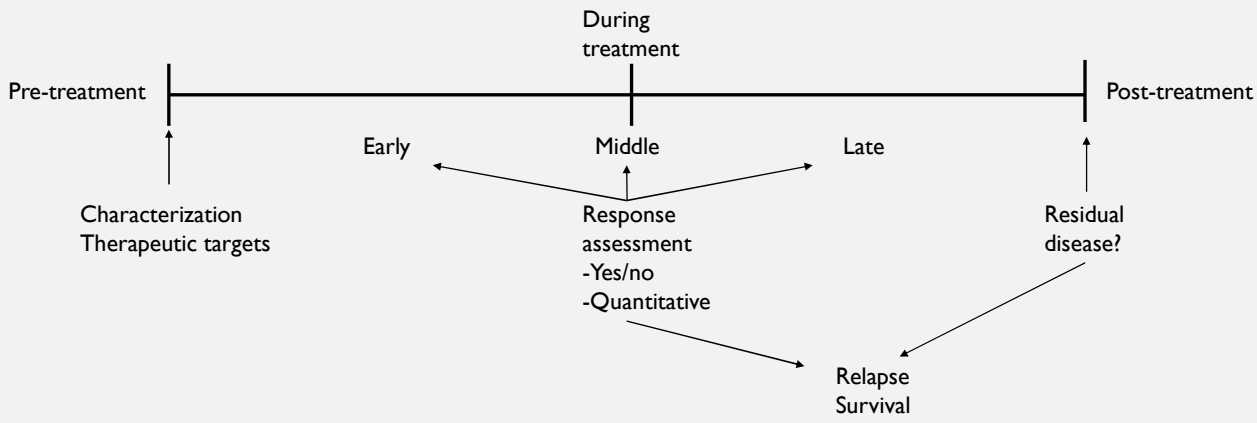
2

Learning objectives

- List potential response biomarker imaging applications
- Describe the difference between prognostic and predictive biomarkers
- Discuss the approach to clinical trials designed to test the accuracy of imaging response biomarkers

3

Imaging to guide cancer therapy



4

How can biomarkers guide cancer therapy?

- Goals in cancer treatment
  - Characterize tumor biology pre-Rx
  - Individualized, specific therapy
  - Static response may be acceptable
- The implied needs for cancer biomarkers
  - Characterize tumor biology
  - Identify targets, predict response
  - Measure tumor response (early!)
  - Relate response to survival

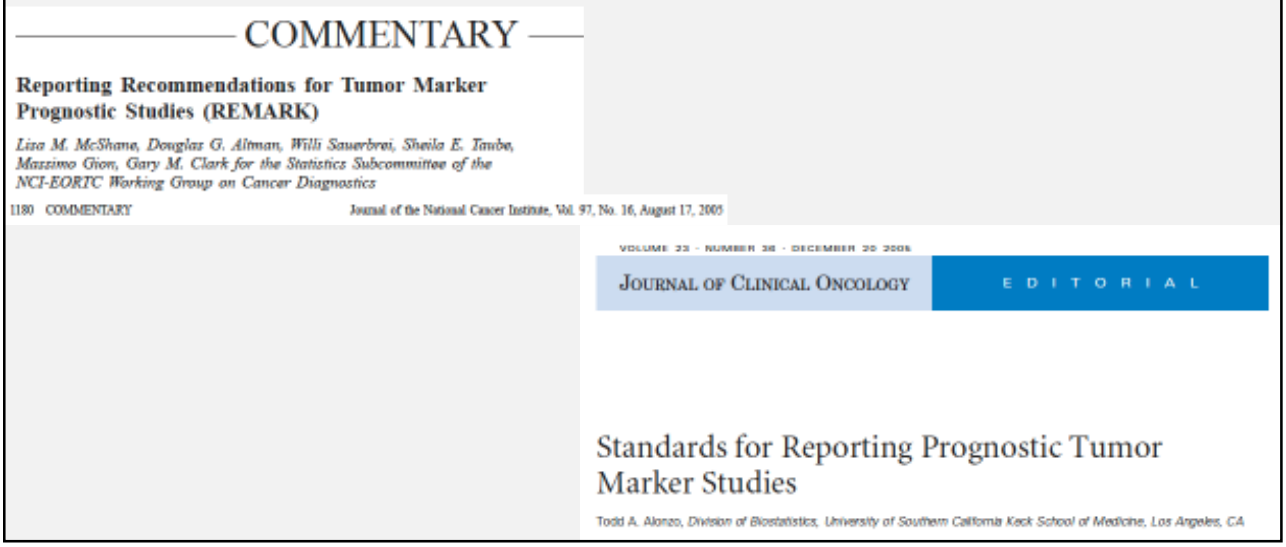
5

How can biomarkers guide cancer therapy?

- Goals in cancer treatment
  - Characterize tumor biology pre-Rx
  - Individualized, specific therapy
  - Static response may be acceptable
- The implied needs for cancer biomarkers
  - Characterize tumor biology – **Prognosis**
  - Identify targets, predict response – **Prediction**
  - Measure tumor response (early!) – **Response**
  - Relate response to survival – **Biologic response**

6

Guidelines for biomarker studies: REMARK



COMMENTARY

Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK)

Lisa M. McShane, Douglas G. Altman, Willi Sauerbrei, Sheila E. Taube, Massimo Gion, Gary M. Clark for the Statistics Subcommittee of the NCI-EORTC Working Group on Cancer Diagnostics

