

Non-surgical Management of NSCLC

Dr. CHAN Siu Hong Oscar

MBChB, FRCR(UK), FRCHK, FHKAM

PDipID, PDip Epidemiology & Biostatistics

Associate Consultant

Department of Clinical Oncology

Pamela Youde Nethersole Eastern Hospital

HKGALI2014-08-27T09_38_08



Pamela Youde Nethersole Eastern Hospital



Disclosure

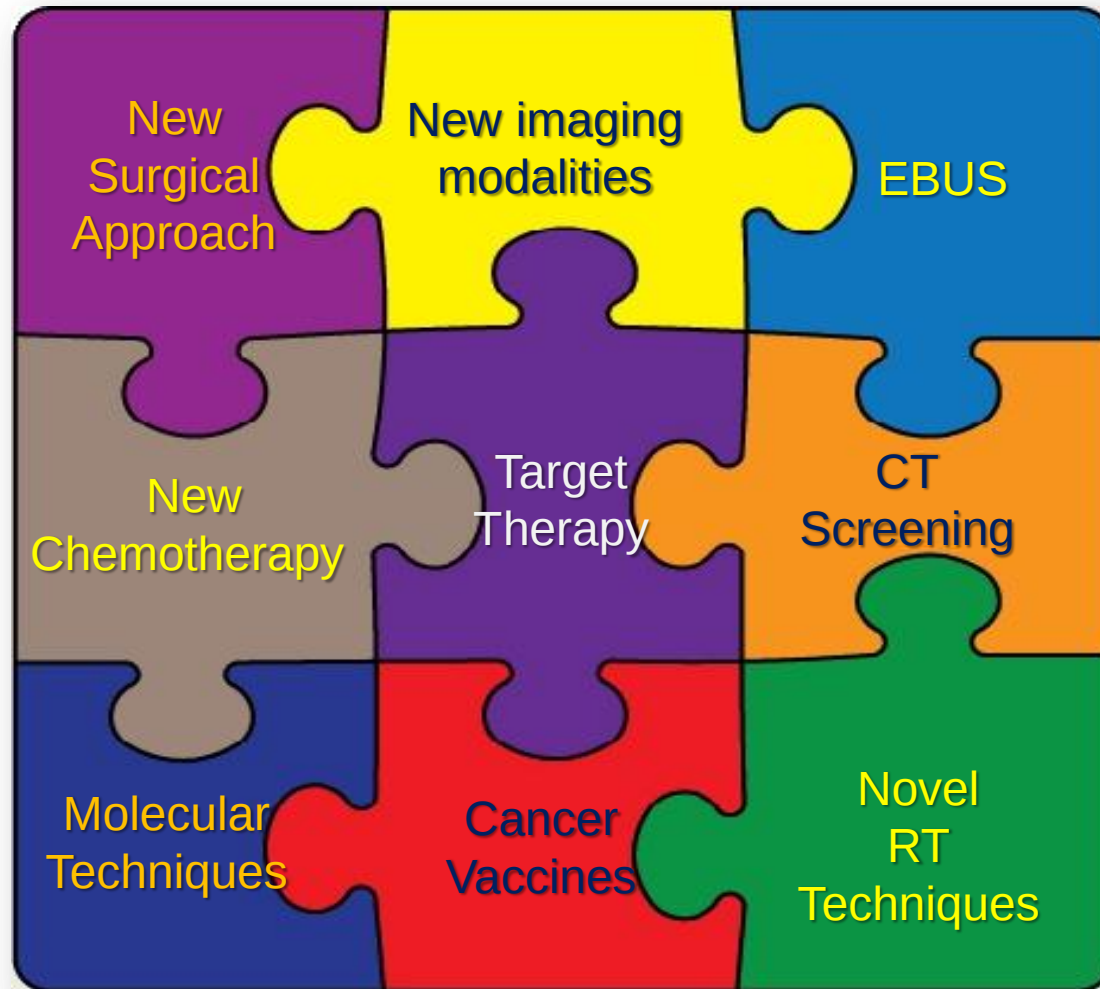
- Honorarium received for speaking activities included:
 - Eli Lilly

Objective

- To understand the indication, efficacy and toxicities of novel target therapy
- To appreciate the indication of chemotherapy and the ways to enhance chemo outcomes
- To know the role of RT in NSCLC
- To be aware of the new techniques in RT and its efficacy and expanding indications



A Rapidly Evolving Field



SYSTEMIC THERAPY

Chemotherapy & Target Therapy



Pamela Youde Nethersole Eastern Hospital



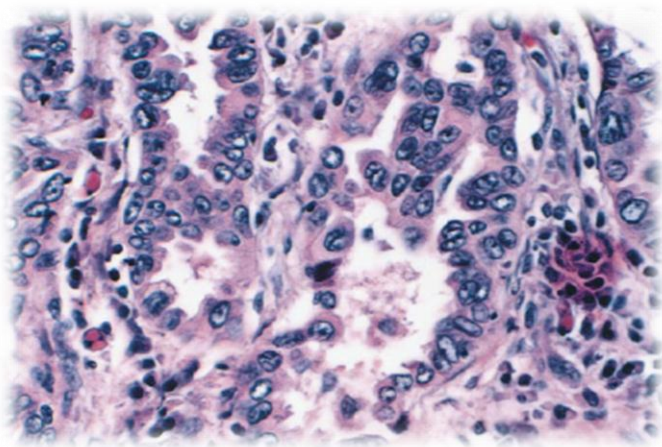
Indication of Systemic Therapy

- As adjuvant therapy in postoperative condition
- As palliative treatment in stage IV disease to reduce symptoms, improve QoL and prolong survival



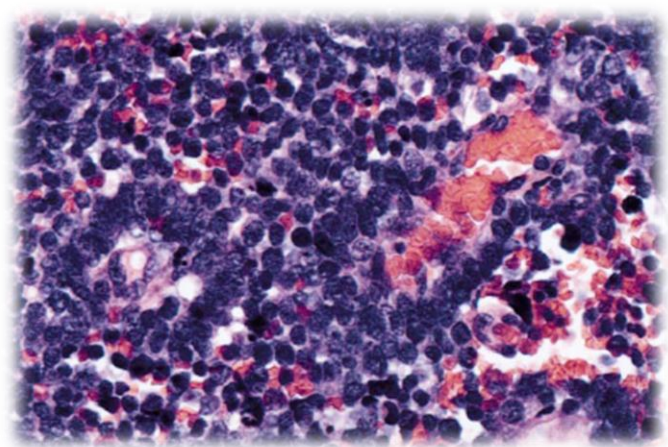
Pathologic Diagnosis

THE OLD PARADIGM



Non-small cell

VS



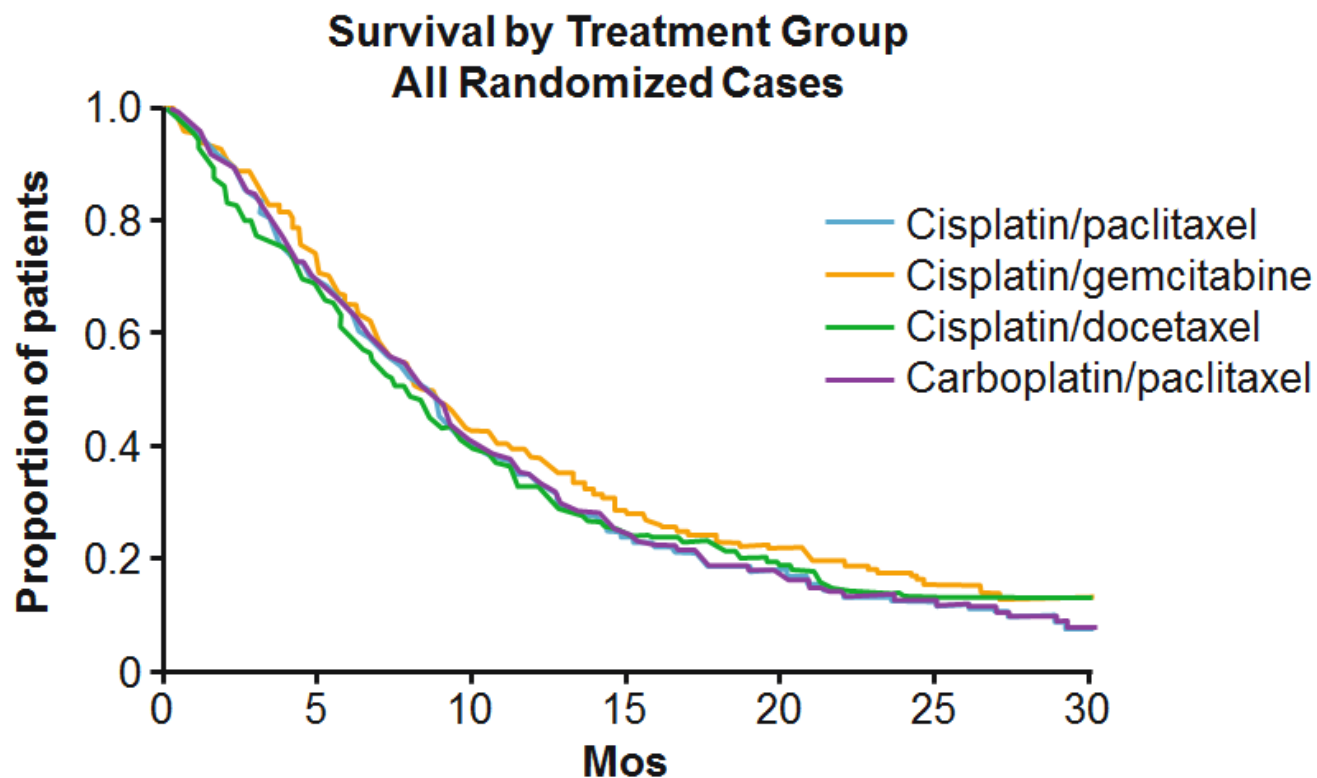
Small cell

JOB DONE

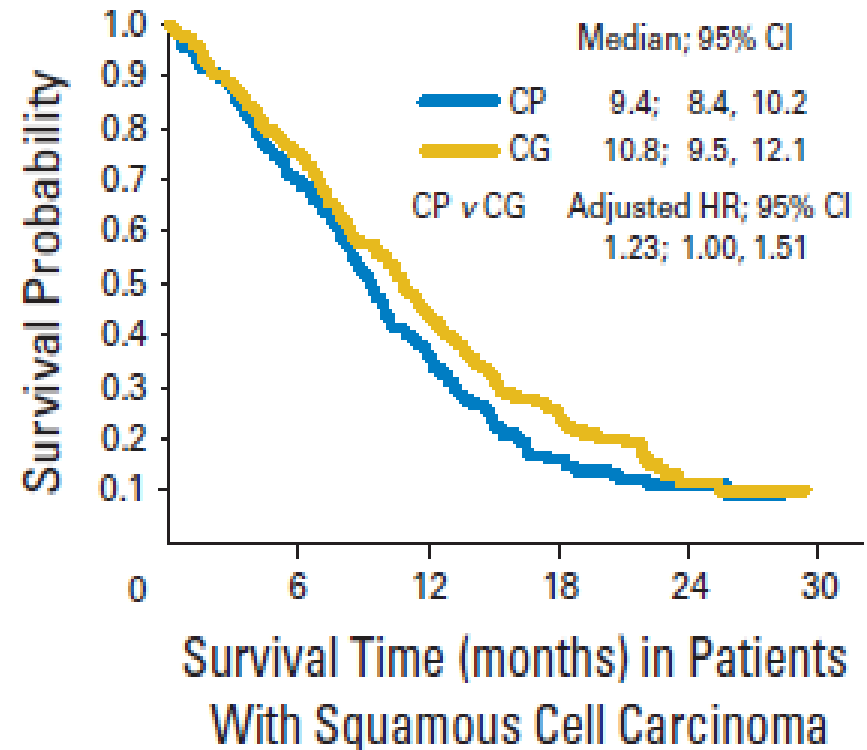
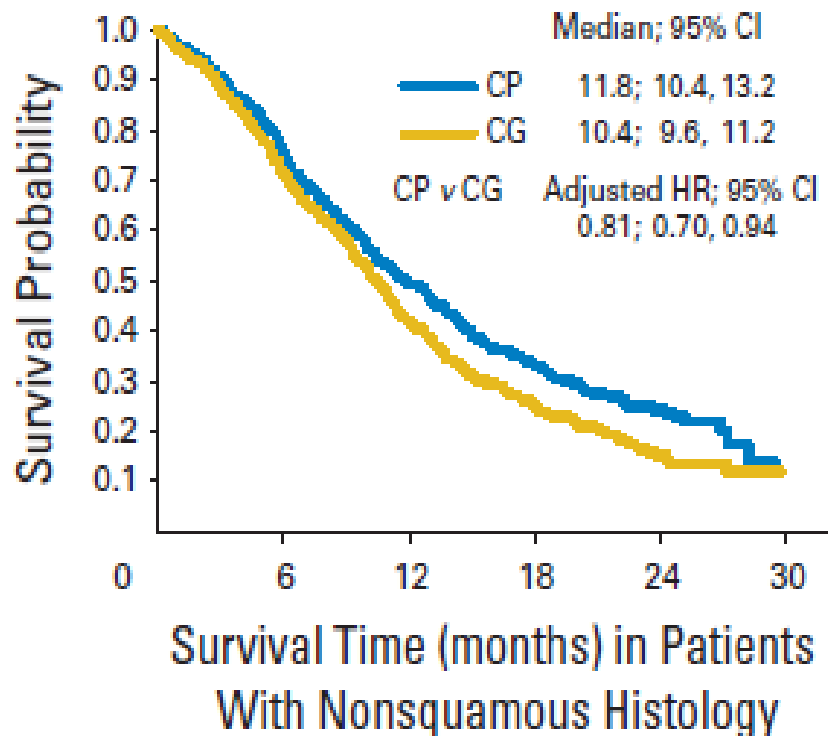


