

Advances in Image Guided Radiation Therapy for Lung Cancer

Noah C. Choi, M.D.

Professor of Radiation Oncology

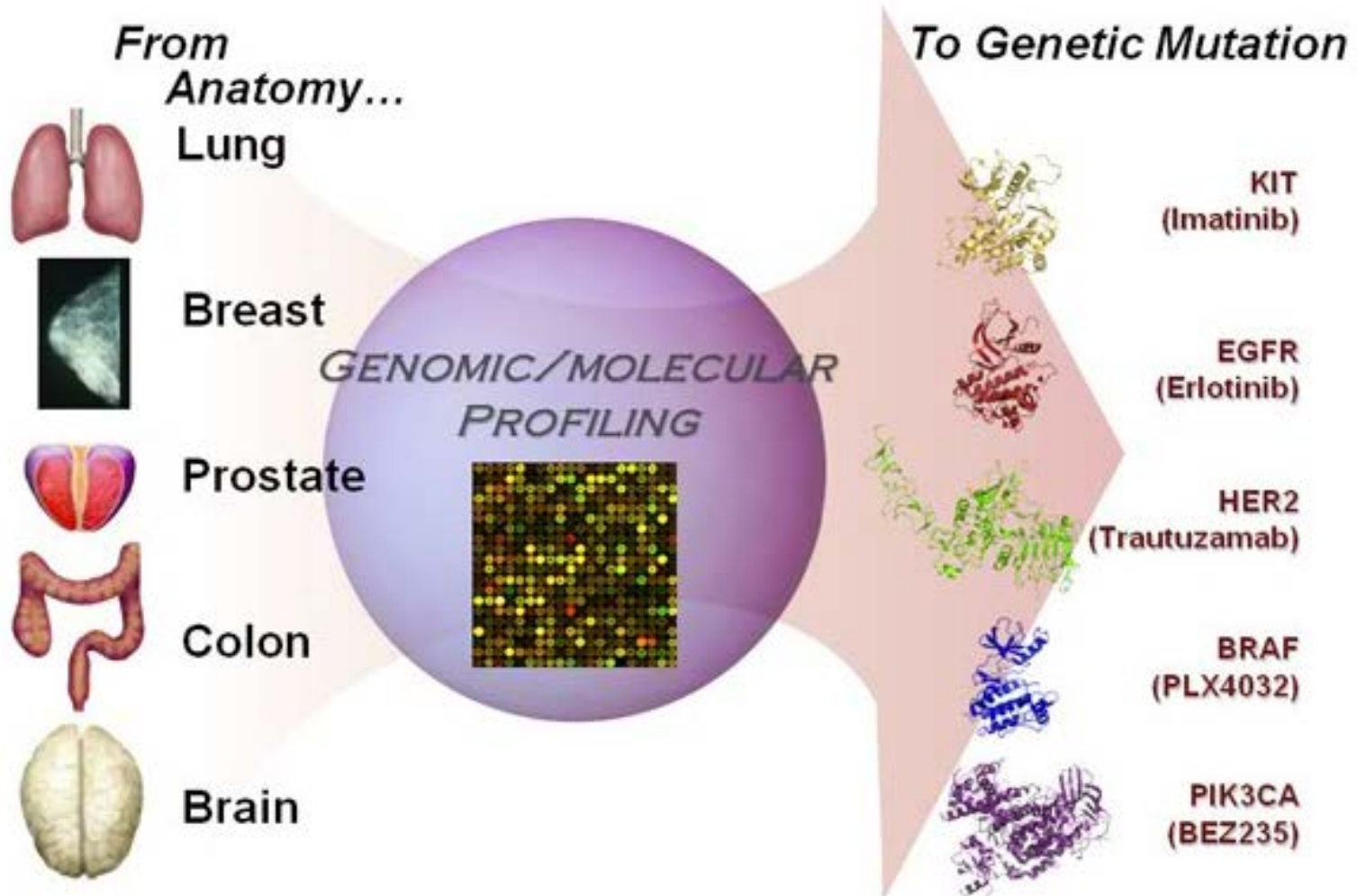
Distinguished Scholar in Thoracic Oncology

MGH Cancer Center

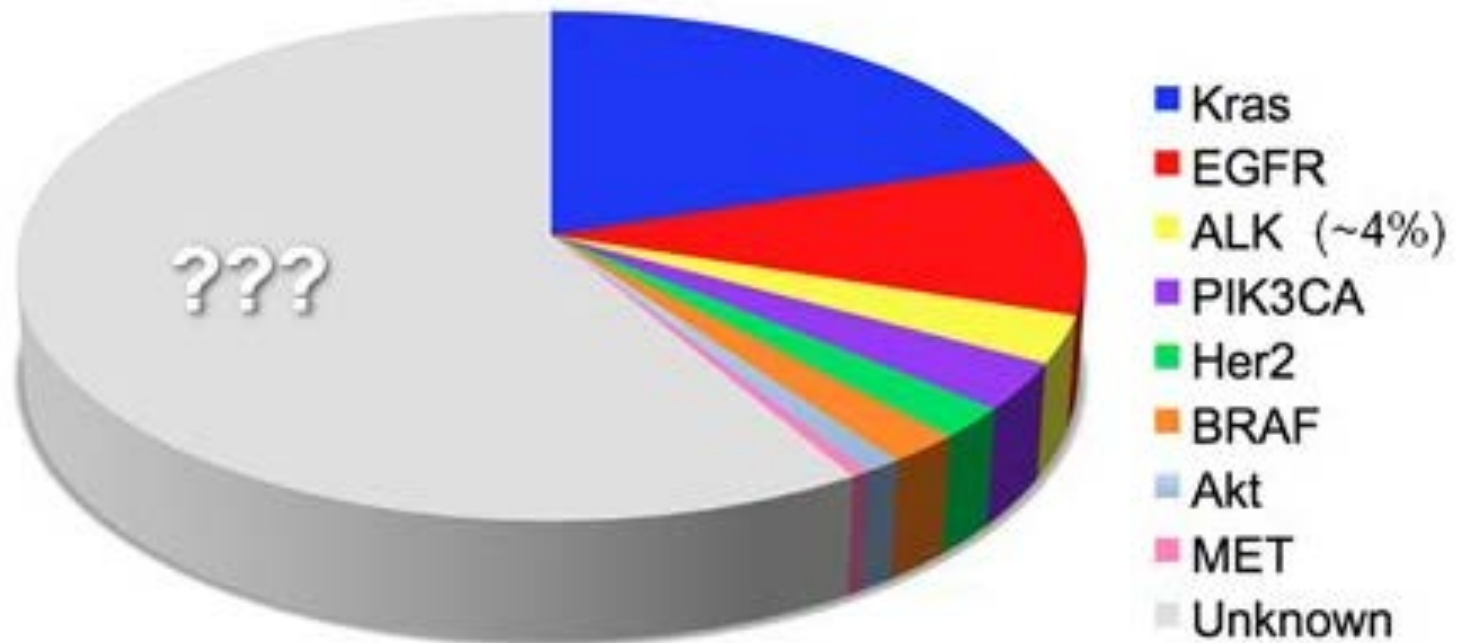
Massachusetts General Hospital

Harvard Medical School

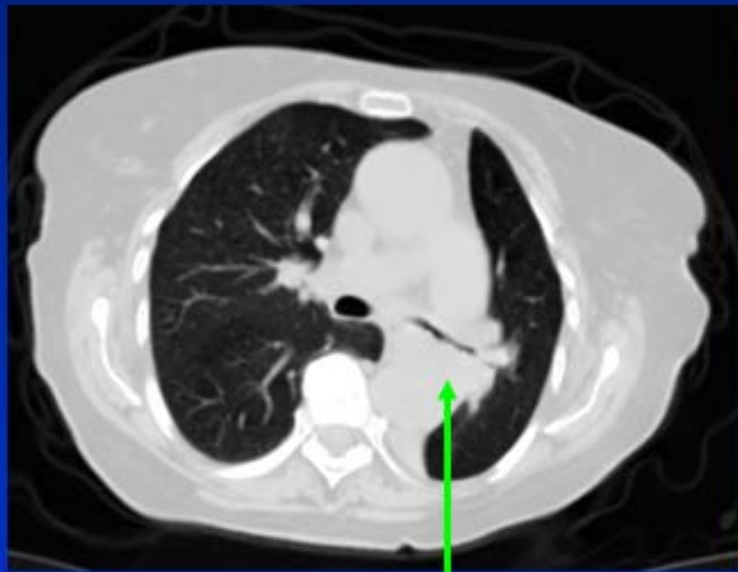
A Paradigm Shift: The Genomic View of Cancer