1180 COMMENTARY Journal of the National Cancer Institute, Vol. 97, No. 16, August 17, 2005

VOLUME 23 · NUMBER 36 · DECEMBER 20 2005

JOURNAL OF CLINICAL ONCOLOGY EDITORIAL

Standards for Reporting Prognostic Tumor Marker Studies

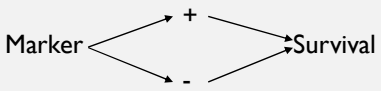
Todd A. Alonzo, *Division of Biostatistics, University of Southern California Keck School of Medicine, Los Angeles, CA*

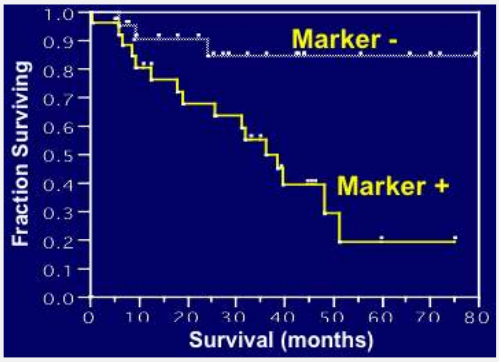
7

Imaging and therapeutic response: Prognosis

8

Study design for prognosis



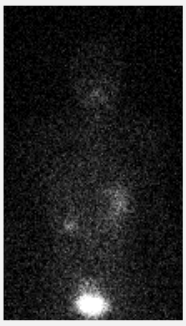


- In vitro examples:
  - Proliferation – Ki67
  - Receptor expression – ER
  - Oncogene expression – HER2

9

FDG predicts survival in recurrent thyroid cancer - Robbins, JCEM, 2006

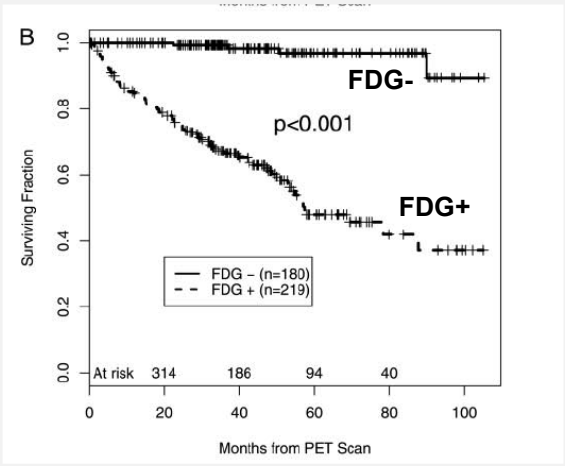
^{131}I-



High TG, Neg Scan

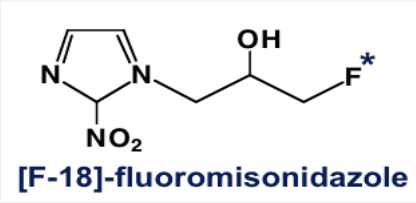
FDG PET

L Cervical LN



10

Imaging hypoxia as the accumulation of a radiopharmaceutical

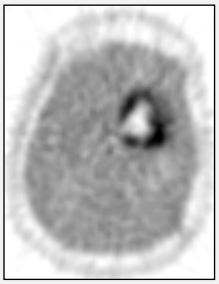


KA Krohn University of Washington

11

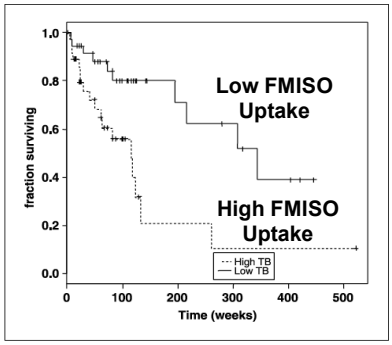
Tumor hypoxia quantified by PET predicts survival

FMISO PET Brain Tumor



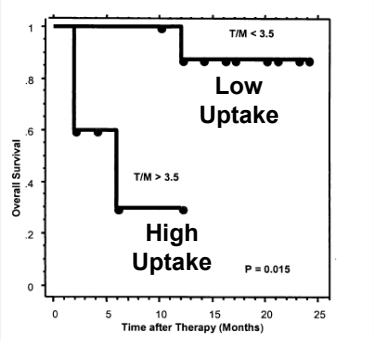
(Spence, Clin Cancer Res, 2008)

FMISO PET H & N Cancer



(Rajendran, Clin Can Res, 2007)

Cu-ATSM PET Cervical Cancer



(Dehdashti, Int J Radiat Oncol Biol Phys, 2003)

12

ACRIN 6684

MULTICENTER, PHASE II ASSESSMENT OF TUMOR HYPOXIA IN GLIOBLASTOMA USING ^{18}F-FLUOROMISONIDAZOLE (FMISO) WITH PET AND MRI

Elizabeth Gerstner, MD, PI

13

ACIN 6684: Hypoxia PET and MRI predict GBM PFS and OS

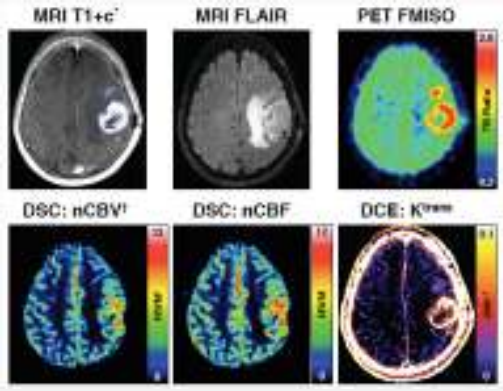


Table 3. Cox Regression Model

	Overall Survival Time			Progression Free Survival		
Parameter	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Univariate Model						
SUVpeak	1.54	1.00, 2.38	0.049*	1.24	0.80, 1.91	0.33
TBmax	1.16	0.75, 1.81	0.50	0.93	0.61, 1.40	0.72
HV	1.00	0.97, 1.03	0.90	1.01	0.98, 1.04	0.36
Mean k	1.17	1.02, 1.34	0.024*	1.10	0.99, 1.23	0.074
Median k	1.32	1.01, 1.72	0.045*	1.30	1.04, 1.63	0.021*
nRCBV	1.11	0.90, 1.37	0.31	1.20	1.05, 1.54	0.0096*
nCBF	1.07	0.88, 1.29	0.51	1.19	1.01, 1.38	0.038*

