

# Criteria for defining resistance to EGFR-TKI's:

Are RECIST appropriate?

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Dept Pulmonary Diseases

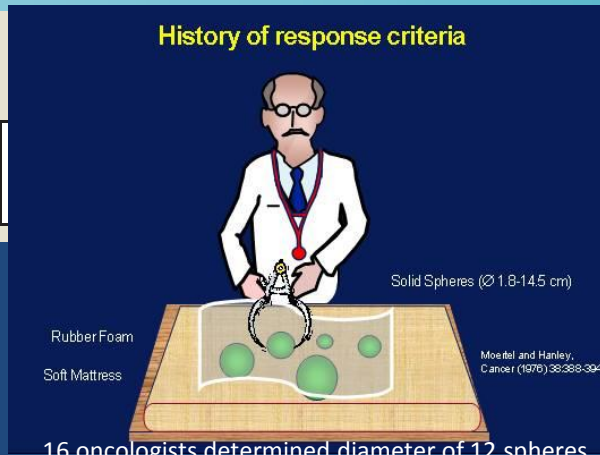
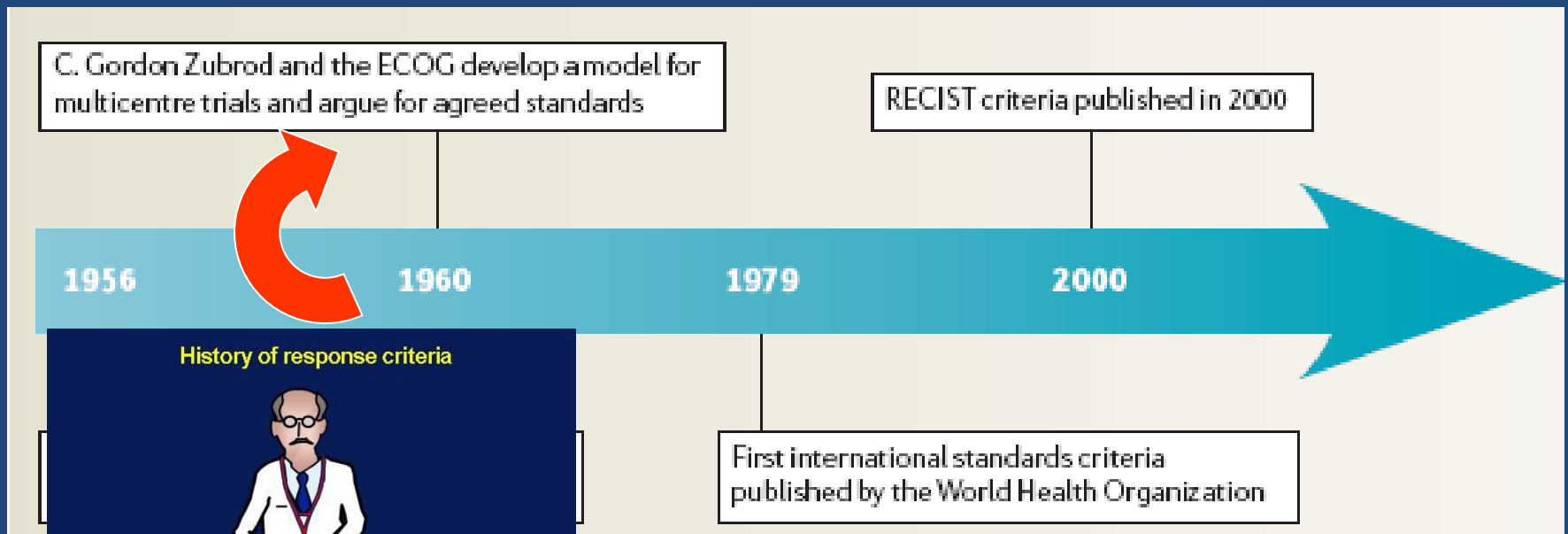
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# How to assess treatment efficacy with EGFR TKI's?

- Radiology (ie. RECIST)
- Molecular imaging (ie PERCIST)
- Tumor biopsies
  - Surrogate tissue?
- Circulating markers (will not be discussed)
  - Circulating “tumor” DNA
- Biology coupled with Clinical judgement

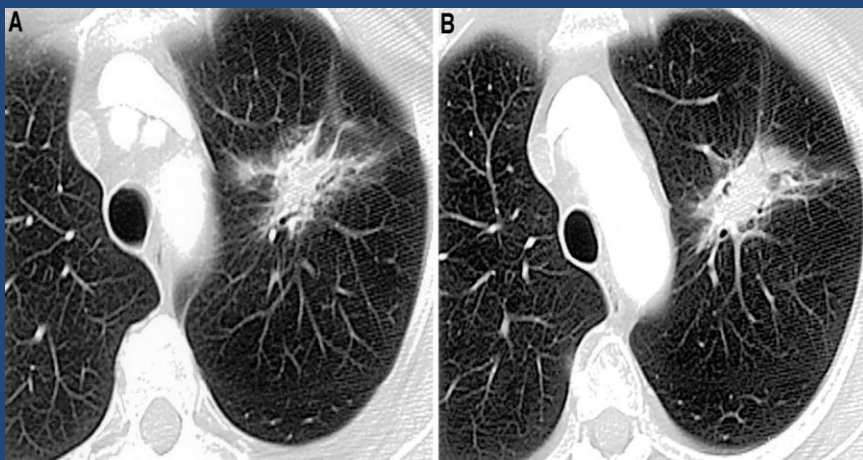
# History of Radiological Response Assessment



16 oncologists determined diameter of 12 spheres  
Area of identical spheres differed:  
At least 25% in 25% of measurements  
At least 50% in 6.8% of measurements  
("false positive for response")

Michaelis and Retain. Nat Rev Cancer  
6;409,2006

# What size has this tumor?



**Intraobserver variability 37%**

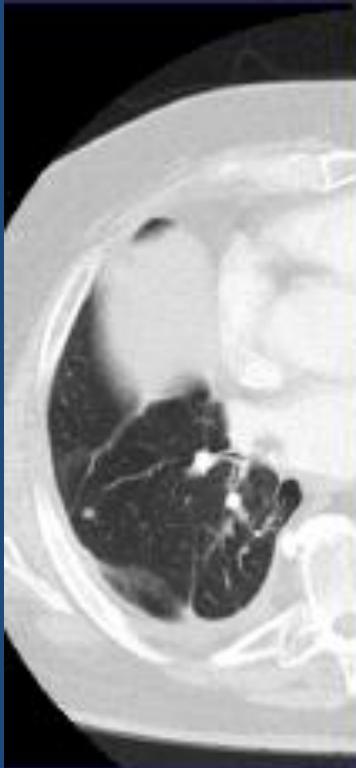
**Interobserver variability 140%**

- 33 patients, 5 observers
- Assessment of PD by RECIST and WHO
- Misclassification
  - RECIST 11.9 (30%)
  - WHO 17 (43%)

