浙江省人民医院
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杭州医学院附属人民医院
PEOPLE'S HOSPITAL OF HANGZHOU MEDICAL COLLEGE

仁爱 | 卓越 | 奉献 | 创新






晚期肺癌寡转移、寡进展的放疗

肿瘤中心放疗科 梁晓东

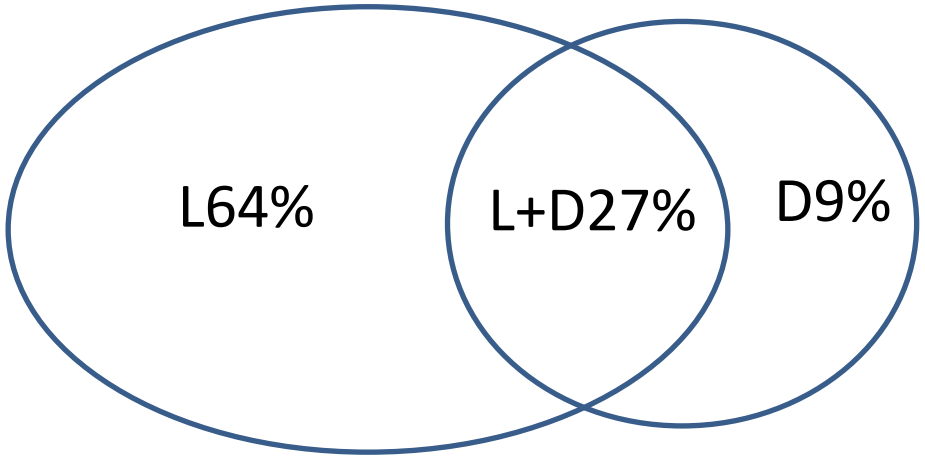
一、晚期肺癌化疗/TKI/免疫治疗的失败模式

晚期NSCLC化疗后失败模式

Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis

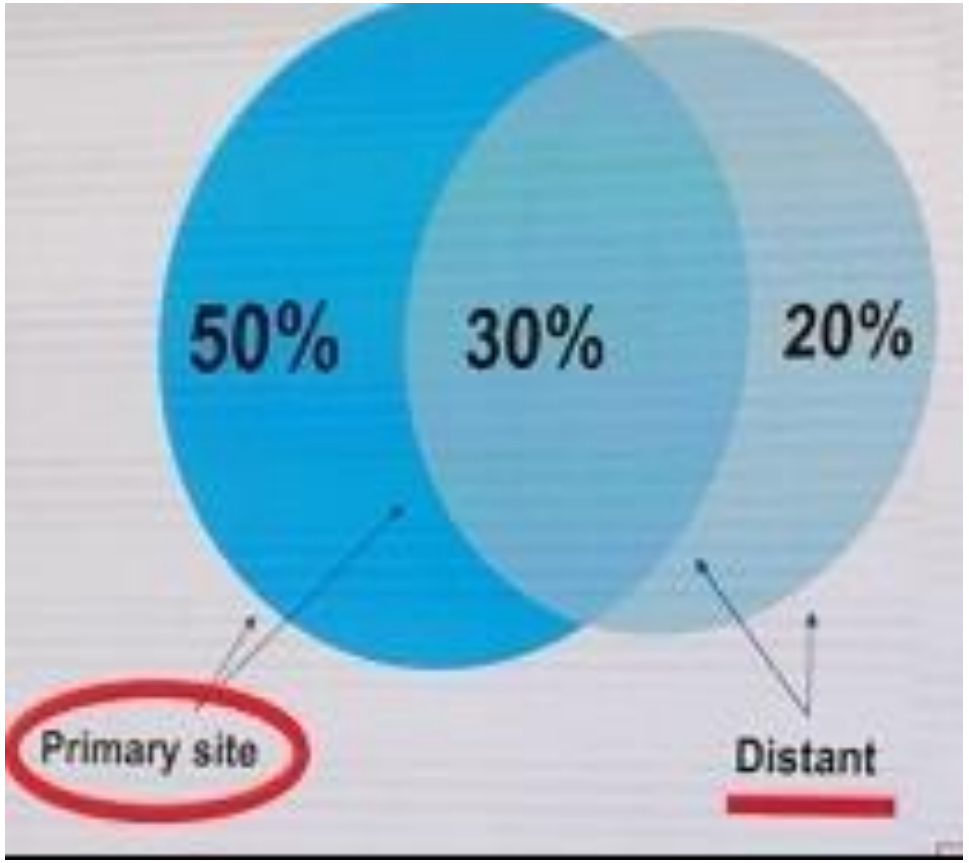
Acta Oncologica, 2009

L只有初始病灶局部进展
D只有新发远处转移
L+D两者同时存在



初始病灶SBRT有助于提高疗效

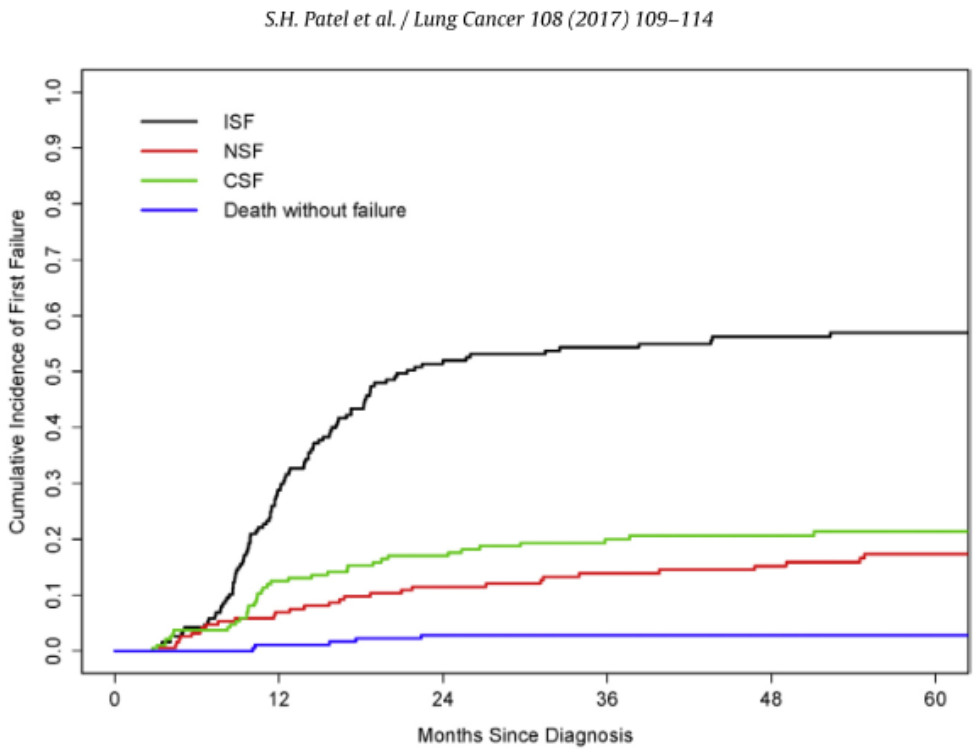
晚期NSCLC系统治疗后的失败模式



寡进展:15-45%

2018 ELCC

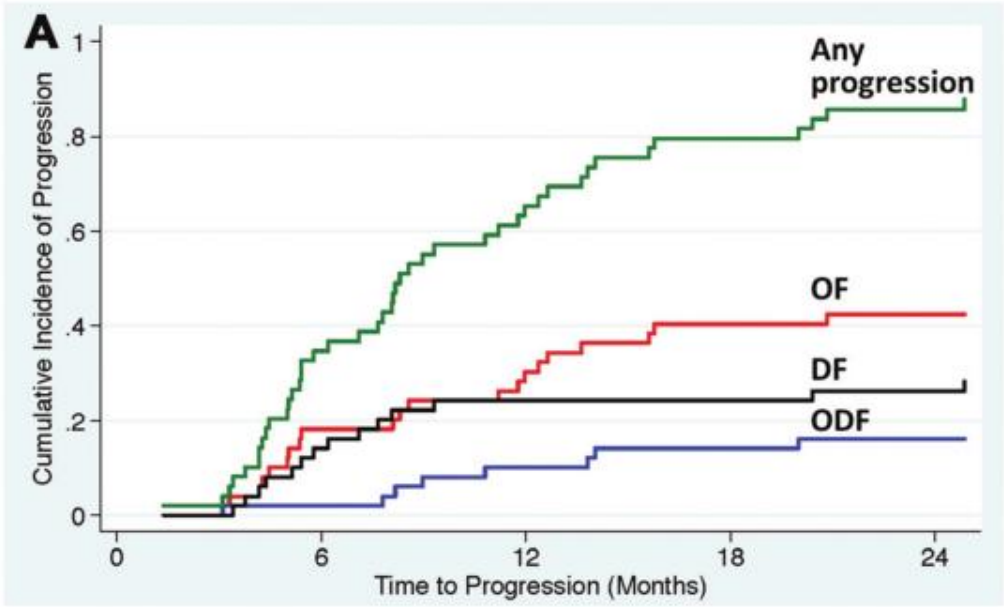
