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Geneva, Switzerland
13-16 APRIL 2016

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# Surgery in Oligometastatic Disease

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**Guangzhou, P.R China**

**13th – 16th April, 2016 Geneva**

广东省肺癌研究所 Guangdong Lung Cancer Institute

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广东省医学科学院 华南理工大学第一临床学院

# Disclosure

- Conducting research sponsored by Roche, Boehringer-ingelheim, AstraZeneca, Pfizer, Novartis, BMS;

- Received the honorarium from Roche, AstraZeneca, Eli Lilly, Sanofi.

# Oligometastases & Oligorecurrence

- Definition
  - A state of metastatic disease that is limited in total disease burden, usually by number of clinically evident or radiographic sites (either 1–3 or 1–5), and that is not rapidly spreading to more sites.

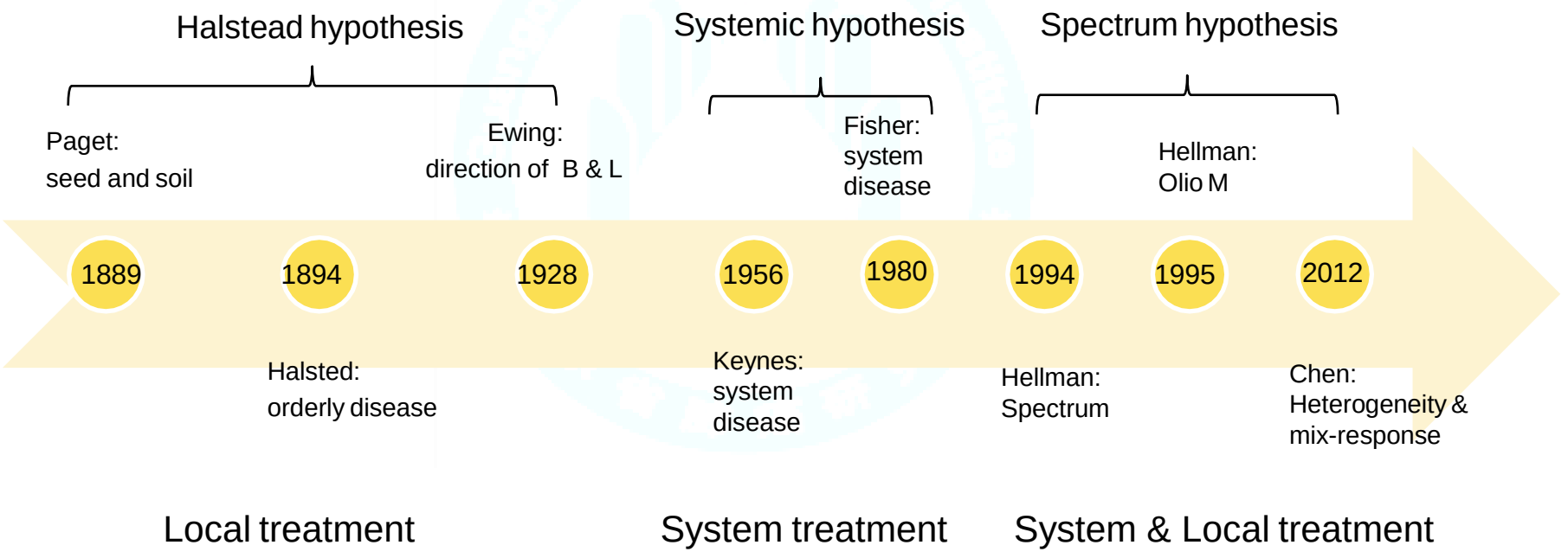
- Clinical implication
  - If the primary site (if still present) is controlled, or resected, and the metastatic sites are ablated (surgically or with radiation), there will be a prolonged disease-free interval, and perhaps even cure.