Genetically-Defined Subsets of NSCLC

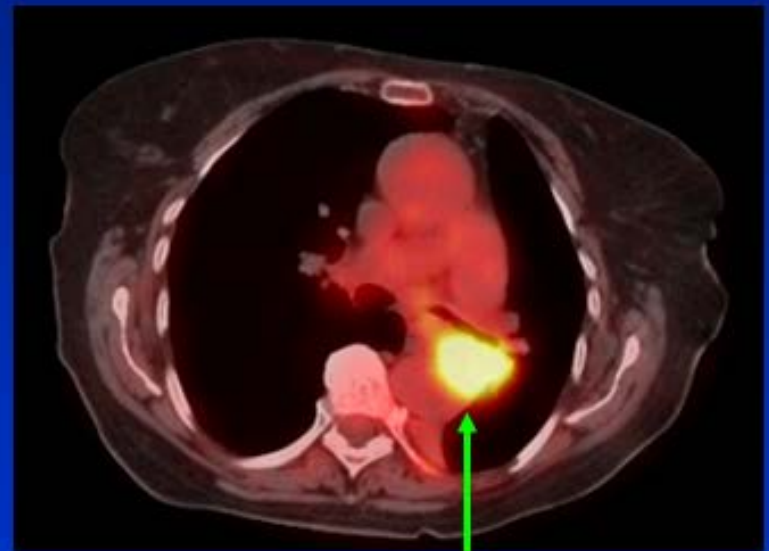


CT Image



Poorly Defined Tumor Margins

Fused CT-PET Image



^{18}F -FDG Avid Tumor

Image of a person who was detected by heat sensor while hiding in a boat under the boat cover.

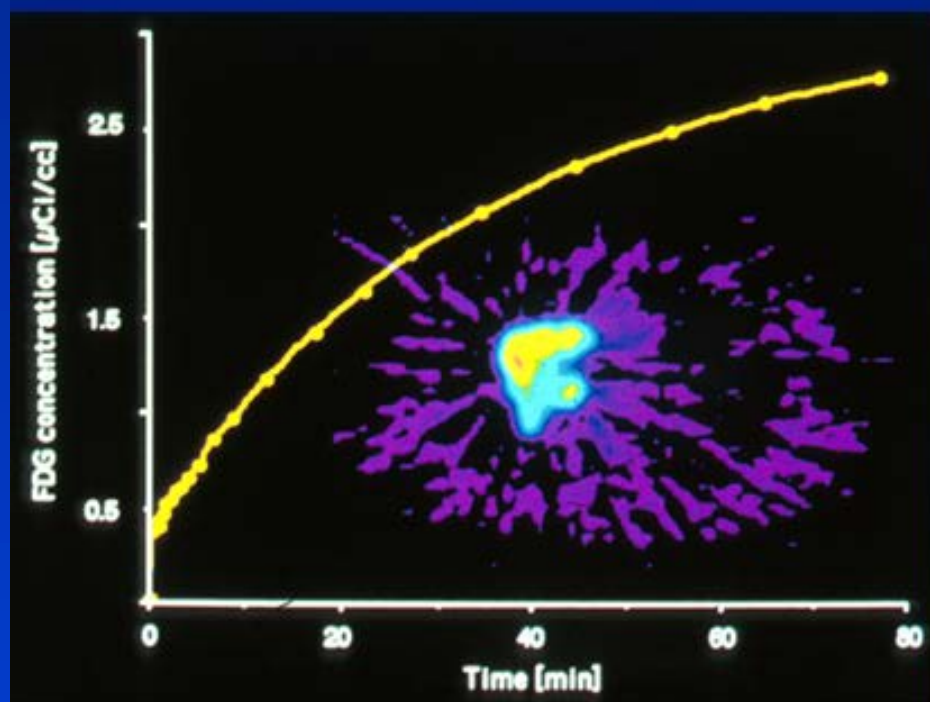


Metabolic sensor FDG PET can detect living cancer cells.

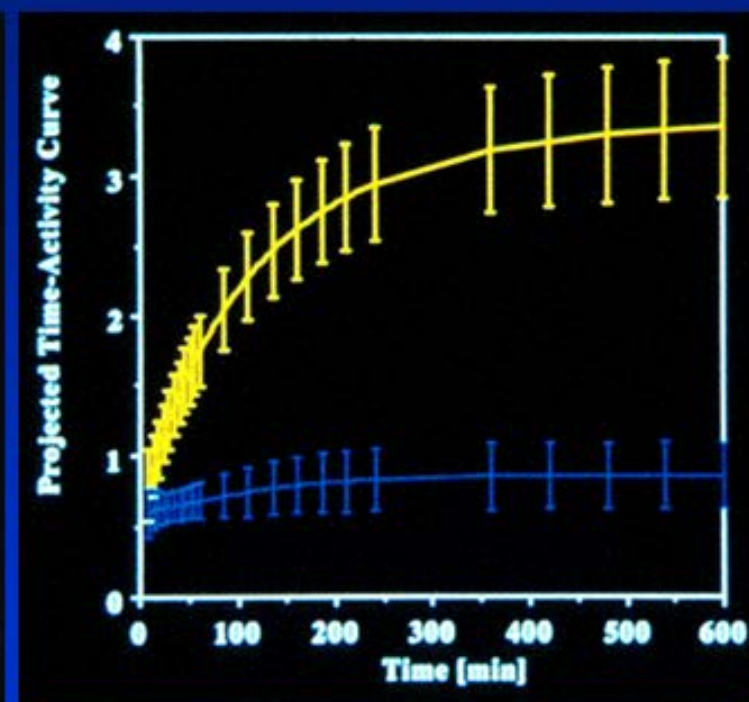
Lung Cancer: 5-yr Survival Rate

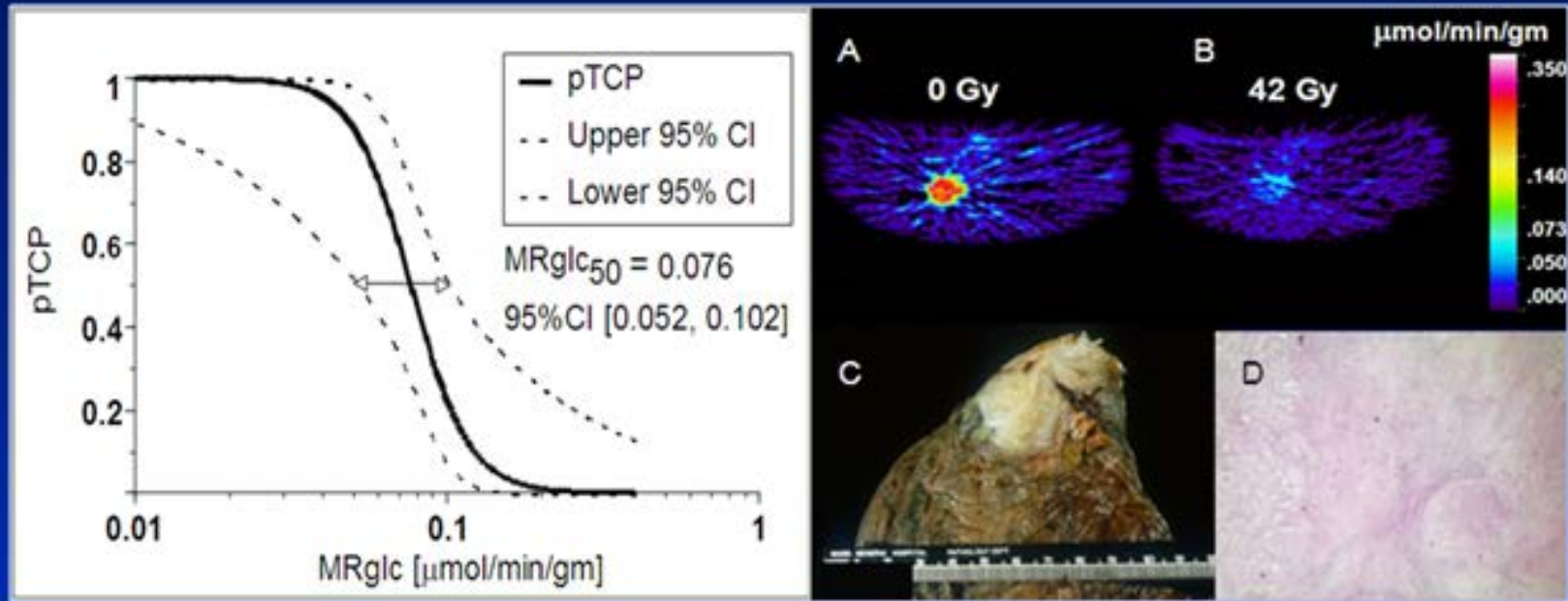
- Stage I: 15% (all cases), S5: 70%
- Stage II: 5%, S5: 50-55%
- Stage III: 40%, S5: 15-20%
- Stage IV: 40%, S5: <3%

