elcc EUROPEAN LUNG CANCER CONFERENCE
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Controlled EGFR mutant disease and one rapidly growing lung nodule

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My disclosure

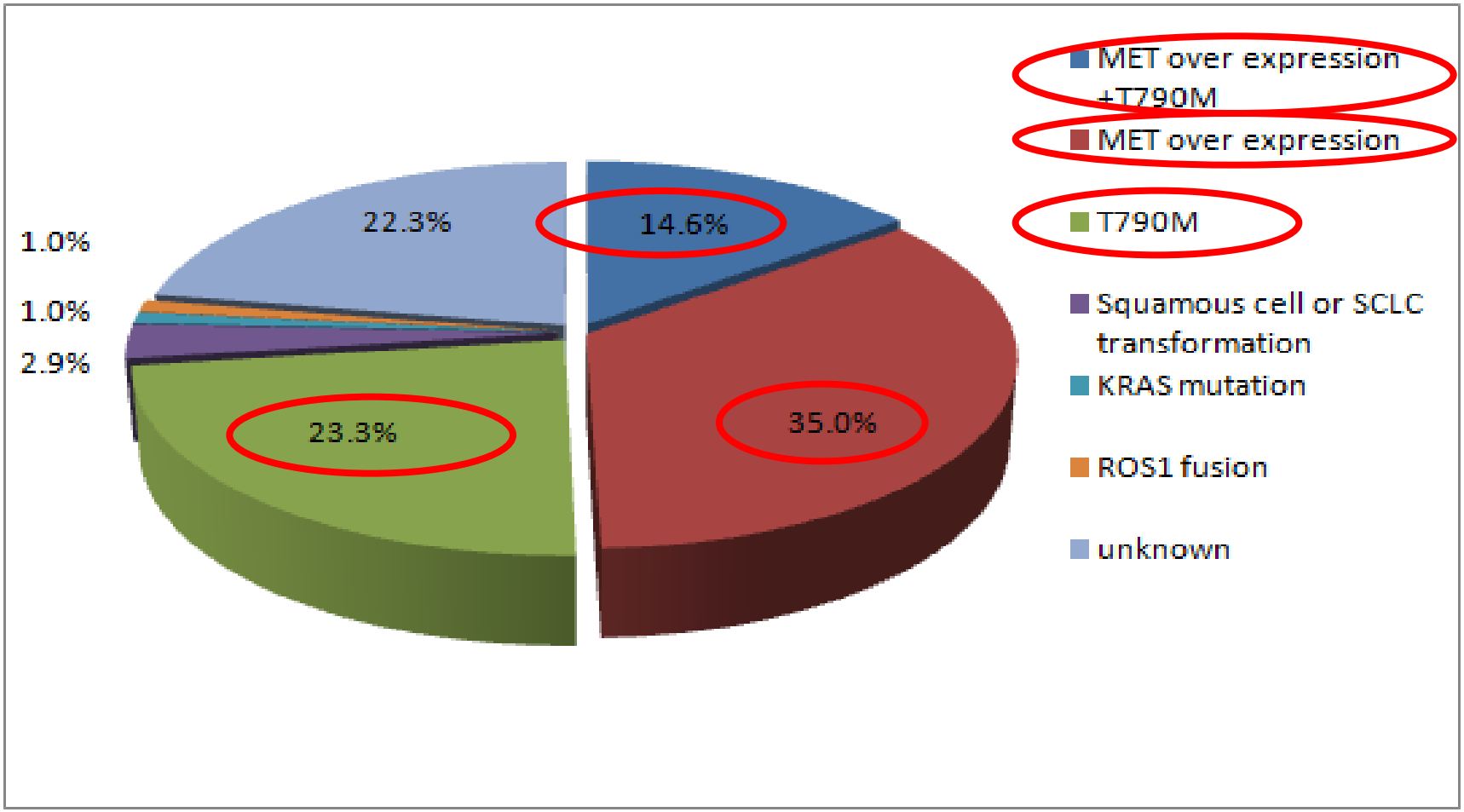
- Speaker fees from Eli Lilly, AstraZeneca, Roche, Pfizer

Studies of EGFR-TKIs in *EGFR* sensitising mutation-positive NSCLC

Study	EGFR-TKI	n	Line	mPFS (M)	mOS (M)
IPASS[1,2]	Gefitinib	132	First	9.5	21.6
WJTOG 3405[3]	Gefitinib	86	First	9.2	30.9
NEJGSG 002[4,5]	Gefitinib	114	First	10.8	27.7
First-Signal[6]	Gefitinib	42	First	8.4	30.6
OPTIMAL[7,8]	Erlotinib	82	First	13.1	22.7
EURTAC[9]	Erlotinib	86	First	9.7	19.3
ENSURE[10]	Erlotinib	110	First	11.0	**NR**
LUX-Lung 3[11]	Afatinib	230	First	11.1	28.2
LUX-Lung 6[12]	Afatinib	242	First	11.0	23.1

1. Mok et al. N Engl J Med 2009;361:947–957; 2. Fukuoka et al. J Clin Oncol 2011;29(21):2866–2874; 3. Mitsudomi et al. Lancet Oncol 2010;11:121–128; 4. Maemondo et al. N Engl J Med 2010;362:2380–2388; 5. Inoue et al. Ann Oncol 2013;24:54–59; 6. Han et al. JCO 2012; 7. Zhou et al. Lancet Oncol 2011;12:735–742; 8. Zhou et al. ASCO 2012 poster. Abs 7520; 9. Rosell et al. Lancet Oncol 2012;13:239–246; 10. Wu et al WCLC 2013; 11.Sequist et al. J Clin Oncol 2013 epub ahead of print; 12. Wu et al. Lancet Oncol 2014

Mechanism for acquired resistance to EGFR TKIs in 103 patients with advanced NSCLC



Gou LL & Wu YL. APLCC 2014

Heterogeneity In NSCLC

Screening for EGFR mutations by direct sequencing in consecutive lung cancer patients
n = 3071(yr 2006.11-2011.5)

→ Only one sample
n = 2765

Patients with paired samples
n = 306

→
- SCLS
- Non adenocarcinoma
- Absence of primary tumor
- Insufficient tumor cells n = 126