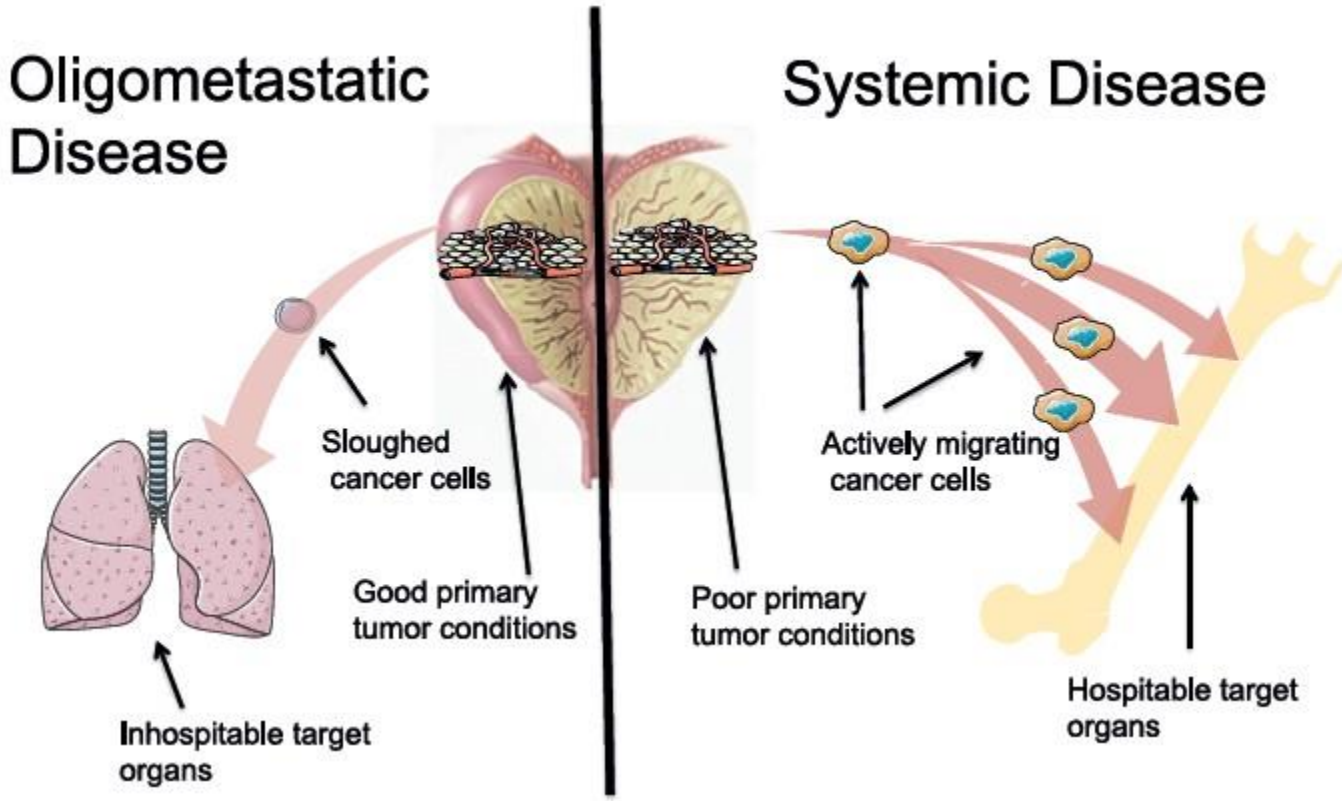
Reyes and Pienta. Oncotarget 2015

# 3 hypothesis of metastases

## Hypothesis and treatment schema



# Oligometastatic disease *versus systemic disease*




Reyes and Pienta. Oncotarget 2015

# Oligometastatic NSCLC

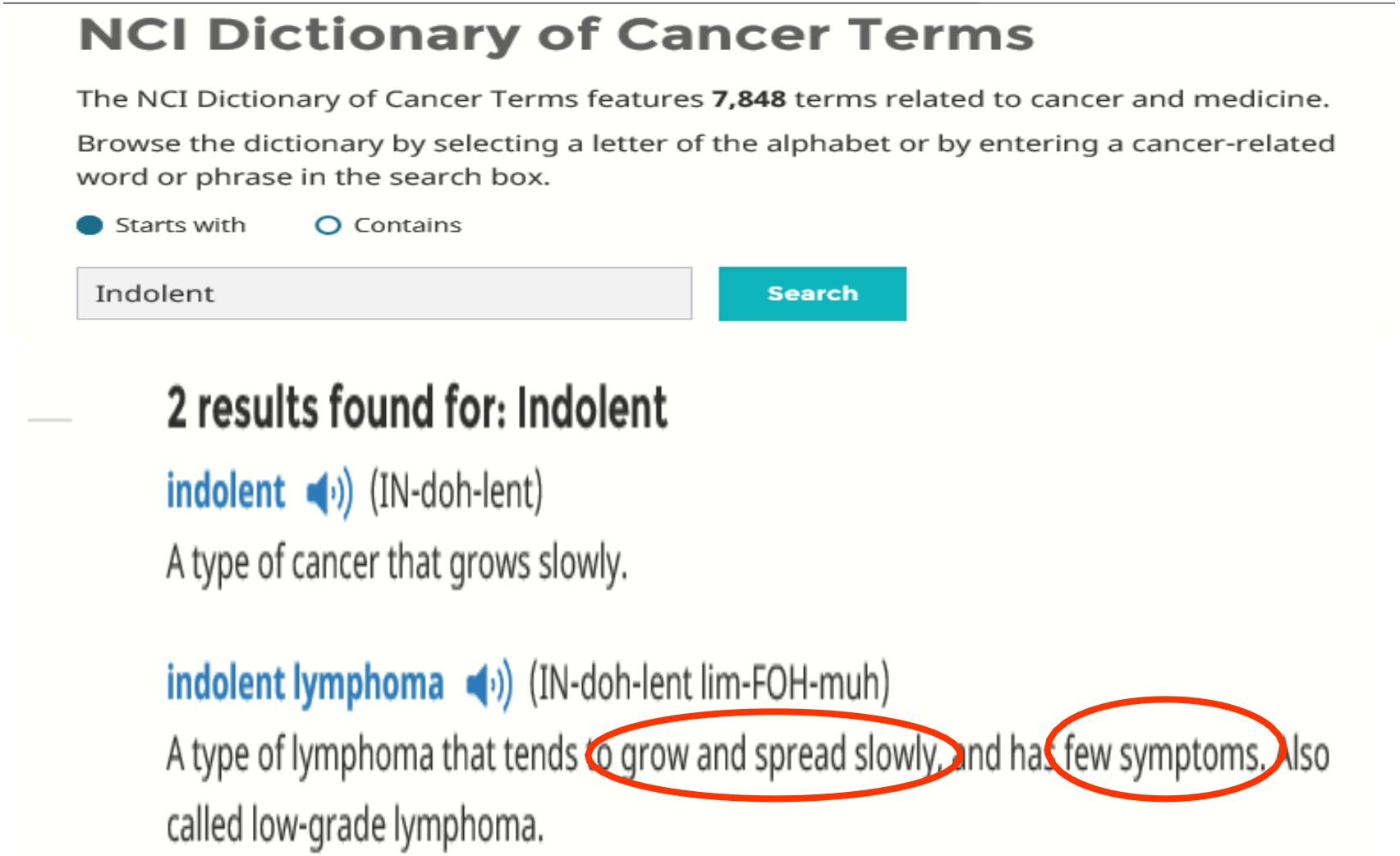
- Oligometastatic NSCLC is usually defined as a subgroup of stage IV NSCLC with a limited number, or number of sites of, metastatic disease[1]

- Only a small subset of lung cancer patients present with such limited metastases:
  - Brain metastasis: ~46% of patients have a solitary lesion[2]
  - Adrenal gland metastasis: ~4% of patients present with isolated adrenal gland metastasis[3]

- Patients with oligometastatic NSCLC may be eligible for, and benefit from, ablative therapy[1]

1. Hellman S, et al. J Clin Oncol 1995; 13(1):8–10;
2. Delattre JY, et al. Arch Neurol 1988;45:741–44;
3. Ettinghausen SE & Burt ME. J Clin Oncol 1991;9:1462–66.

# New concept in lung cancer: the Indolent Lung Cancer



## NCI Dictionary of Cancer Terms

The NCI Dictionary of Cancer Terms features **7,848** terms related to cancer and medicine.

Browse the dictionary by selecting a letter of the alphabet or by entering a cancer-related word or phrase in the search box.

Starts with  Contains

Indolent  Search

### 2 results found for: Indolent

**indolent** (IN-doh-lent)

A type of cancer that grows slowly.

**indolent lymphoma** (IN-doh-lent lim-FOH-muh)

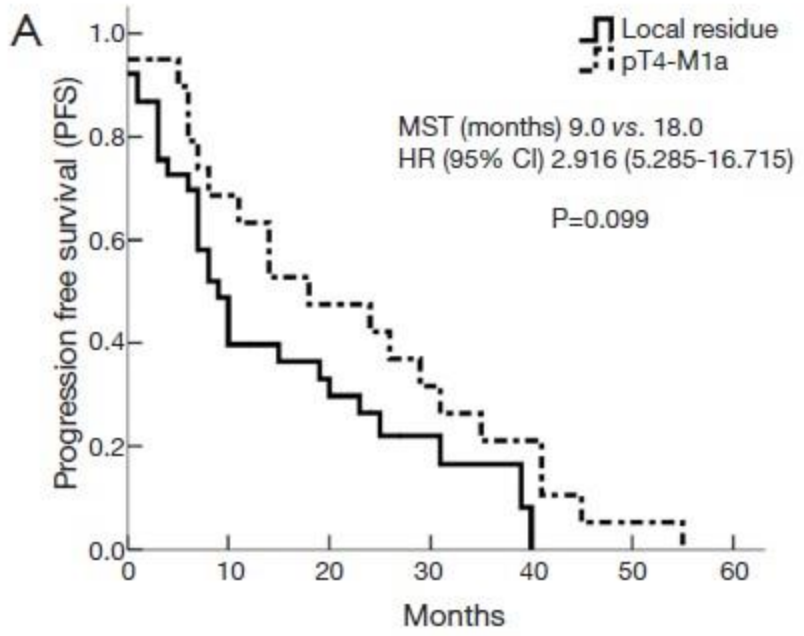
A type of lymphoma that tends to grow and spread slowly, and has few symptoms. Also called low-grade lymphoma.