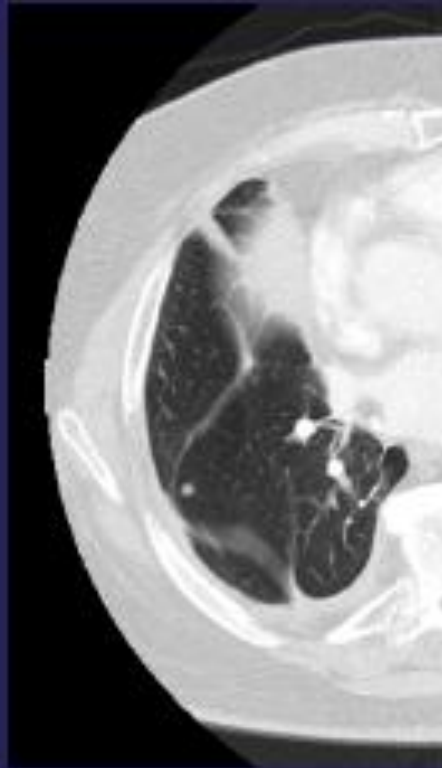
# Response assesment by RECIST



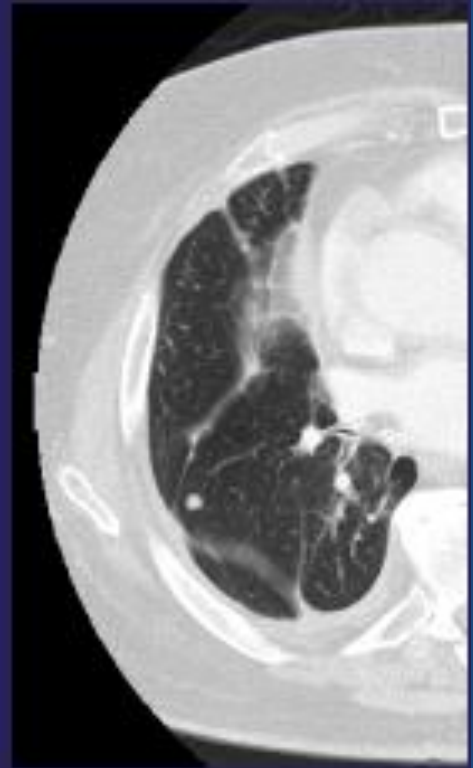
# Response assesment by RECIST



**Apr 2010**

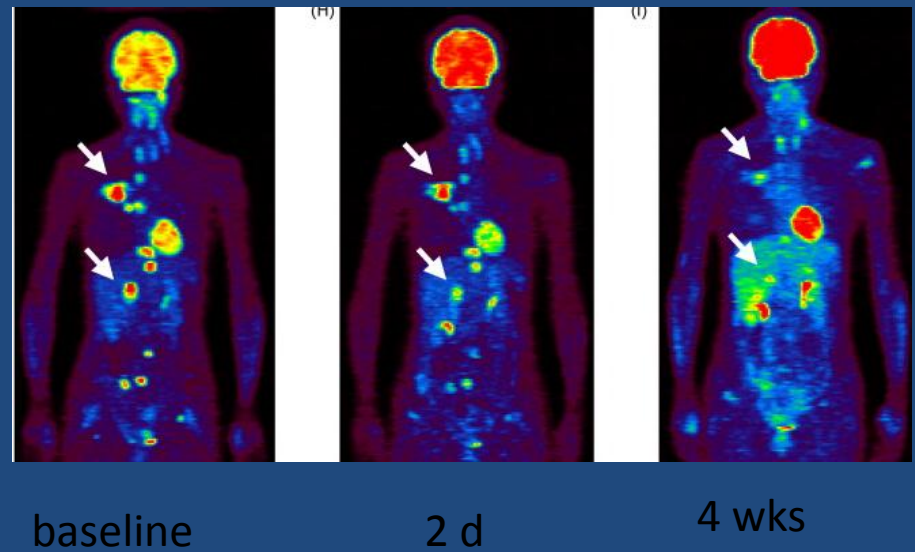
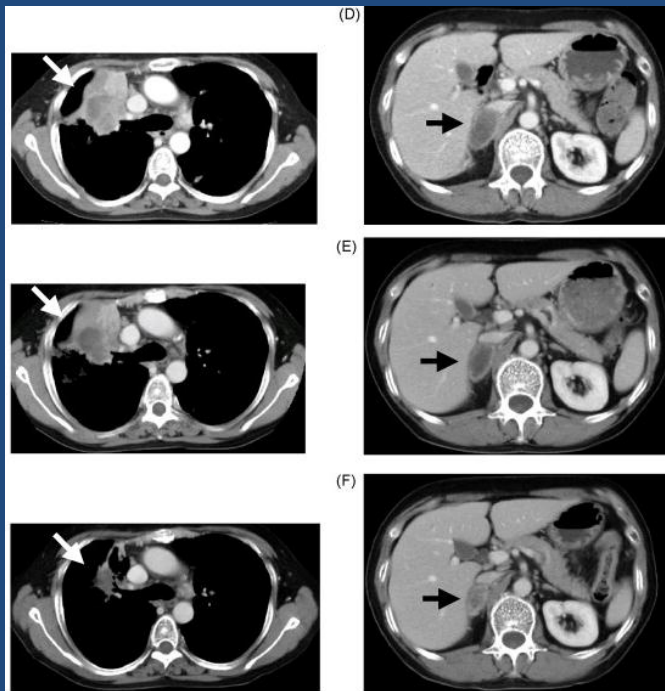


**Jun 2010**



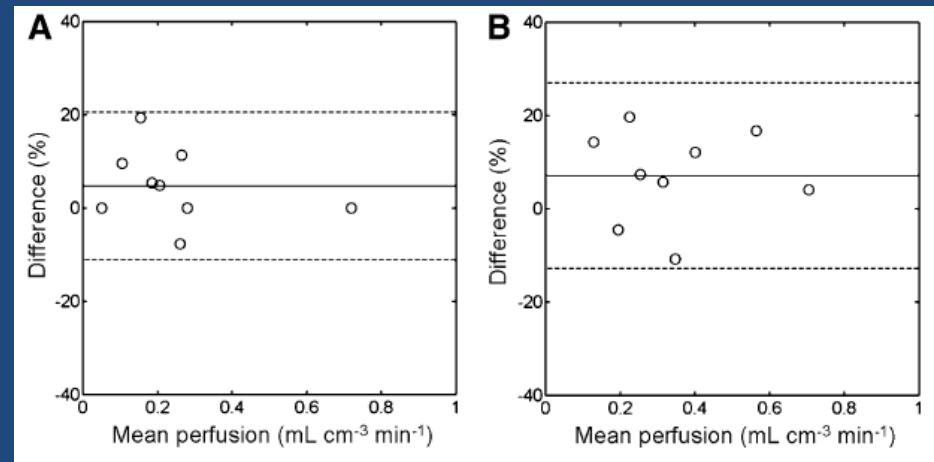
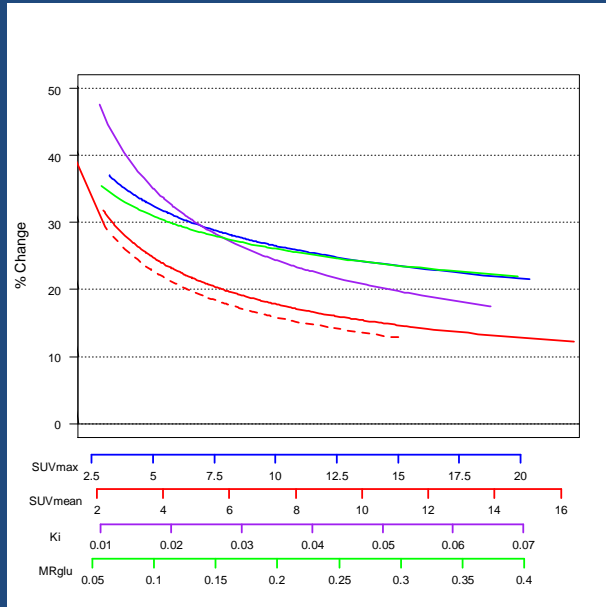
**Aug 2010**