Reaching a Plateau

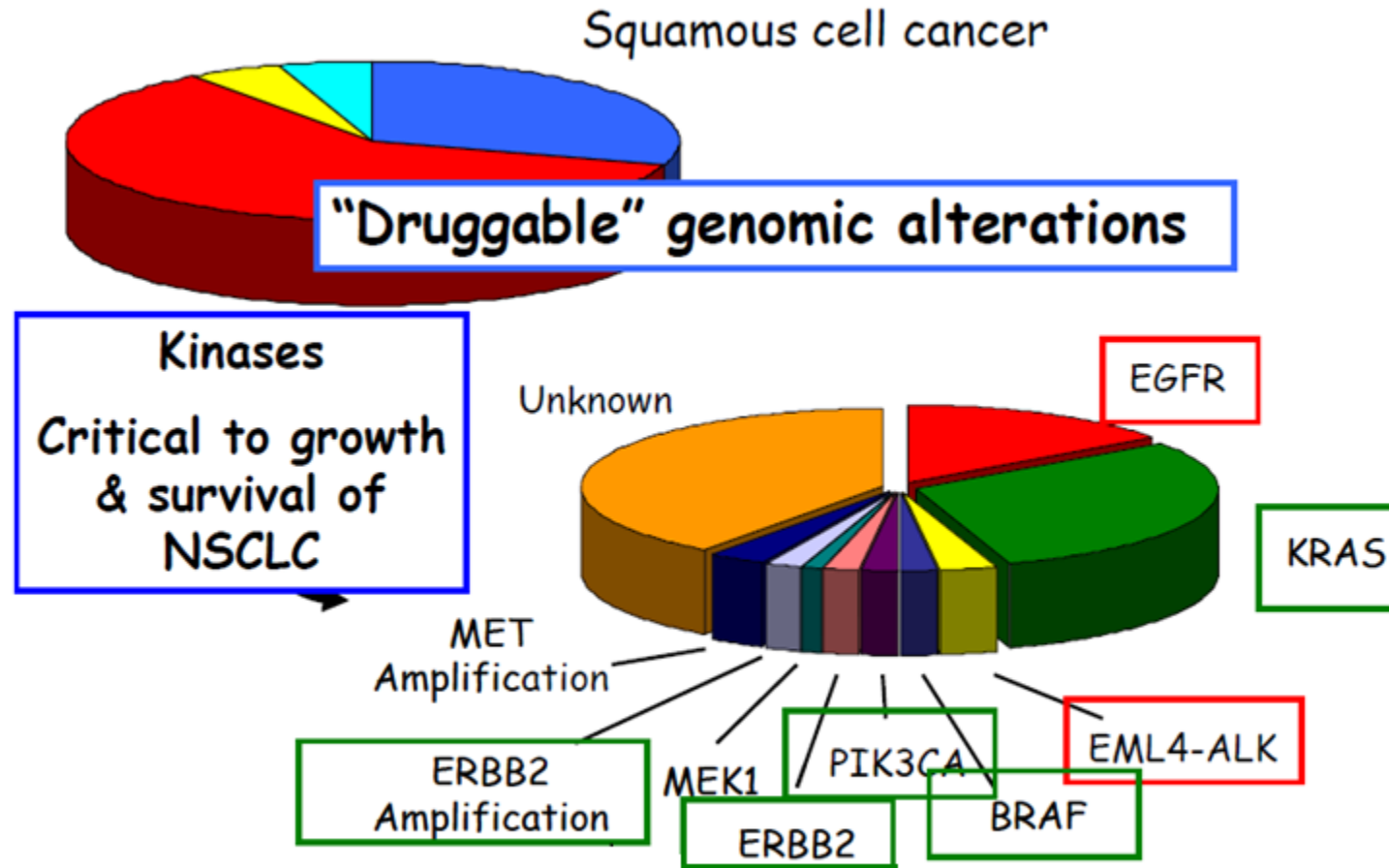
ECOG 1594: OS



Histology Matters



The Genomic Era

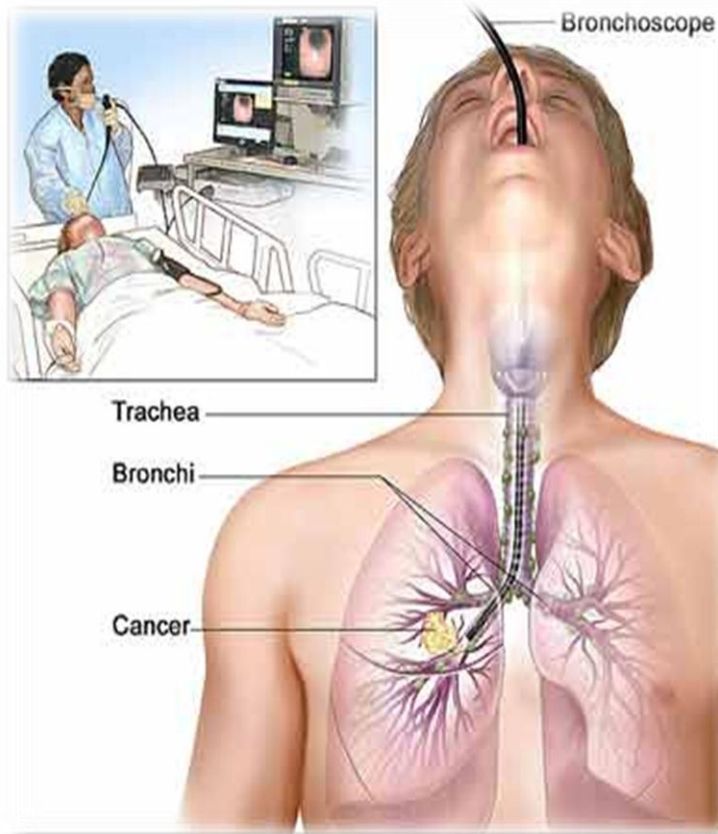


Adequate Tissue is the Issue

- Tissue biopsy: Bronchoscopy, EBUS, EUS, image guided biopsy
- Good liaison with operators
- Re-biopsy upon progression (identify resistant mechanism)



Traditional Methods



Bronchoscopy



Mediastinoscopy

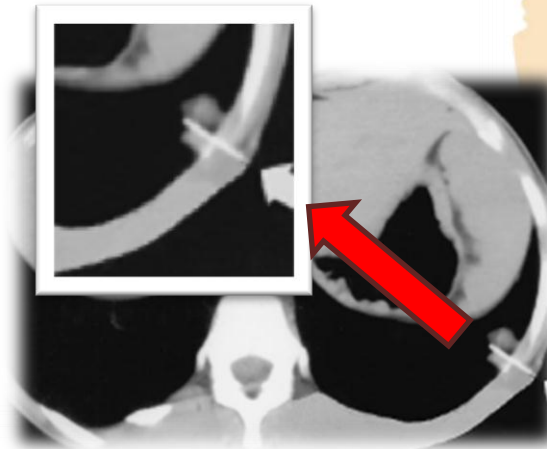
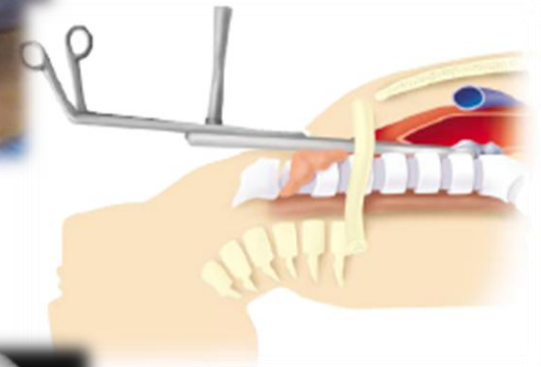
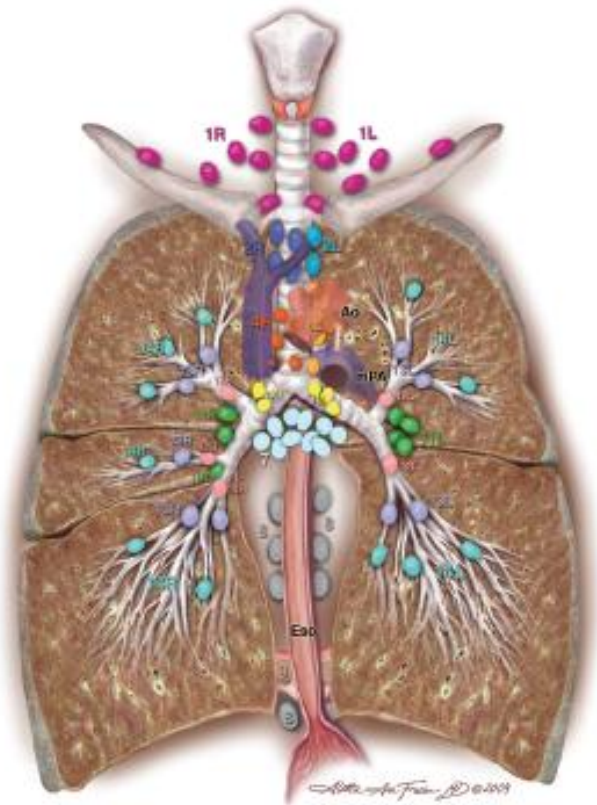
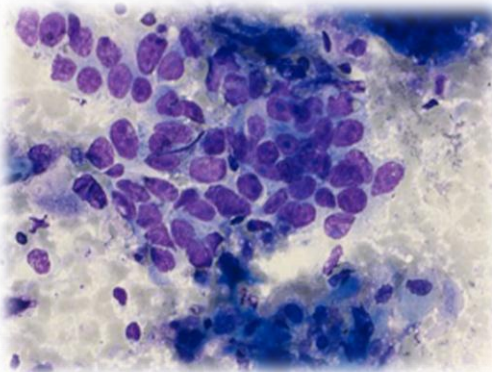


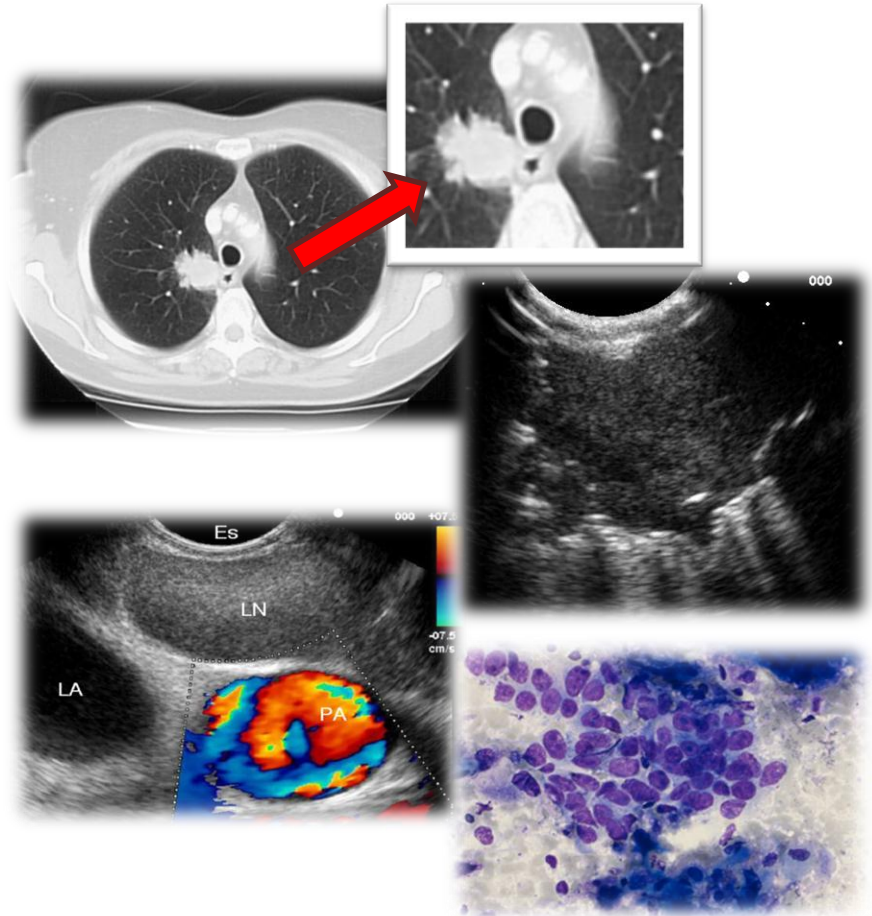
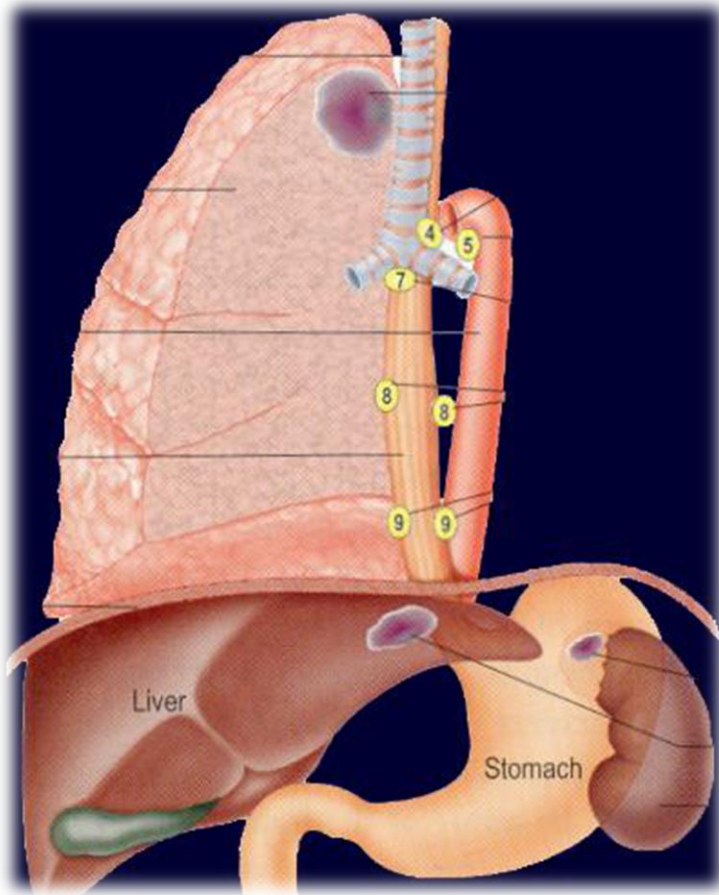
Image-Guided Biopsy



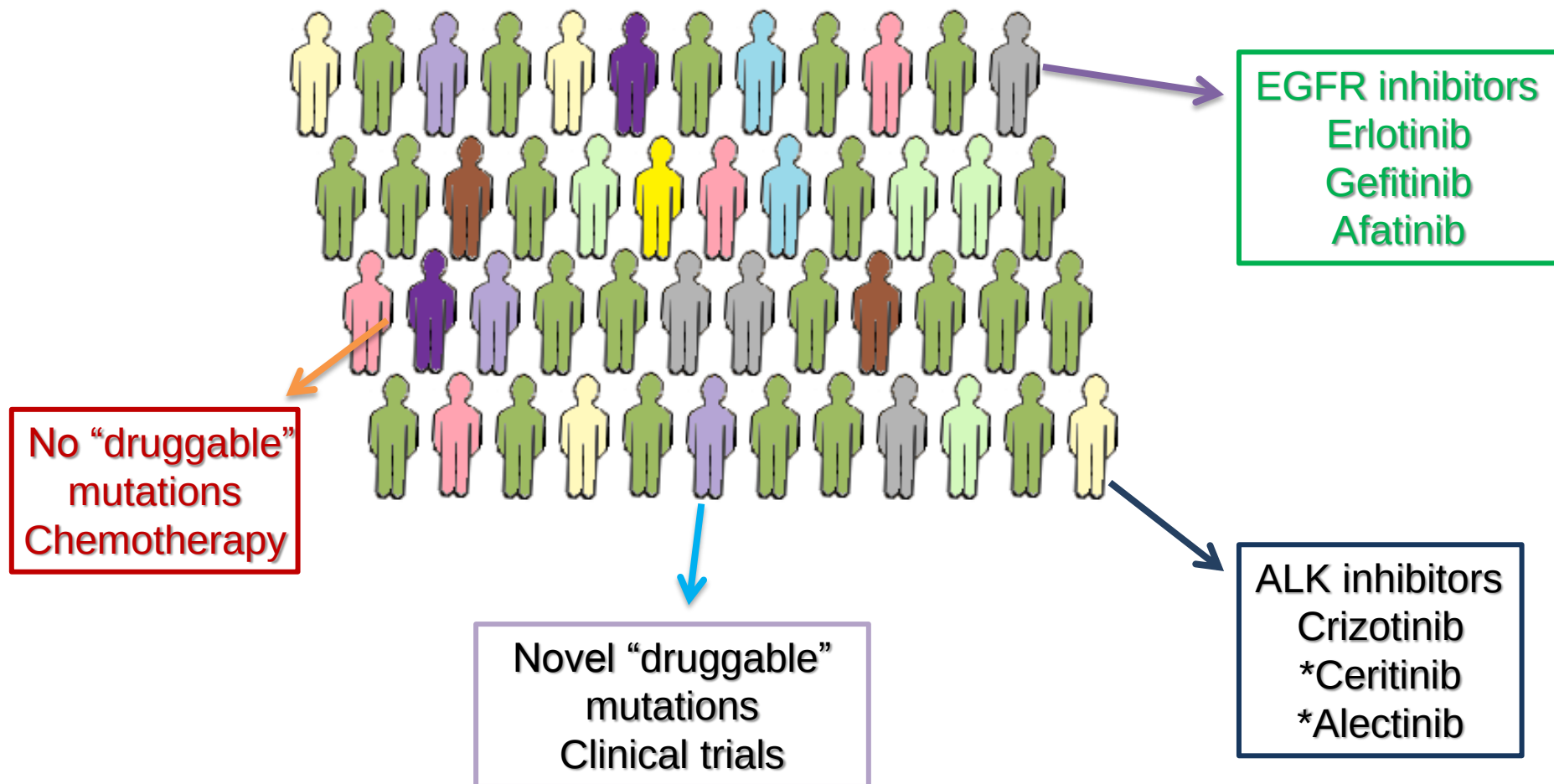
Endobronchial USG (EBUS)