Eligible for heterogeneity analysis
n = 180

→ TKI therapy
n = 38

Non TKI therapy
n = 142 cases

Synchronous
n =40

Metachronous
n = 102

Primary lesions at different time points
n = 39

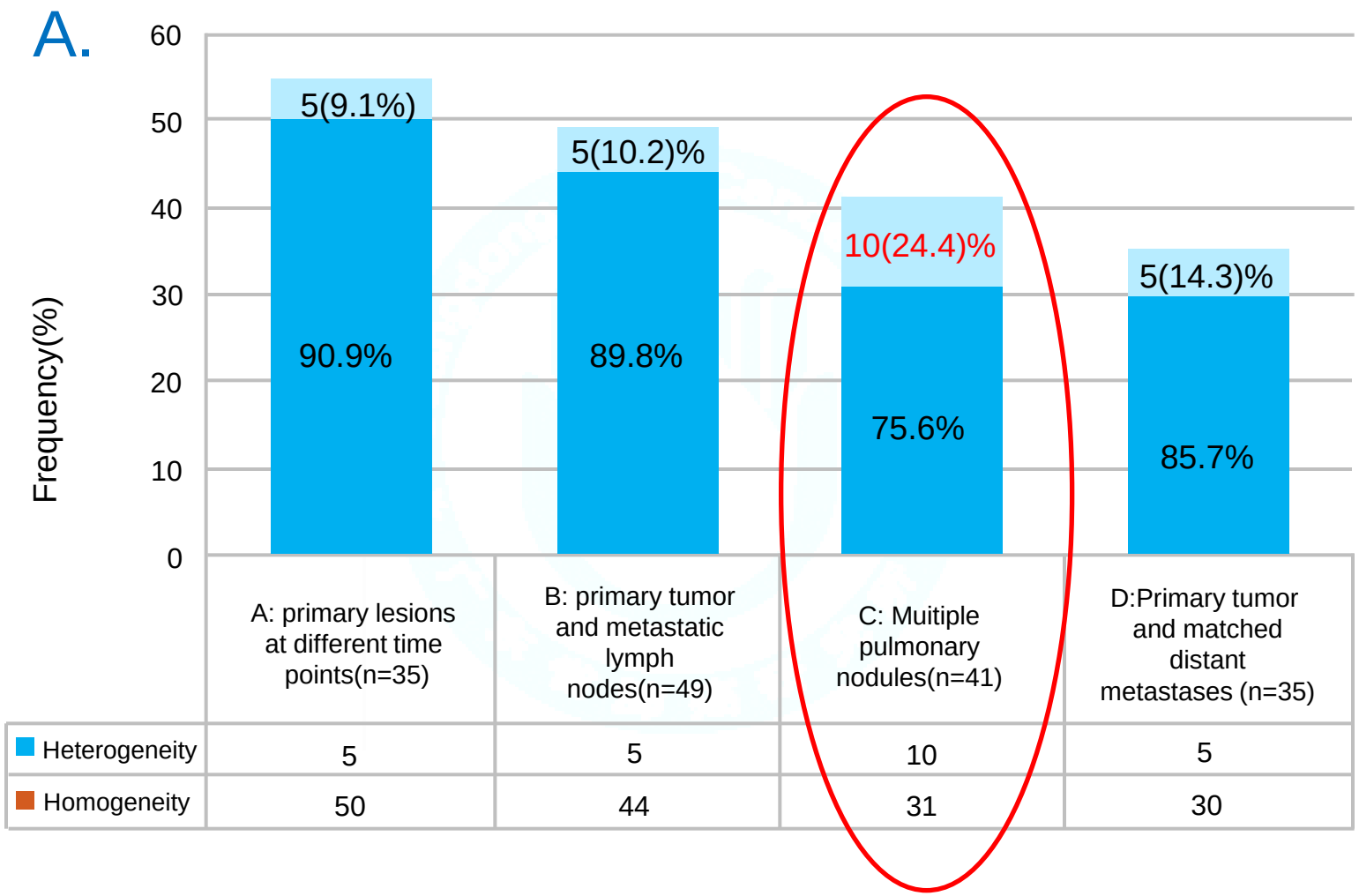
Primary tumor and metastatic lymph nodes
n=41

Muitiple pulmonary nodules
n=38

Primary tumor and matched distant metastases
n=24

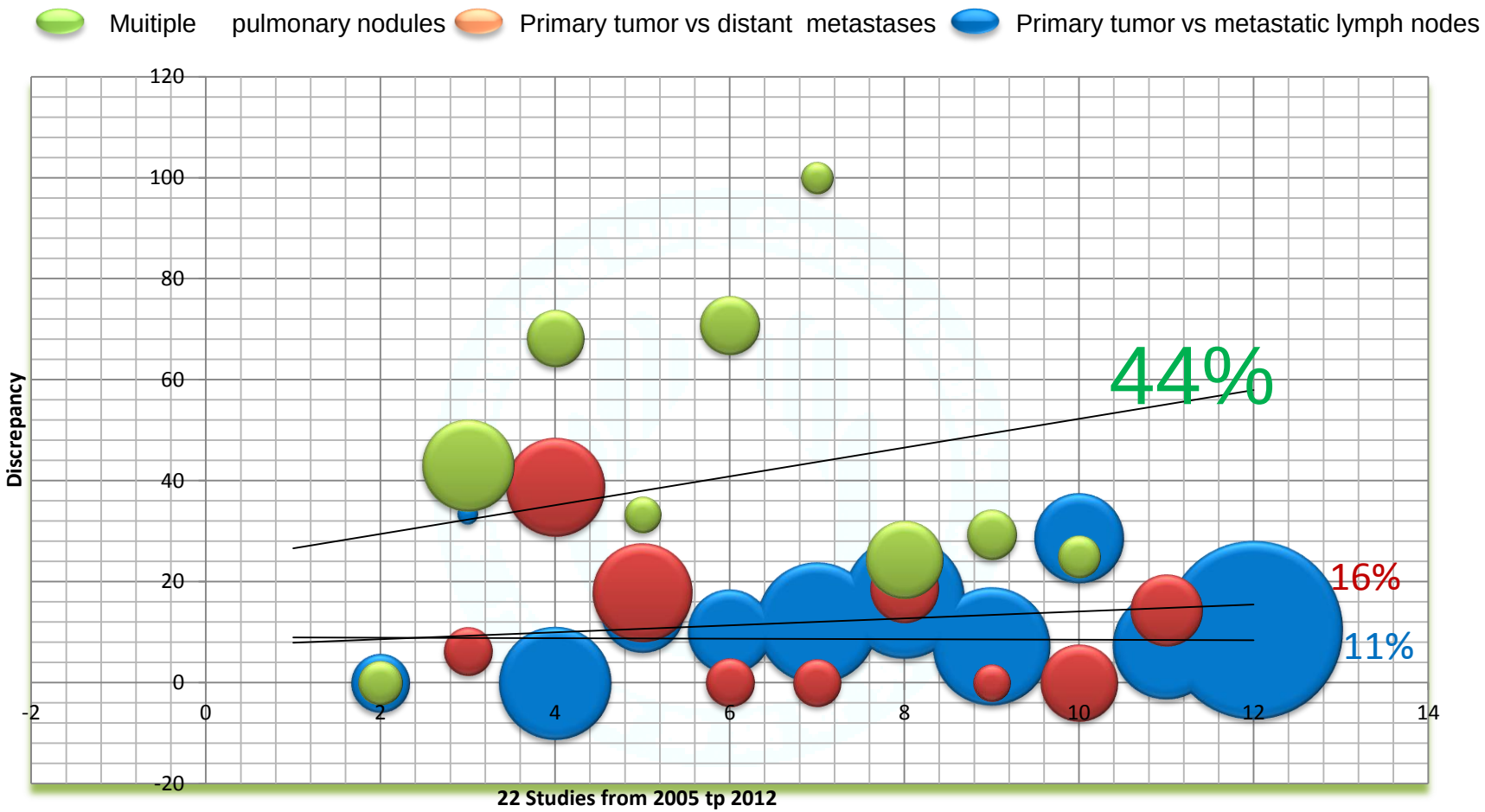
Chen, Zhong & Wu, Oncologist 2012

Discordance rate was 13.9% in the 180 paired samples multiple pulmonary nodules(24.4%)