1代TKI



超过50%单独初始部位进展

1-2代TKI

J Thorac Oncol. 2015



单独初始部位进展47.0%
单独远转20.4%
联合失败32.6%

3代TKI（泰瑞莎）

Lung Cancer 2019 149–155

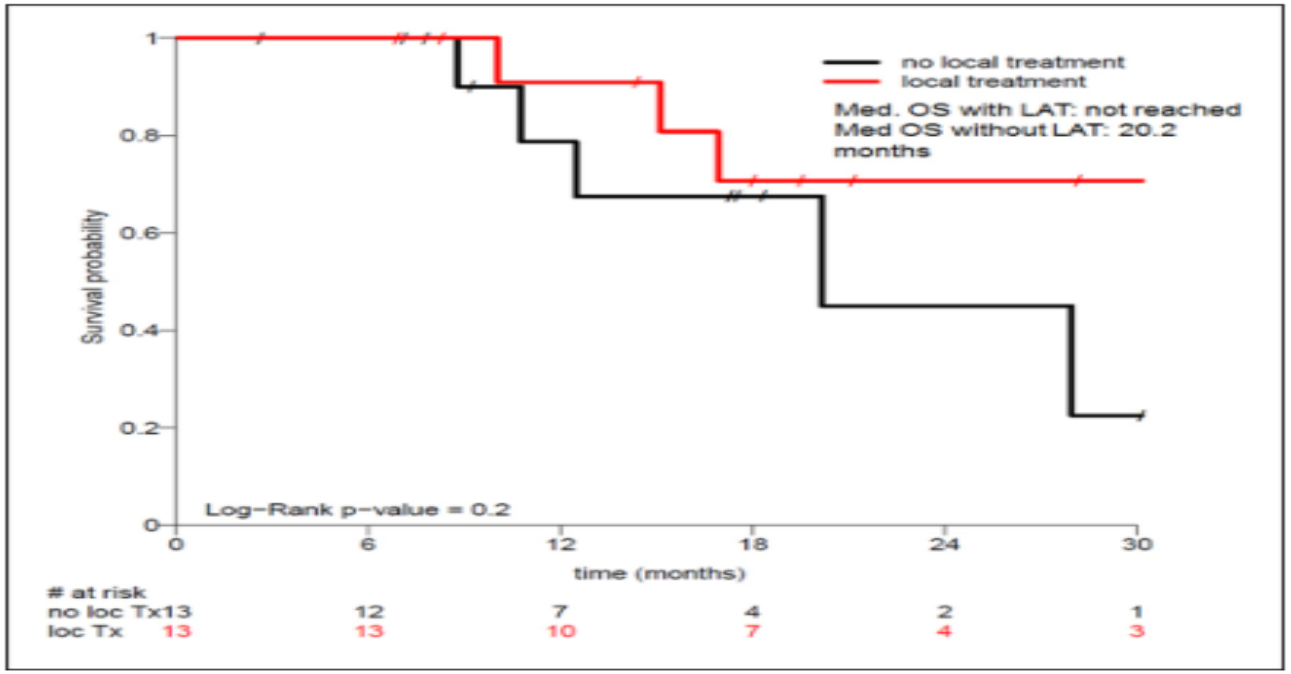


Fig. 2. OS in oligo-PD with/without LAT.

泰瑞莎治疗后进展的患者中73%为寡进展
局部治疗潜在获益更大

免疫治疗获得性耐药

Oncotarget 2018

Clinical and molecular features of innate and acquired resistance to anti-PD-1/PD-L1 therapy in lung cancer

33例患者获得性耐药
20例（60.6%）原有部位进展
22例（66.7%）进展患者为孤立部位进展

Acquired resistance to PD-1 blockade in NSCLC

Memorial Sloan Kettering Cancer Center

Adam J. Schoenfeld, Hira Rizvi, Danish Memon, Jia Luo, Isabel R. Preeshagul, Jennifer L. Sauter, Andrew J. Plodkowski, Chad Vanderbilt, Martin L. Miller, Matthew D. Hellmann

Memorial Sloan Kettering Cancer Center, New York, NY, USA

Abstract # 9621

Background

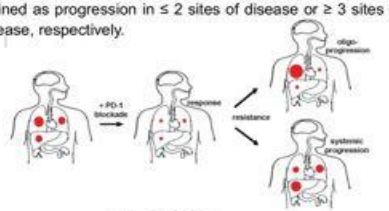
- Although durability is the trademark characteristic of response to PD-1 blockade, acquired resistance can occur.
- The frequency, patterns, and survival outcomes of patients with acquired resistance to PD-1 blockade in NSCLC are not well established.