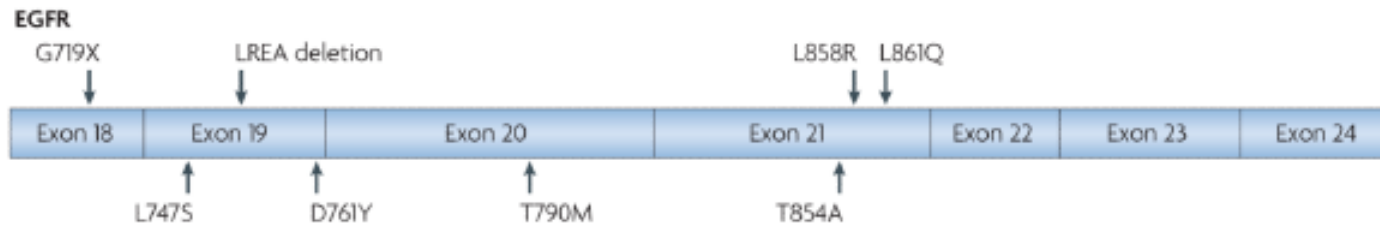
Esophageal USG



Genotype Directed Therapy



Biology of EGFR Mutation

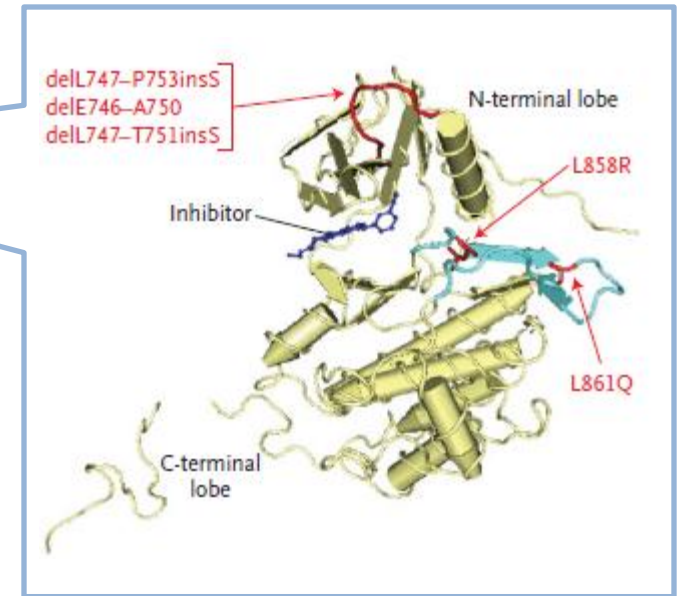
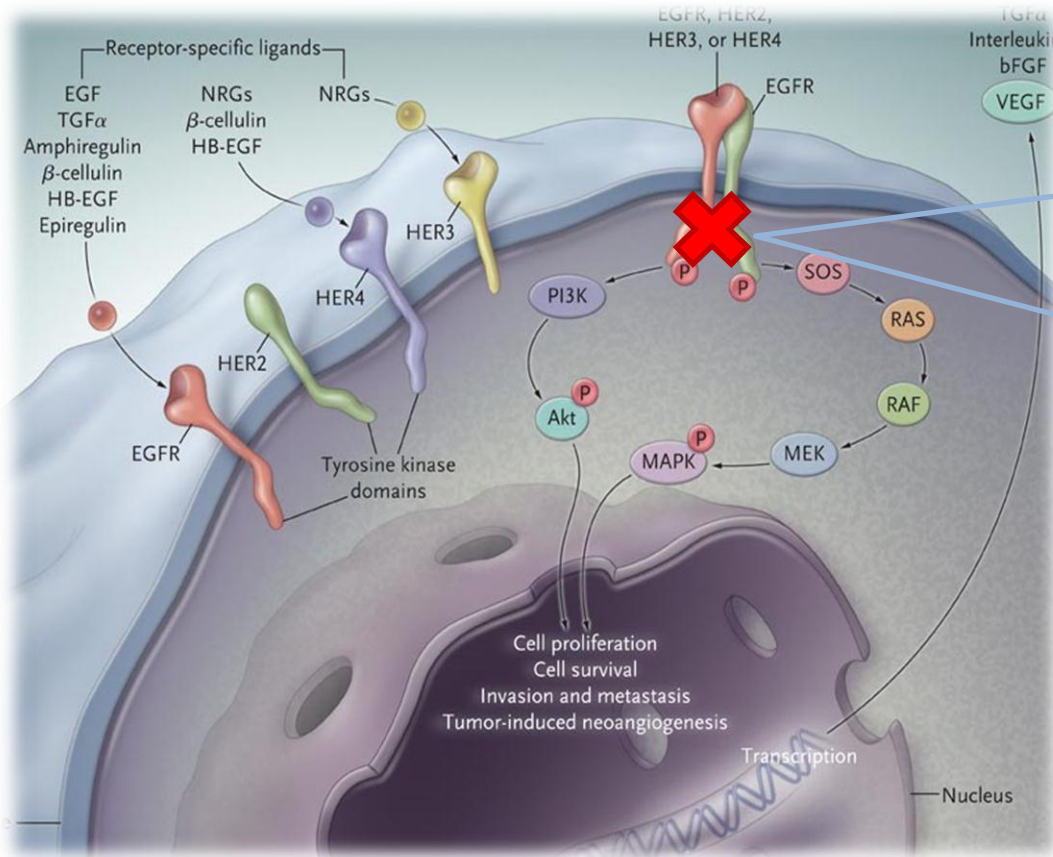


- Almost exclusive within exon 18-21
- Encode TK domain
- Constitutively active
- Addicting oncogene: dependant on aberrant kinase signaling for survival

W Pao et al. Nat Rev Cancer 2010; L Paz-Ares et al. J Cell Mol Med 2010



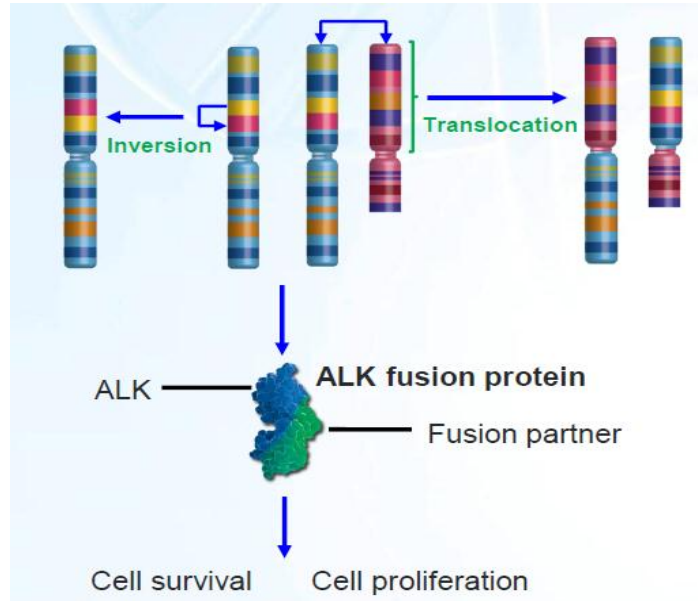
How do EGFR-TKIs work?



NEJM 2004, 2008

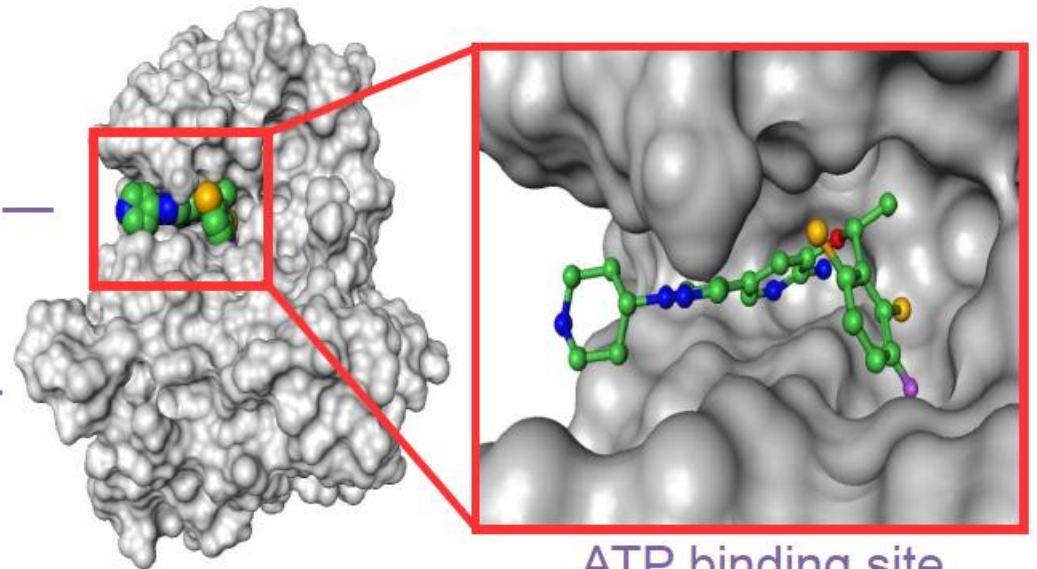


ALK Inhibitor



Crizotinib —

ALK —

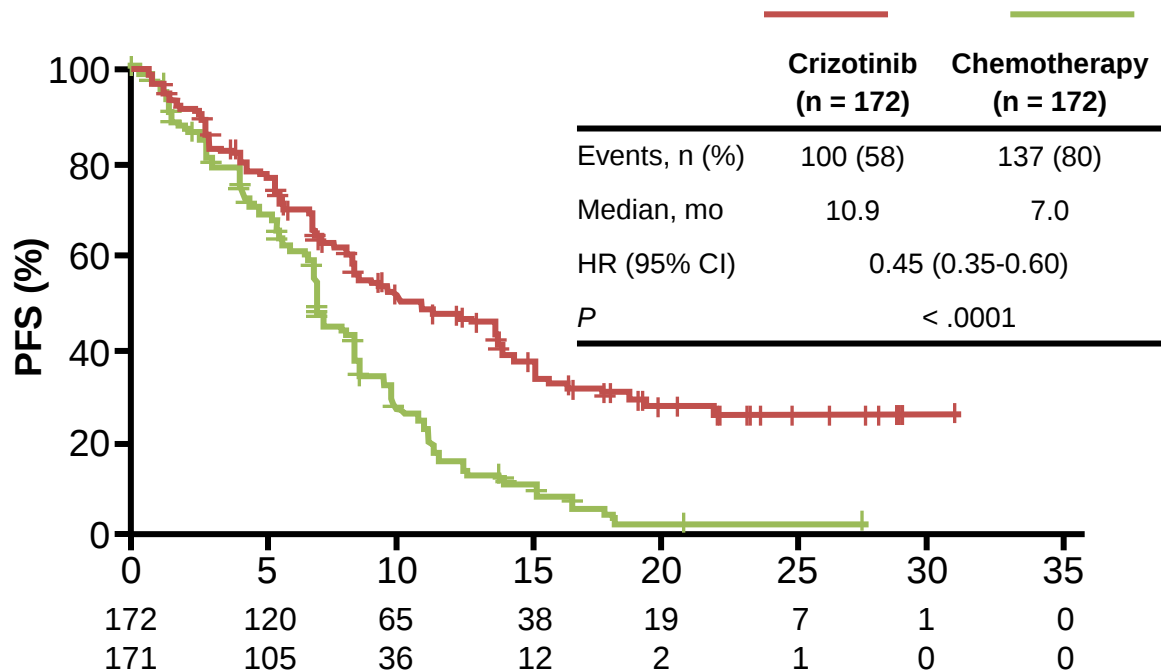


ATP binding site

Phase III Data

- Phase III trial (N = 344) ALK-positive patients with nonsquamous NSCLC and no prior systemic treatment for advanced disease

Progression-Free Survival



- PFS benefit seen across all subgroups

— Eg, age, sex, smoker, time since Dx

- ORR: 74% with crizotinib vs 45% with chemo ($P < .0001$)

*Carboplatin or cisplatin.