Chen, Zhong & Wu, Oncologist 2012

Discrepancies of EGFR mutation between primary tumor and metastasis in lung cancer: 22 studies (17% in1392 cases)



Discrepancy was peak at multiple pulmonary nodules of 44%

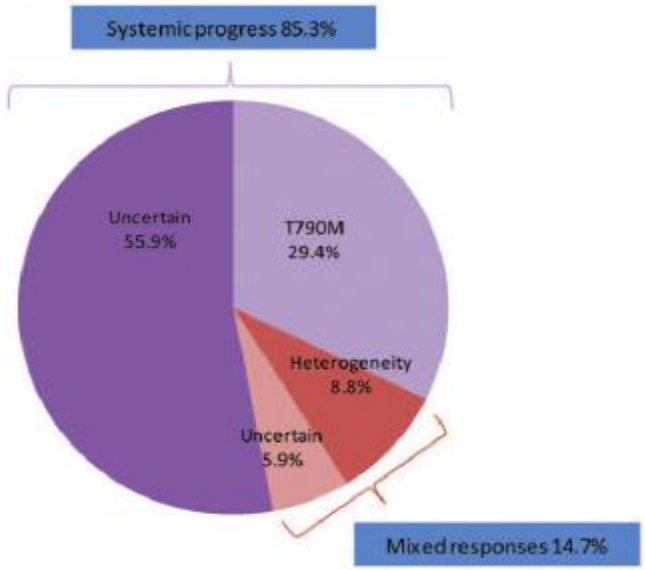
T790M: Heterogeneity & Mix-Response

A

Date	2011-01-18		2011-05-26		2011-06-28
Therapy	Baseline	Erlotinib 4 months		Erlotinib+ Cetuximab 2 cycles	
Left upper lobe	Del		NA		Del
		PR-72%		PR-38%	
Retroperitoneal			WT		NA
		PD- New		PR-68%	
Adrenal gland					
		N			

B

The frequency of observed drug resistance mechanisms (n=34)



echanism:
se

Local treatment maybe important in this setting

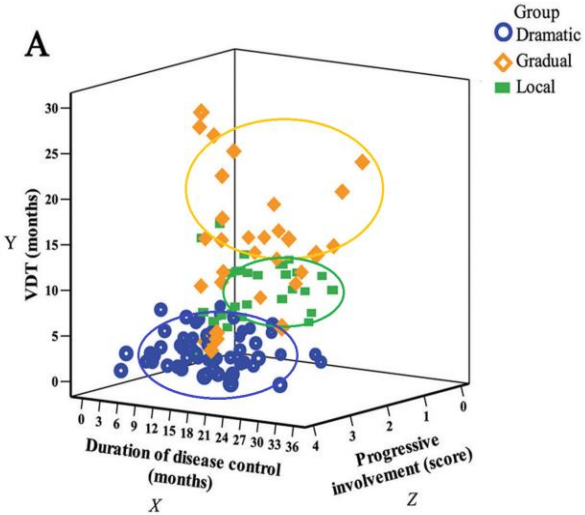
Chen ZY, Zhong WZ, Wu YL et al. Oncologist 2012

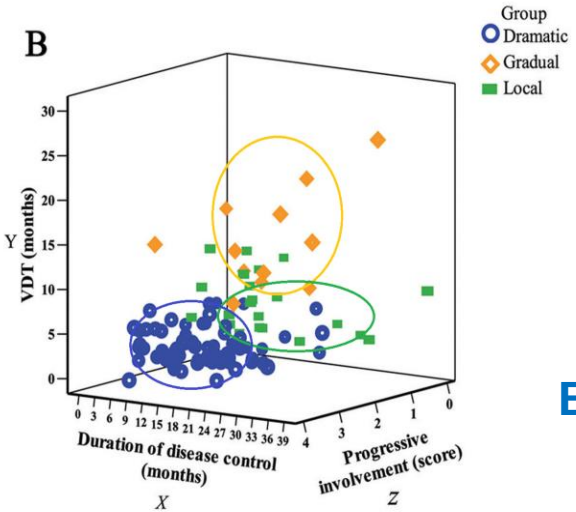
Contents lists available at SciVerse ScienceDirect

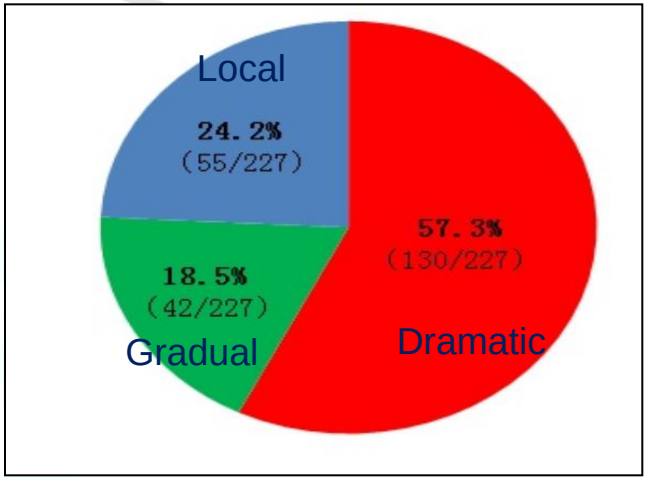
Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Clinical modes of EGFR tyrosine kinase inhibitor failure and subsequent management in advanced non-small cell lung cancer







120 trials Pts, training set

107 non-trial Pts validating set

Based on Clinical factors:

- **Tumor burden**
  - **Target lesions**
  - **non-target lesions**
- **EGFR TKI exposure time**
- **Symptom**

Yang JJ, Chen HJ, Wu YL ,et al. Lung Cancer 2013

EGFR TKI failure in NSCLC

Treated by T790M

Dramatic progression

- Disease control ≥3 months
- Compared with previous assessment, rapid increment of tumour burden
- Symptom deterioration

Chemotherapy

Gradual progression

- Disease control ≥6 months
- Compared with previous assessment, minor increment of tumour burden
- Symptom benefit