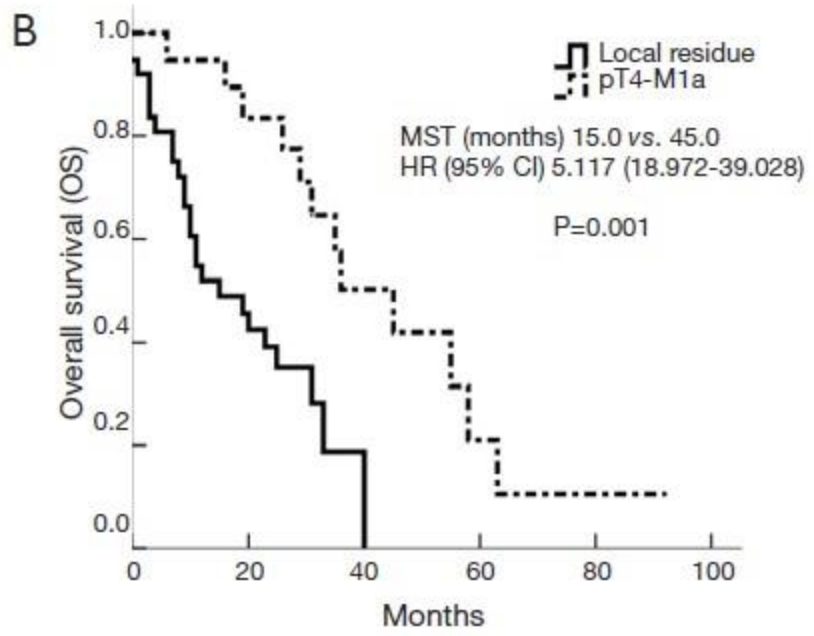
# Definition of indolent Lung Cancer

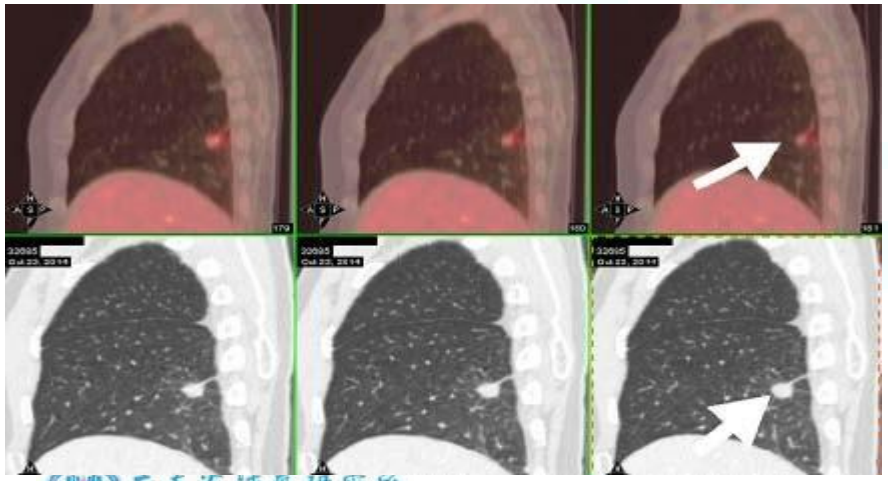
- 4122 asymptomatic individuals aged 50 years or older who were current or former heavy smokers for 5 years.
- Volume doubling time (VDT) was classified as
  - fast growing, at less than 400 days;
  - slow-growing at 400-599 days;
  - indolent at 600 days or more.

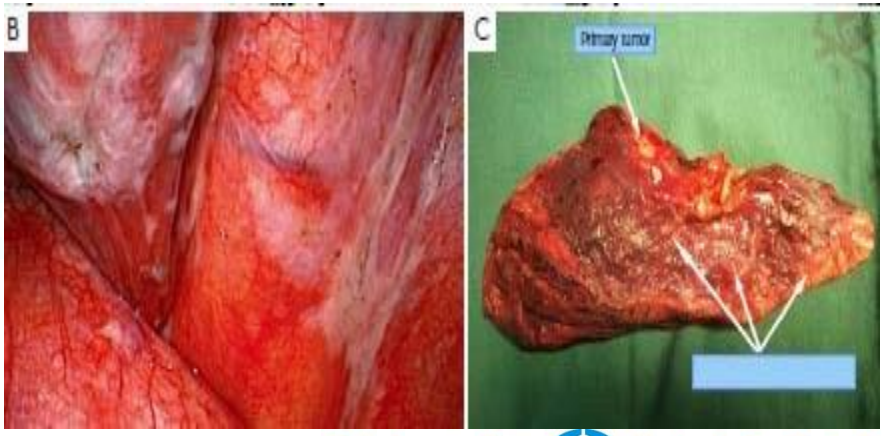
Veronesi (Milan, Italy) et al. *Annals of Internal Medicine 2013*

# Indolent advanced NSCLC



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Zhong & Wu, JTD 2015

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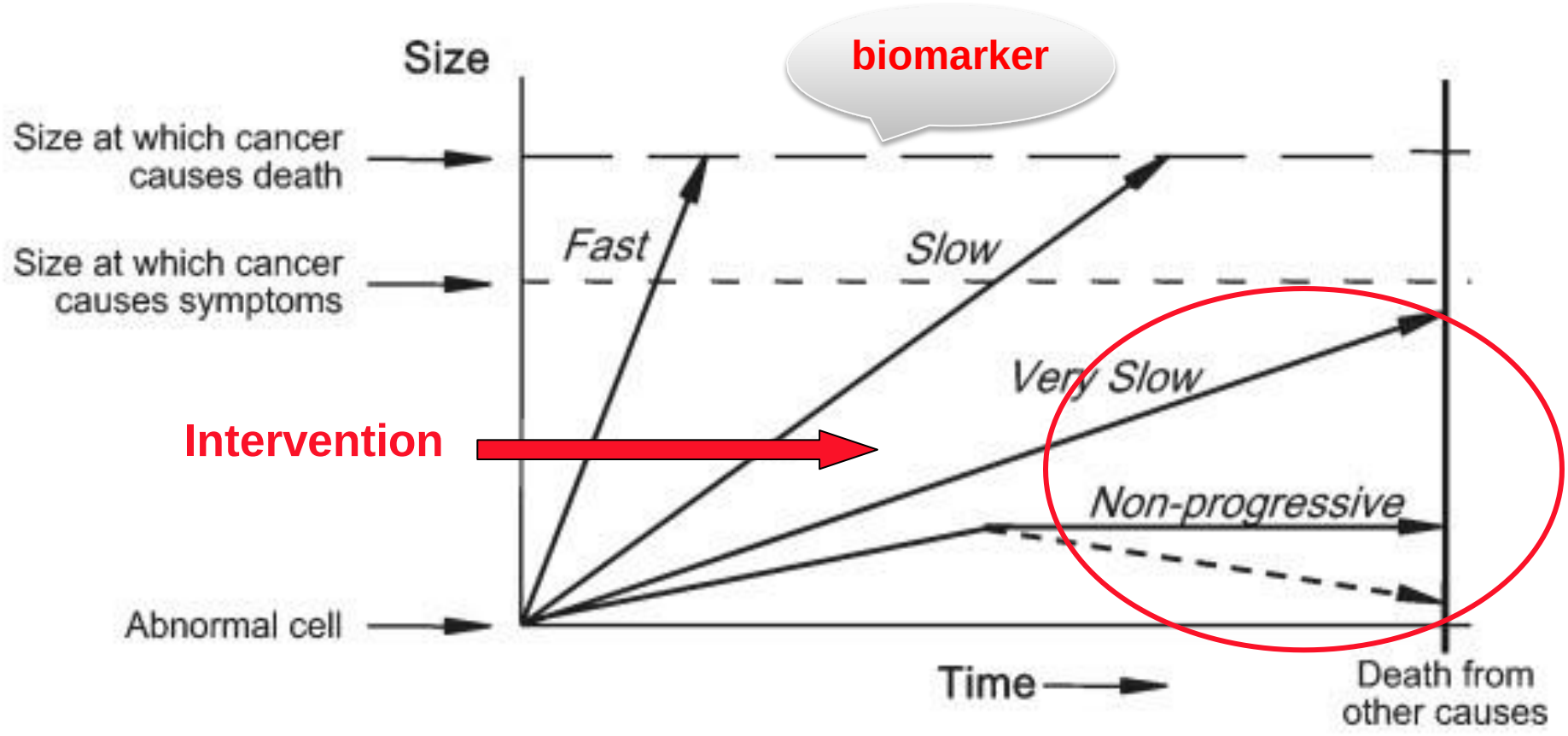
# Model of indolent and aggressive cancer




Henson DE, Siddiqui H et al. Overdiagnosis in cancer. J Natl Cancer Inst. 2010 May 5;102(9):605-13.

# Proposals for the Revision of the M Descriptors in the Forthcoming TNM staging of Lung Cancer

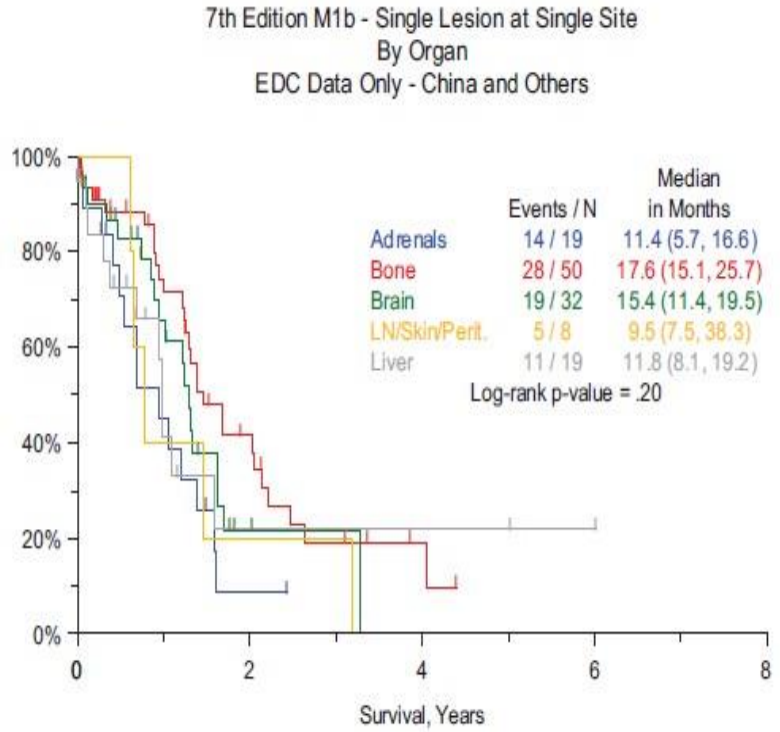



FIGURE 5. Single lesion at single site by organ—China and others.