EGFR-TKI as 1st Line Therapy

Study	Regime	Response rate (%)	P-value	PFS (mths)	P-value	OS (mths)	P-value
First-SIGNAL	GC vs Gefitinib	38 Vs 85	0.002	6.7 Vs 8.4	0.0084	26.5 Vs 30.6	NS
IPASS	PJ vs Gefitinib	47 Vs 71	<0.001	6.3 Vs 9.5	<0.001	21.9 Vs 21.6	NS
WJTOG	CD vs Gefitinib	32 Vs 62	<0.001	6.3 Vs 9.2	<0.0001	NR	NS
NEJ002	PJ vs Gefitinib	31 Vs 74	<0.001	5.4 Vs 10.8	<0.001	23.6 Vs 30.5	NS
EURTAC	G/D+C/J vs Erlotinib	15 Vs 58	<0.0001	5.2 Vs 9.7	<0.0001	19.5 Vs 19.3	NS
LUX3	AC vs *Afatinib	23 Vs 56	0.001	11.1 Vs 6.9	0.001	NA	NA

G=Gemcitabine, C=Cisplatin, P=paclitaxel, J=carboplatin, D=docetaxel; NR=not reached, NA=not available, A = Pemetrexed, NS=not significant

*Afatinib has not registered in HK



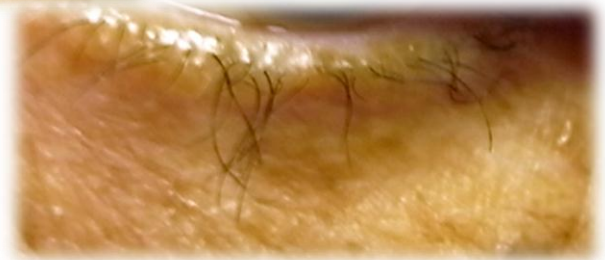
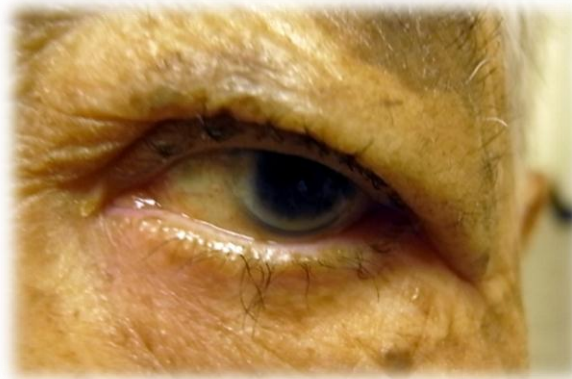
Pamela Youde Nethersole Eastern Hospital



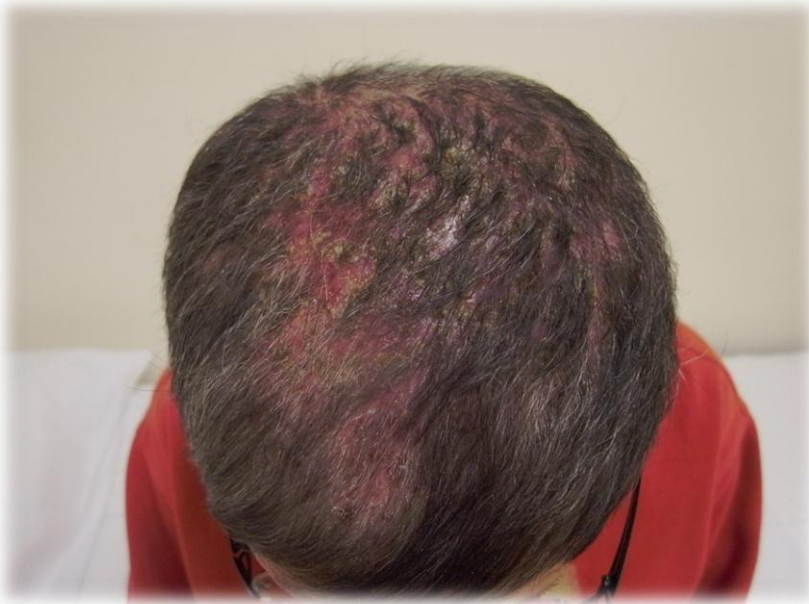
Toxicity of EGFR-TKIs



Toxicity of EGFR-TKIs



Toxicity of EGFR-TKIs



CHEMOTHERAPY

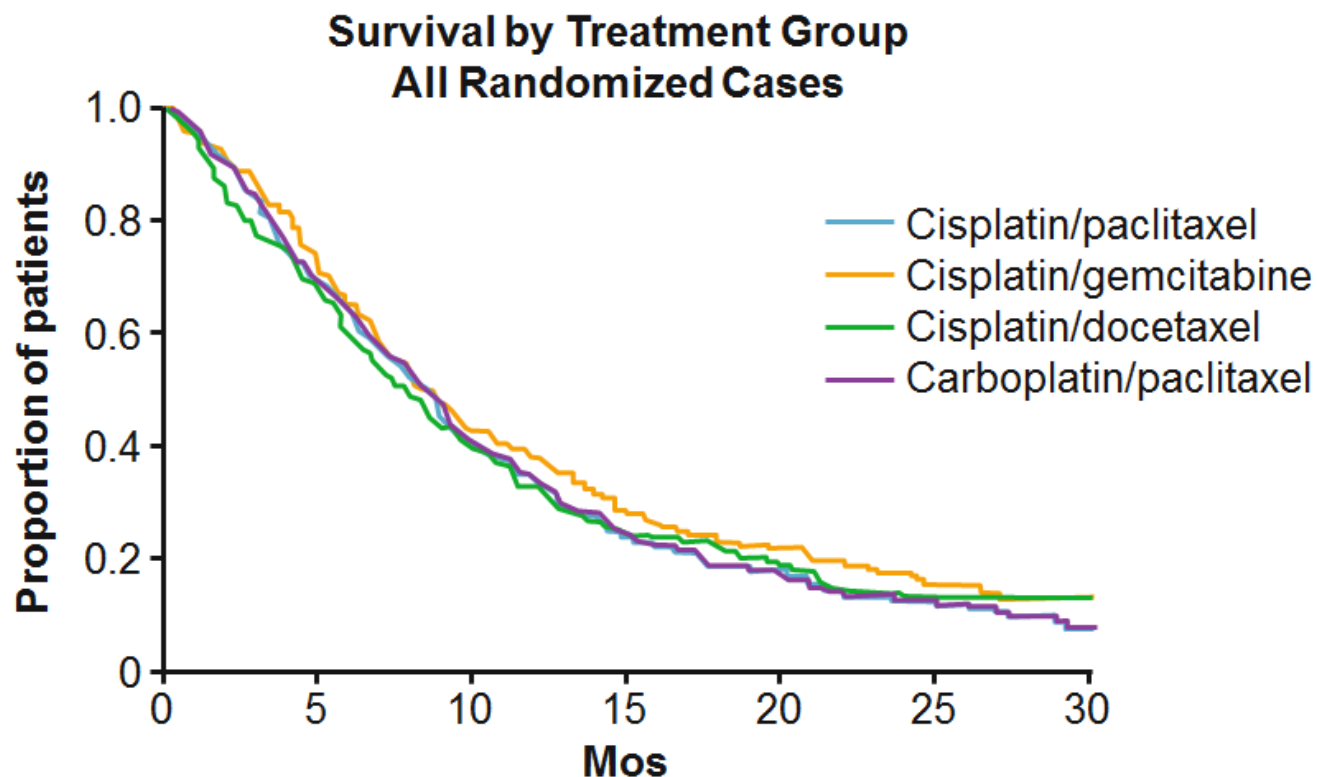


Pamela Youde Nethersole Eastern Hospital



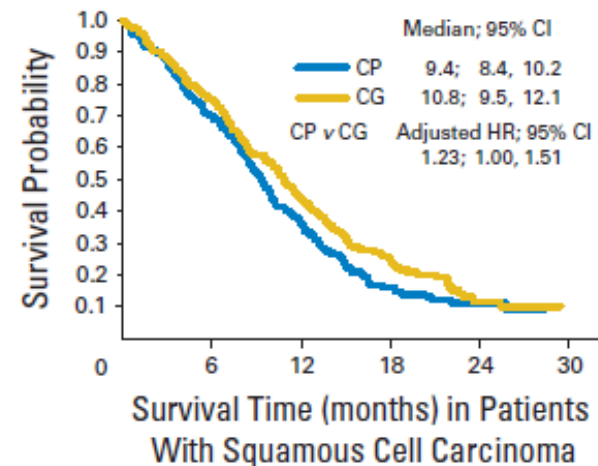
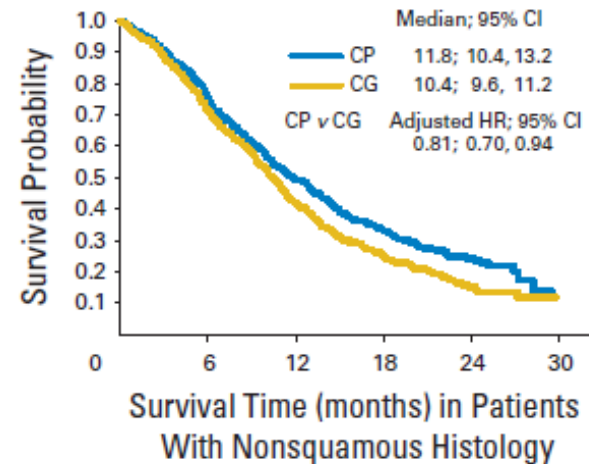
Reaching a Plateau

ECOG 1594: OS



Histology Dependent

- Similar efficacy in 3G platinum doublets
- Different toxicity profiles
- Pemetrexed most favourable toxicity profile
- Convenient administration schedule
- Pemetrexed more effective in adenoCA but less efficacious in Sq. CC



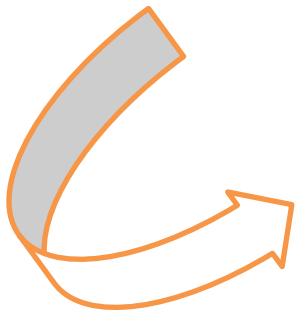
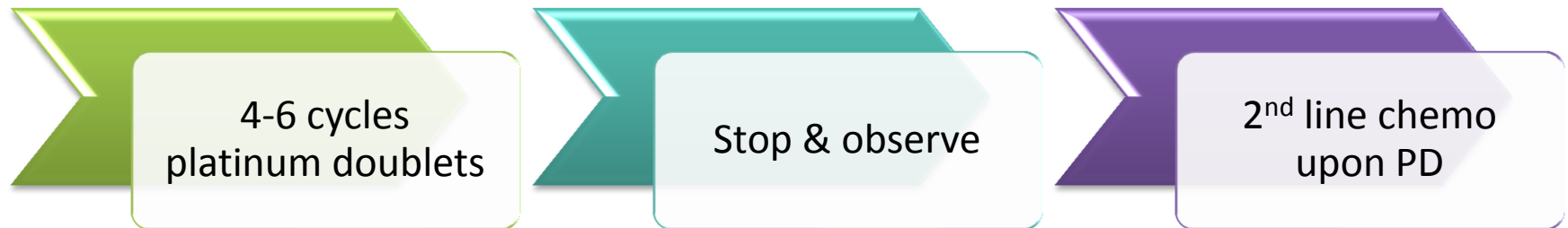
Ways to Enhance Chemo Outcome

- Maintenance therapy
 - Continuation vs switch maintenance
- Combination with targeted therapy
 - Adding anti-angiogenic mAB like bevacizumab
 - Adding anti-EGFR mAB like cetuximab



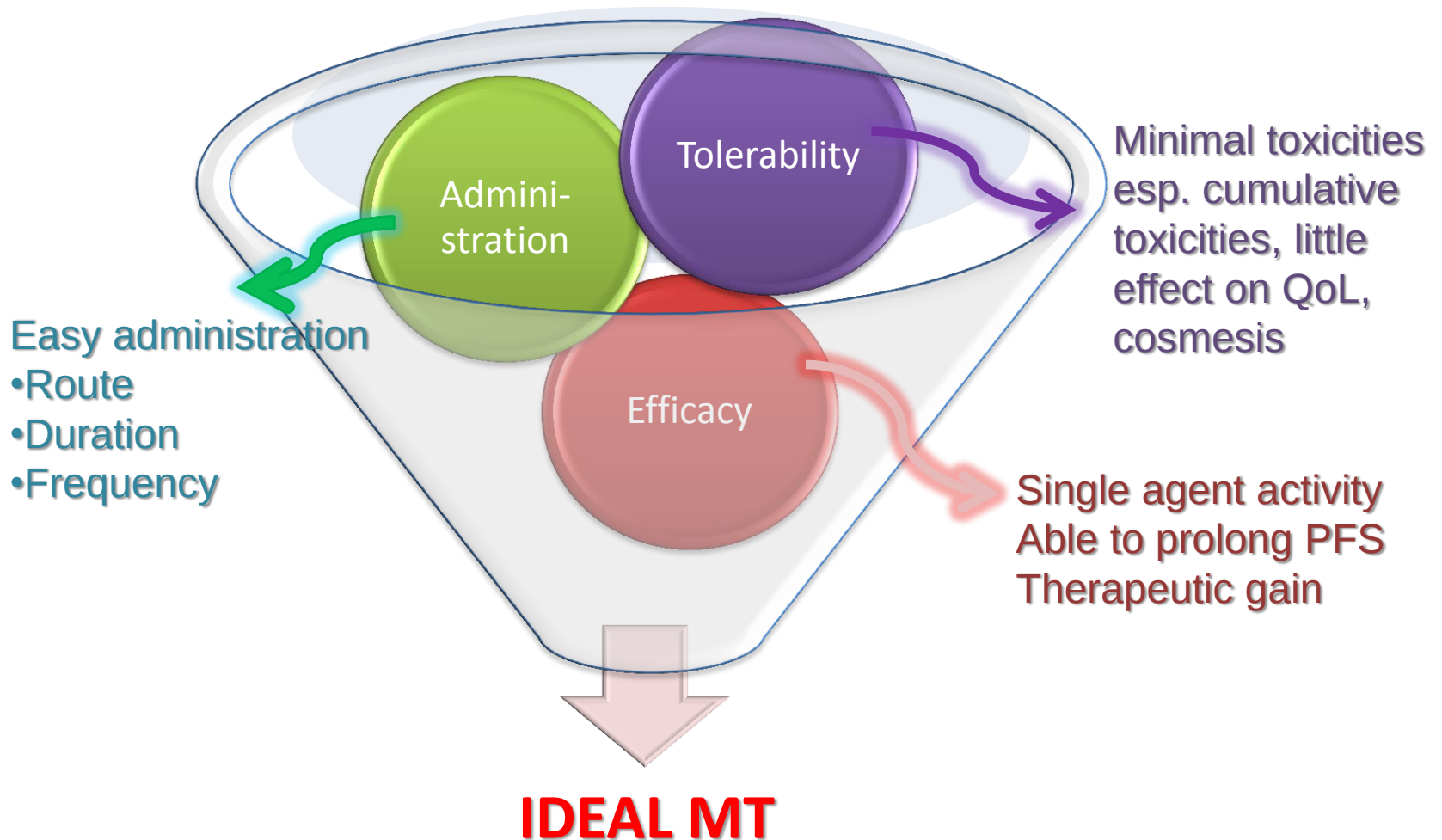
The Tradition Chemo Paradigm

Before the blooming of new cytotoxics & identification of various molecular markers...



Stage IV NSCLC. A. In patients with stage IV NSCLC, first-line chemotherapy **should be stopped at four cycles** in patients who are **not responding to treatment**. The Panel consensus is that first-line chemotherapy should be administered **for no more than six cycles in patients with stage IV NSCLC**.