Continuation of EGFR-TKIs

Symptom

Switch Chemo

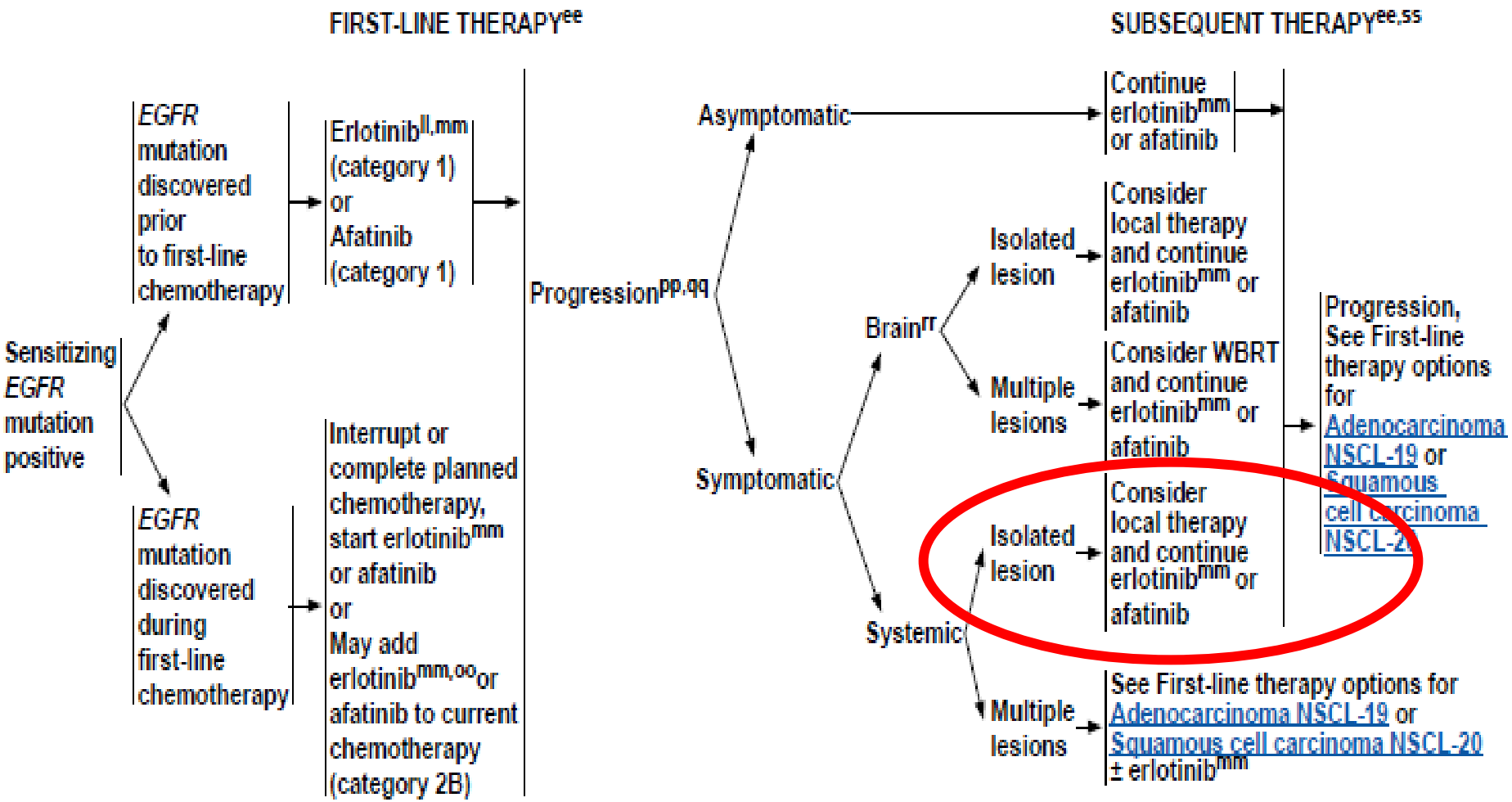
Local progression

- Disease control ≥3 months
- Solitary extracranial progression or intracranial progression
- Symptom benefit

Continuation of EGFR-TKIs plus local intervention

Modified from Yang et al. Lung Cancer 2013;79:33–39

SENSITIZING EGFR MUTATION POSITIVE[a]

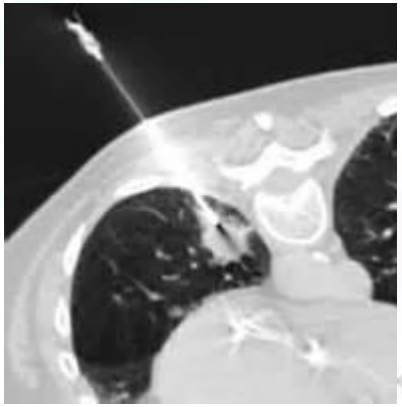


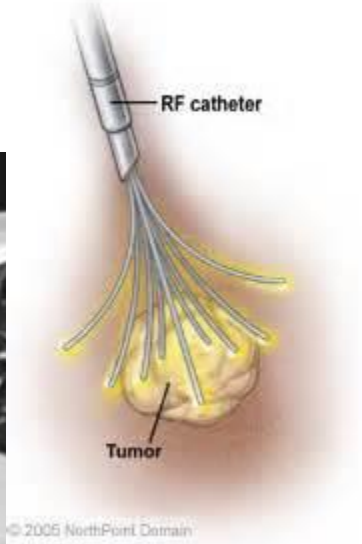
What is local treatment?

VATS

SBRT

Ablation





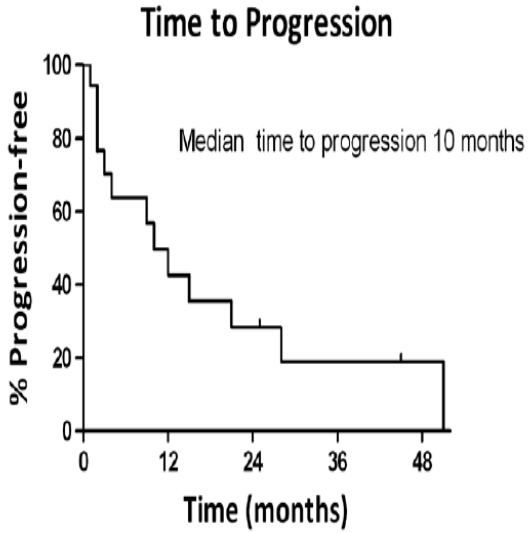
J Thorac Oncol. 2013 Mar;8(3):346-51. doi: 10.1097/JTO.0b013e31827e1f83.

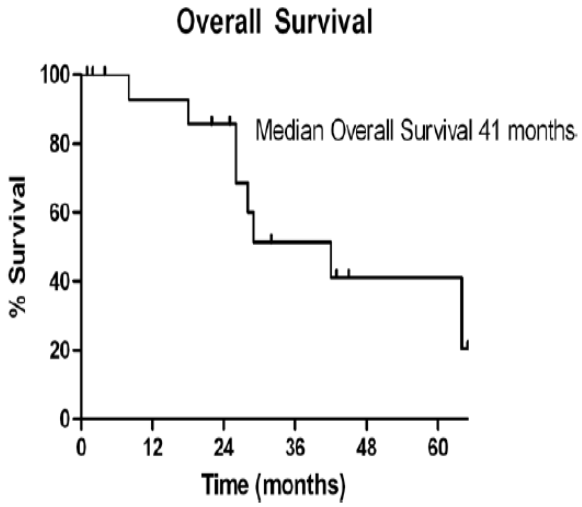
Local Therapy with Continued EGFR Tyrosine Kinase Inhibitor Therapy as a Treatment Strategy in EGFR-Mutant Advanced Lung Cancers That Have Developed Acquired Resistance to EGFR Tyrosine Kinase Inhibitors.

Yu HA, Sima CS, Huang J, Solomon SB, Rimner A, Paik P, Pietanza MC, Azzoli CG, Rizvi NA, Krug LM, Miller VA, Kris MG, Riely GJ.

*Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine; †Thoracic Service, Department of Surgery; ‡Department of Epidemiology and Biostatistics; §Department of Radiology; and ‖Department of Radiation Oncology Memorial Sloan-Kettering Cancer Center, Weill Cornell Medical College, New York, New York.