FDG Uptake Curve in Untreated Lung Cancer



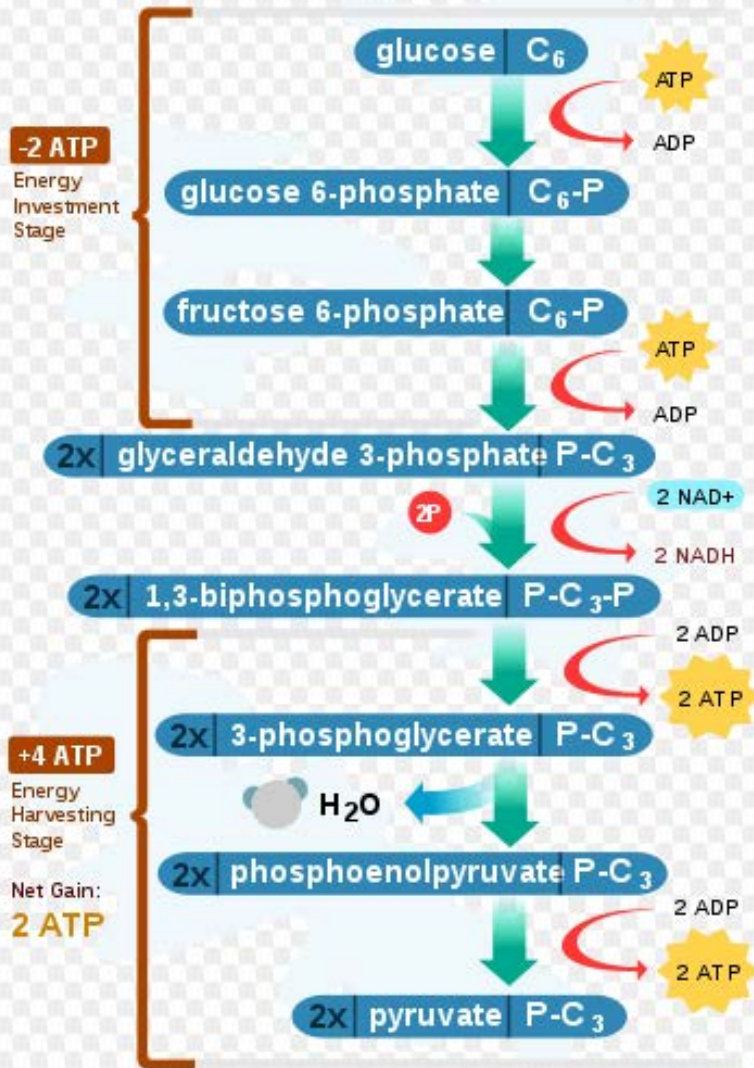
FDG Uptake Curve before and after RT in Lung Cancer



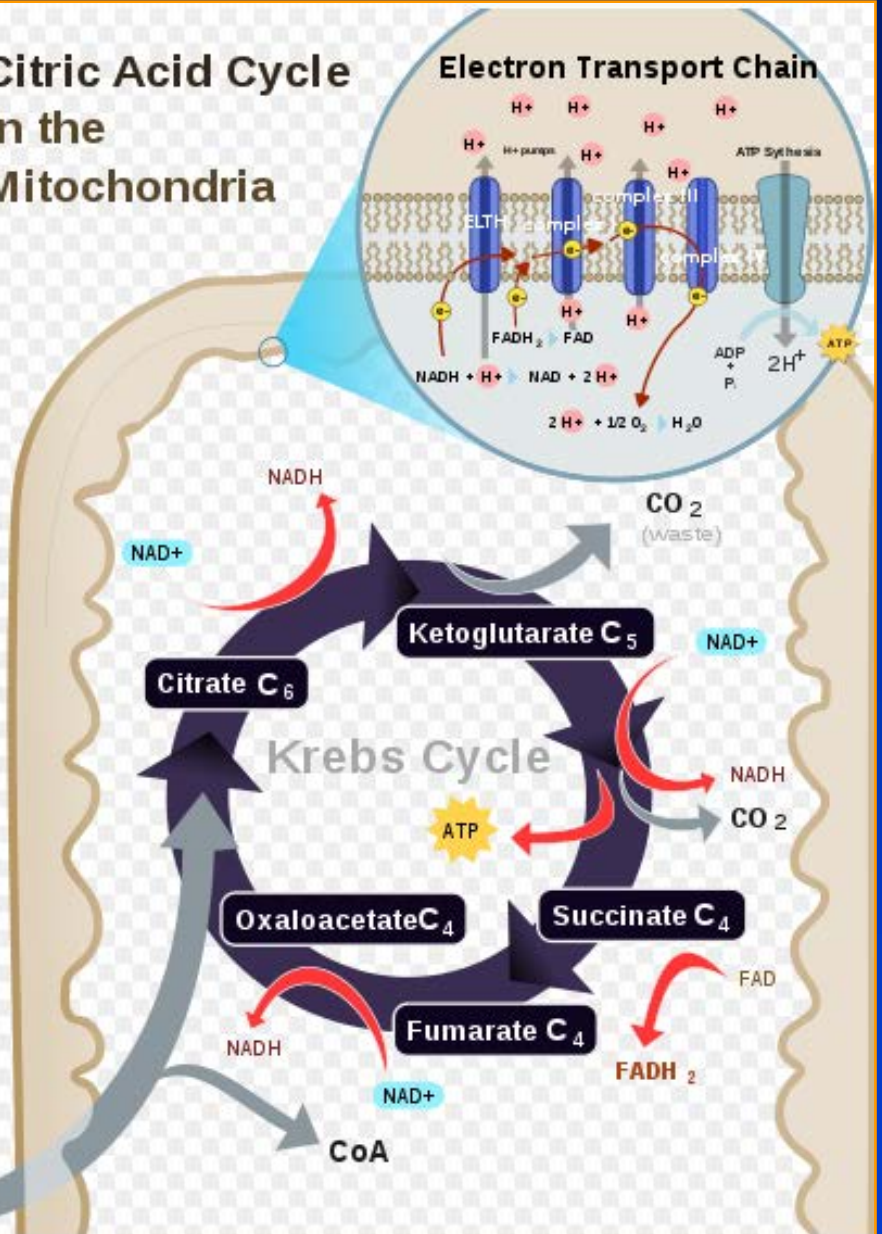


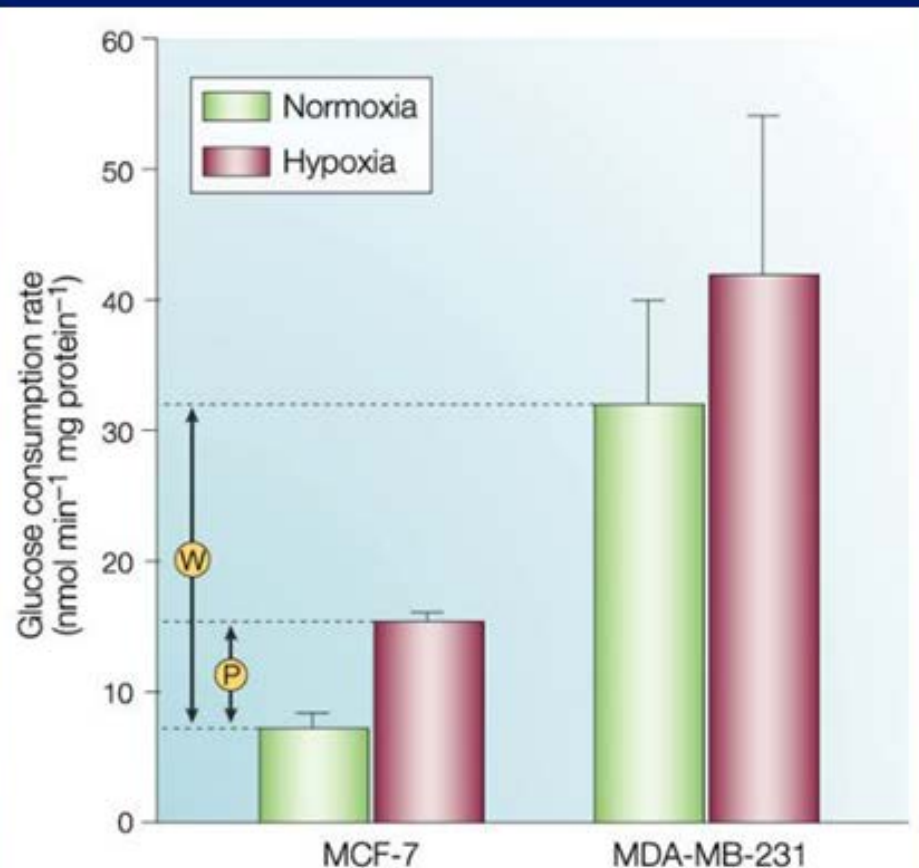
Legend: pTCP: Probability of histopathologic complete tumor control. Colored picture on the right: (A). ¹⁸F-FDG PET images before and (B) after neoadjuvant RCT. Marked decrease in ¹⁸F-FDG uptake (MRglc) was realized in response to RCT. (C). Resected right upper lobe showed what appeared to be gross residual tumor, but (D). Histopathologic examination showed extensive necrosis with no residual cancer cells.