Gerstner, Clin Cancer Res, 22:5079, 2016

14

Imaging and therapeutic response: Prediction

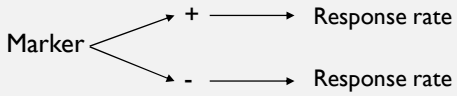
15

Outcomes for cancer imaging: Prediction

- Predictor or response to specific therapy:
  - Positive – predicts who will respond
  - Negative – predicts who will **not** respond

16

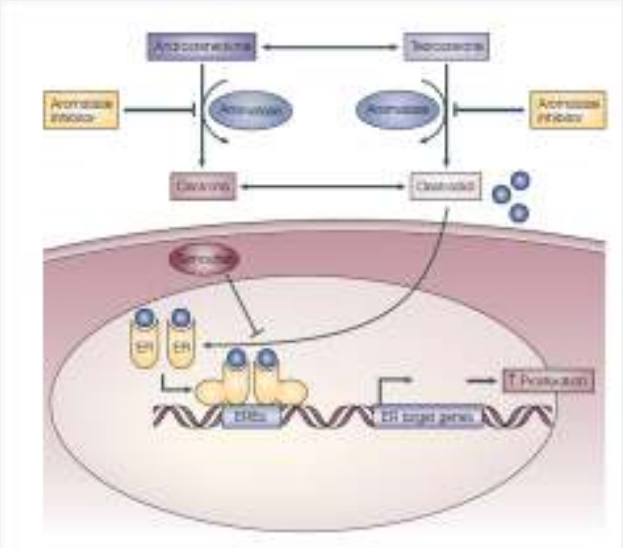
Study design for prediction



- In vitro examples:
  - ER – Endocrine therapy for breast cancer
  - HER2 – trastuzumab for breast cancer

17

Targeted breast cancer therapy:
The estrogen receptor (ER) and endocrine treatment

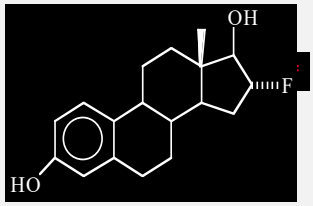


(Johnson and Dowsett, Nar Rev Cancer 3:821, 2002)

18

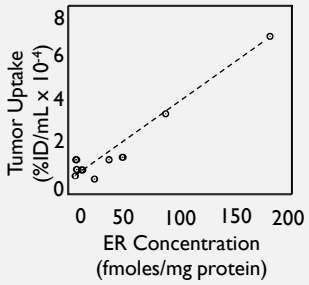
^{18}F-Fluoroestradiol (FES): PET Estrogen Receptor (ER) Imaging

Provides a Quantitative Estimate of ER Expression



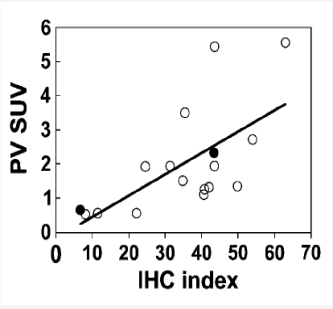
(Kieswetter, J Nucl Med, 25: 1212, 1984)

vs Radioligand Binding



(Mintun, Radiology 169:45, 1988)

vs IHC



(Peterson, J Nucl Med 49: 367, 2008)

19

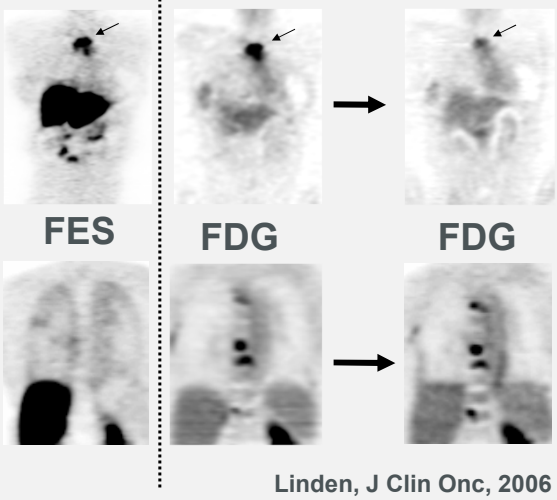
FES uptake predicts breast cancer response to hormonal therapy

Example 1

- Recurrent sternal lesion
- ER+ primary
- Recurrent Dz strongly FES+

Example 2

- Newly Dx'd met breast CA
- ER+ primary
- FES-negative bone mets



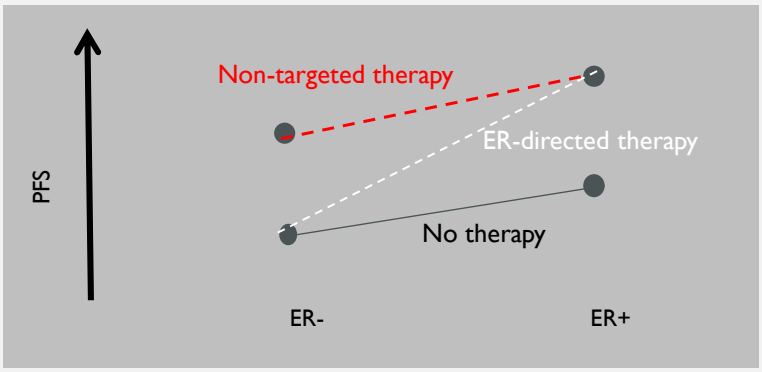
Excellent response after 6 wks Letrozole

No response to several different hormonal Rx's

Linden, J Clin Onc, 2006

20

Cancer carkers: Prognostic, predictive, or both?