- 18/184 treated by local therapy in 7 years
  - No CNS PD
  - Median new systematic therapy: 22 months

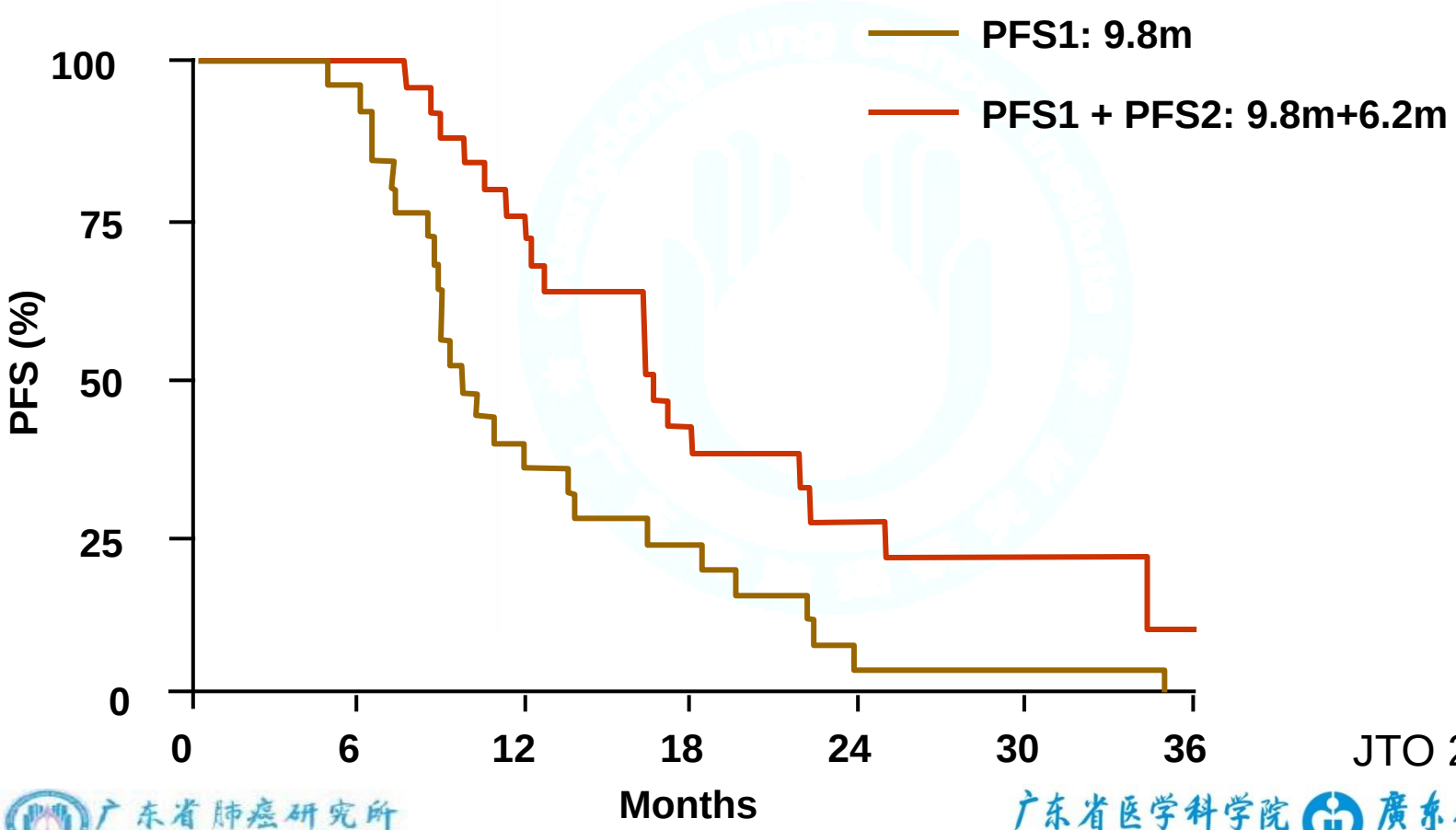




Performed	
Total	18
Lung	15
Radiofrequency ablation	2
Stereotactic radiotherapy	1
Radiation therapy	1
Lobectomy	7
Wedge resection	1
Pneumonectomy	3
Lymph node (supraclavicular)	
Radiation therapy	1
Adrenal gland	
Adrenalectomy	2

Local Ablative Therapy of Oligoprogressive Disease Prolongs Disease Control by Tyrosine Kinase Inhibitors in Oncogene-Addicted Non–Small-Cell Lung Cancer

Andrew J. Weickhardt, MBBS, DmedSc, Benjamin Scheier, MD,* Joseph Malachy Burke, MD,* Gregory Gan, MD,‡ Xian Lu, MSc,‡ Paul A. Bunn, Jr., MD,* Dara L. Aisner, MD, PhD,§ Laurie E. Gaspar, MD, MBA,‡ Brian D. Kavanagh, MD, MPH,‡ Robert C. Doebele, MD, PhD,* and D. Ross Camidge, MD, PhD**



JTO 2012

Lung Cancer 79 (2013) 33–39

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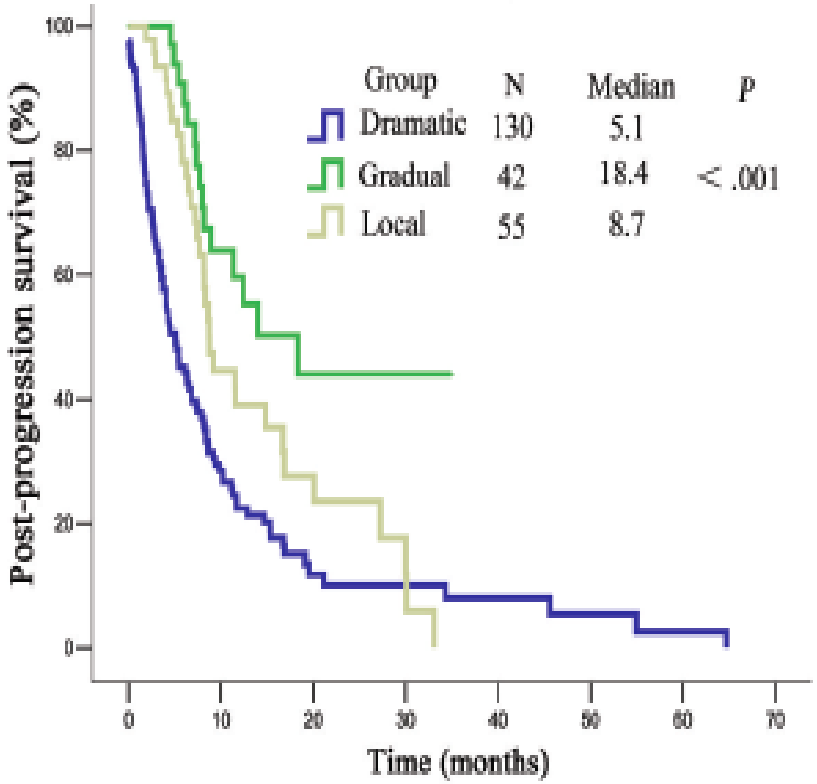
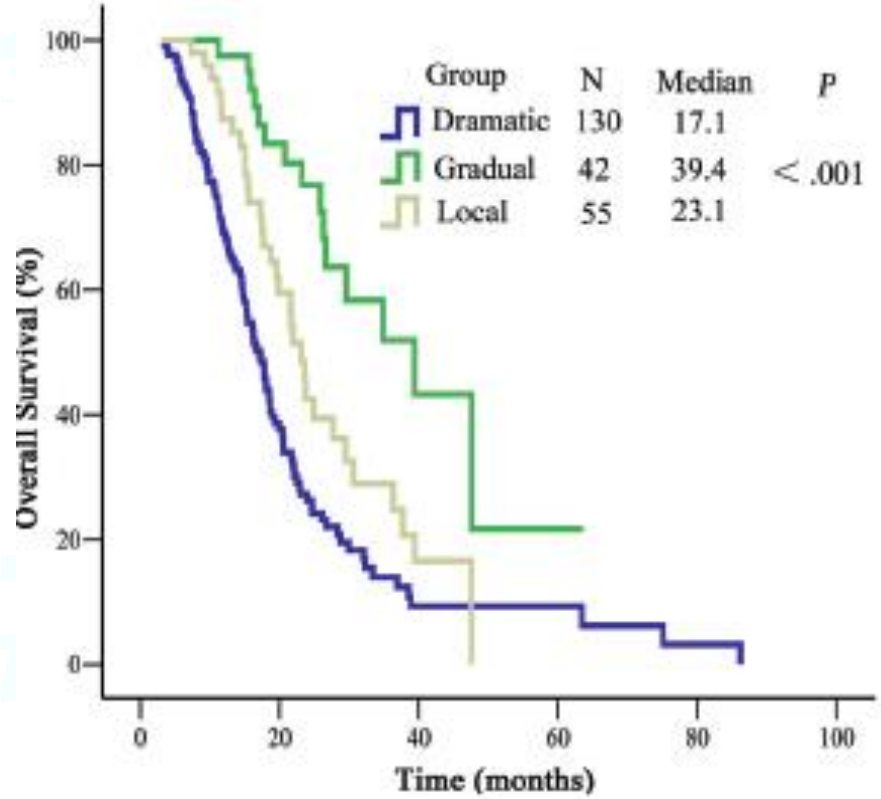