# Prediction of response to gefitinib with FDG-PET



# What constitutes a PET response?

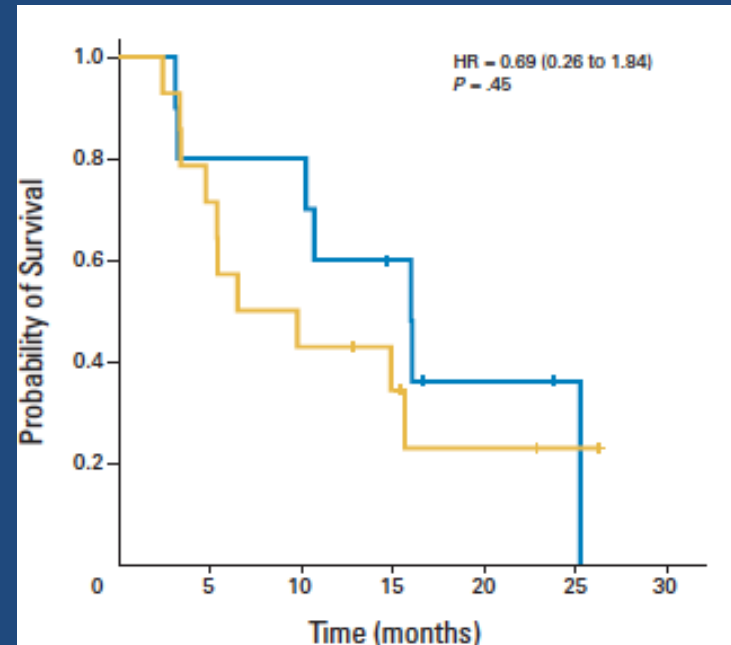
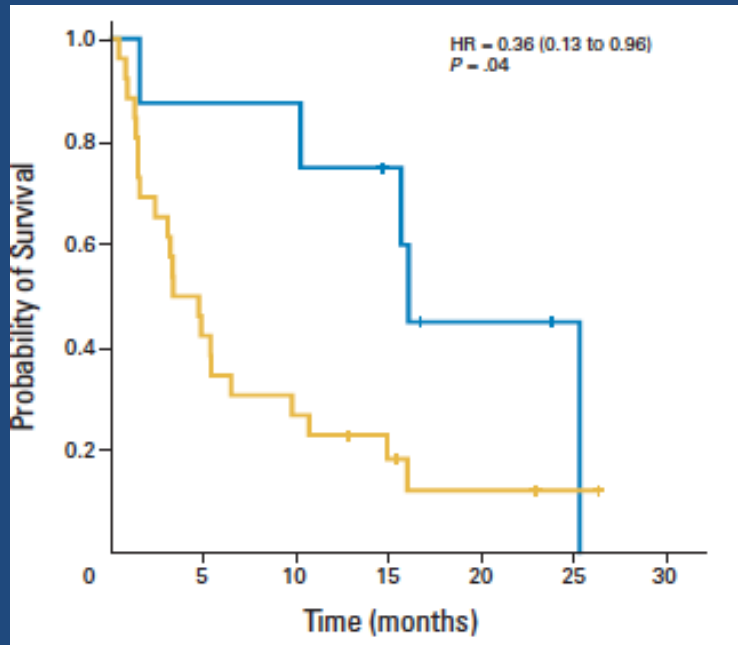
## Repeatability studies of FDG



>20% decrease in FDG (SUV mean) or 1.17 absolute difference for low SUV values.



# Tracers are important: Early FDG not FLT PET “predicts” OS

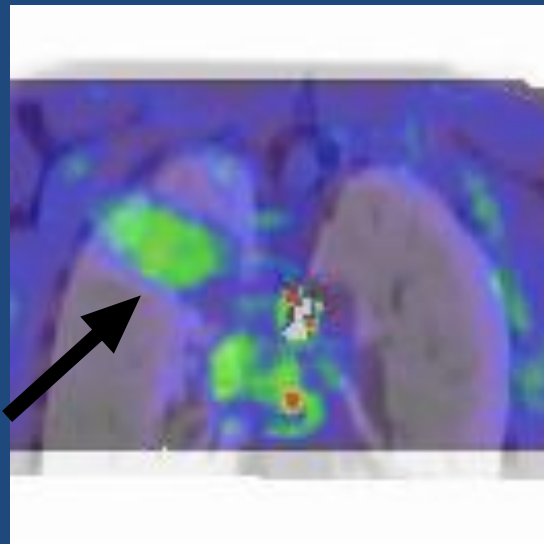


# Molecular imaging studies defining progression on EGFR – TKI's

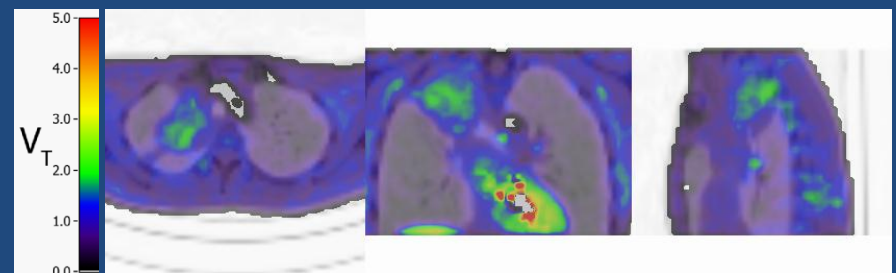
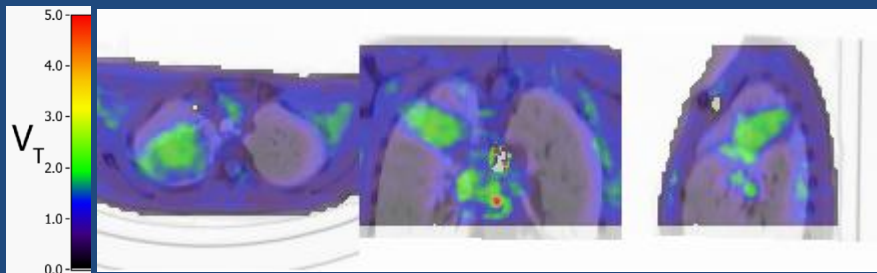
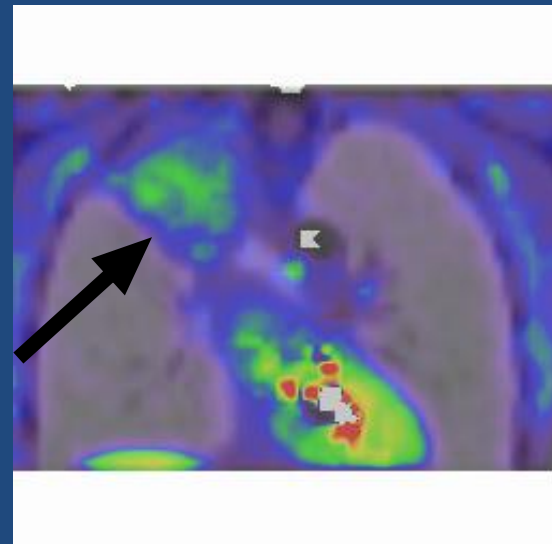
- No reports in the literature.
- Animal studies suggest same thresholds for FDG (and FLT) may be applied.

# Advanced molecular imaging: $^{11}\text{C}$ -erlotinib PET

2009, exon 19 del

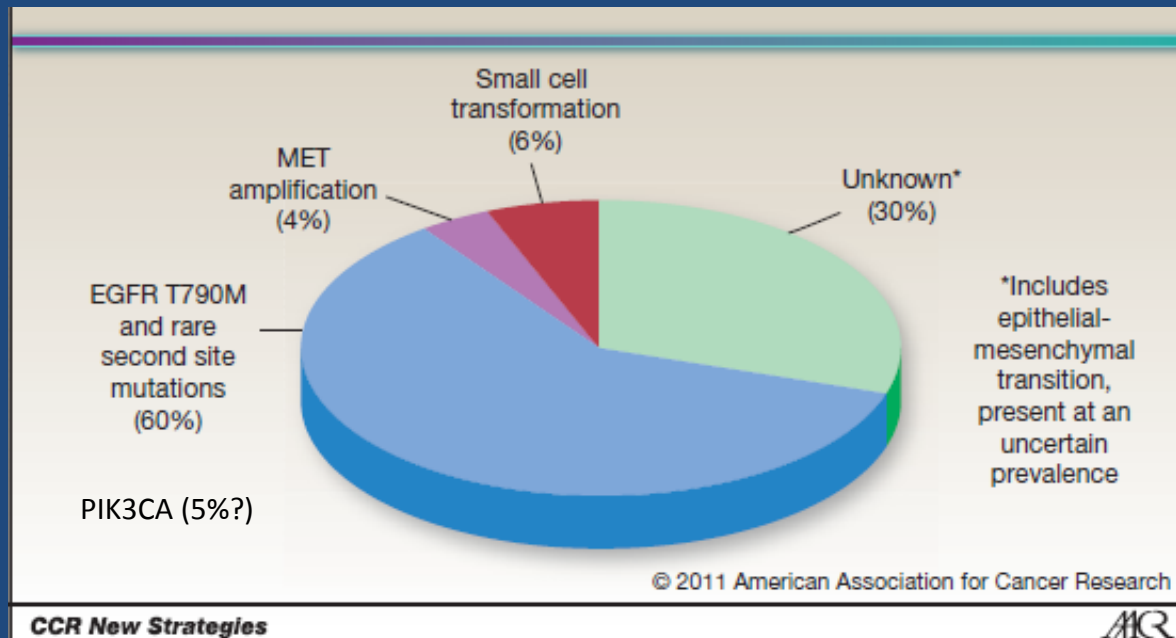


2011, exon 19 del + T790M



# Characteristics of tumours with acquired resistance to EGFR TKI

Frequency of acquired resistance mechanisms for EGFR-TKIs. Pooled data from the 2 largest rebiopsy series.