Prerequisites of MT

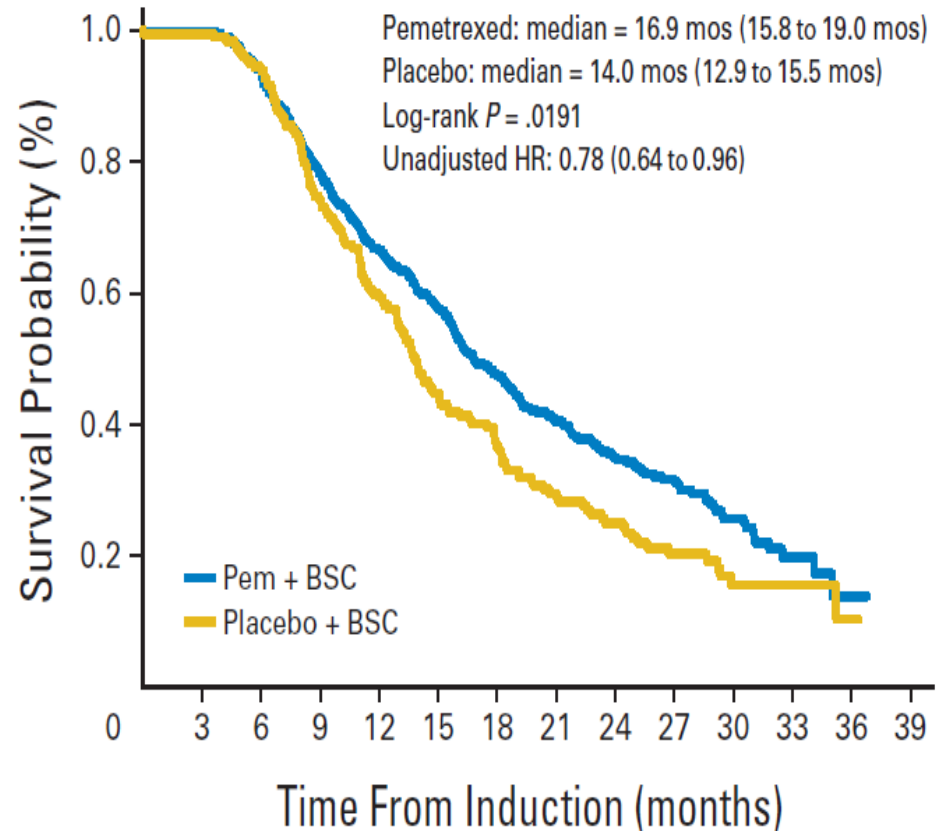


Maintenance Therapy

Continuation Vs Switch

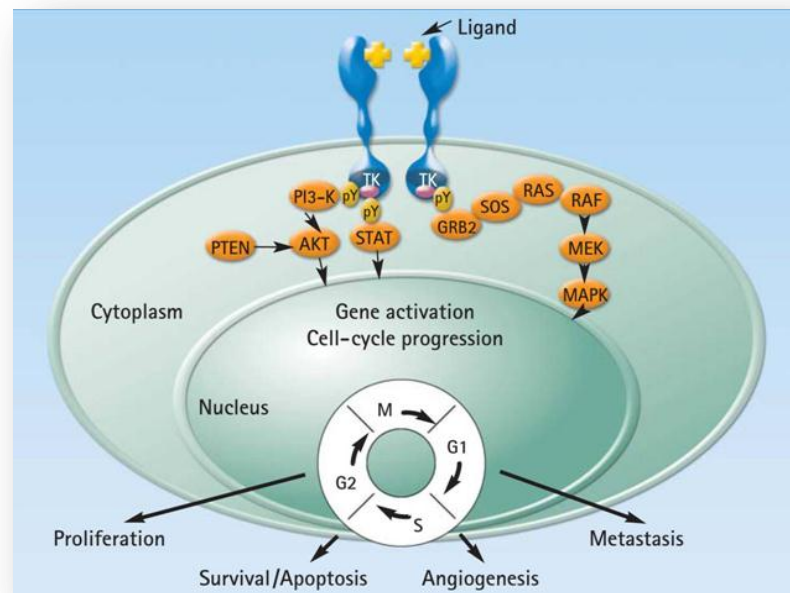
Currently available options:

- Pemetrexed
- Bevacizumab
- Erlotinib



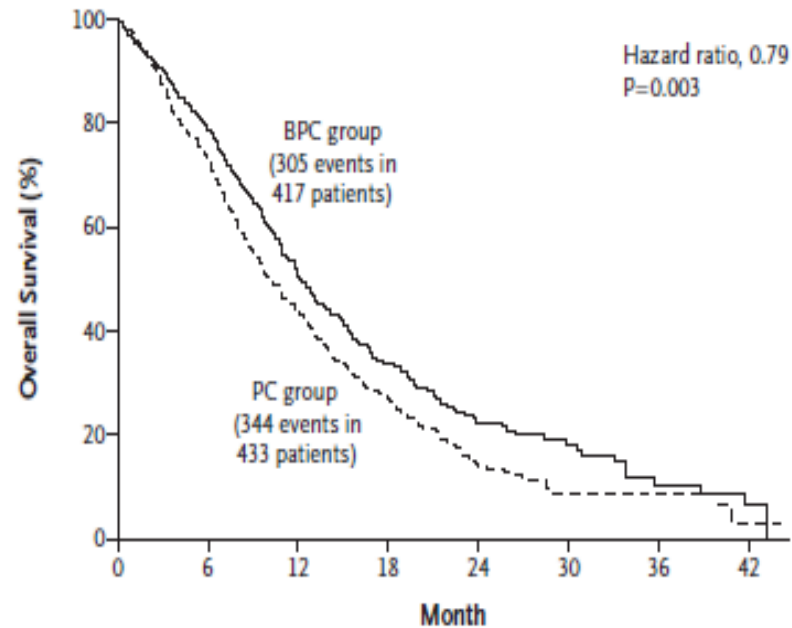
Addition of MABs

Anti-EGFR



Addition of MABs

Bevacizumab



Addition of MAB

	Study details	Participants	Response rate	Progression-free survival	Overall survival
E4599 (2006) ¹	First-line paclitaxel-carboplatin bevacizumab vs paclitaxel-carboplatin alone	878	35% vs 15% (p<0.001)	6.2 months vs 4.5 months (HR 0.66; p<0.001)	12.6 months vs 10.3 months (HR 0.83; 95% CI 0.70-0.99; p=0.003)
LUME-Lung1 (2014) ¹	Second-line docetaxel plus nintedanib vs docetaxel plus placebo	1314	All histologies: 4.4% vs 3.3% (p=0.3067); adenocarcinoma: 4.4% vs 3.6% (p=0.4770); with progression-free survival	4.5 months vs 3.9 months (HR 0.83; 95% CI 0.70-0.99; p=0.0359); adenocarcinoma with progression within 9 months after start of first-line treatment: 10.9 months vs 7.9 months (HR 0.75, 95% CI 0.60-0.92; p=0.0073)	

Table: Randomised trials assessing the addition of targeted therapy in non-small-cell lung cancer

We need good biomarkers!!

Toxicity of Chemotherapy

- Newer agents are less toxic
 - Less myelotoxic
 - Less alopecia
- Better supportive agents:
 - Antiemetics: Aprepitant ; 5HT₃ antagonist
 - GCSF/ PEG-GCSF
- Other common side effects:
 - Neuropathy, skin rash, edema, hypersensitivity
 - Renal impairment, cation loss