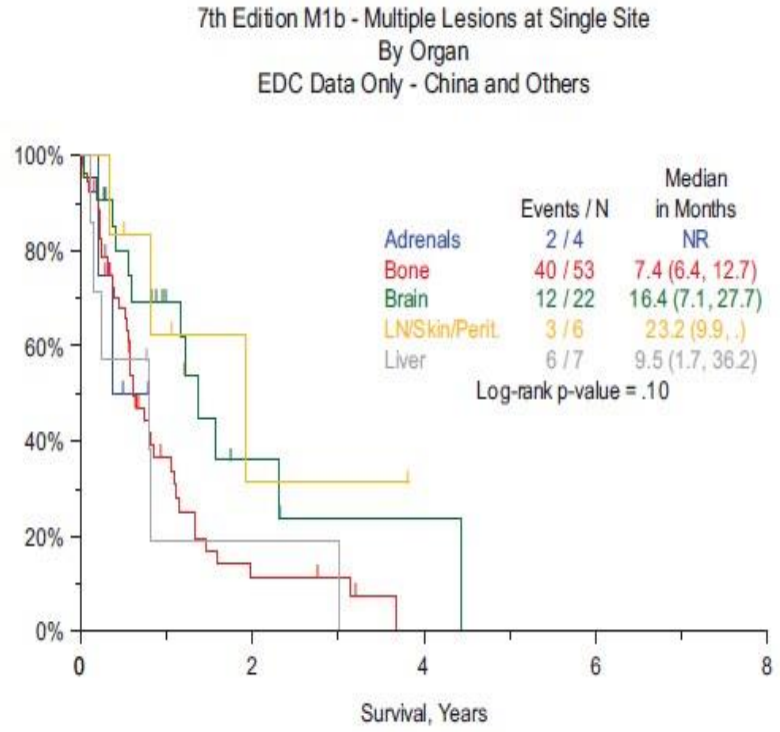
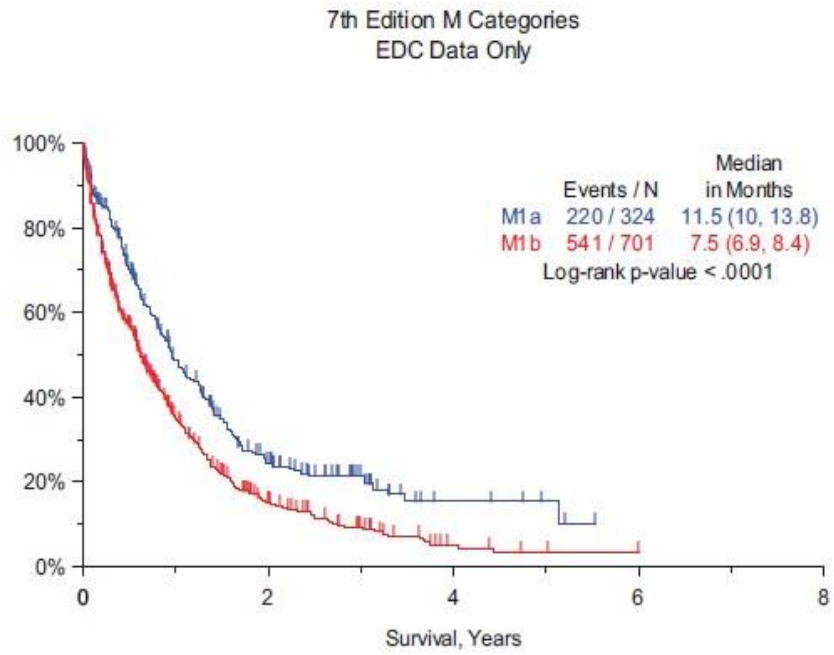



FIGURE 7. Multiple lesions at single site by organ—China and others.

Eberhardt et al. JTO 2015

# Proposals for the Revision of the M Descriptors in the Forthcoming TNM staging of Lung Cancer



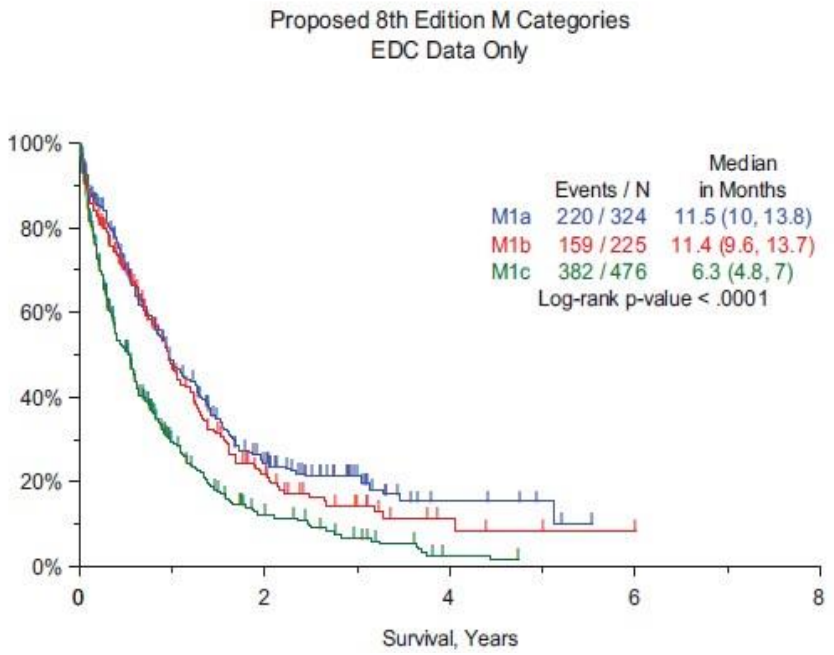




**TABLE 3.** Prognostic Impact of Single and Multiple Metastatic Lesions in a Single Organ versus Multiple Metastatic Sites

| | | Overall Survival | | |
|---|---|---|---|---|
| **Proposed Category** | **Variable** | **n/N (%)** | **HR (95% CI)** | ***P* Value** |
| M1a | M1a | 324/1025 (32) | Reference level | |
| M1b | M1b, single organ/lesion | 225/1025 (22) | 1.11 (0.91, 1.36) | 0.308 |
| M1c | M1b, single organ/multiple lesions | 229/1025 (22) | 1.63 (1.34, 1.99) | <0.001 |
| | M1b, multiple organs | 247/1025 (24) | 1.85 (1.52, 2.24) | <0.001 |

*P* value from score $\chi^2$ test in Cox regression.
HR, hazard ratio; 95% CI, 95% confidence interval.

Eberhardt et al. JTO 2015

# Oligometastases:Two Scenarios

- **Oligometastases ---**Treatment naïve
  - Location and number,
  - Synchronou or metachronous
  - Extra-cranial, extra-adrenal metastasis
- **Oligorecurrence ---** Treated

# Key prognostic factors for patients with oligometastatic NSCLC

**1. Number and site of metastatic disease**

**2. Pathologic staging of lymph node involvement**

Prognostic factors

**3. Status of primary lung lesion**

**4. Metachronous vs. synchronous disease**

# Number and site of metastatic disease

- Lower number of metastatic sites associated with better clinical outcome
  - >2 sites of disease associated with shorter PFS (*P*=0.002)[1]

- Brain and adrenal gland versus other sites such as bone or liver:
  - There is little published data on surgical treatment of oligometastasis from NSCLC outside of the brain and adrenal gland, mostly only case studies
  - In clinical practice we do not operate on bone or liver NSCLC metastasis because of poor prognosis

PFS, progression-free survival.