21

Imaging and therapeutic response: Response

22

Outcomes for cancer imaging: Response

- Accuracy of response assessment
  - Response or not - R versus NR
  - Degree of response – residual disease versus CR
- Surrogate outcome measure
  - Predictor of DFS, OS

23

Categories of response

ANATOMIC	FUNCTIONAL
• Complete response	• Complete metabolic response
• Partial response	• Partial metabolic response
• Stable disease	• Stable metabolic disease
• Progressive disease	• Progressive metabolic disease

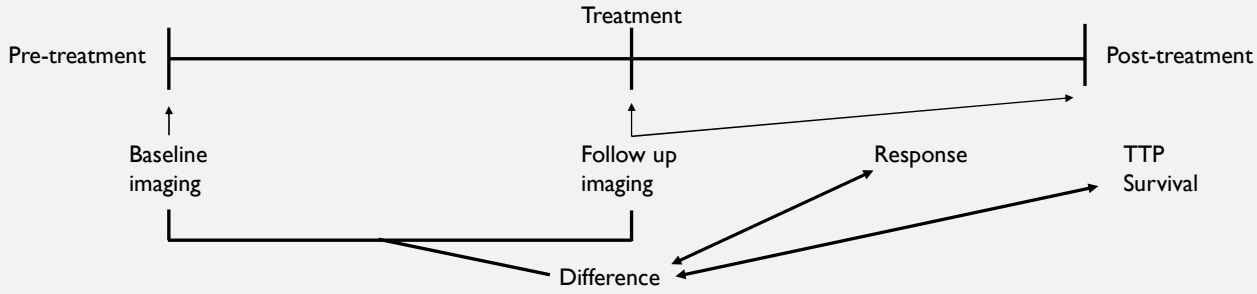
24

Pseudoprogression

- The scan looks worse, but the patient is responding to the treatment
- Very difficult or impossible to differentiate from true progression
  - Usually, only time will tell

25

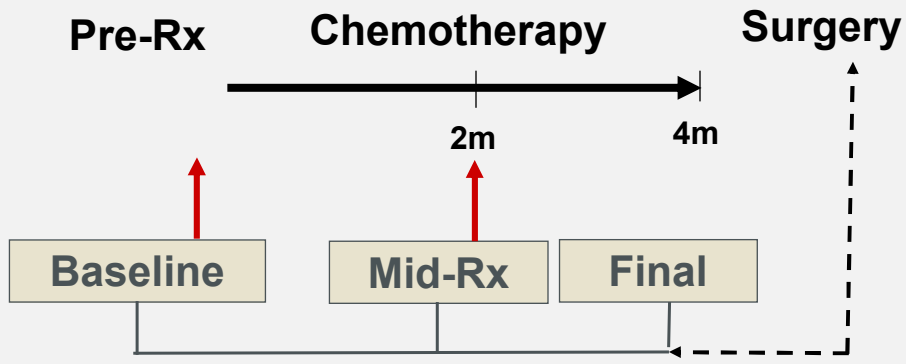
Study design for response



- Outcomes:
  - Sensitivity, specificity, ROC AUC for response
  - Predictor of TTP, Survival

26

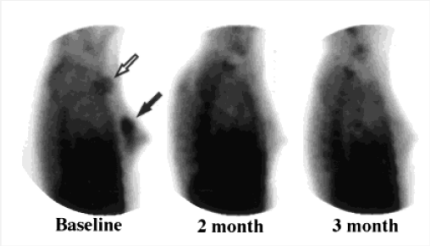
Functional and molecular imaging response
Neo-adjuvant therapy of locally advanced breast cancer (LABC)



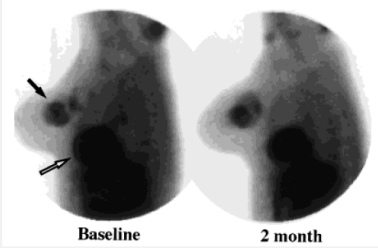
27

Change in MIBI uptake predicts response

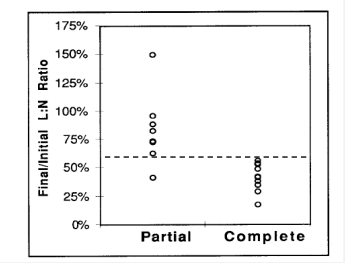
Pathologic Complete Response



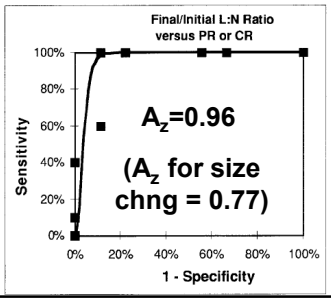
Progressive Disease



Uptake vs Response



ROC for CR versus PR



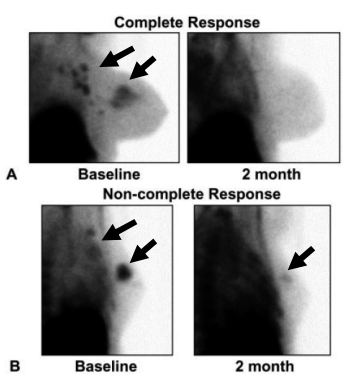
(Mankoff, Cancer, 1998)