Cancer treatment is costly



1423

250mg bd/ 30 day



THE BIG MAC INDEX



416

800mg/ cycle



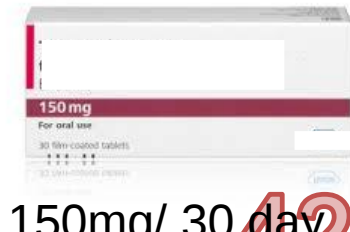
5 frs. of SBRT
in HA

24



Median household
Income in 2013

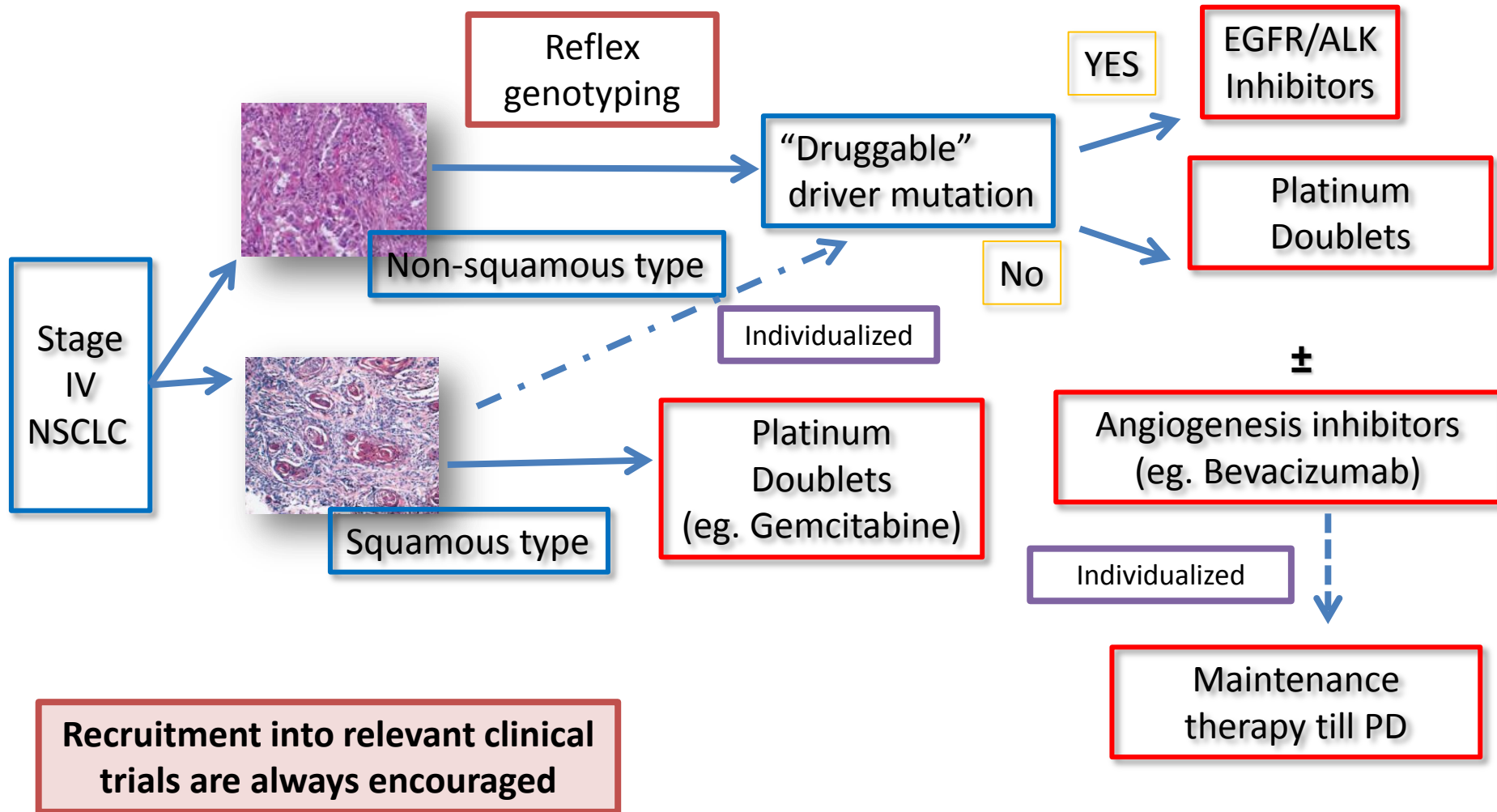
596



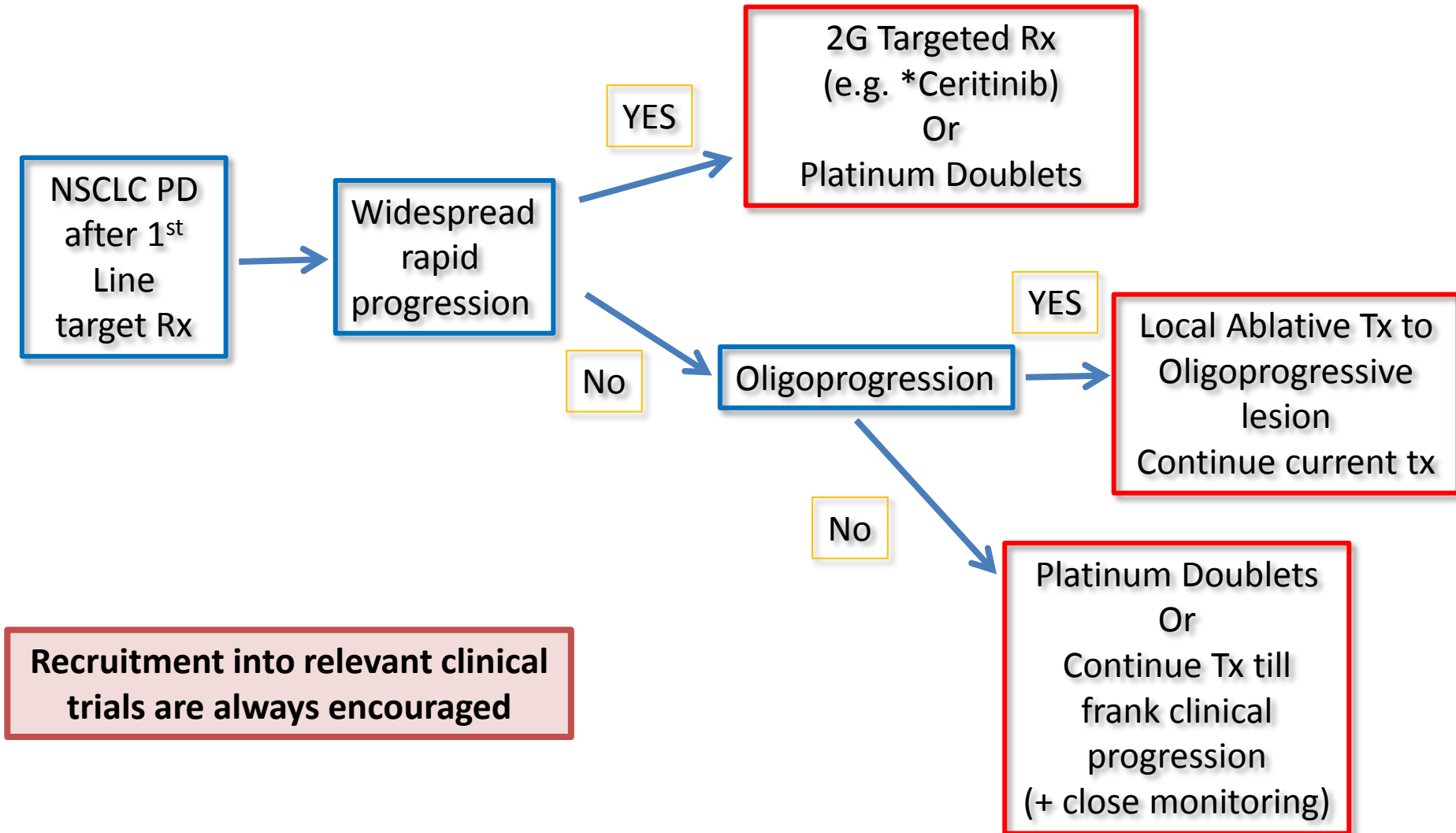
150mg/ 30 day

427

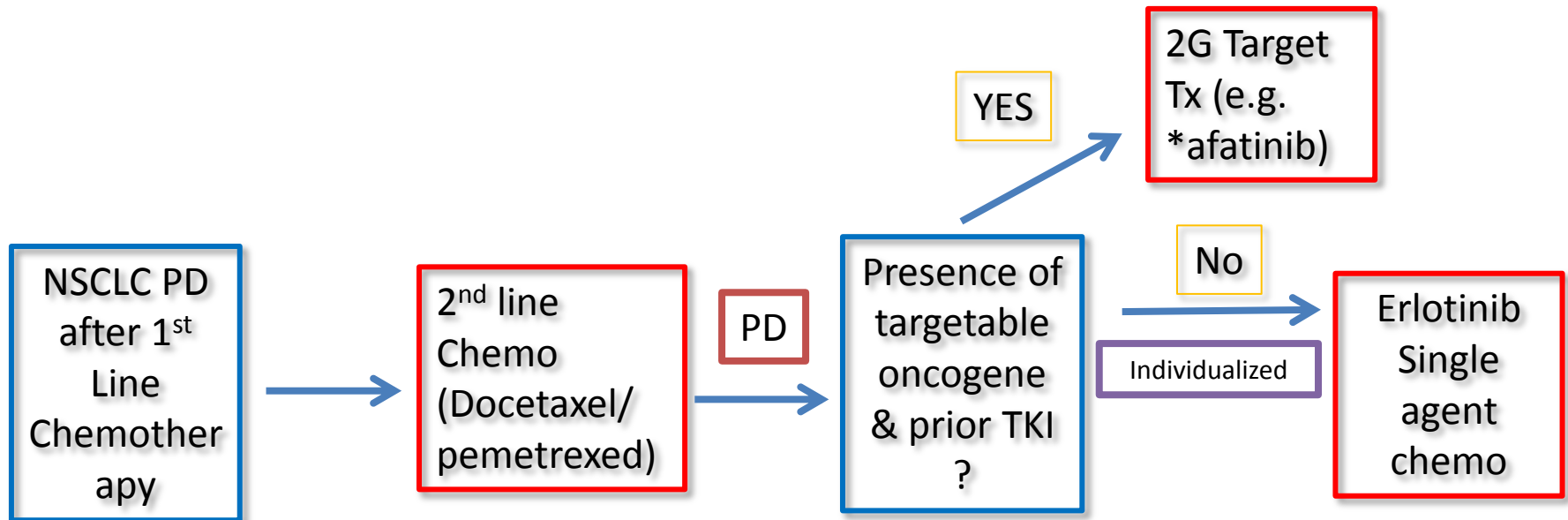
1st Line Rx for Stage IV Disease



Progression After Targeted Therapy

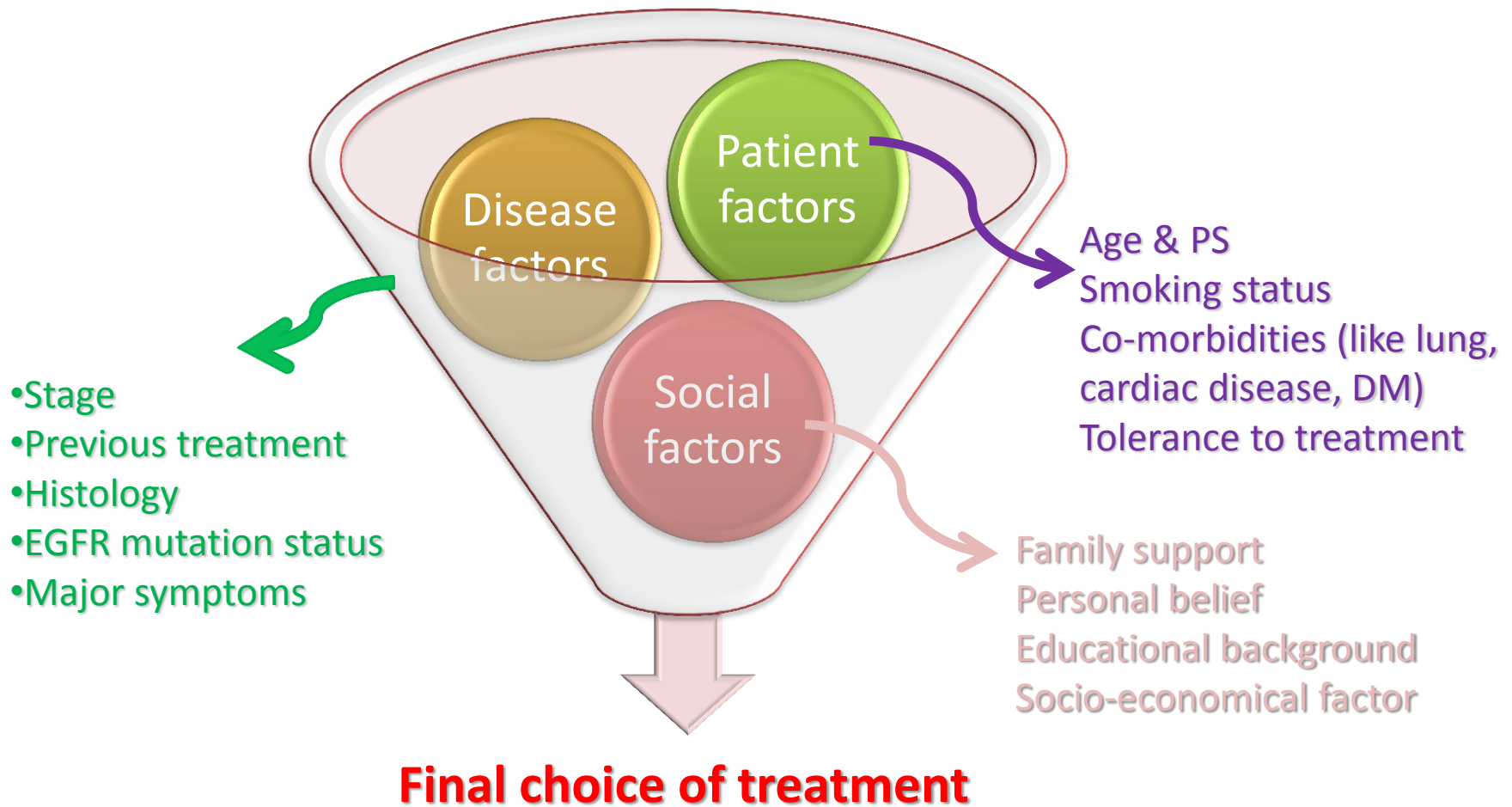


Subsequent Rx After 1L Chemotherapy



Recruitment into relevant clinical trials are always encouraged

Choice of Treatment



RADIOTHERAPY

New RT techniques and facilities are revolutionizing the role of RT in treating not only early disease but metastases as well...



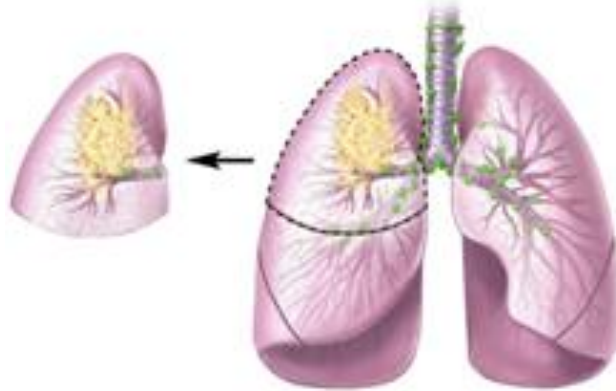
Tradition Indication of RT

- Radical RT in medically inoperable CA lung
- Concurrent with chemotherapy in stage III disease
- Palliation of symptoms in stage IV disease



Treatment of Early Stage CA Lung

**Lobectomy & Systematic
Lymph Node Dissection**



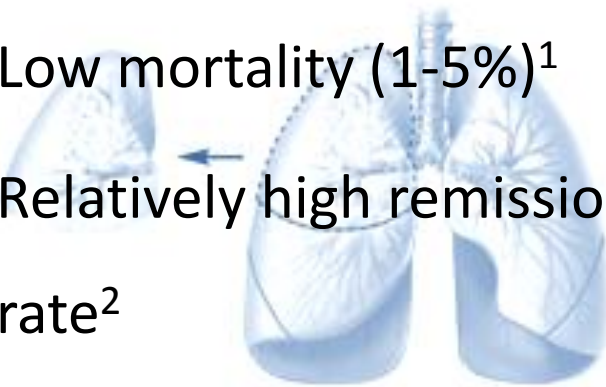
**Conventional
Radiotherapy**



Treatment of Early Stage CA Lung

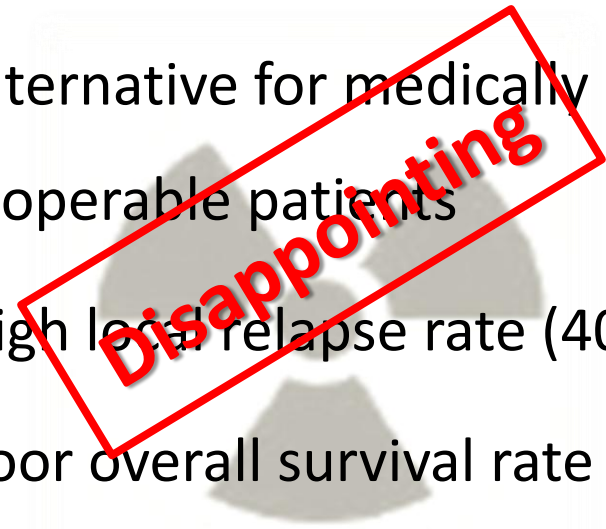
Lobectomy & Systematic Lymph Node Dissection

- Standard of care
- Low mortality (1-5%)¹
- Relatively high remission rate²
- Less morbidity in VATS



Conventional Radiotherapy

- Alternative for medically inoperable patients
- High local relapse rate (40%)³
- Poor overall survival rate (3yr OS 34%)³



1. Haasbeek et al. *Oncologist* 2008
2. Rami Porta R et al. *JTO* 2007
3. Qiao X et al. *Lung Cancer*. 2003



Limitation of Lobectomy

- Not suitable for frail elderly with multiple comorbidities
 - Median age of lung cancer is 70-yr-old¹
 - Death rate in octogenerian up to 9.4%²
- High morbidity rate ³
- Reduction in QoL
 - ↓ Lung volume & postoperative pain⁴
- 5-15% required bilobectomy & pneumonectomy³
 - ↑ complications and postoperative death rate

1. *HK Cancer Registry*

3. *Allen et al. Ann Thorac Surg 2006*

2. *Damhuis et al. Lung Cancer 2006*

4. *Sarna et al. Chest 2004*



Elements of SABR

Accurate
Immobilization

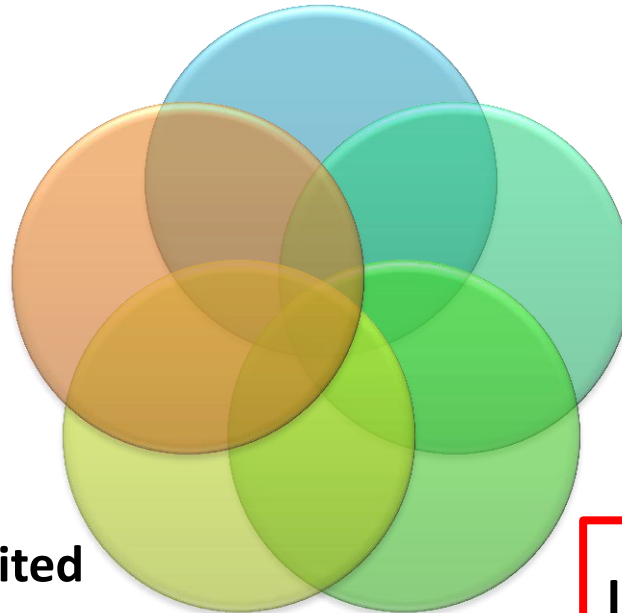
QA & Dosimetry

High Conformity

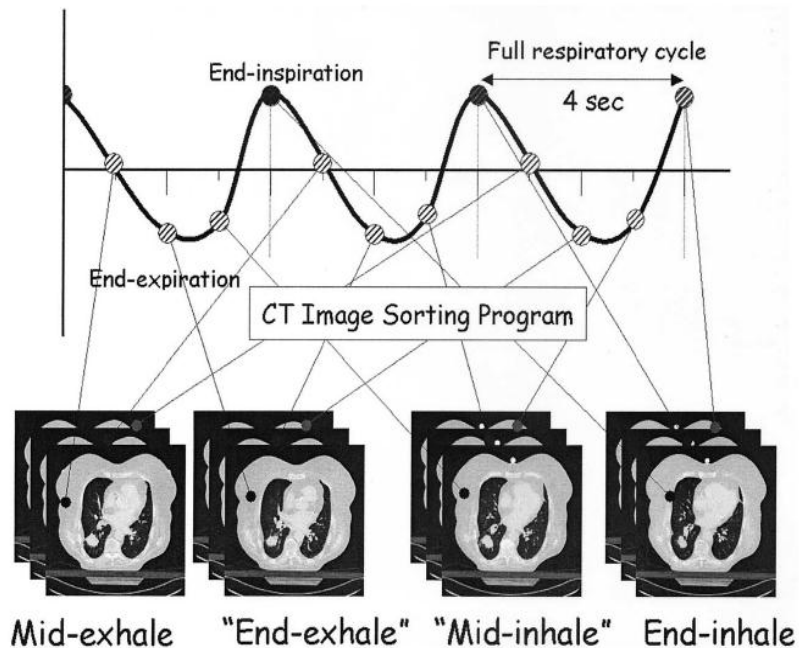
Tumor Motion
Management

High Dose in Limited
Fractions

Image Guidance



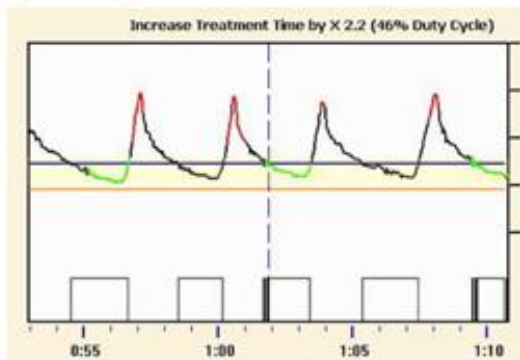
Tumor Motion Management



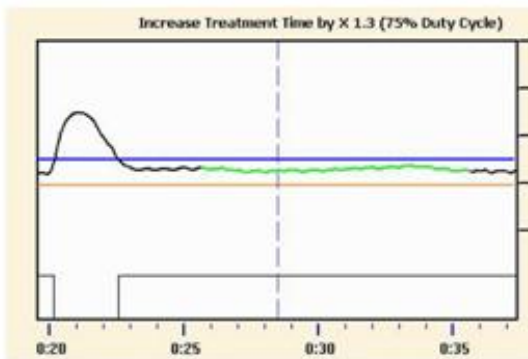
4D-CT ITV Based Approach

Tumor Motion Management

Gating



Voluntary Breath-hold



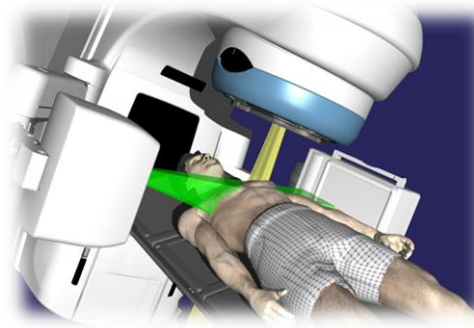
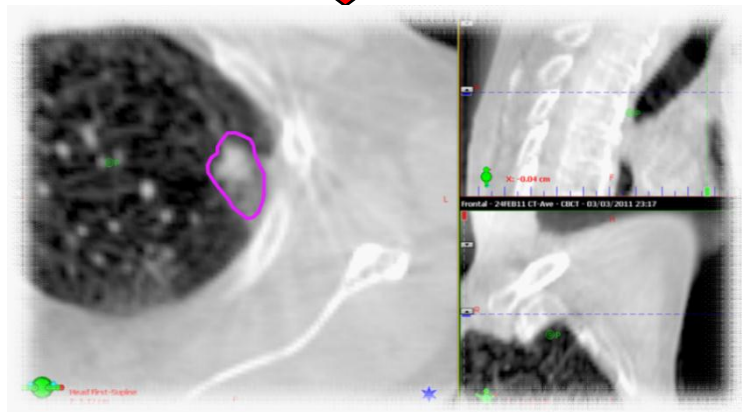
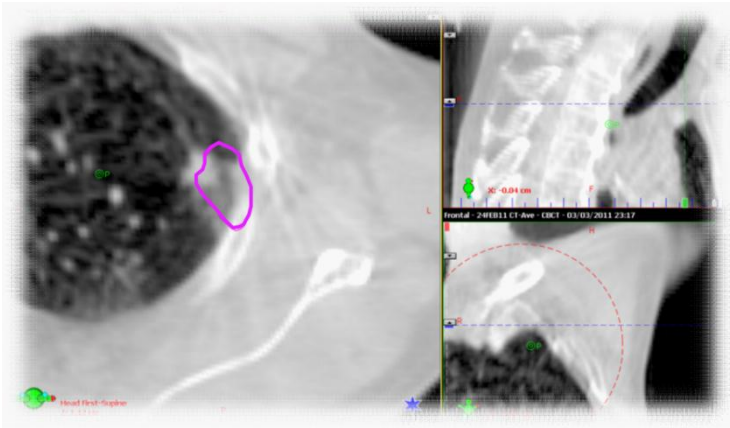
Active Breath Coordinator™