Glycolysis in the Cytoplasm



Citric Acid Cycle in the Mitochondria





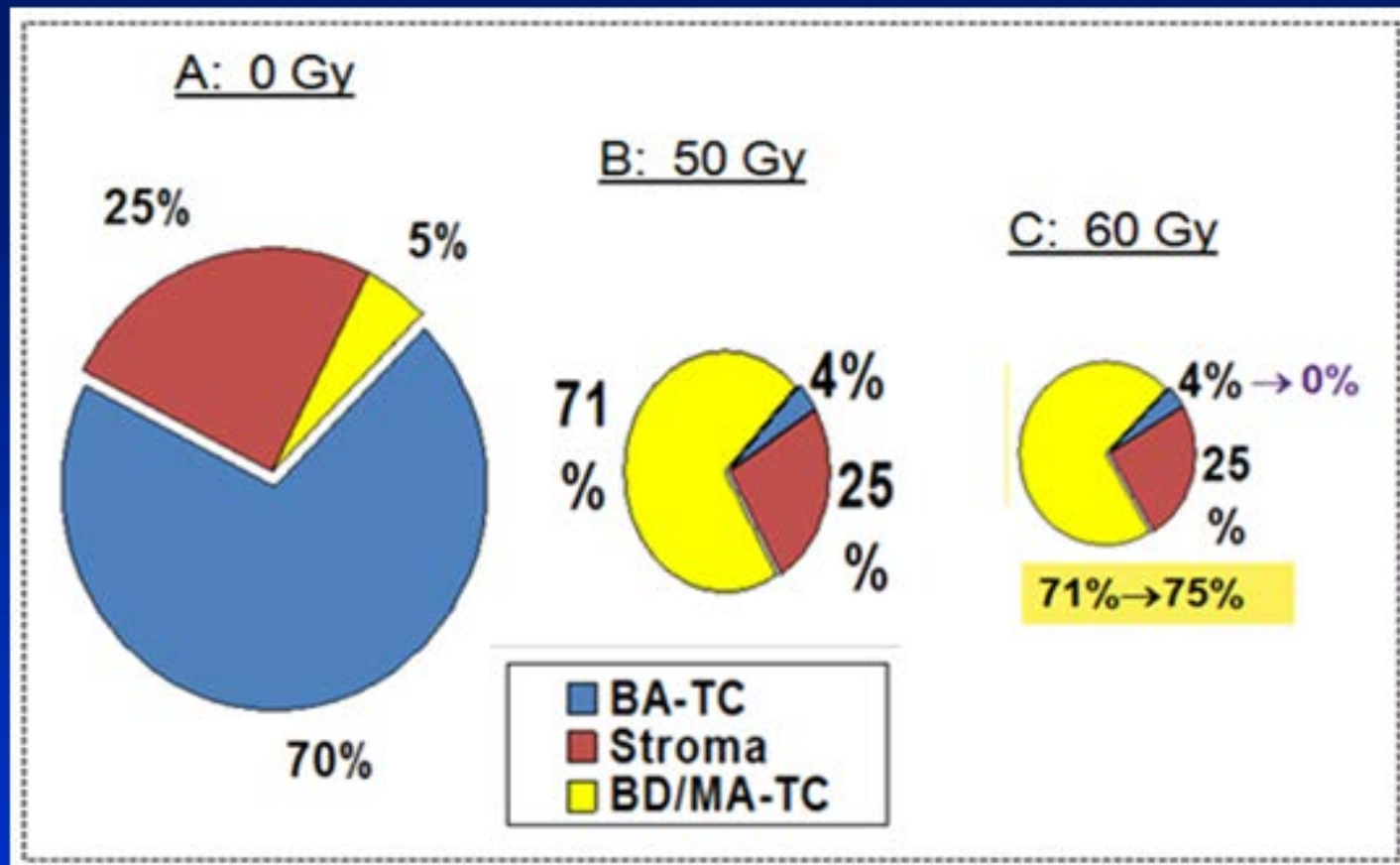
Nature Reviews | Cancer

Glucose consumption is reduced in the presence of oxygen — the **Pasteur effect (P)**. However, the more aggressive cell line, MDA-MB-231, has much higher glucose consumption in the presence of oxygen than the MCF-7 cells with a non-invasive phenotype — the **Warburg effect (W)**.

Rationale/Hypothesis

- (1). FDG uptake requires phosphorylation of FDG to FDG-6-Phosphate by living cells. Therefore, no uptake may mean no living cells.
- (2). Thus, FDG uptake is an ideal surrogate biomarker for cell's response to therapy.

Elements of solid tumor and response of each to RT



Model A: Represents baseline tumor model that contains biologically alive tumor cells (BA-TC, 70%), tumor stromal cells (stroma, 25%) and biologically dead but metabolically alive tumor cells (BD/MA TC, 5%).

Discovery of Timely Metabolic Response Biomarker for Its Potential in Guiding Personalized Radiotherapy

To search for a metabolic response biomarker that is capable of guiding individualized RT for patients with inoperable NSCLC, we conducted a prospective clinical trial, “**Partners protocol 03-282: Bioimaging in Radiotherapy for Lung Cancer**” in which glucose metabolic rate (MR_{glc}) of lung cancer was measured with ¹⁸F-FDG PET at baseline, 10 days, 3 months (m), 6 m and 12 m after RT or RCT.

This was awarded NIH/NIBIB Grant R01 EB002907 (PI: Noah Choi).