1. Hasselle MD, et al. J Thorac Oncol 2012;7:376-381.

# Different treatment strategies for primary and metastatic disease

| Treatment of primary lesion | Treatment of metastatic disease | Location of metastatic disease | Outcome |
|---|---|---|---|
| [redacted] | | | |
| Surgery | Gamma knife SRS ± WBRT | Solitary brain metastasis | 5-year survival: 10.4%[2] |
| [redacted] | | | |
| Surgery | Surgery | Adrenal metastasis | 5-year survival: 7–60%[5] |
| [redacted] | | | |

OS, overall survival; SBRT, stereotactic body radiotherapy; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy

1. Jabbour SK, et al. J Thorac Dis 2011; 3: 4–9 2. Flannery TW, et al. Lung Cancer 2003; 42(3): 327–333 3. Patchel RA, et al. N Engl J Med 1990; 322(8): 494–500 4. Mintz AH, et al. Cancer 1996; 78(7): 1470-1476 5. Villaruz LC, et al. Curr Oncol Rep 2012; 14: 333–341 6. Holy R, et al. Strahlenther Onkol 2011; 187(4): 245–251.

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# Synchronous versus metachronous disease

- Optimal disease-free interval (DFI) to distinguish synchronous and metachronous disease has not been agreed upon, but usually defined as 6 months
- A longer DFI is generally associated with better prognosis

**Patients receiving adrenalectomy for oligometastatic NSCLC (review of 10 studies, n=114)[1]**

| DFI | Median overall survival, months | P-value |
|---|---|---|
| [redacted] | | |
| >6 months (metachronous) | 31 | |

Tanvetyanon T, et al. J Clin Oncol 2008;26:1142–47.

# Treatment of oligometastatic NSCLC
# Extra-cranial, extra-adrenal metastasis

## Frequency: 6.7 % (193/2872) consecutive NSCLC

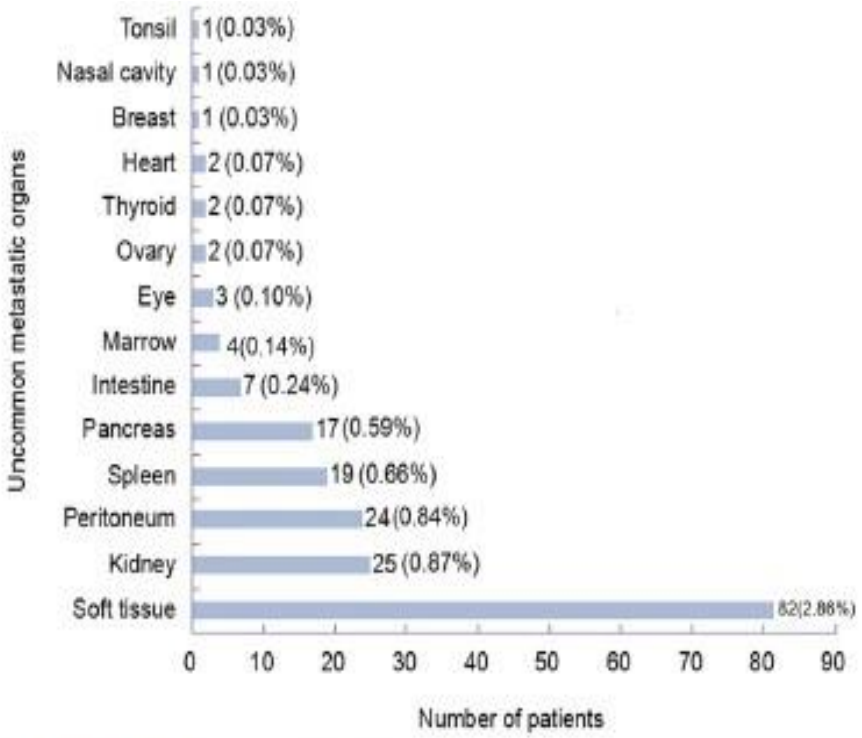



**Fig. 1** The frequency of uncommon metastases

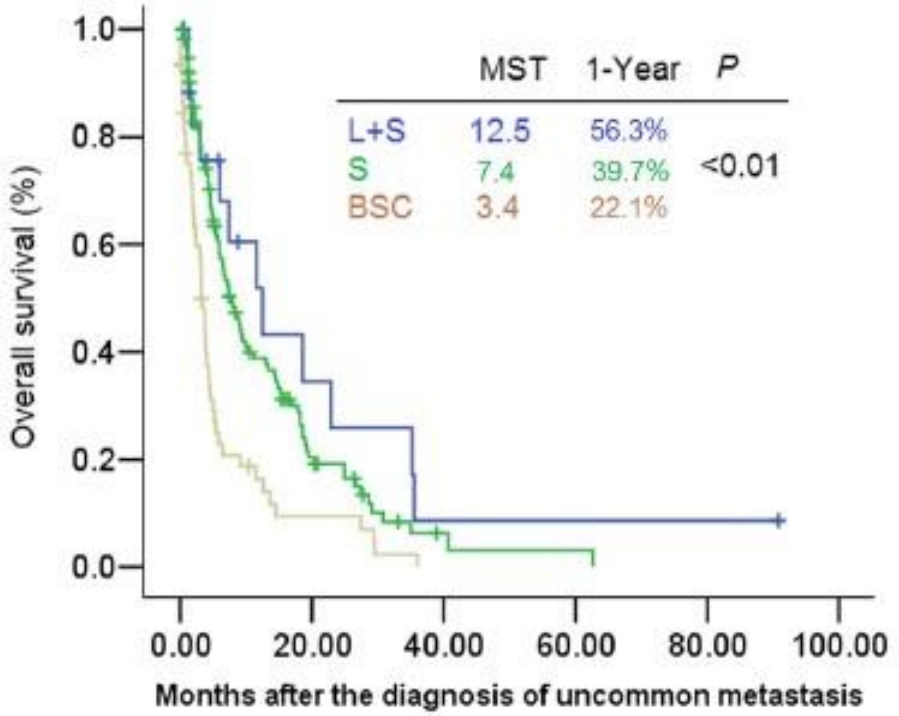



**Fig. 4** Survival from the time of the uncommon metastasis diagnosis in patients who received different treatments. Abbreviations: S, systemic treatment; L, local treatment; B, best supportive care

Niu & Wu et al. BMC Cancer 2016

# Survival by location of Oligometastases

2176 patients /49 eligible studies

Surgical metastatectomy: 55% of studies
Stereotactic radiosurgery for brain: 35%
SABR: 10%

| Location of oligometastases | | No. patients (*n*) | MS range (months) | Overall MS (months) |
|---|---|---|---|---|
| Brain | Status of primary lung tumor | | | |
| All patients | Controlled or uncontrolled | 1436 | 5.9–52 | 13.6 |
| All patients | Controlled | 1082 | 6.8–52 | 19.7 |
| Solitary Metastasis | Controlled or uncontrolled | 294 | 5.9–52 | 9.3 |
| Solitary Metastasis | Controlled | 215 | 6.2–52 | 19.7 |
| Mixed | Controlled (all) | 431 | 13–30.9 | 20 |
| Adrenal | Controlled (all) | 190 | 11–21 | 17 |
| Lung (one study only) | Controlled (all) | 76 | 40 | n/a |

Key determinants of long-term survival:
definitive treatment of the primary tumor;
a long disease-free
lack of intra-thoracic nodal metastasis.