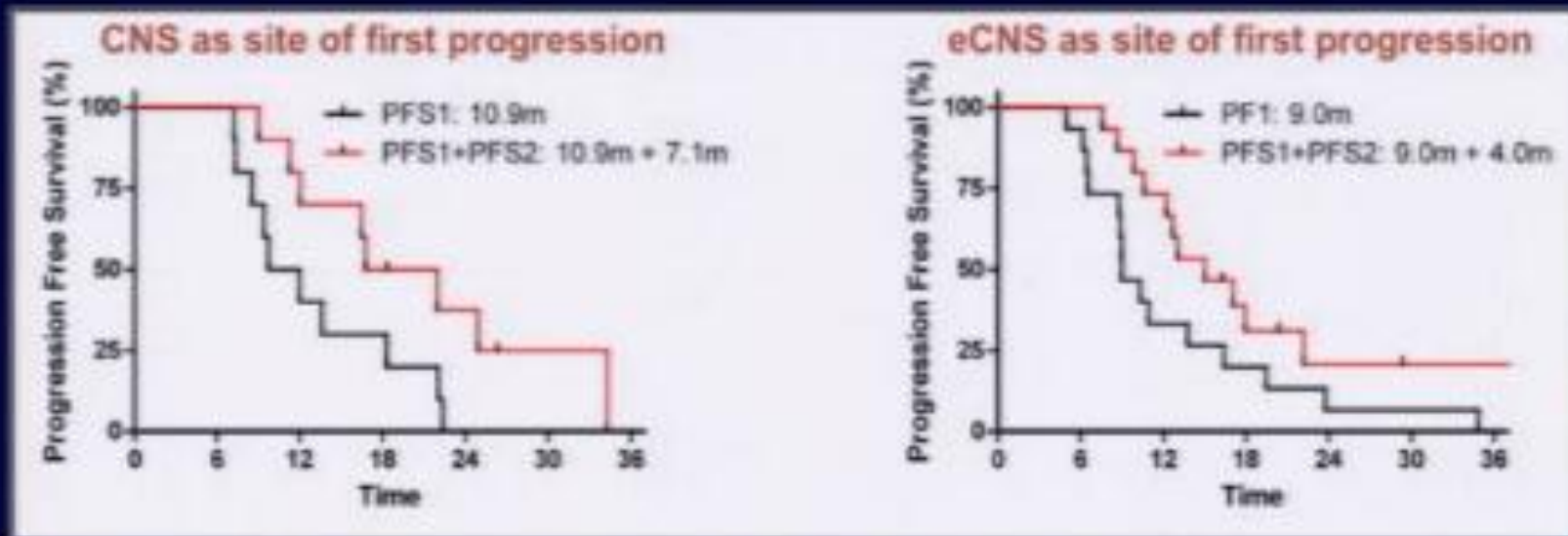
All maintained mutated EGFR genotype

# What is the clinical problem?

- Single focus of progression
  - Sanctuary sites (CNS)
  - Outside these – tumor burden low
- Slow multifocal progression –total sum of disease < at presentation
- Rapid multifocal progression

# Local Therapy in Acquired Resistance: University of Colorado Experience

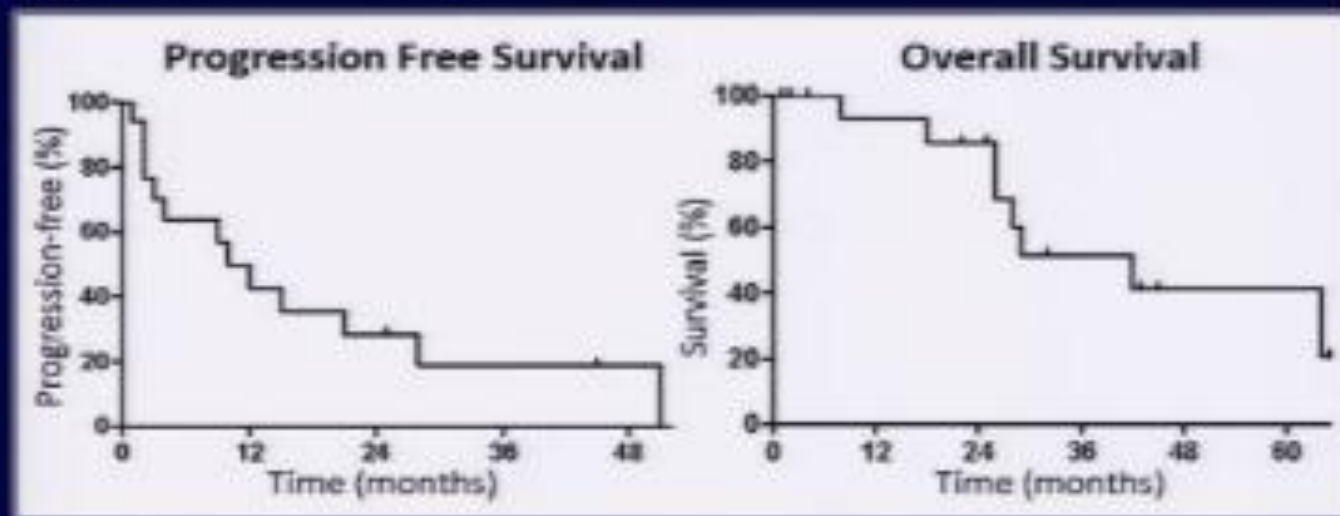
- 65 pts (38 ALK+, 27 EGFR mut'n+) of whom 51 (28 ALK, 23 EGFR) progressed
- 25 (49%) with CNS (no LMC) or  $\leq 4$  extracranial sites of progression



- Particular value in those w/CNS as first site of PD
  - acquired resistance vs. sanctuary site w/inadequate dosing

# Local Therapy in Acquired Resistance: MSKCC

- 18/184 pts/7+ yrs underwent local therapy for extracranial PD
  - CNS PD excluded
- From time of local therapy
  - Median TTP: 10 months
  - Median time to new systemic Rx: 22 months
  - Median OS: 41 months