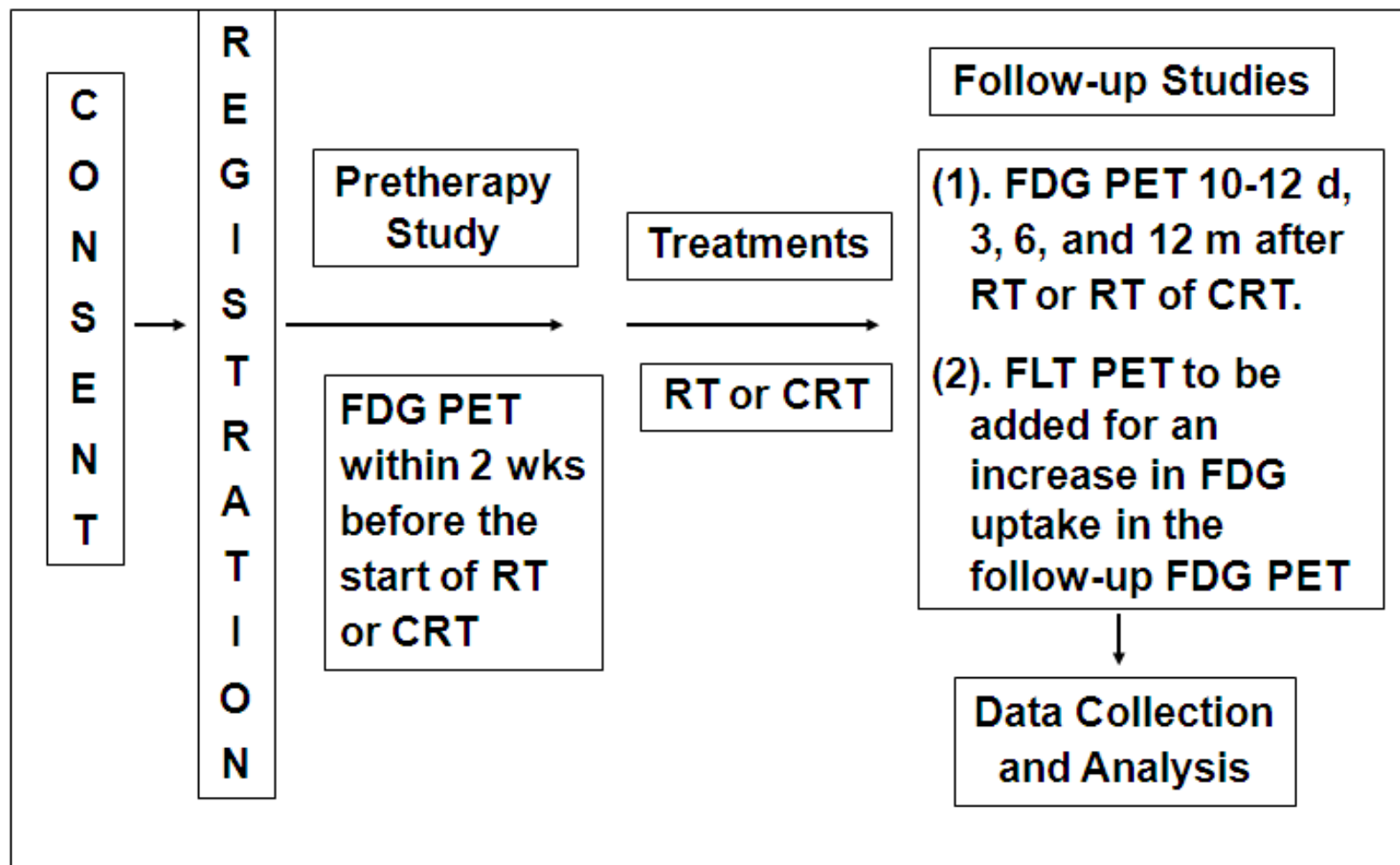
Specific aims of this study were:

- (1). Determine the time-course of metabolic tumor response using ^{18}F -FDG PET, after RCT or RT in lung cancer and identify the earliest time point where the maximum metabolic tumor response (MRgIc-MMR), defined with the nadir of residual ^{18}F -FDG uptake, is realized.
- (2). Determine the association between the levels of MRgIc-MMR and subsequent complete tumor control at 12 months and beyond.

Specific aims of this study were:

- (3). Determine the values of MRglc-MMR that correspond to tumor control probability (TCP) of $\geq 95\%$, 90% , 75% and 50% at 12 months and beyond, and their robustness in predicting tumor control.
- (4). Determine the optimum cutoff value of MRglc-MMR based on its predicted tumor control probability (TCP), sensitivity and specificity.

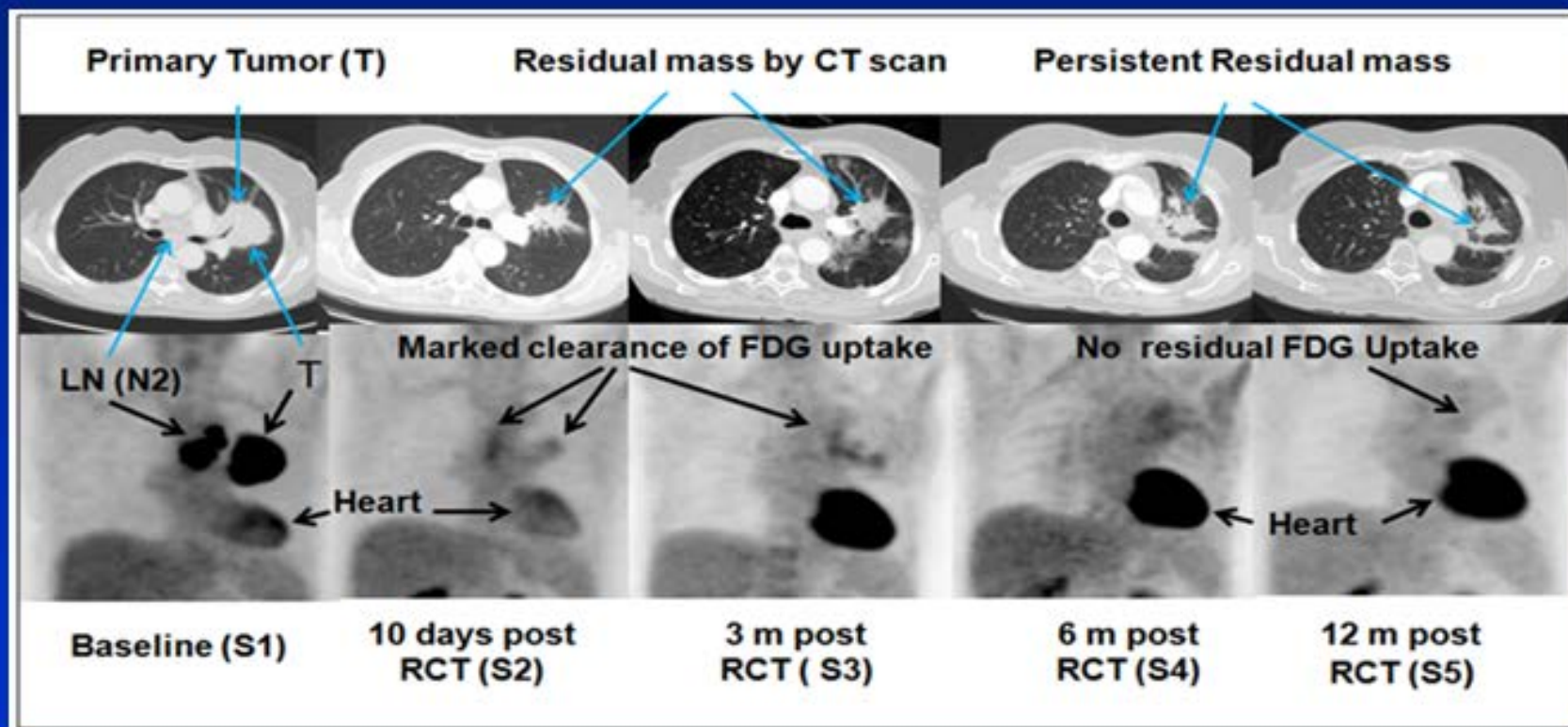
Study Schema (Partners Protocol 03-282)



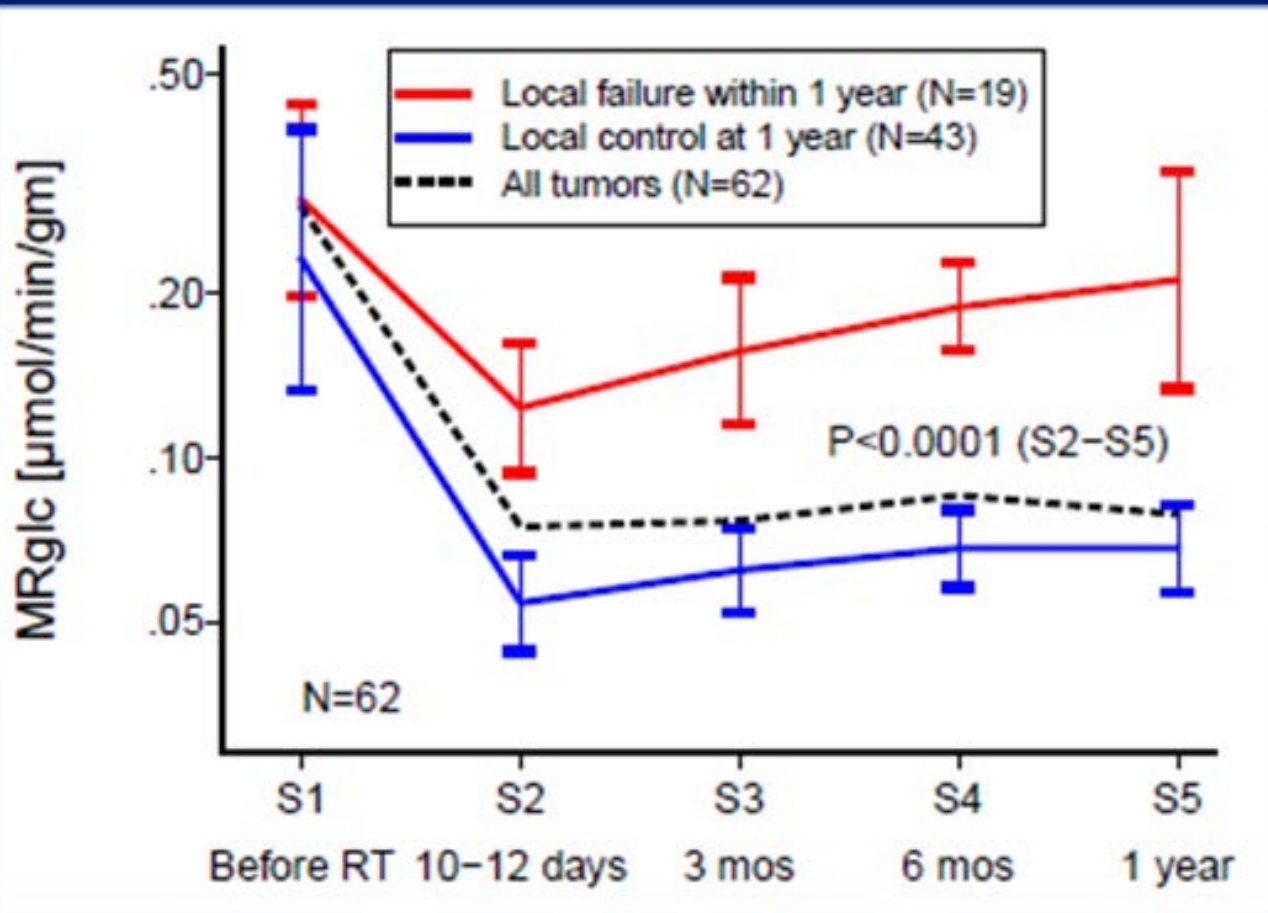
Tumor Stages, Histology and the Proportion of Tumors that met Study End Point (SEP)