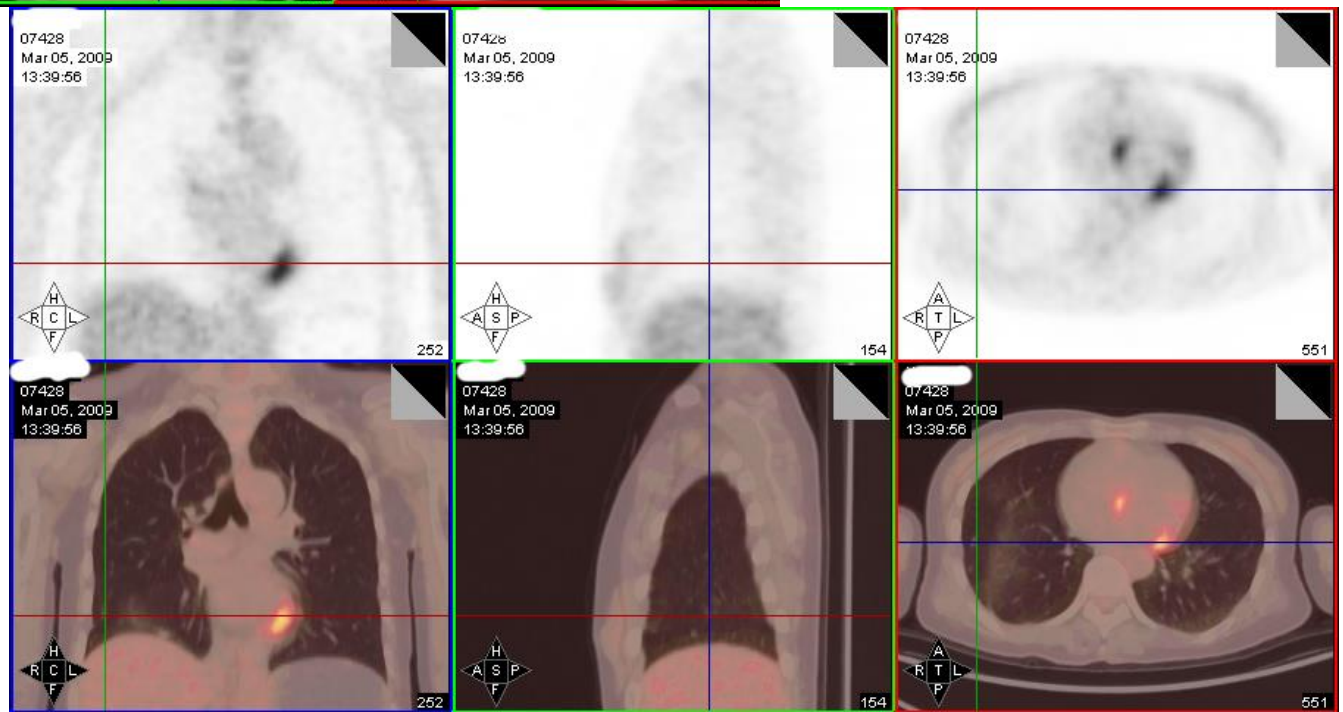
Yang JJ. & Wu YL et al. Lung Cancer 2013

Case 1 from GLCI

- Female, 44y, no smoking, no cancer family history
- Right lower lobectomy in July 5,2007. diffuse nodes on lung and chest wall (incompletely resection);
- Post-operative stage is sT2N2M1 stage IV adenocarcinoma;
- 4 cycles doublet chemo with Gemcitabine and carboplatin.
- March 2009 showed nodes on lung and chest wall，PFS 20 months;
- Tumor tissue test: EGFR21 mutation;
- Erlotinib oral qd from March 2009