# Slow multifocal progression

## Treatment beyond progression

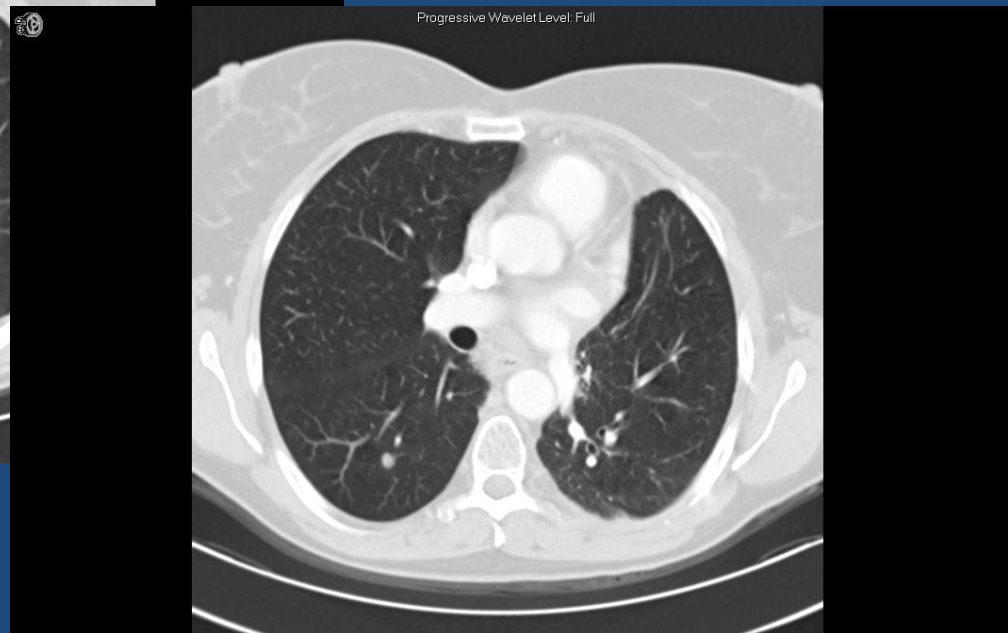
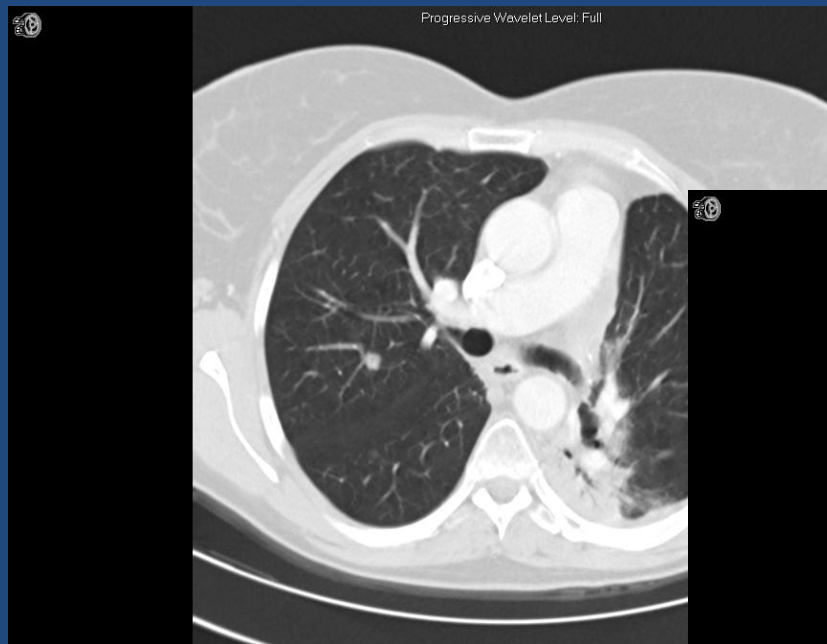
- Few clinical data
- Most suggest TBP may be worthwhile in terms of patient benefit
- Need prospective trials
  - How to “prove” this concept?



## Ms B. 24-06-1961

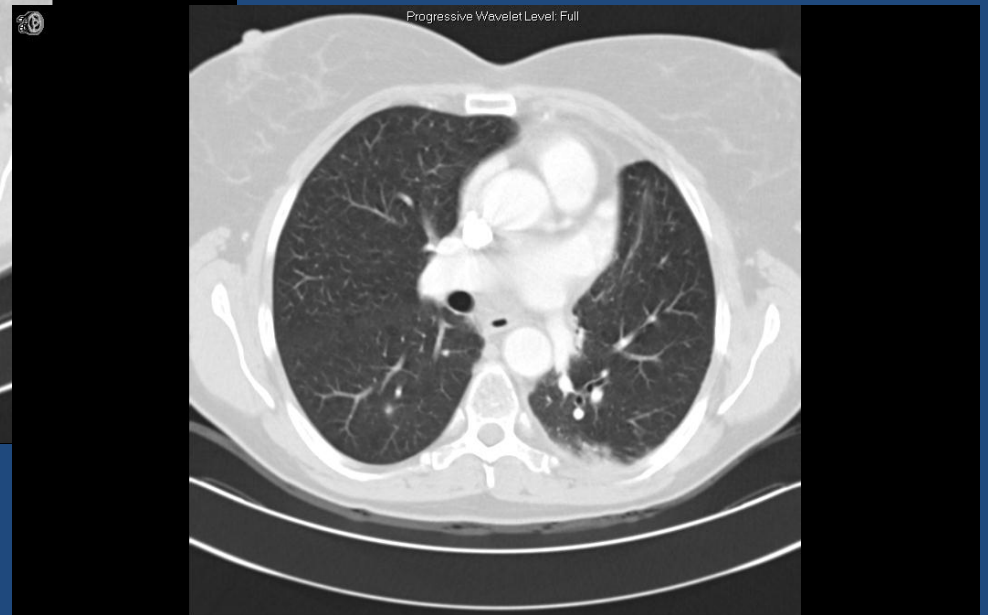
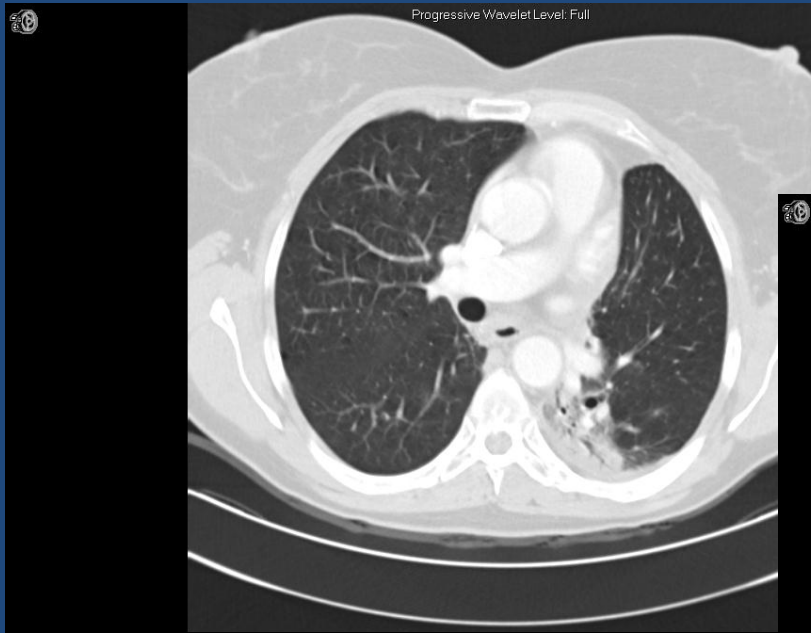
- Nov. 2005 pT2N2M0 adenocarcinoma LUL
- Lobectomy + adjuvant Cx-RT
- May 2006 local recurrence
  - Chemotherapy pem-cisplatin: PR
- January 2007 intrapulmonary metastasis