28

Functional imaging predicts outcome

^{99m}Tc-MIBI Serial Imaging

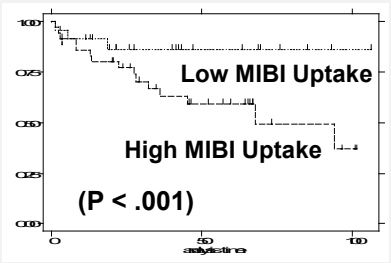
Change in Uptake Predicts Response



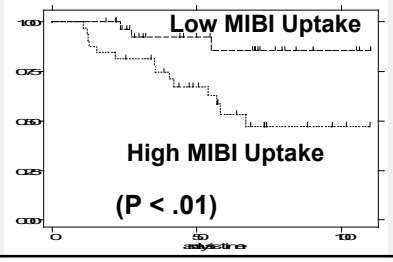
Residual Uptake Predicts Outcome

Disease-Free Survival

(N=62)



Overall Survival

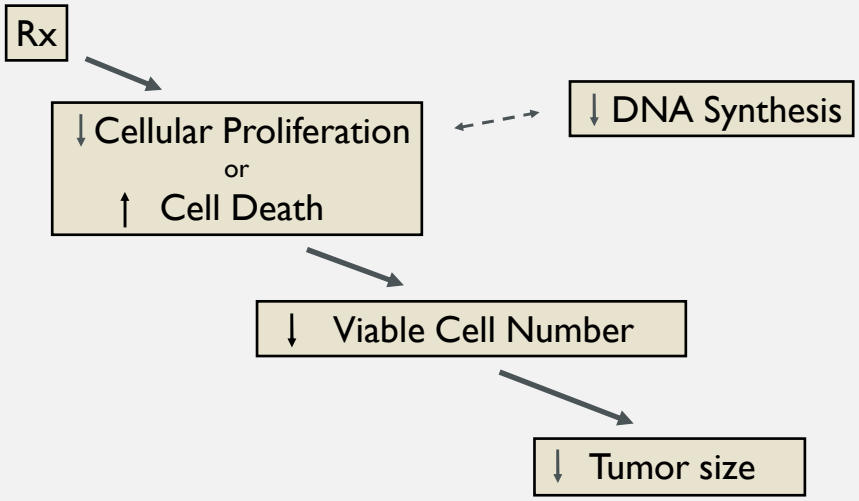


(Dunnwald, Cancer, 103: 680, 2005)

29

Biologic events in response to successful cancer therapy

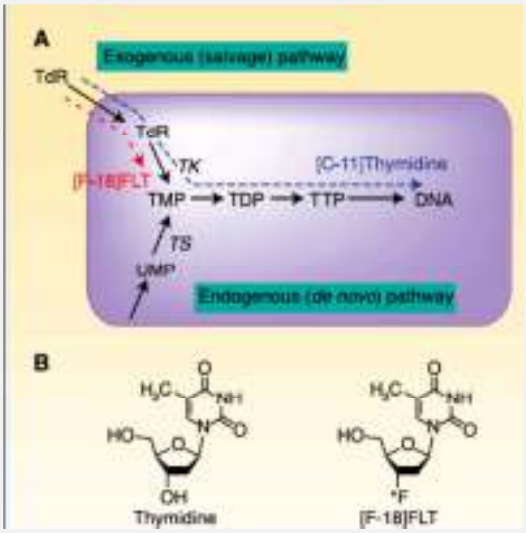
Rationale for measuring rarly response by cell proliferation imaging