Real time Position Management

Image Guidance (IGRT)



Image Guidance



Cone beam CT



SABR IS NOT VENDOR SPECIFIC



High Local Control Rate

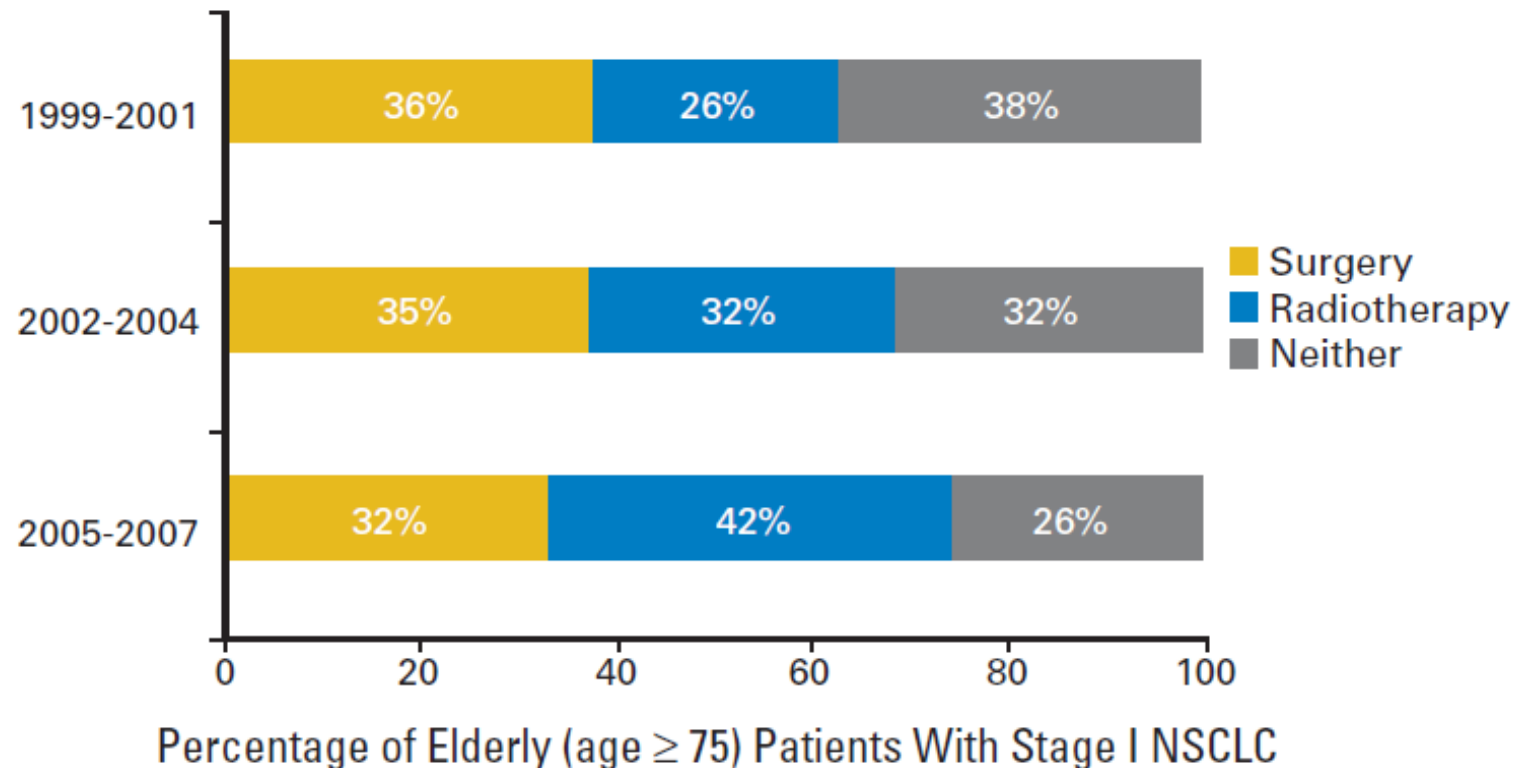
- Local control rate $\geq 85\%$
- Suitable for medically inoperable patients
- May challenge surgery in future!

Study	Total dose (Gy)	Daily dose (Gy)	Reference point	Local control	Median follow-up time
Uematsu <i>et al.</i> , 2001 (21, 23)	50–60	10	80% margin	94%(47/50)	36 months
Arimoto <i>et al.</i> , 1998 (24)	60	7.5	Isocenter	92%(22/24)	24 months
Timmerman <i>et al.</i> , 2003 (19)	60	20	80% margin	87%(30/37)	15 months
Onimaru <i>et al.</i> , 2003 (25)	48–60	6–7.5	Isocenter	80%(20/25)	17 months
Wulf <i>et al.</i> , 2004 (26)	45–56.2	15–15.4	80% margin	95%(19/20)	10 months
Nagata <i>et al.</i> , 2005 (28)	48	12	Isocenter	97%(44/45)	30 months
Lee <i>et al.</i> , 2003 (27)	30–40	10	90% margin	90%(8/9)	21 months
Fakiris <i>et al.</i> , 2009 (29)	60–66	20–23	80% margin	88%(70)	50 months
Baumann <i>et al.</i> , 2009 (30)	45	15	67% margin	92%(57)	35 months
Timmerman <i>et al.</i> , 2010 (31)	60	20	80% margin	98%(54/55)	36 months

IJROBP 2011

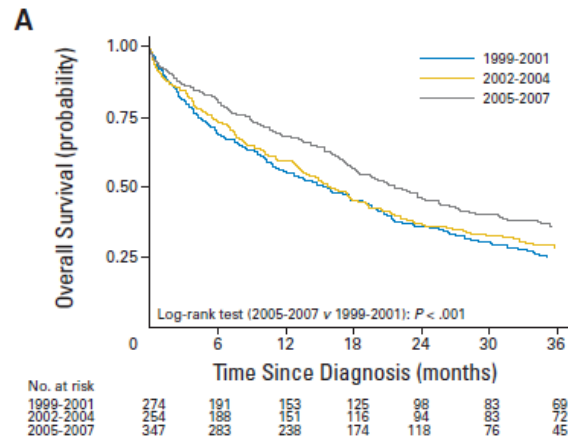


Dutch Population Based study

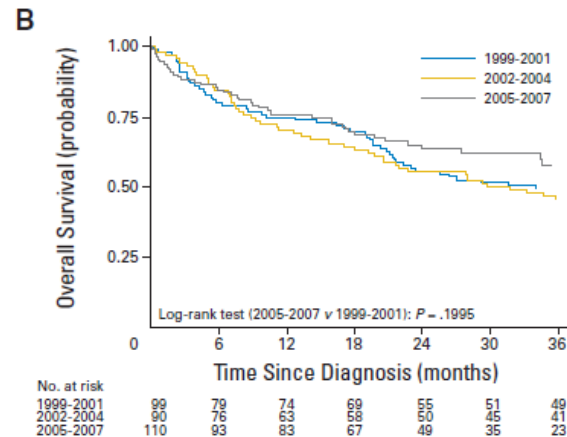


Dutch Population Based study

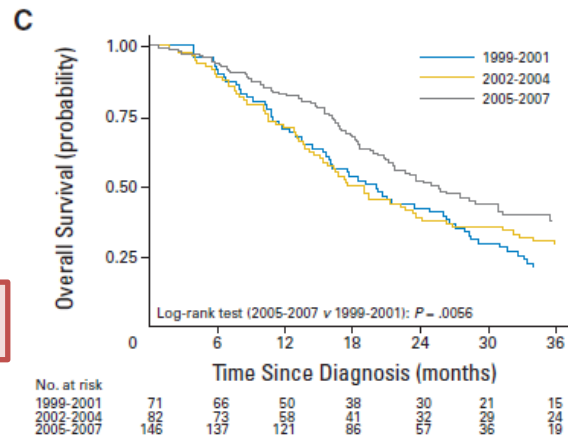
Overall



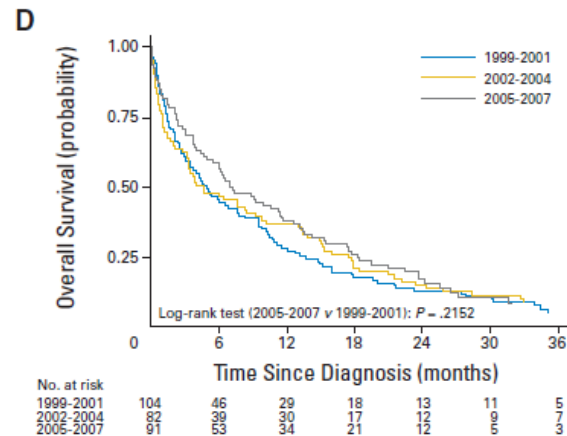
Surgery



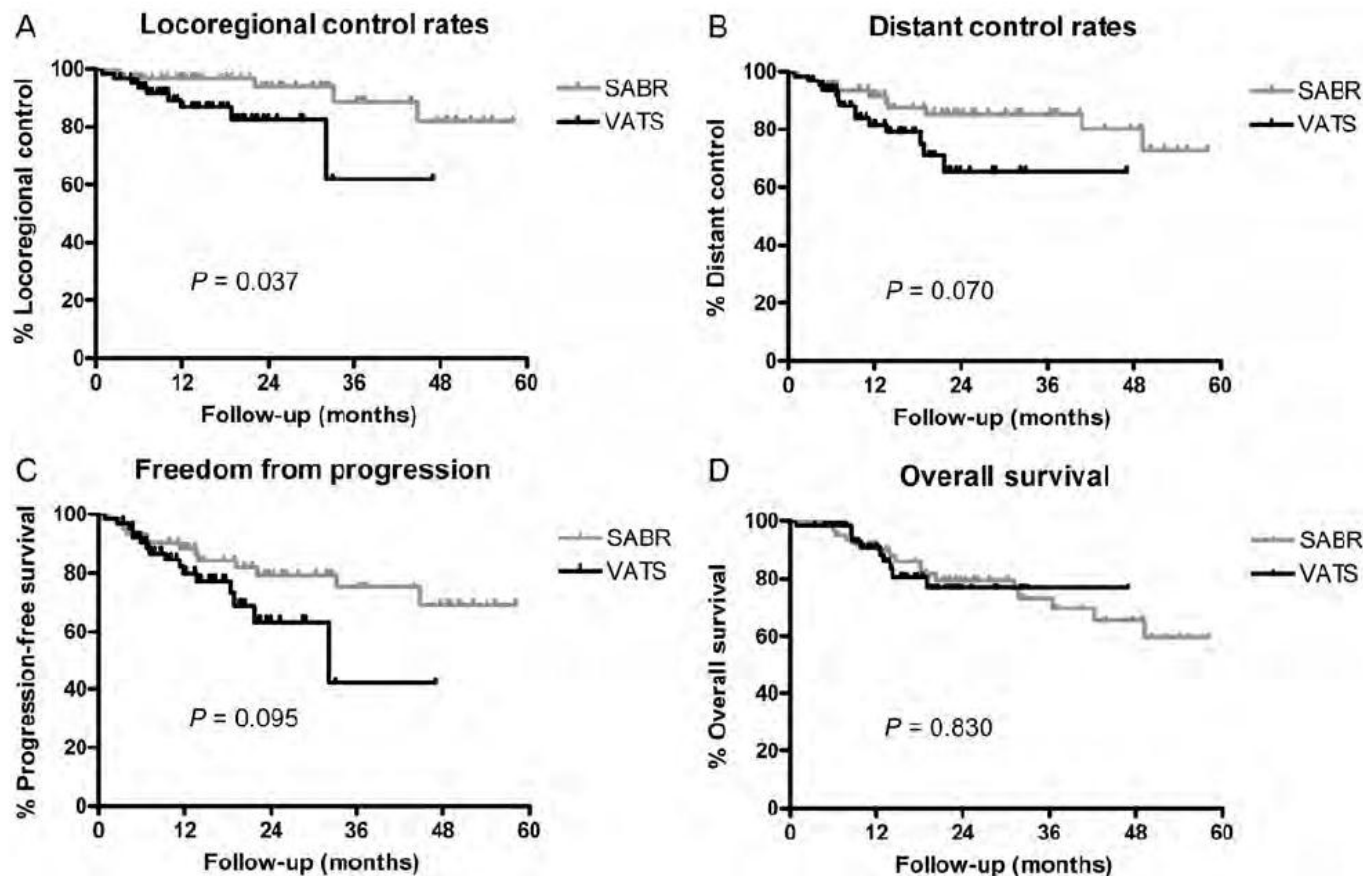
Radiotherapy



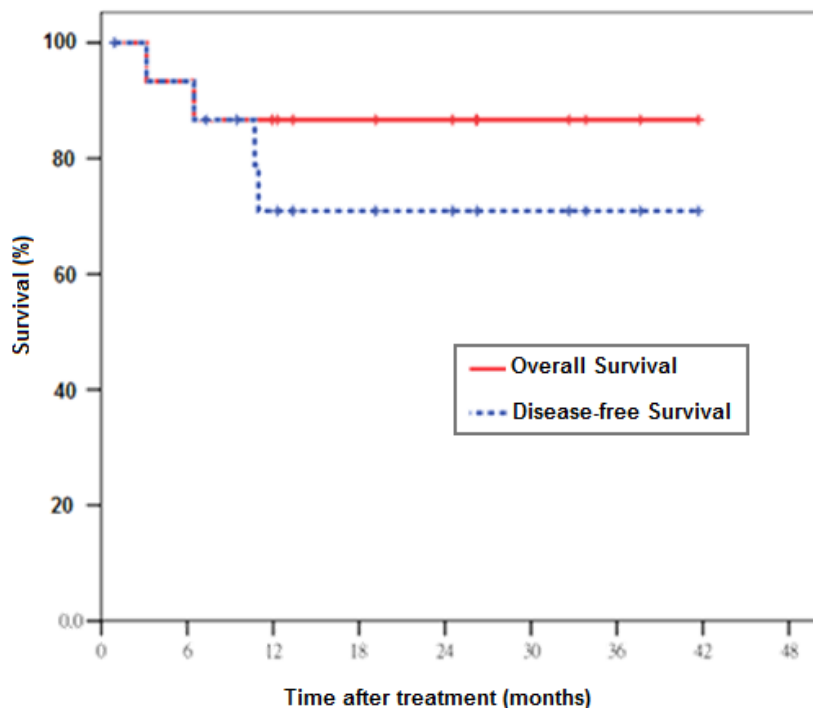
No Treatment



Propensity Score-matched Analysis



Early Outcome in PYNEH

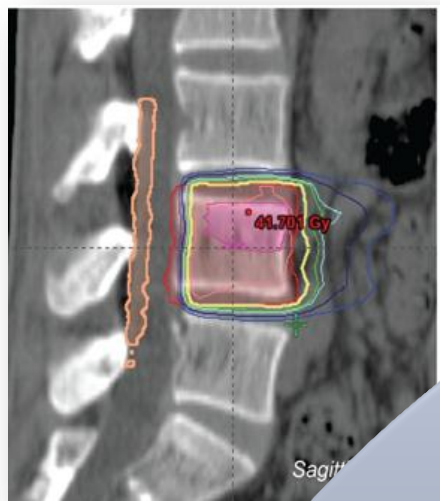


Oscar SH Chan et al. HKMJ, 2012

- SBRT started in 2008 in PYNEH
- 16 stage I patients treated so far
- >90% Local control rate
- 2-yr OS ~ 87%, DFS 71%
- No treatment related death or Grade 3 toxicity