19-01-2007

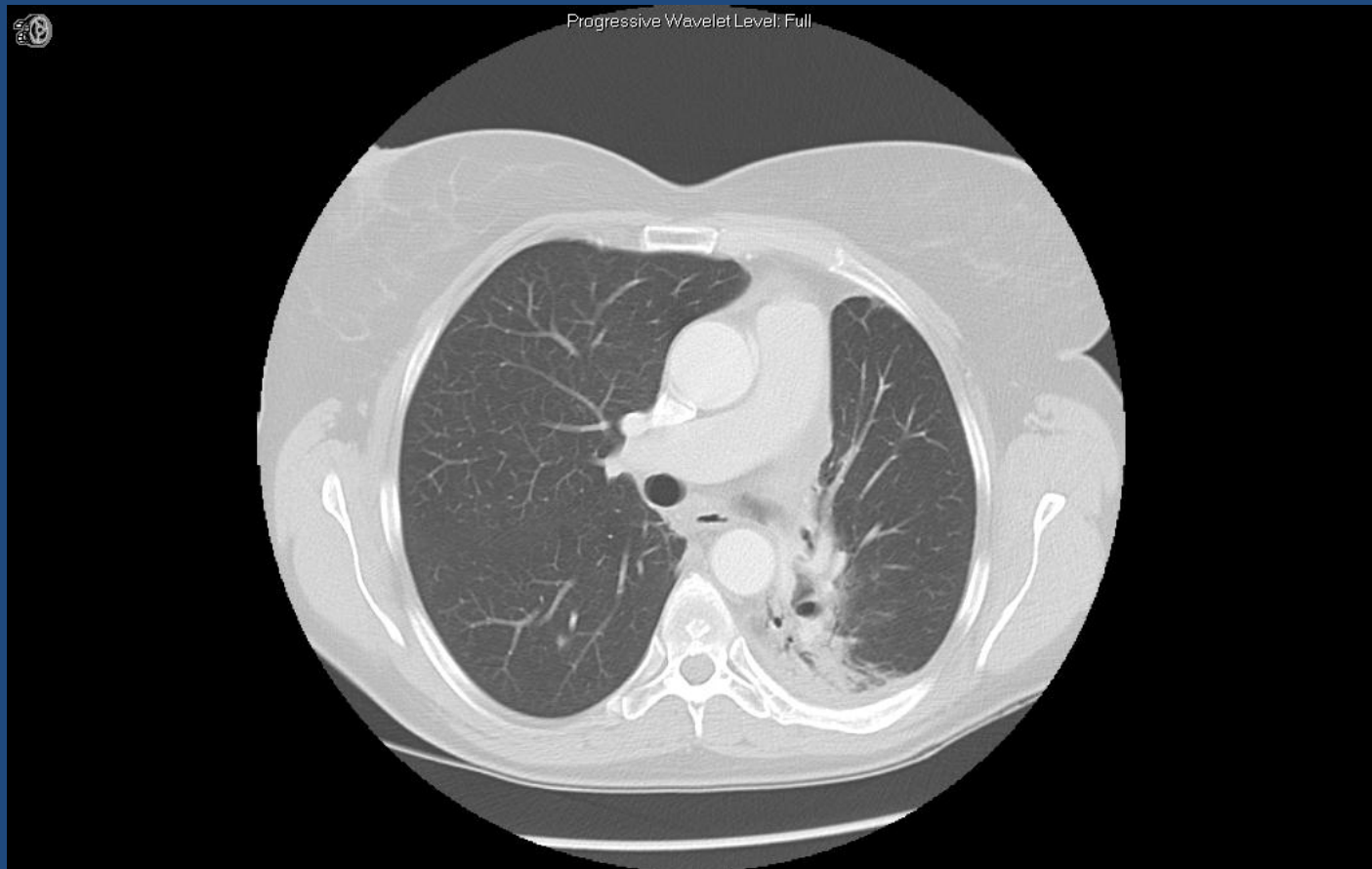


- EGFR mutation analysis primary tumor LBK:  
del exon 19
- R/ erlotinib 150 mg/dg

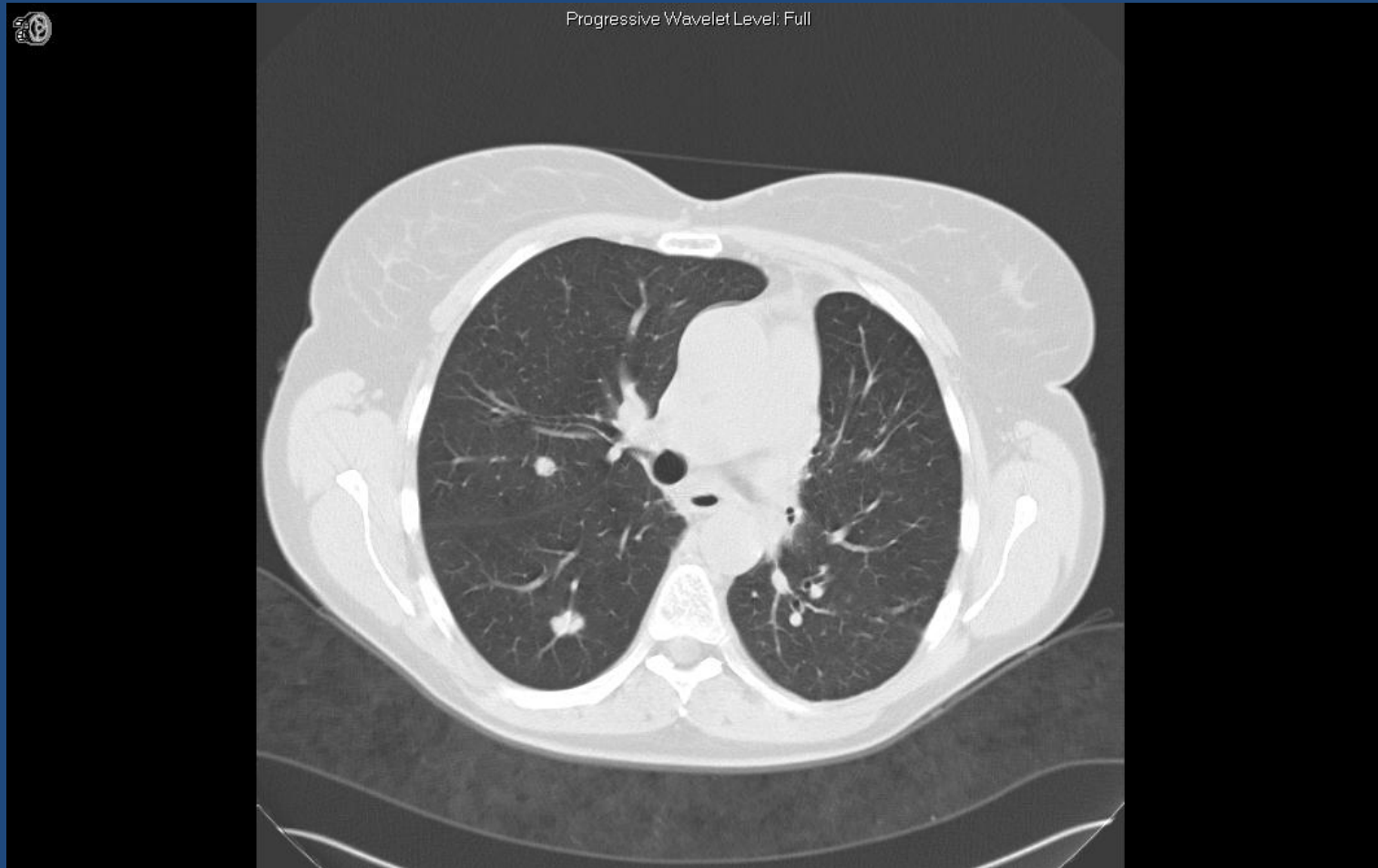
01-05-2007



26-09-2007



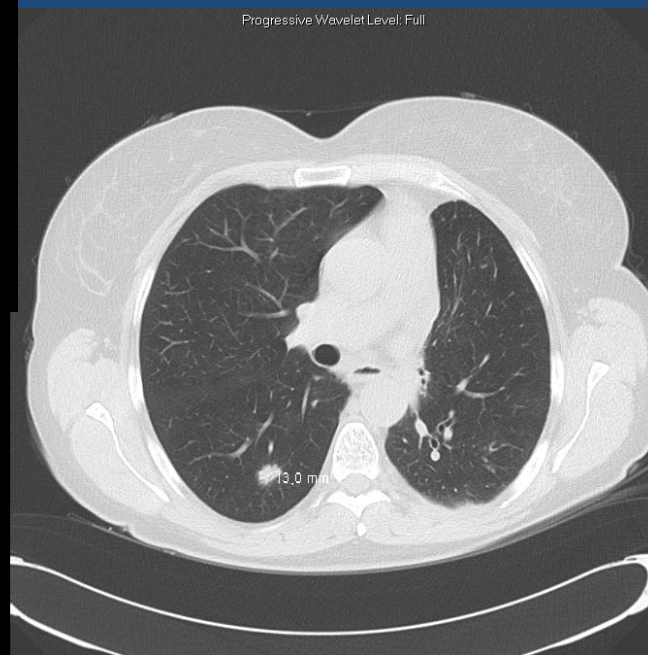
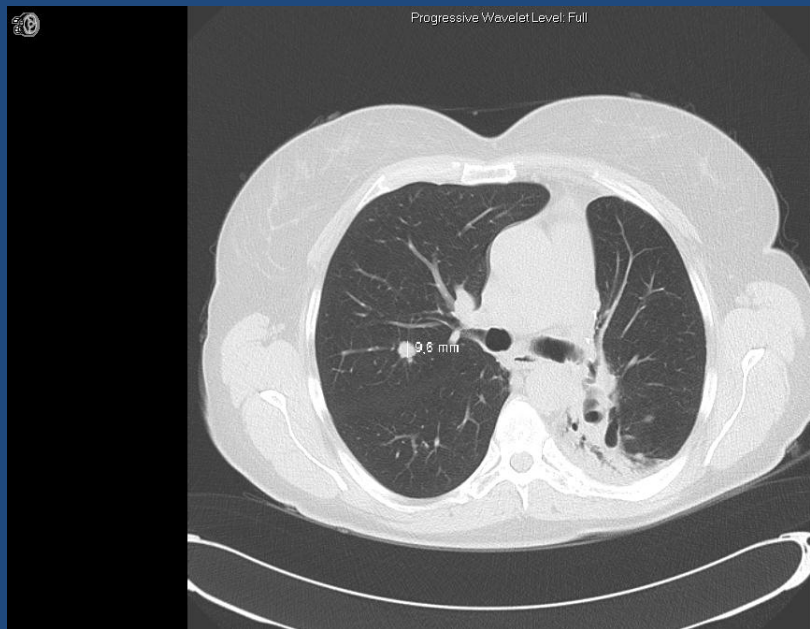
# 15-12-2009