30

Thymidine incorporation pathways

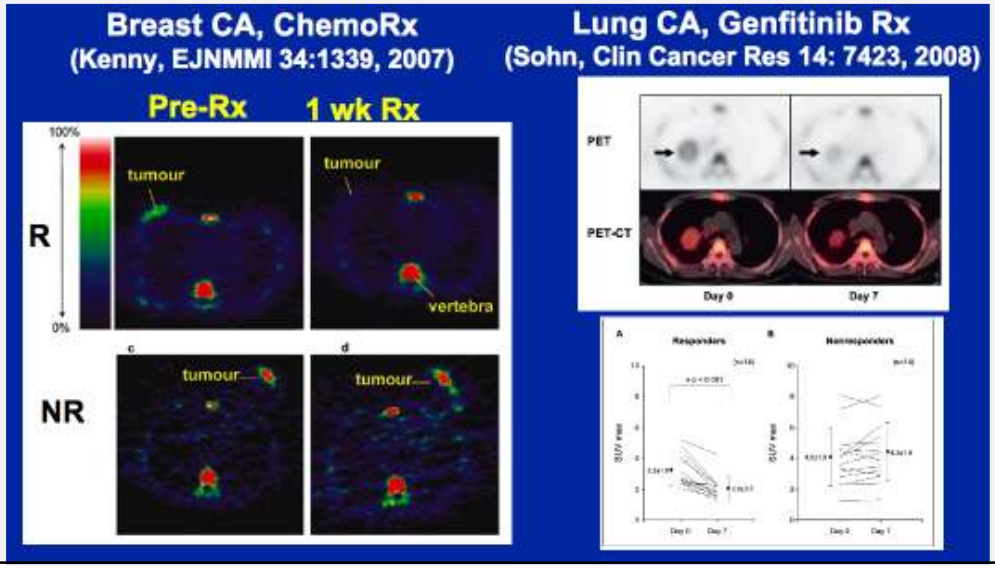
Imaging tumor proliferation



Mankoff and Eary, Clin Cancer Res 14:7159, 2008

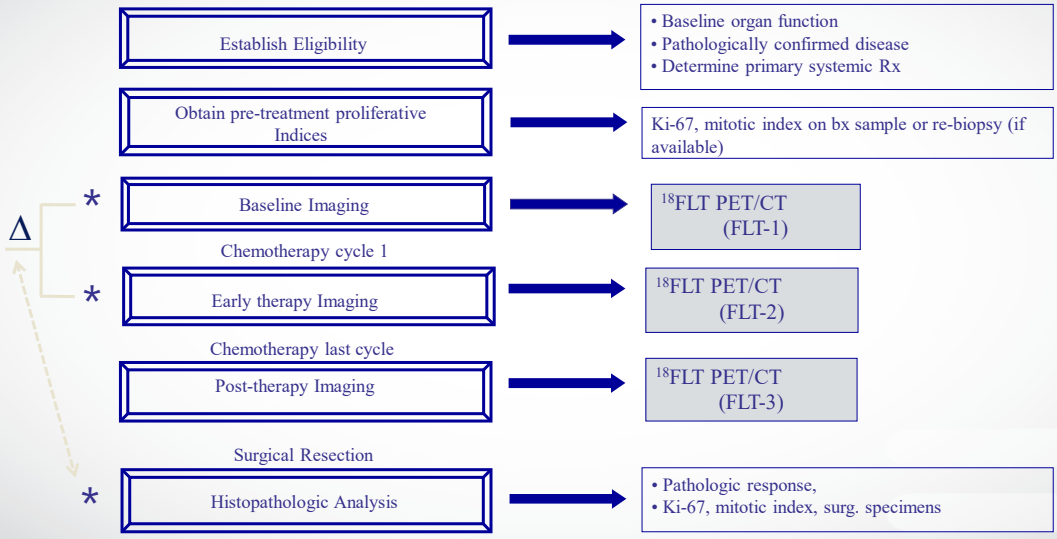
31

Early response measured by ^{18}F-fluorothymidine (FLT) PET/CT



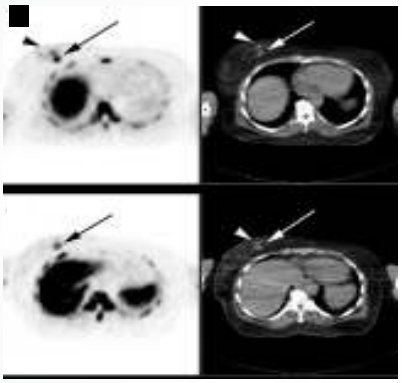
32

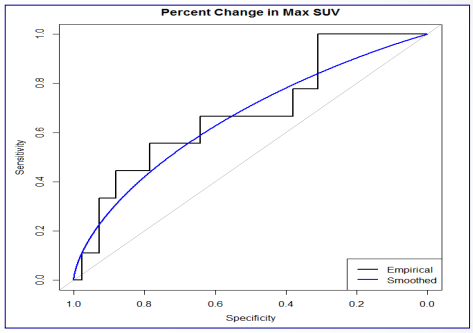
ACRIN 6688: Phase II Study of FLT-PET in Invasive Breast Cancer



33

ACRIN 6688: FLT PET to Measure Early Breast Cancer Response (PI: Lale Kostakoglu)





Best ΔSUV_{max} cut-off for predicting pCR = -51% (sensitivity 56%;specificity 79%).

(Kostakoglu, J Nucl Med, 2015)

34

Imaging and therapeutic response: Biologic response

35

Outcomes for cancer imaging: Biologic response

- Can functional/molecular response better predict outcome?
  - Predict DFS, OS, etc.
  - And what are the biologic insights
- Surrogate outcome measures?

36

Goals of anti-cancer therapy

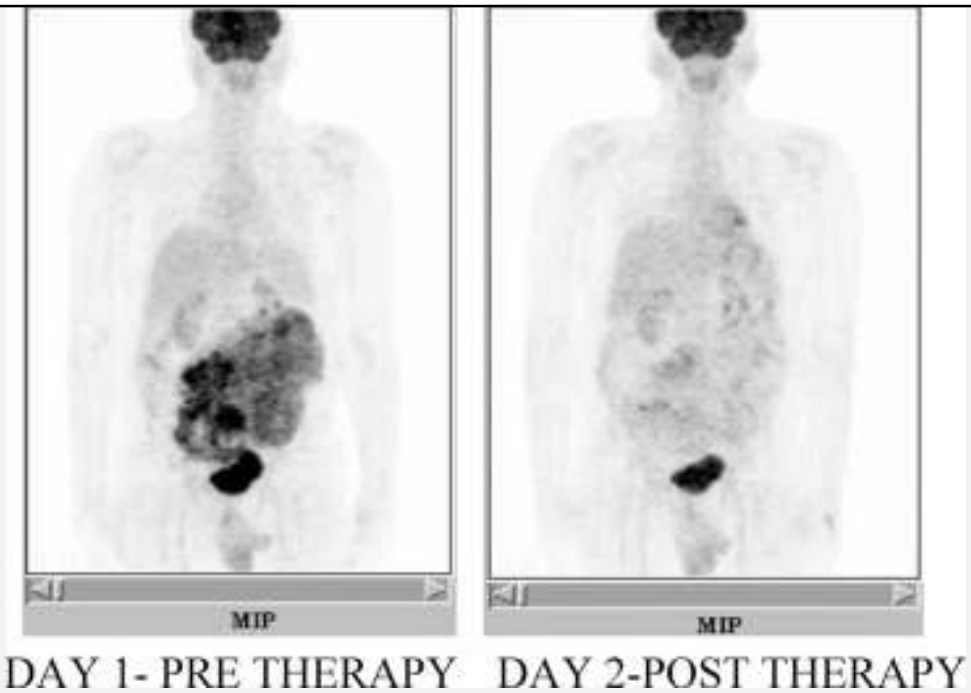
- Improve quality of life
- Improve duration of life
- Shrinking tumors in isolation not a goal of therapy
  - Anatomic response not a strong surrogate for clinical endpoints