Ashworth A et al. meta- analysis Lung Cancer 2013

# Treatment of oligometastatic NSCLC
# Overview of treatment strategies

- Surgery and radiosurgery are the two most common methods of tumour ablation
- Radiosurgery is less invasive and useful for patients ineligible for surgery[1]
- Additionally, evidence suggests SBRT may be more applicable to limited extracranial metastasis to multiple organs compared with surgery[2]
- Multidisciplinary combinations of surgery, radiotherapy and systemic treatment can be used

SBRT, stereotactic body radiotherapy.

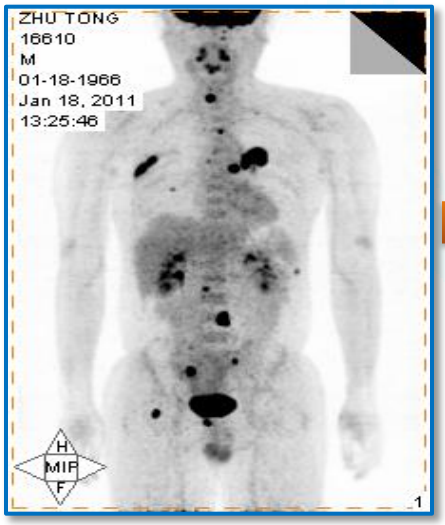
1. Villaruz LC, et al. Curr Oncol Rep 2012; 14: 333–341;
2. Corbin KS, et al. J Clin Oncol 2013;31:1384-1390.

# Oligometastases:Two Scenarios

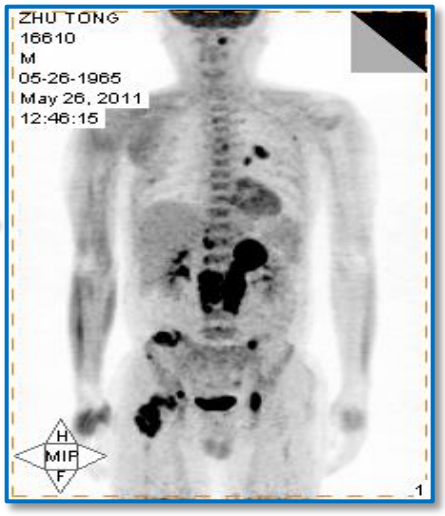
- Treatment naive
- Oligorecurrence -- Treated
  - Focus on driver gene mutant NSCLC patients

# Heterogeneity and Mixed response to Systemic Therapy

| Mixed response To systemic therapy | Primary tumor | Metastases | Percentage |
|---|---|---|---|
| 1 | ↓ | ↑ | 8%(12/155) |
| 2 | ↑ | ↓ | 10%(16/155) |
| 3 | ↓ | ↓ ↑ | 12%(19/155) |

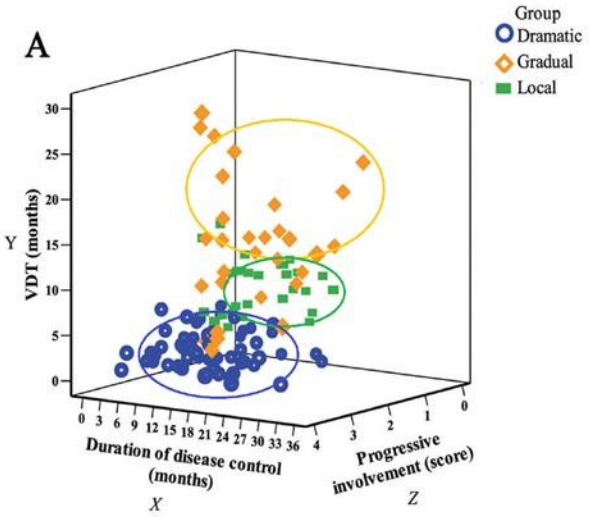



**4 months TKI therapy**

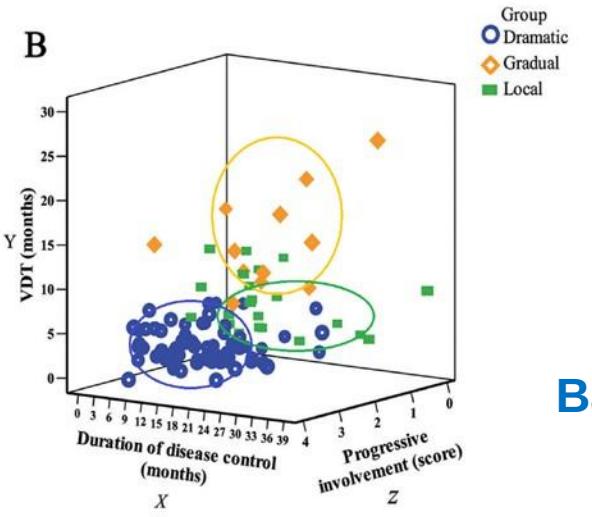



Chen, Zhong & Wu et al, Oncologist 2012

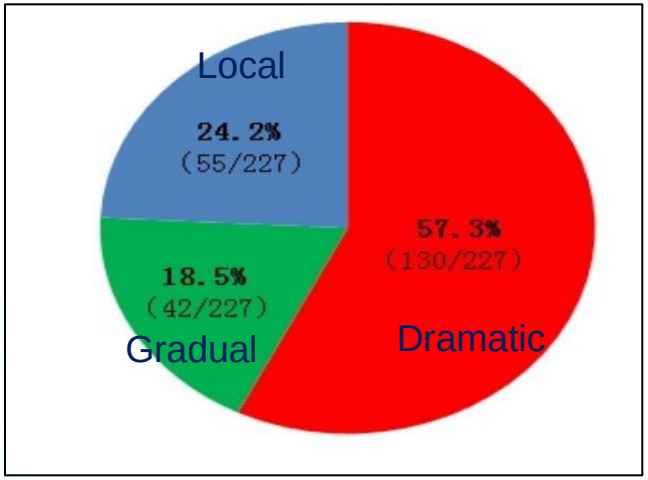
# Clinical modes of EGFR TKIs failure and management schema of EGFR mutant NSCLC




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

**Dramatic progression**
Disease control ≥3 months;
Compared with previous assessment, rapid increment of tumor burden;
Symptom deterioration.

**Gradual progression**
Disease control ≥6 months;
Compared with previous assessment, minor increment of tumor burden;
Symptom benefit.

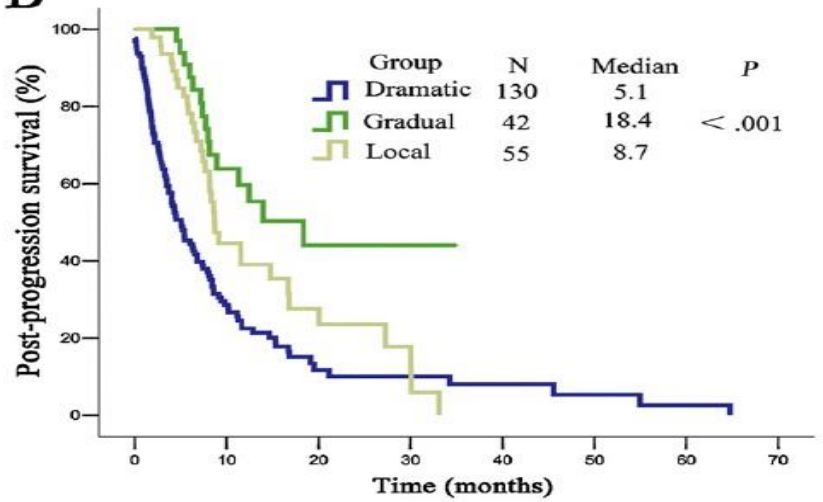
**Local progression**
Disease control ≥3 months;
Solitary extracranial progression or intracranial progression;
Symptom benefit.