Expanding the Indications

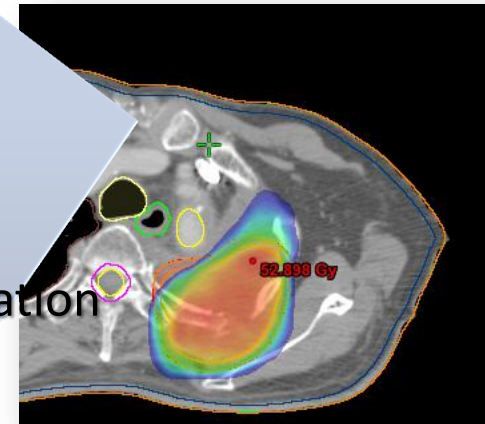


Primary
NSCLC

Oligo-
metastases

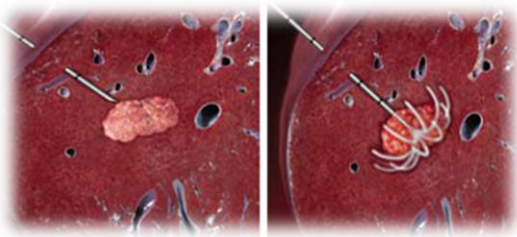
Oligo-
residual/
progressive

Re-
irradiation

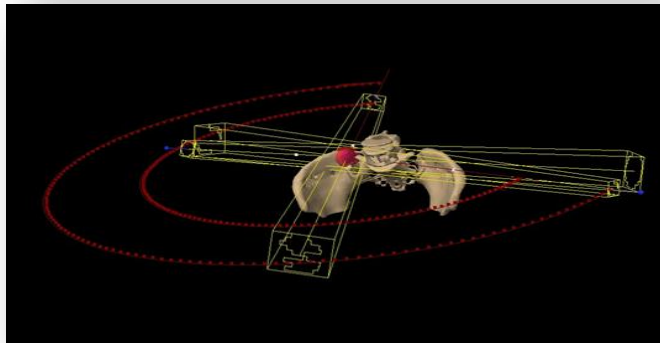
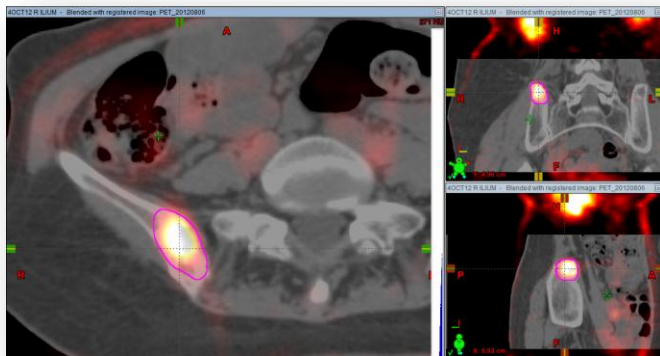


Management of Oligometastases

- Coined by Weichselbaum & Hellman in 1995
- An intermediate state of metastases limiting to specific organs in limited numbers
- Metastatic facility not fully developed
- Applicable to **oligoprogressive** disease as well

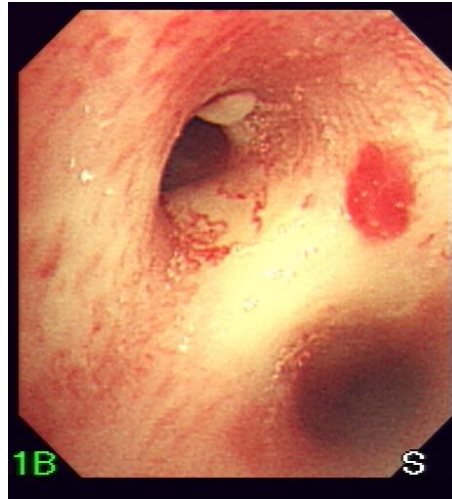
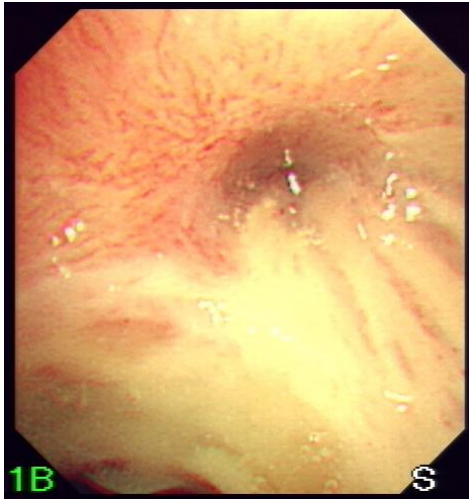


Management of Oligometastases



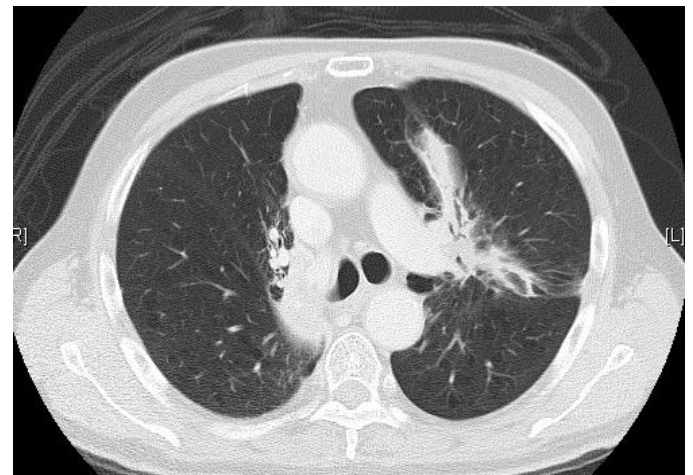
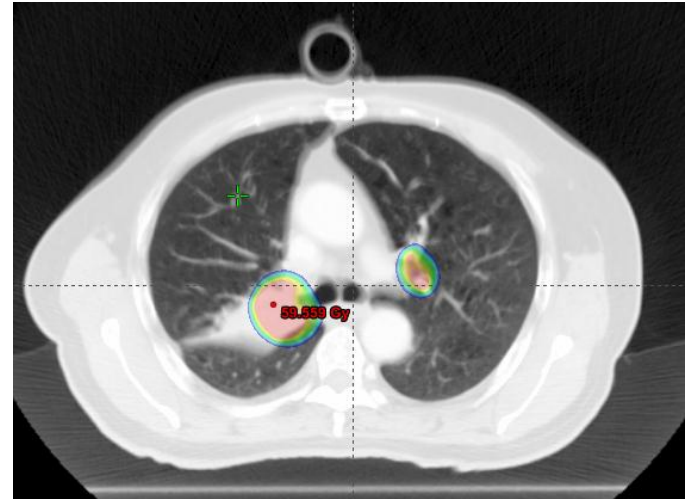
60-yr-old lady with recurrent NSCLC at R ilium, 1 yr after tx of stage I CA Lung. SABR delivered followed by 4 cycles of CDDP-pemetrexed. Disease free for 12 mths.

Pulmonary Toxicities

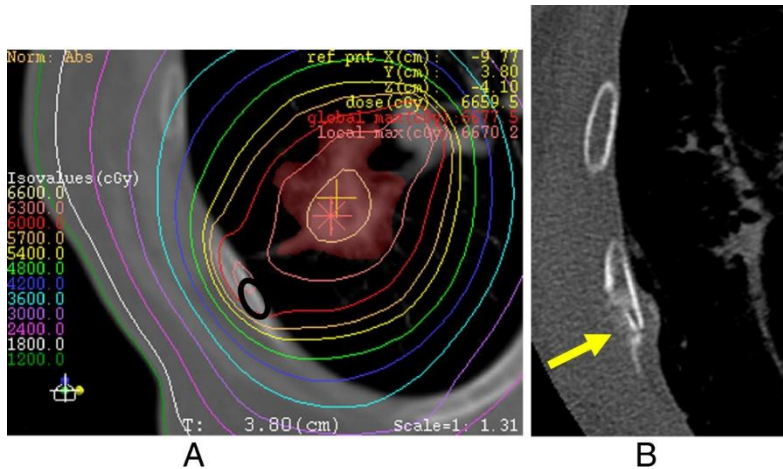


Bronchial Atresia Telangiectasia

Minimize the hot spots in centrally located tumors (<105% dose)



Chest Wall Toxicities

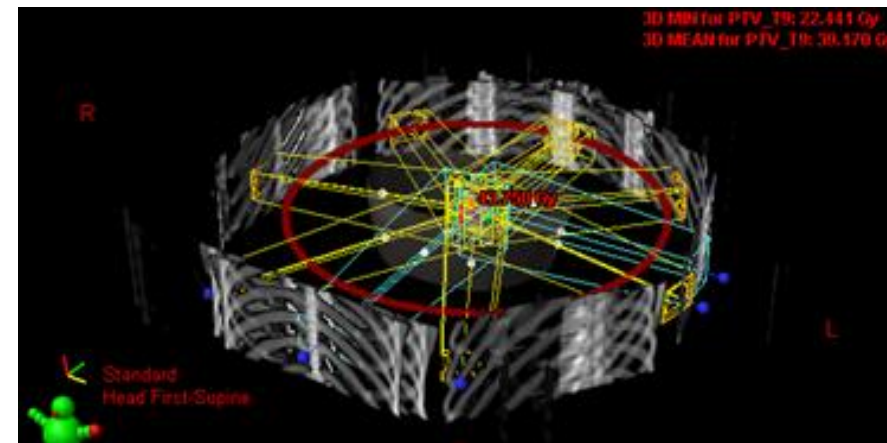
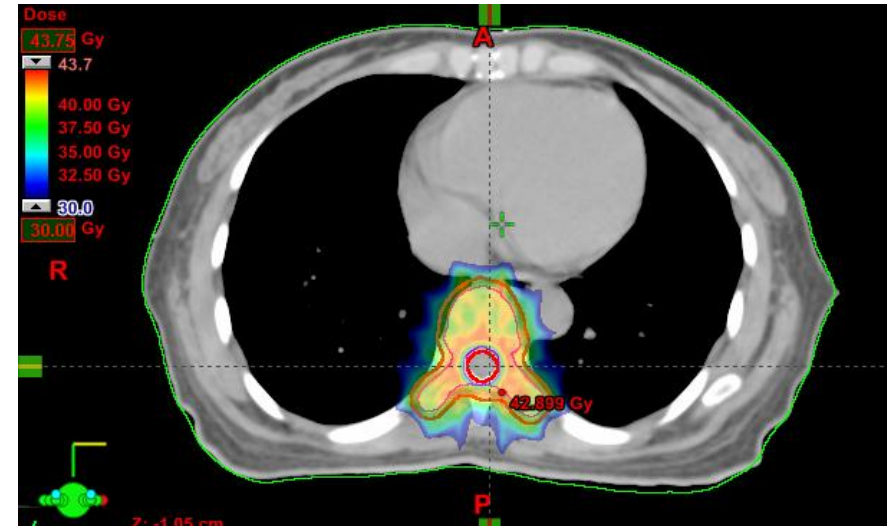
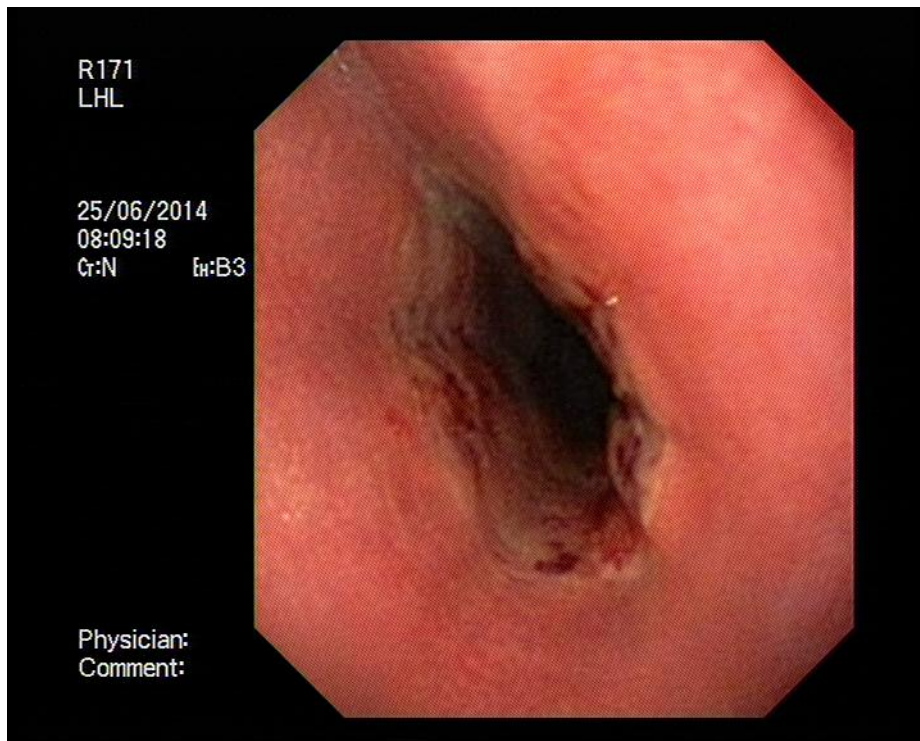


Rib fracture incidence up to 40%
but majorities are asymptomatic



Chan et al HKMJ 2012
Nambu et al BMC Cancer 2013

Esophageal Toxicities



Palliative Radiotherapy

- In sanctuary site, like brain
- Pain relief
- Relieve obstruction
- Haemostasis



Take Home Message

- Identification of biomarkers and applying specific target therapy improves survival
- Chemotherapy still plays important role in pts without druggable targets
- Maintenance therapy and adding biologics improves survival
- SABR is safe and effective in early NSCLC
- Application of SABR is expanding