37

Functional imaging for response assessment

- Functional changes precede anatomic changes
- Functional changes can exist in the absence of anatomic changes
  - Cytostatic therapies
- More examples of functional imaging as predictive of clinical endpoints

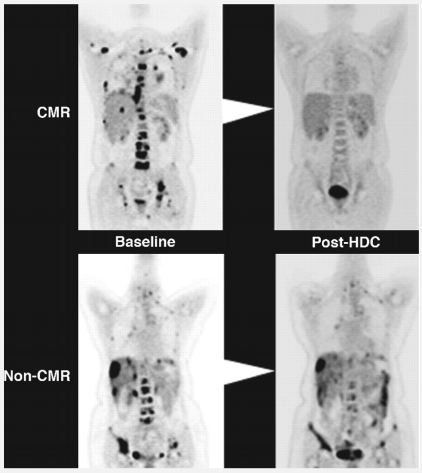
38

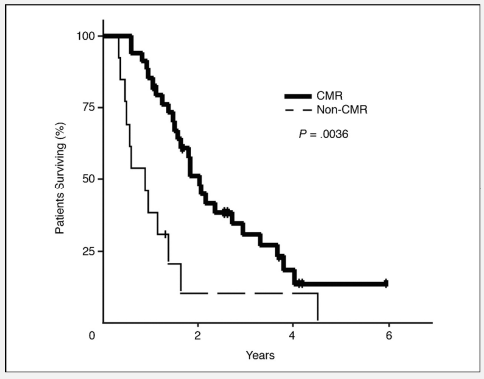


Sinto *et al.* Clin Nucl Med. 2008, 33(7): 486-487.

39

PET response after chemotherapy predicts survival





Cachin et al. J Clin Oncol 2006

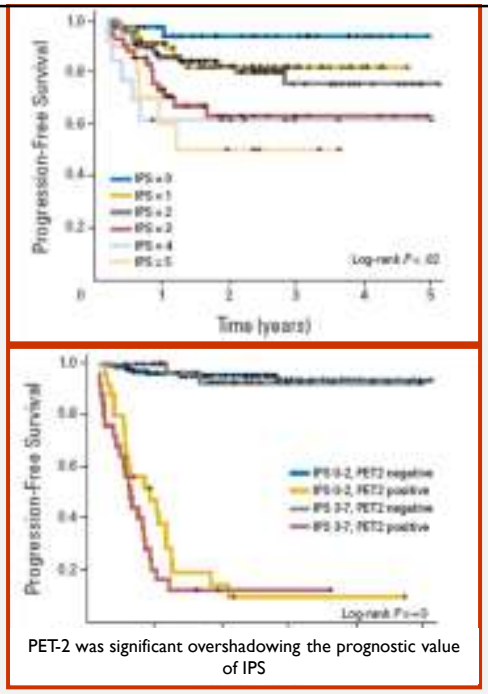
40

Advanced Stage HL

- 260 HL patients, prospective
  - unfavorable stage IIA 26%
  - stage IIB 27%
  - stage III-IVB 47%
- End-point: 2yr PFS, med f/u 2.2 y
- 79% CR; 16% prog <6mo; 4% relapse
  - PPV 86%
  - NPV 95%
  - Sens and spec: 81% and 97%
  - 2-yr PFS for PET2- vs PET2+ 95% vs 13%,

Positive PET definition uptake > MBP

(courtesy of Lale Kostakoglu)



PET-2 was significant overshadowing the prognostic value of IPS

Gallamini et al. J Clin Oncol. 2007 ;25:3746

41

Post-therapy FDG PET predicts survival in lymphoma
Zanoni, Q J Nucl Med Mol Imag 55:633, 2011

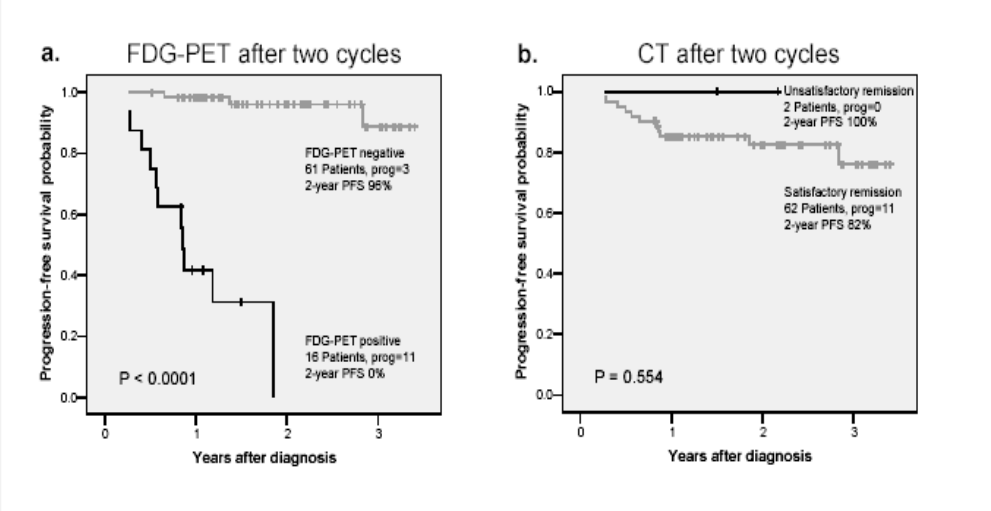
TABLE 1—*Prognostic value of end-treatment 18F-FDG PET for Aggressive NHL and HL*