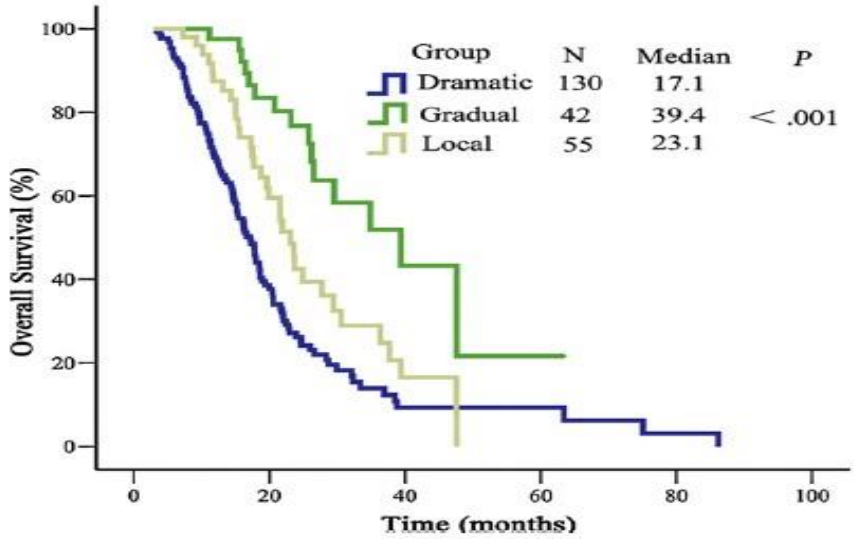
**Chemotherapy**

**Continuation of TKIs**

**Continuation of TKIs plus local intervention**

**B**




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

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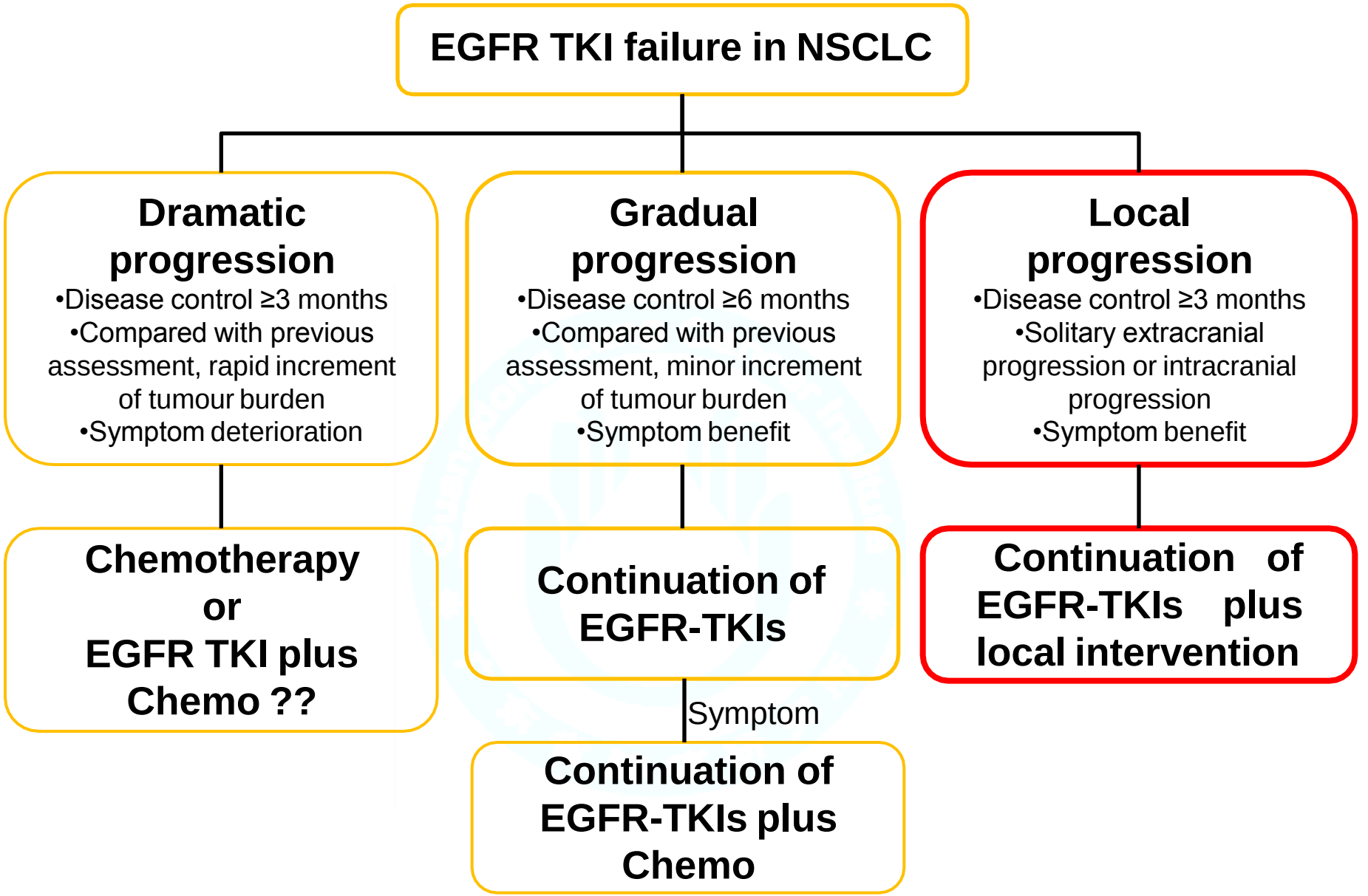





Modified fromYang et al. Lung Cancer 2013;79:33–39

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

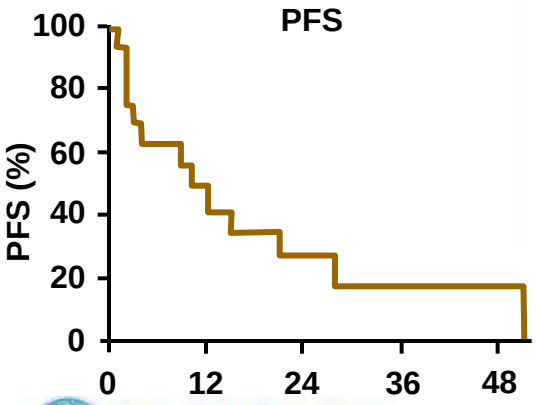
**Local Therapy with Continued EGFR Tyrosine Kinase Inhibitor Therapy as a Treatment Strategy in EGFR-Mutant Advanced Lung Cancers That Have Developed Acquired Resistance to EGFR Tyrosine Kinase Inhibitors.**

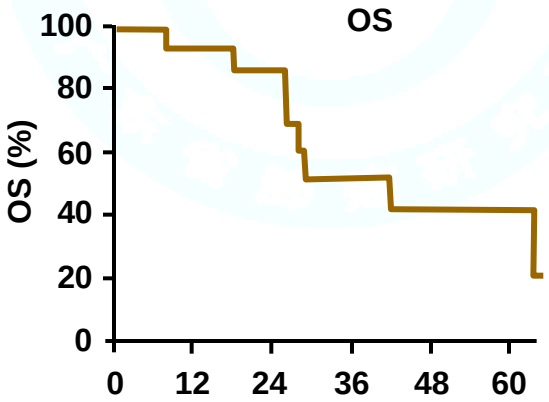
MSKCC

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.