Progression metastasis RLL as per RECIST

- Erlotinib was continued. Because of skin toxicity the dose was reduced to 100 mg/dg

# 23-03-2010

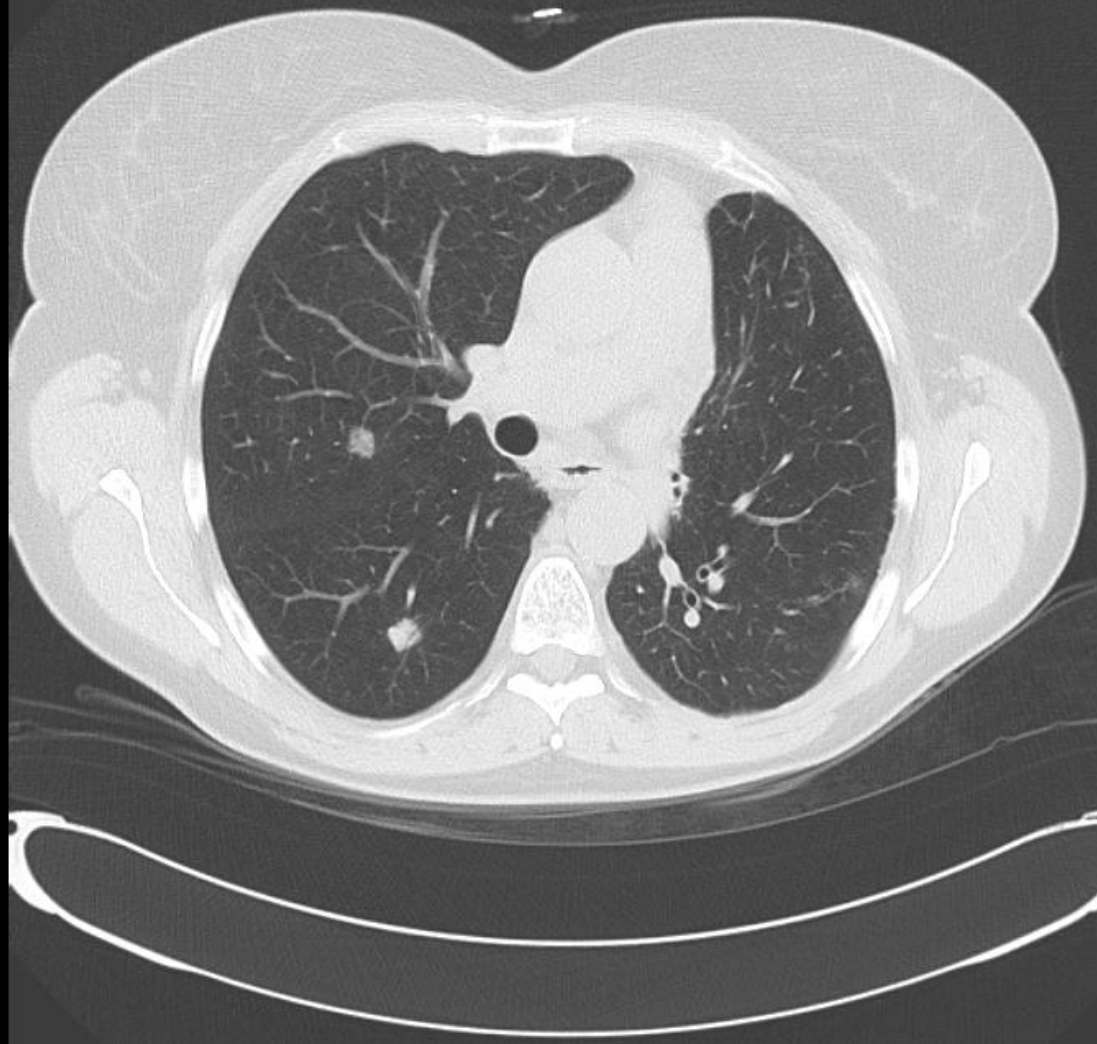




22-06-2010



Progressive Wavelet Level: Full



- Patient wants to emigrate to Canada to join her son
- Immigration authorities do not grant permission since she is treated with erlotinib
- Patient asks: if you remove these two nodes can I go without treatment?

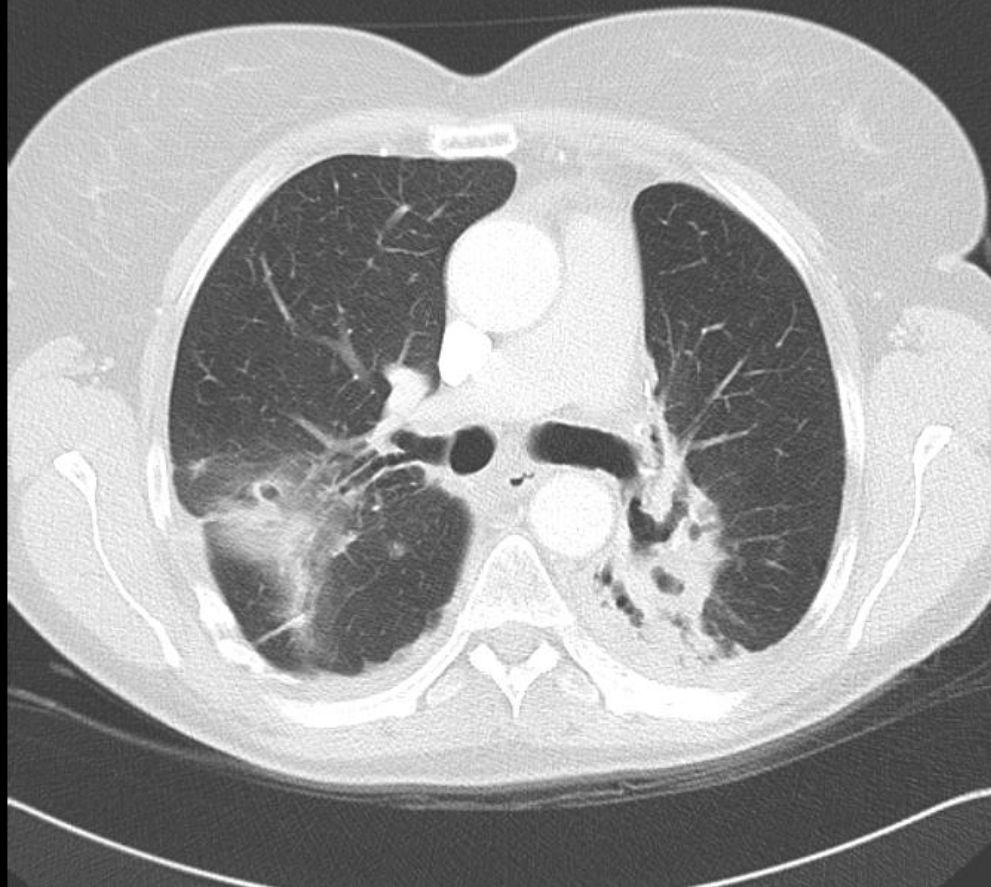
- FDG-PET/CT scan: FDG uptake in both lesions in the RLL and RUL. Physiological uptake elsewhere
- MDTB: I ask the surgeon to do 2 wedge resections and all others think this is crazy