AUTHOR	Patients (n°)	DISEASE	NOTES	FOLLOW-UP (months)	PFS PET+ vs PET−
Zinzani 1999 [10]	44	LH/LNH	Abdominal mass in all	20	1 yr: 15% *vs* 95% 2 yr: 0% vs 95%
Jerusalem 1999 [11]	54	LH/LNH	RM in 24	21	1 yr: 0% vs 86%
Mainty 2000 [12]	24	LH/LNH	RM in 24	20	50% vs 75%
Mikhaeel 2000 [13]	45	Aggressive LNH	RM in 17	30	1 yr: 0% vs 85%
Spaepen 2000 [14]	93	Aggressive LNH	RM in 24	22	2 yr: 4% vs 85%
Jarwoid 2002 [15]	38	Aggressive LNH	-	15.5	1 yr: 8% vs 88%
de Wit 2001 [16]	37	LH	RM in 37	25.6	54% vs 96%
Weihrauch 2001 [17]	28	LH	RM in 28	28	1 yr: 40% vs 95%
Spaepen 2001 [18]	60	LH	RM in 43	31	2 yr: 4% vs 85%
Mikhaeel 2002 [19]	65	LH	-	36	1 yr: 0% vs 93%

Abbreviations: RM: residual mass; PET+ positive; PET− negative

42

Early interim FDG-PET and prognosis



(courtesy of A Shields, Karmanos Cancer Center)

M Hutchings, Blood, 2006

43

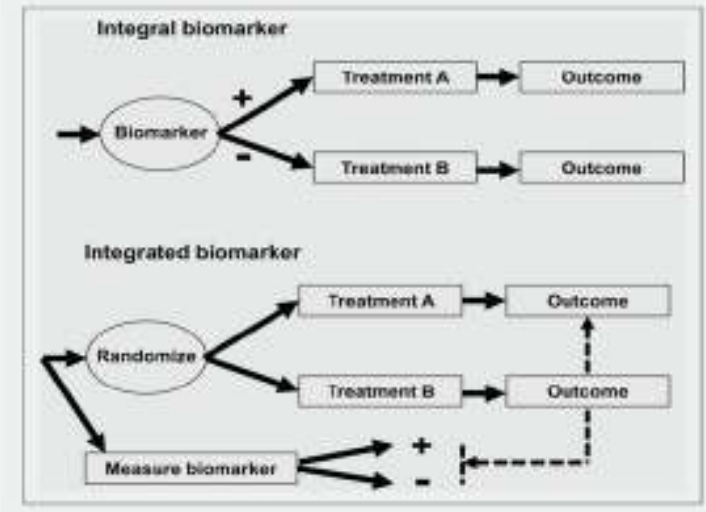
Example: Rectal cancer neoadjuvant therapy

- Meta-analysis of 34 studies
  - Most studies showed FDG PET/CT predictive of pathologic response to neoadjuvant therapy
- Pooled cohort of 1526 patients
- Pooled response cutoff of 63%

Maffione et al., AJR 2015

44

Imaging biomarker in cancer trials: Integrated vs integral markers

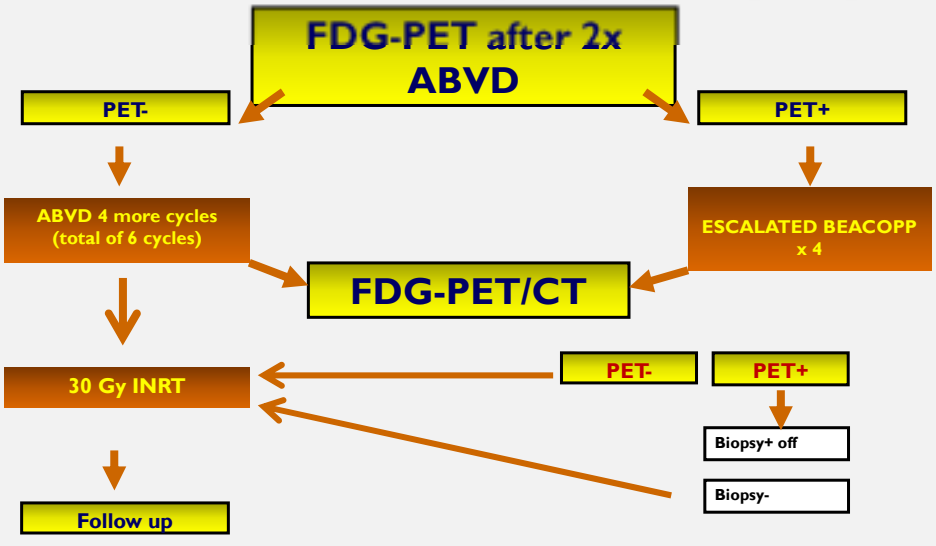


(Mankoff, J Nucl Med 55:525, 2014)

45

ECOG PI: R Advani

ECOG 2410 Trial in bulky early stage HL (n=144)



PFS at 36 mo

46

Imaging as a biomarker: Summary

- Imaging to guide treatment – imaging as a disease biomarker
  - Prognosis – How aggressive is the disease?
  - Prediction - Will the treatment work?
  - Response - Is the treatment working?
  - Biologic eesponse
    - Can response predict survival?
    - Can we use insights from imaging to adapt therapy?

47