- Among184 excranial PD (7+ y)，18 cases with EGFR M+ received local treatment
  - mTTP：10 months
  - Median to systemic treatment: 22 months
  - mOS： 41months



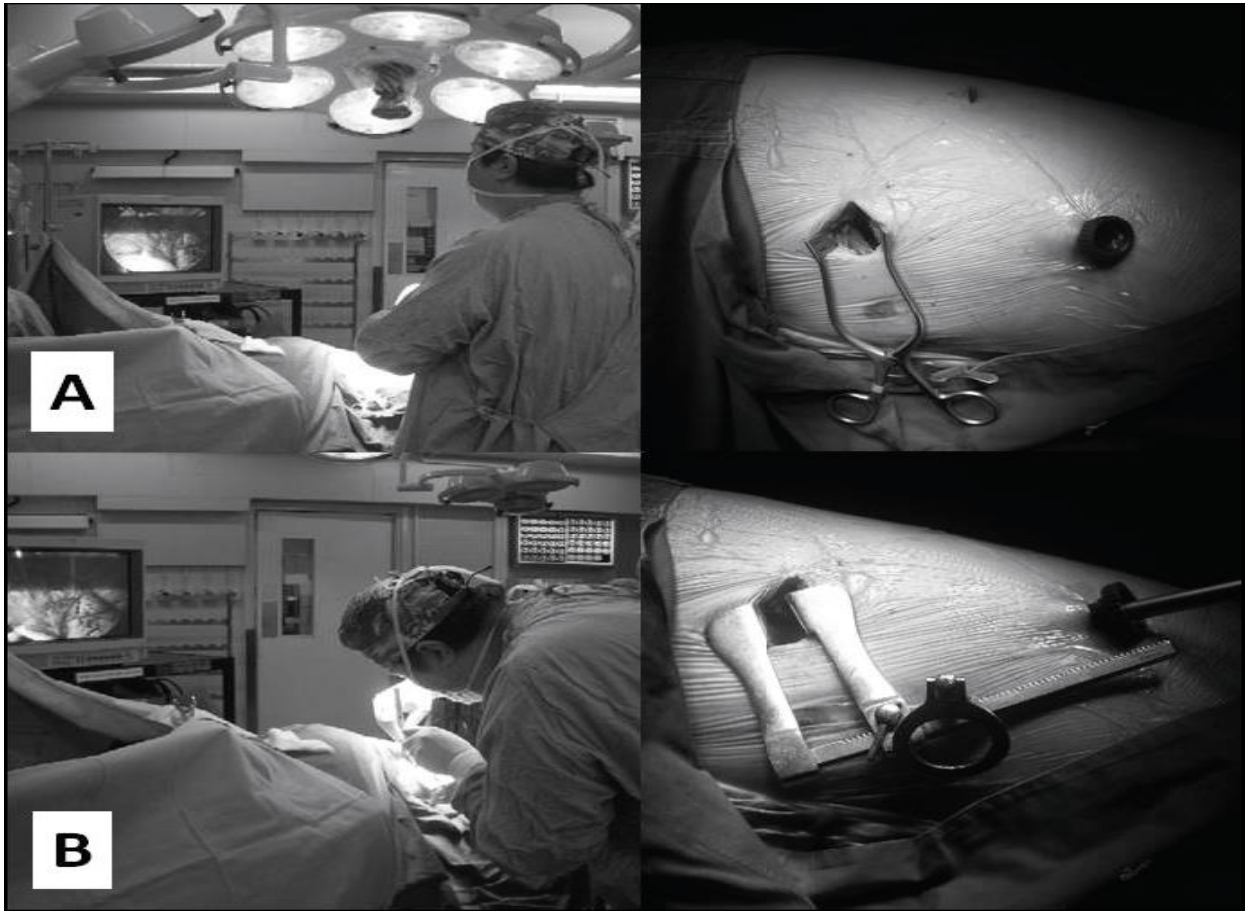

| Performed | |
|---|---|
| Total | 18 |
| Lung | 15 |
| Radiofrequency ablation | 2 |
| Stereotactic radiotherapy | 1 |
| Radiation therapy | 1 |
| Lobectomy | 7 |
| Wedge resection | 1 |
| Pneumonectomy | 3 |
| Lymph node (supraclavicular) | |
| Radiation therapy | 1 |
| Adrenal gland | |
| Adrenalectomy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

# The optimal local treatment

- Minimally invasive (or noninvasive)
- Administered quickly and efficiently
- Not have a lengthy recovery period
- Not impede delivery of other local or systemic treatment
- Have a high rate of local control

Folkert et al. Clin Adv Hematol Oncol 2015

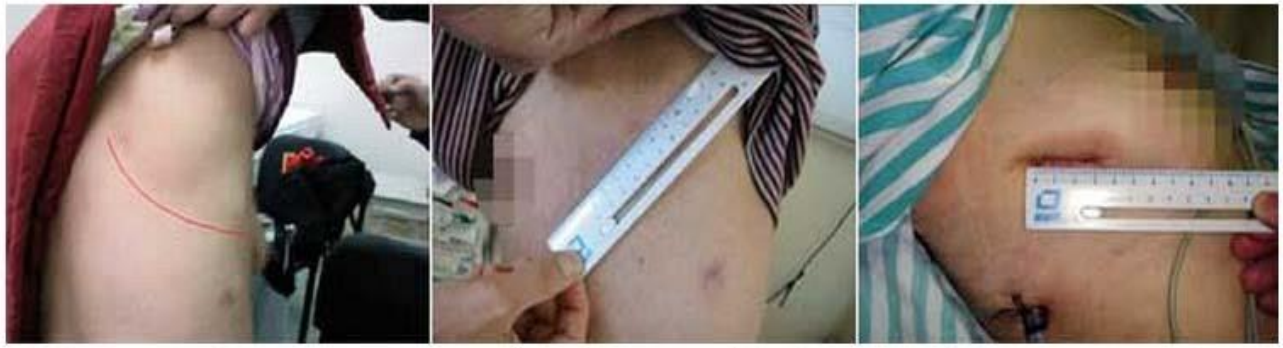
# Thoracic surgery technique improved



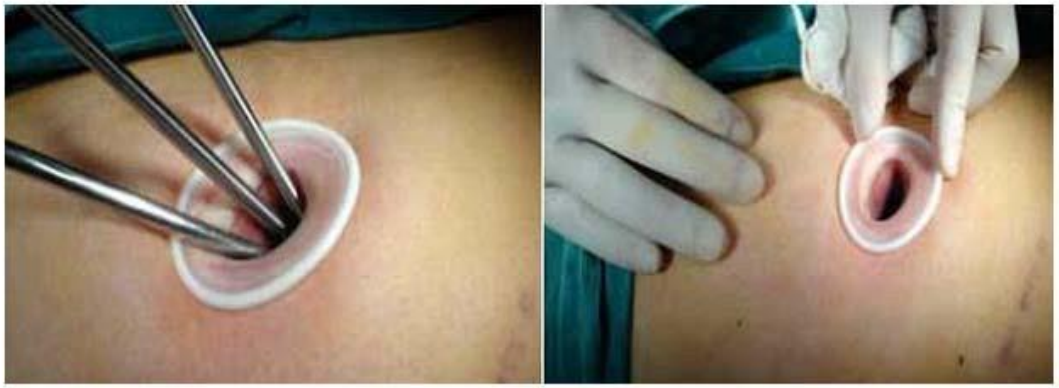

complete VATS

assist VATS

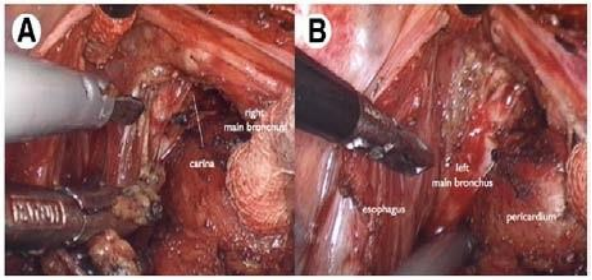
# The minimal thoracic surgery – Single port lobectomy



分别是传统的后外侧大切口（红线轨迹），保留胸肌切口，单操作口（切口大小由20-30cm减少到3-4cm）



单孔胸腔镜手术：只需要3cm左右的切口完成肺癌根治术



# Key concepts for treating patients with oligometastatic NSCLC

Multi-disciplinary treatment

Intervention should be minimally invasive

Treatment strategies for primary lung tumour and metastatic disease

# Conclusions

- There is a subtype of stage IV NSCLC patients with oligometastatic or oligorecurrence NSCLC that could achieve long-term survival following aggressive treatment
- Prognostic factors can identify patients most likely to benefit from local therapy
- A multidisciplinary approach is needed to treat oligometastatic or oligorecurrence NSCLC

# Remaining challenges and future directions

- How to define slowly or indolent progression of oligometastases or oligorecurrence?
  - Molecular characteristic analysis
  - Advancing imaging technique
- What is the best choice of local treatment?
  - Limited clinical data – RCT or perspective study?
  - Individual treatment based on ……
- What is the best strategy of multidisciplinary treatment.

## HARMONIOUS FAMILY
相亲相爱的一家人 >>


# Thank you!