<i>Primary Tumors</i>	<i>Tumors met SEP</i>
Stage I (n=31)	20/31 (65%)
Stage II (n=13)	8/13 (62%)
Stage IIIA (n=45)	22/45 (49%)
Stage IIIB (n=27)	16/27 (59%)
NSCLC (n=91)	48/91 (53%)
SCLC (n=19)	14/19 (74%)
CI diagnosis (n=6)	4/6
<i>Total: 116</i>	<i>66/116 (57%)</i>

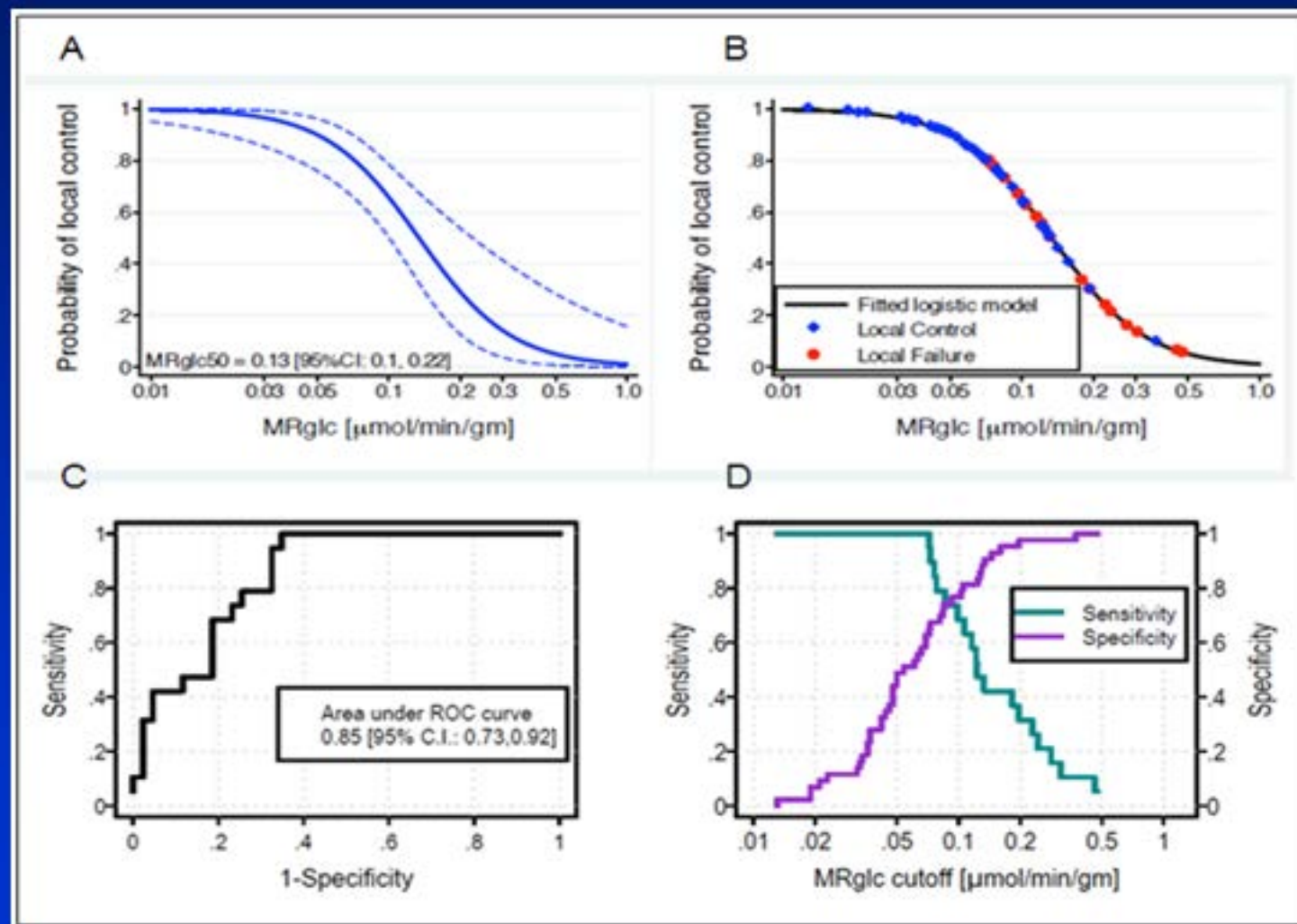
A sample case for illustration of differences between anatomical and metabolic responses of lung cancer to RCT by serial ^{18}F -FDG PET/CT studies.



Time-course of metabolic response measured with MRglc before and at intervals after radiotherapy or chemoradiotherapy



Logistic model of tumor control probability as a function of residual MRglc (^{18}F -FDG uptake) after RCT or RT



(A). Logistic model of tumor control probability (TCP) as a function of residual MRglc measured with ^{18}F -FDG uptake 10 days after RCT or RT,

(B). A robust fit is shown of the regression line of the logistic model superimposed on the actual data points,

(C). Area under the receiver operating characteristic (ROC) curve,

(D). Model probability cut-off curves with sensitivity and specificity values [11].

Cutoff values of MRglc and SUVmax of residual ^{18}F -FDG Uptake and their corresponding TCP, Sensitivity and Specificity