Surgery + 1st L chemo
PFS: 20 months

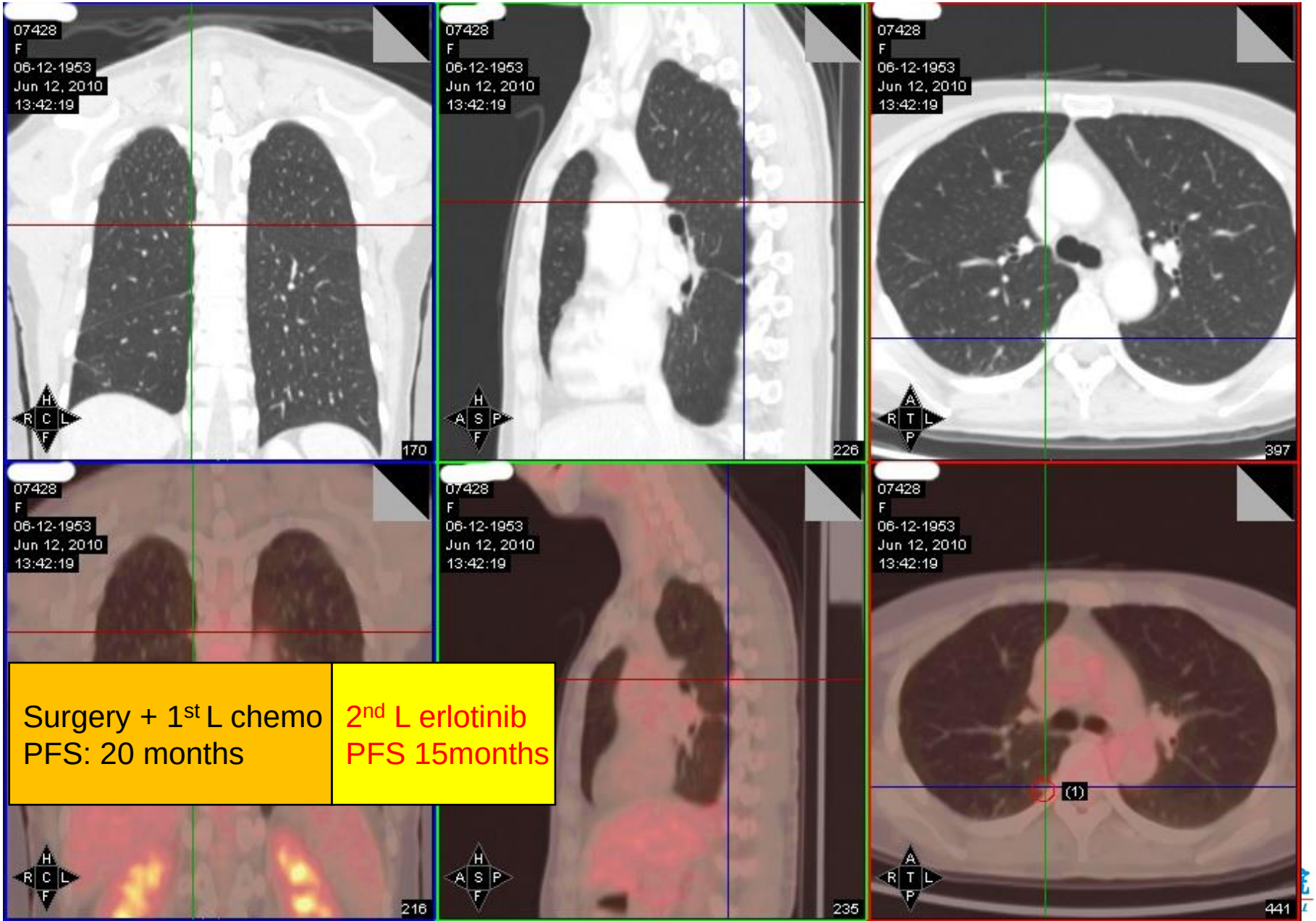
- March 5, 2009
- Base line imaging



- April 24,2009
- Erlotinib one months, PR-CR

广东省肺癌研究所
Guangdong Lung Cancer Institute

- June 12 2010: new lesions and CEA 51.33ng/ml ⇧



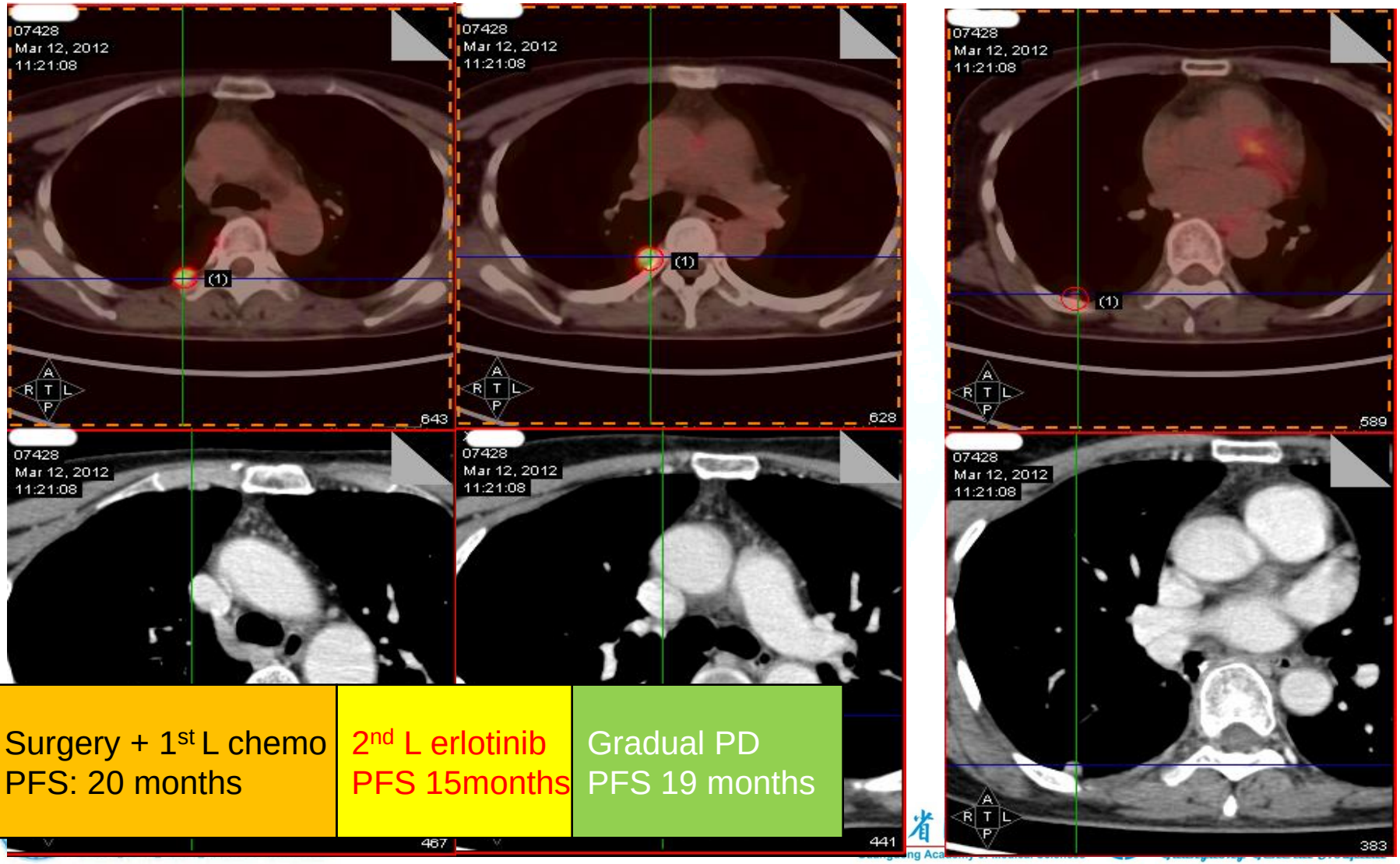
Surgery + 1st L chemo
PFS: 20 months

2nd L erlotinib
PFS 15months

What is your option?