- Segment resection RLL (I) and wedge resection RUL (II)
- PA (I): adenocarcinoom EGFR del19 en T790M
- PA (II): idem.
- pT4N0

# 14-12-10



Progressive Wavelet Level: Full

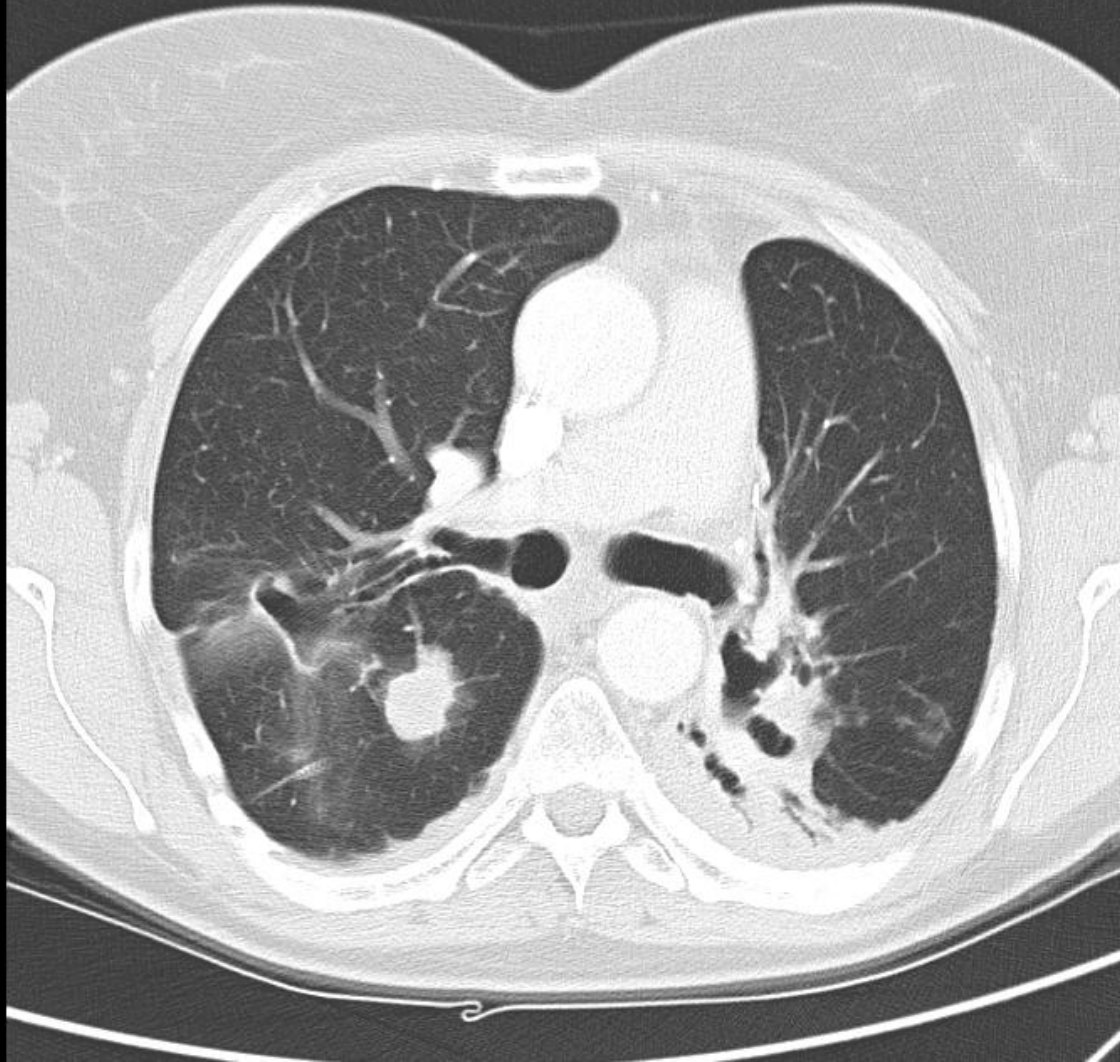


- Aug 2011: novel (?) lesion RLL.

13-09-2011



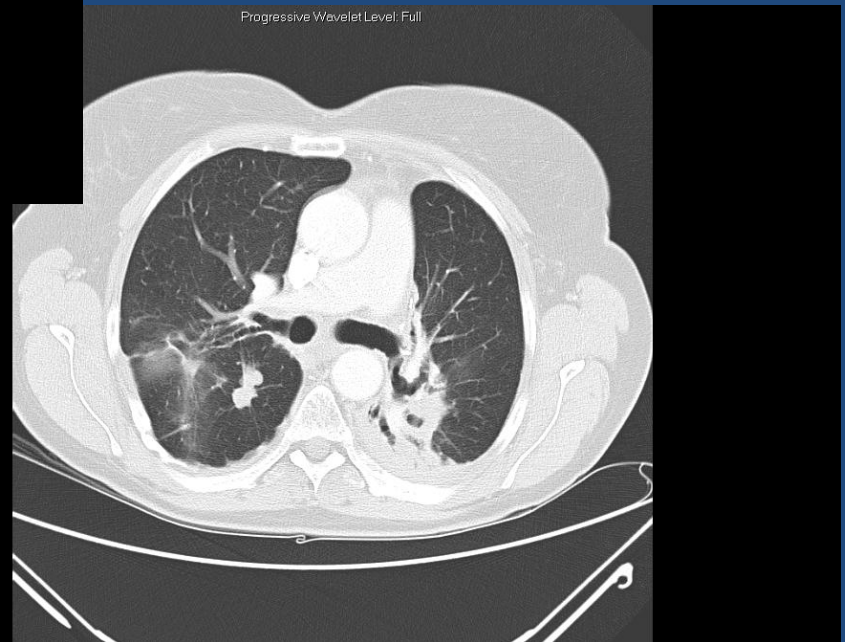
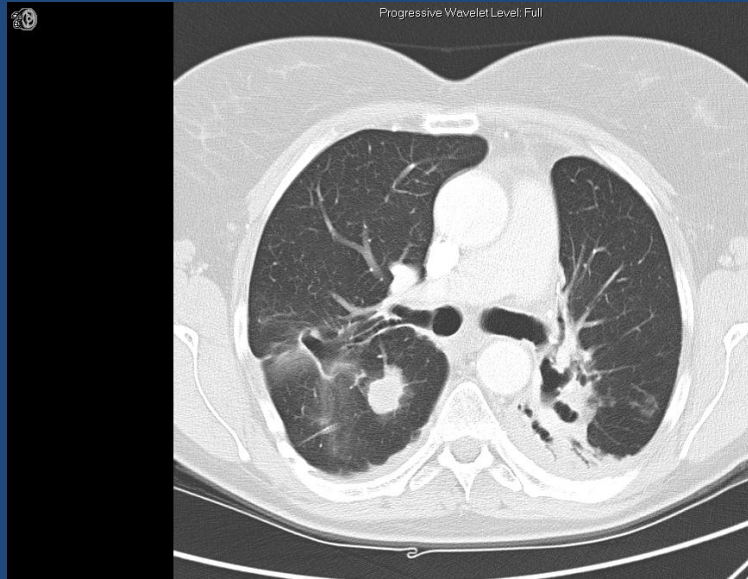
Progressive Wavelet Level: Full



- TTP: adenocarcinoma EGFR del19
- R/ erlotinib 100 mg/day



# 14-02-2012



# Conclusions

- RECIST criteria are the best we have
- PD by RECIST does not necessarily imply a change of treatment
- Consider local therapies for single site progression (and continue EGFR-TKI)