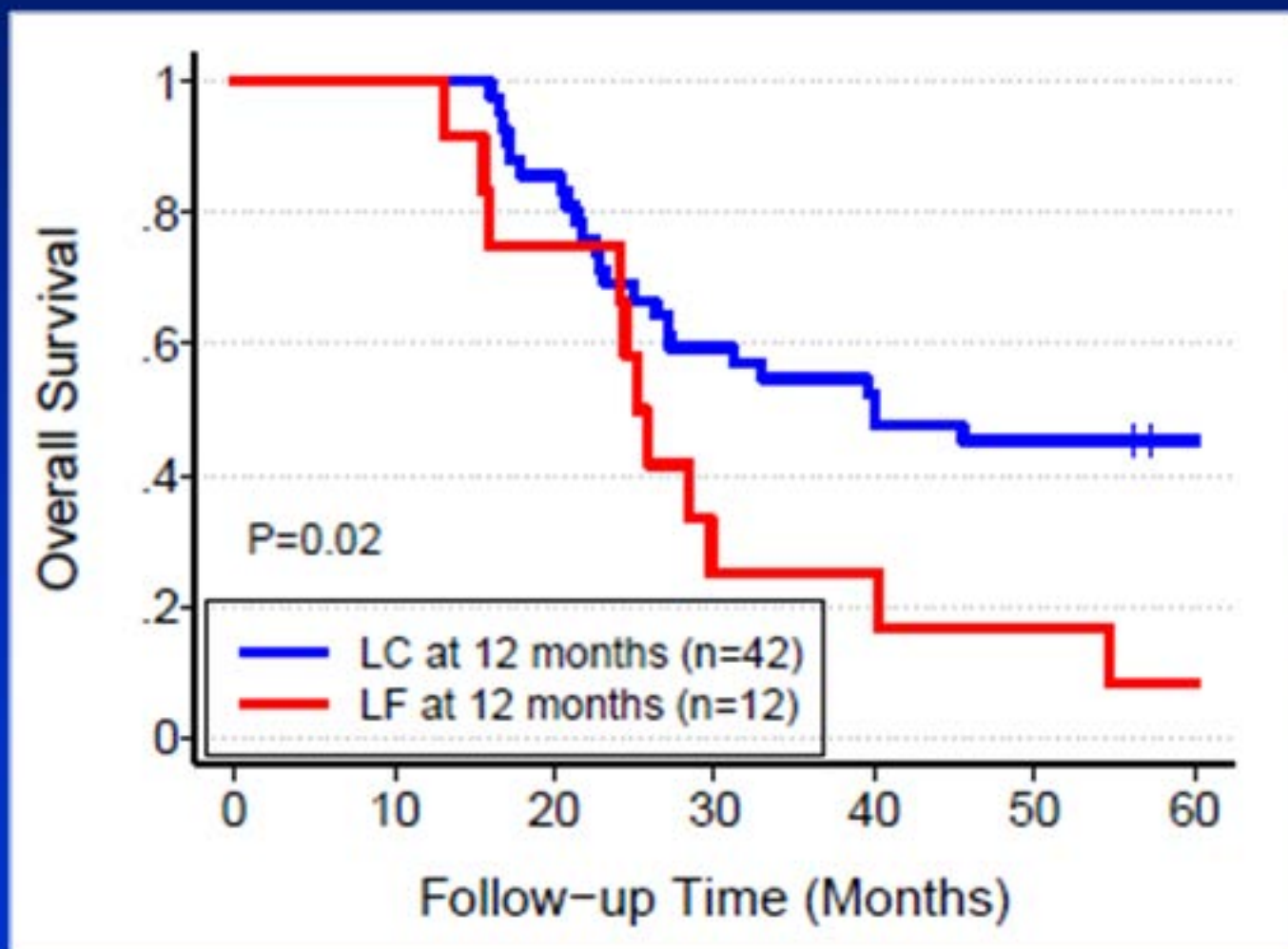
Cutoff values of MRglc ($\mu\text{mol}/\text{min}/\text{gm}$) by SKM at S2	Cutoff values of SUVmax ^a at S2	TCP (%) ^b	Sensitivity ^c	Specificity ^d
≤ 0.036	≤ 0.92	95	100%	19%
≤ 0.050	≤ 1.14	90	100%	44%
≤ 0.061	≤ 1.32	85	100%	53%
≤ 0.071	≤ 1.45	80	100%	63%
≤ 0.092	≤ 1.75	70	74%	74%
≤ 0.134	≤ 2.48	50	42%	91%

Among the ranges of cut-off values,

MRglc-MMR ≤ 0.071 $\mu\text{mol}/\text{min}/\text{gm}$ and SUVmax ≤ 1.45 carry predicted TCP 80%, sensitivity 100% and specificity 63% and are optimum cutoff values. It is also named Metabolic Response Biomarker (MRB).

This means that with this cutoff value, 100% of patients with residual cancer will be identified for boost dose RT to residual cancer while it also carries 37% false positivity.

Overall survival according to local tumor control status by landmark analysis



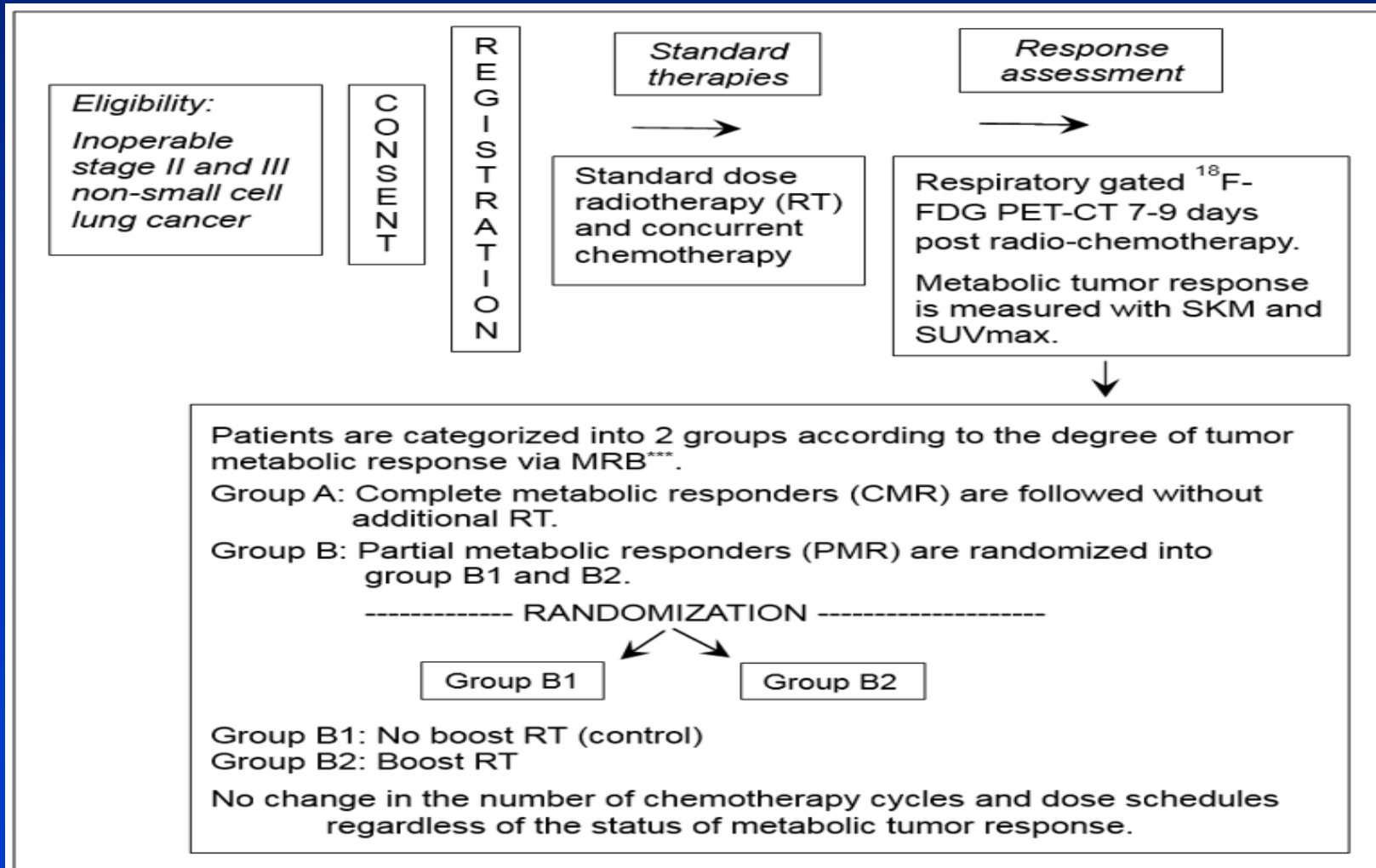
Conclusions

1. The nadir values of FDG uptake at S2 after RT of RCT are inversely correlated with TCP and likely represent remaining tumor burden.
2. MRB (metabolic response biomarker) is residual glucose metabolic rate representing the maximum metabolic response (MRglc-MMR) with the value of $\leq 0.071 \mu\text{mol}/\text{min}/\text{gm}$ by SKM and ≤ 1.45 by SUVmax and carries predicted TCP 80%, sensitivity 100% and specificity 63%.