- Switch to doublet chemo
- Switch to 2nd EGFR TKI as afatinib
- Continue erlotinib
- Continue erlotinib plus local therapy
- Rebiopsy for T790M

- Continue erlotinib to March 12, 2012: most lesions are stable but one lesion enlarged in PET-CT: Diameter 1.4cm, SUVmax 8.2，and CEA 58.49ng/ml



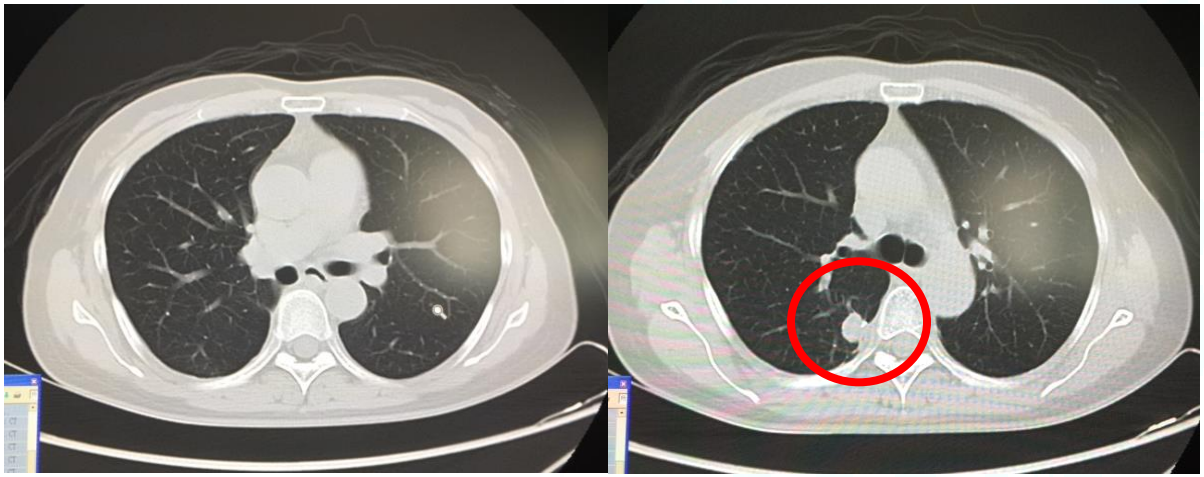
Surgery + 1st L chemo PFS: 20 months	2nd L erlotinib PFS 15months	Gradual PD PFS 19 months

What is your option?

- Switch to doublet chemo
- Switch to 2nd EGFR TKI as afatinib
- Continue erlotinib
- Continue erlotinib plus local therapy
- Rebiopsy for T790M

- March 22, 2012:
  - Right upper lobe wedge resection via thoracoscopy
  - Histology : adenocarcinoma
  - EGFR exon 21 L858R positive；
  - T790M and c-MET negative

Aug 13 2012 CT scan: new lesion on right lung



- CEA dynamic changing

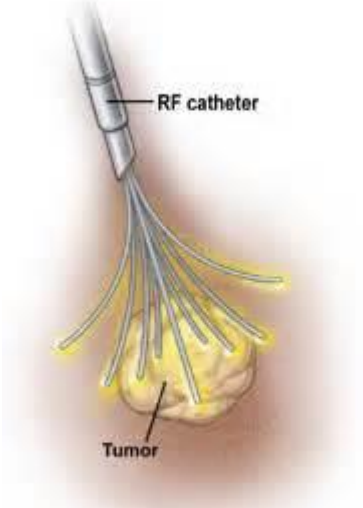
03/2012	58.49
04/2012	39.48
06/2012	44.73
08/2012	71.39

Surgery + 1st L chemo PFS: 20M	Erlotinib 39 months		
	2nd L erlotinib PFS 15M	Gradual PD PFS 19M	Wedge resection PFS: 5M

What is your option?

- Switch to doublet chemo
- Switch to 2nd EGFR TKI as afatinib
- Continue erlotinib
- Continue erlotinib plus local therapy
- Rebiopsy for T790M

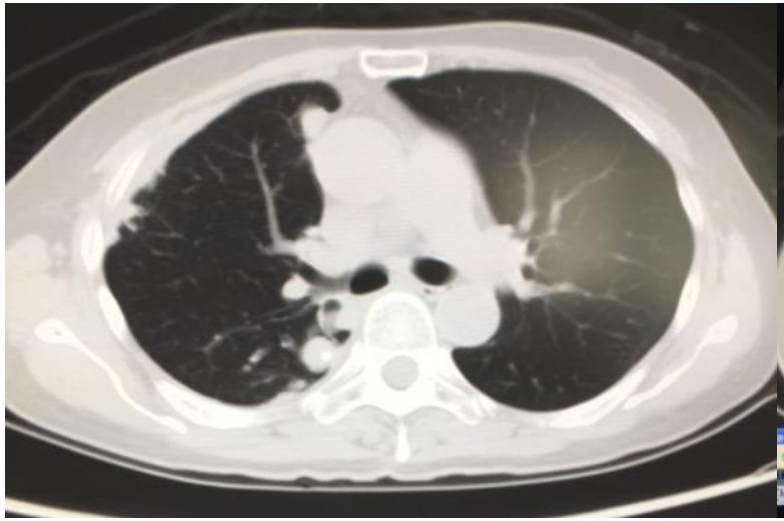
- Aug. 17, 2012:
- radiofrequency ablation for right lung lesion
- PS 1, asymptom on follow-up



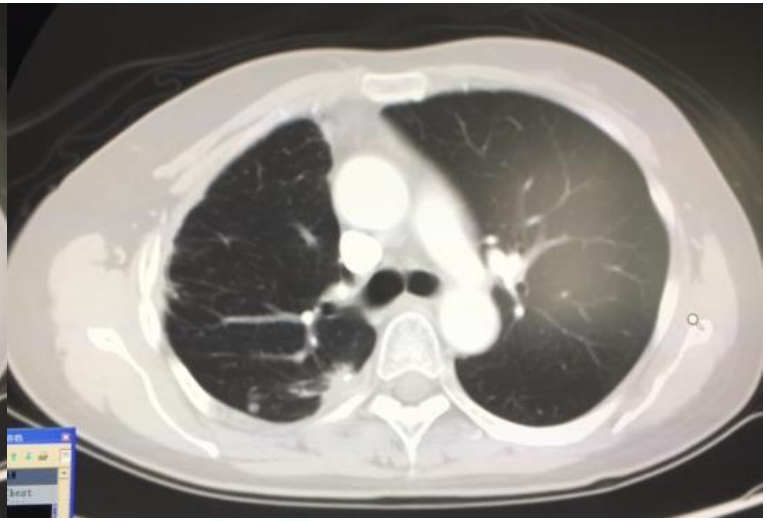
Mar 11, 2013 | Nov 04, 2013, PD? | May 12, 2014, PD

Surgery + 1st L chemo PFS: 20M	Erlotinib 60 months				
	2nd L erlotinib PFS 15M	Gradual PD PFS 19M	Wedge resection PFS: 5M	RF Ablation PFS 15M	Continue E PFS: 6M

The patient was switched to Chemotherapy and now still alive



June 2014, switch to
Pemetrexed doublet 4 cycles



Mar 19, 2015, PR

Summary

- Resistance to EGFR TKIs is heterogeneity
- Local therapy is rational when
  - **Controlled EGFR mutant disease and one or two rapidly growing lung nodules**

16TH WORLD CONFERENCE ON LUNG CANCER

IASLC

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

WWW.IASLC.ORG

Abstract Submission Open	January 2015
Registration Open	January 2015
Abstract Submission Deadline	April 24, 2015
Abstract Notifications	June 22, 2015
Early Registration Deadline	June 26, 2015
Late Breaking Abstract Submission Deadline	July 10, 2015
Regular Registration Deadline	July 24, 2015

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FIGHTING LUNG CANCER