Objectives

- To explore patterns and outcomes of patients with acquired resistance to PD-1 blockade in NSCLC.

Methods

- All patients with NSCLC treated with PD-1 blockade at MSKCC were examined.
- Acquired resistance was defined as initial CR/PR (by RECIST) followed by progression/death.
- Oligo vs systemic patterns of acquired resistance were defined as progression in ≤ 2 sites of disease or ≥ 3 sites of disease, respectively.



Results

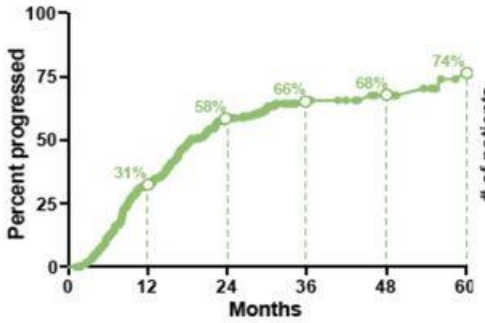
Sites of Disease	Baseline of responders	Oligo-progression	Systemic Progression
Lung	52 (63%)	27 (34%)	27 (69%)
Lymph node	45 (54%)	28 (35%)	30 (77%)
Pleura	34 (41%)	0 (0%)	6 (15%)
Adrenal gland	17 (20%)	12 (15%)	7 (18%)
Liver	18 (22%)	6 (8%)	3 (8%)
Bone	25 (30%)	6 (8%)	14 (36%)
Brain	8 (10%)	5 (6%)	0 (0%)
Other	22 (27%)	2 (3%)	5 (13%)

Distribution of disease sites and pattern of progression

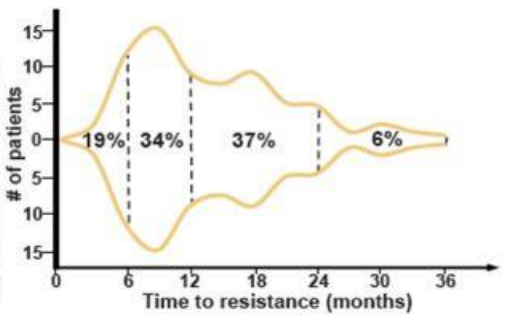
Results

Timing of Acquired Resistance After Initial Response

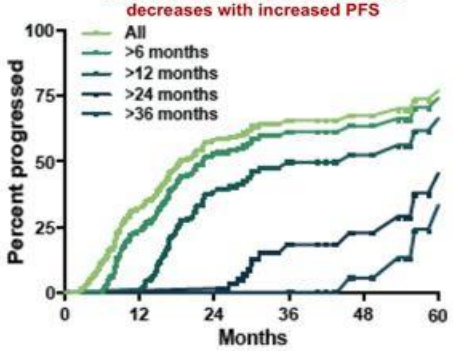
74% of patients with initial response will develop acquired resistance at 5 years