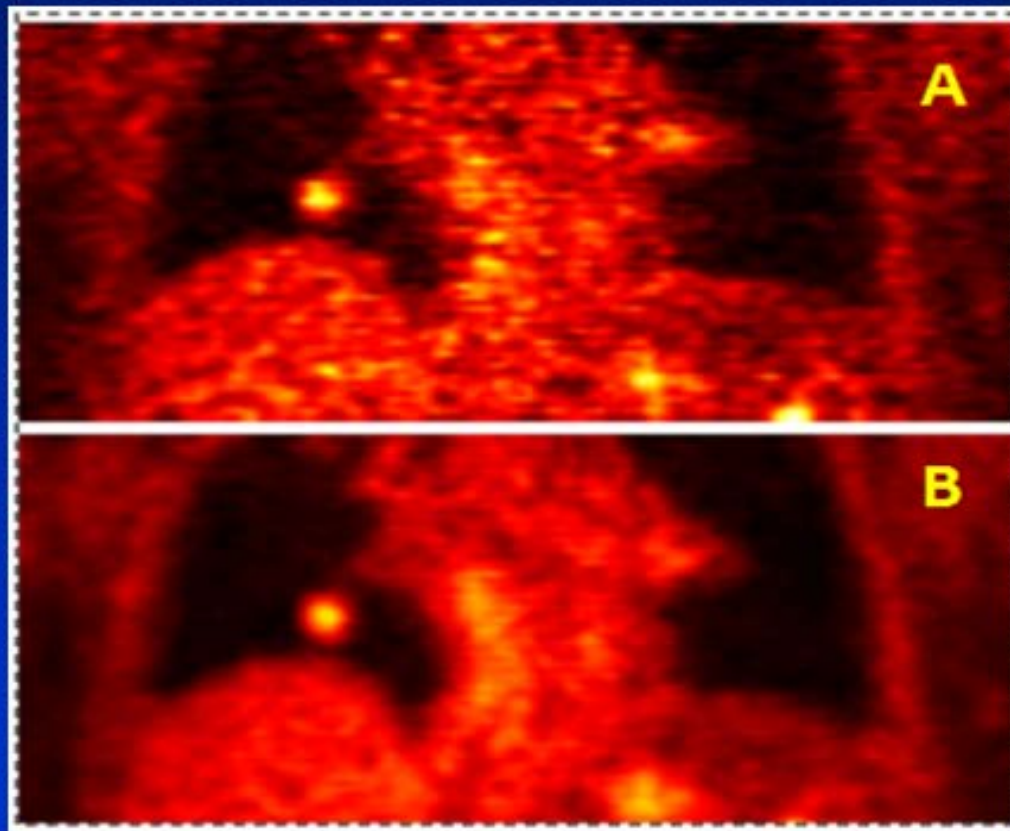
Follow-Up Validation Study

- A phase II randomized trial for validation of the robustness of MRB for guiding individualized RT.

Study Schema



PET IMAGING PROTOCOL



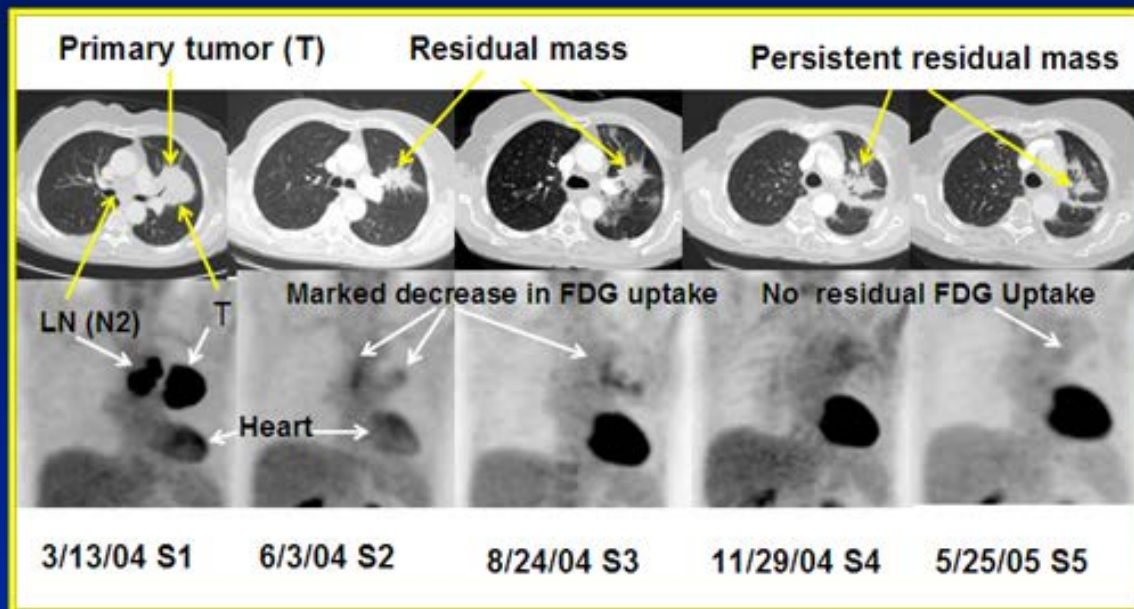
Respiratory Gated (A) and ungated (B) images of right lower lobe lung cancer by ^{18}F -FDG PET. The boundary of the tumor image is much sharper in images A (gated) than B (ungated).

Primary Objective:

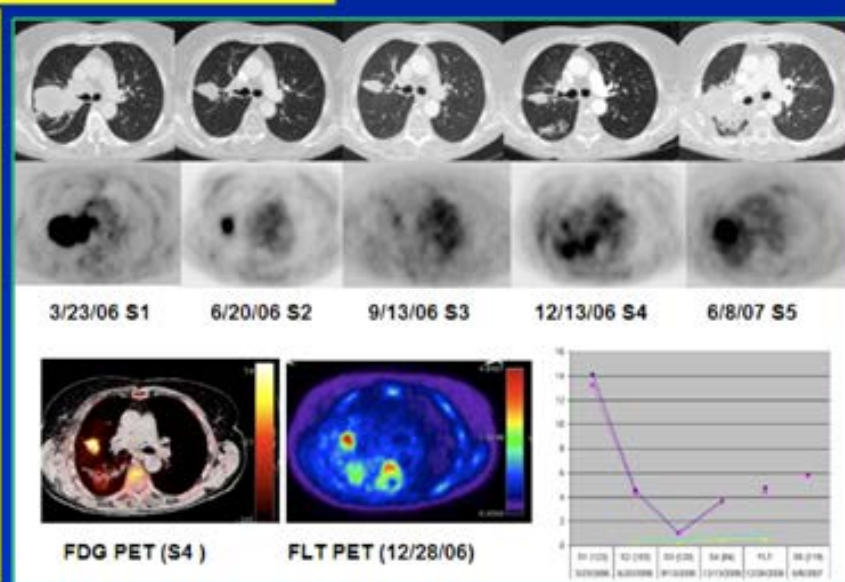
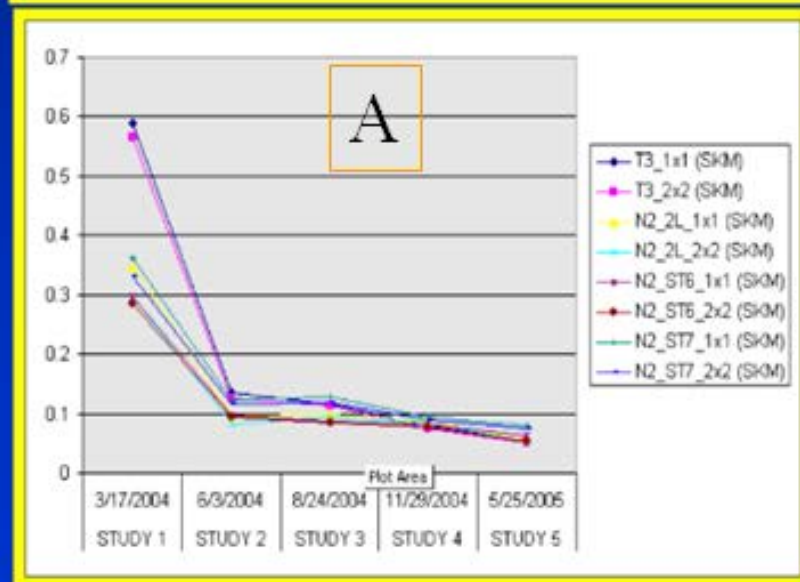
- [1]. Determine the robustness of MRB for its capability in classifying metabolic tumor response into two groups: CMR vs. PMR.

Secondary Objectives:

- [1]. Determine the significance of MRB for an increase in overall survival.
- [2]. Determine the efficacy of boost RT for local tumor control.
- [3]. Determine the tolerance of boost RT.



Two
Sample
cases



Overall Conclusions

1. Glucose metabolism (GM) is an essential cellular function and its altered status in response to therapy can be measured in vivo non-invasively.
2. Enhanced GM (Warburg's effect) in cancer cells can be exploited for response monitoring and guiding personalized therapy.
3. MRB determined in our study is a potential candidate biomarker for optimized radiotherapy. Validation of this MRB is being planned.

Acknowledgements

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