Rate of acquired resistance varies over time

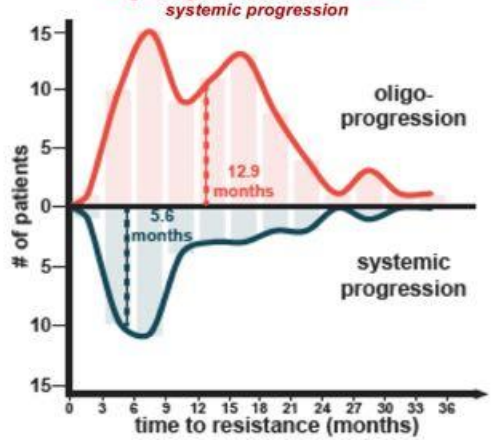


Actuarial rate of acquired resistance decreases with increased PFS

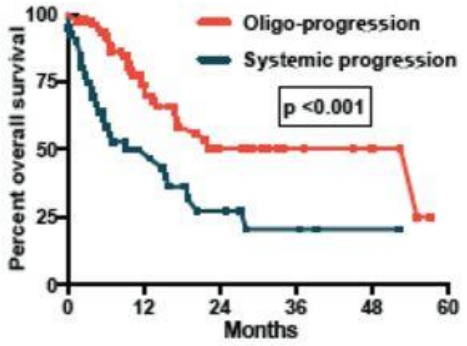


Systemic vs Oligo-progression After Initial Response and Outcomes by Therapy

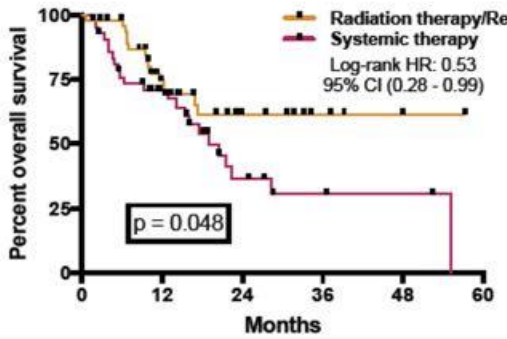
Oligo-progression occurs later than systemic progression



Patients with oligo-progression have improved post-progression OS

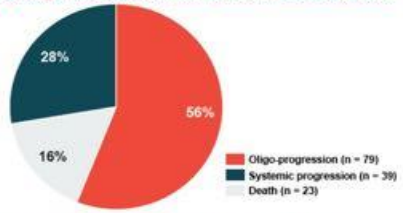


Patients treated with locally directed therapy have improved OS

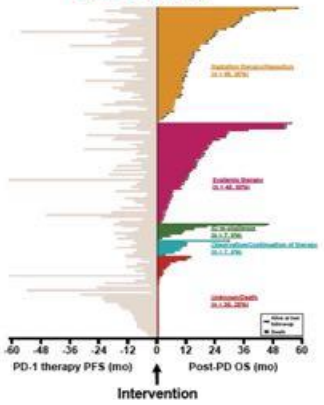


Results

Oligo-progression is common after initial response



PFS on PD-1 therapy and OS post PD-1 by type of therapy



Conclusions

- Acquired resistance to PD-1 blockade is common in NSCLC.
- Risk of acquired resistance is lower in biomarker-enriched patients and with increased duration of response.
- Patterns of acquired resistance is commonly oligo in nature, which is amenable to locally-directed therapy and can be associated with improved survival.
- Differences in organ-site distribution and post-progression survival suggest distinct biology associated with acquired resistance.

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Acquired resistance to PD-1 blockade in NSCLC

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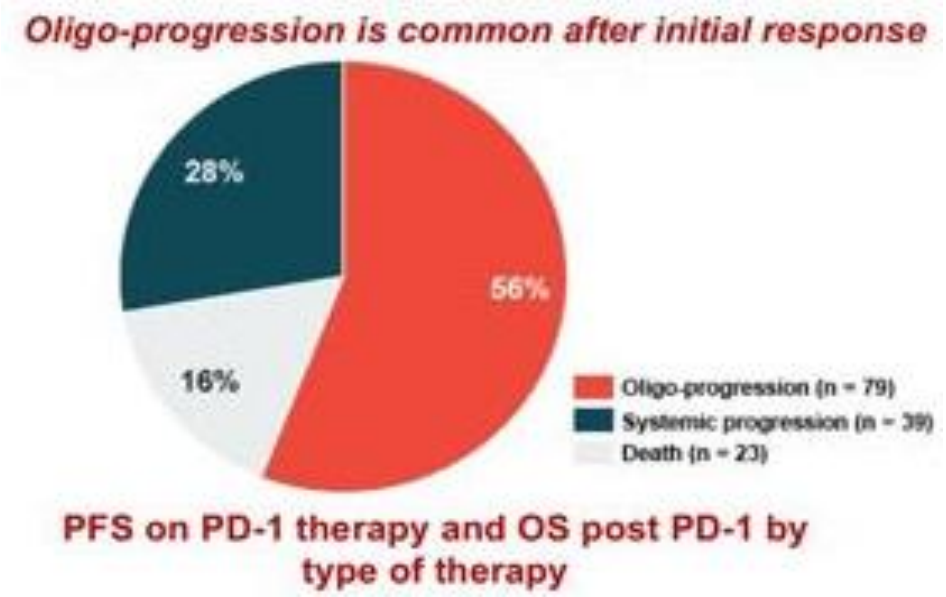
ASCO 2020 **Abstract # 9621**



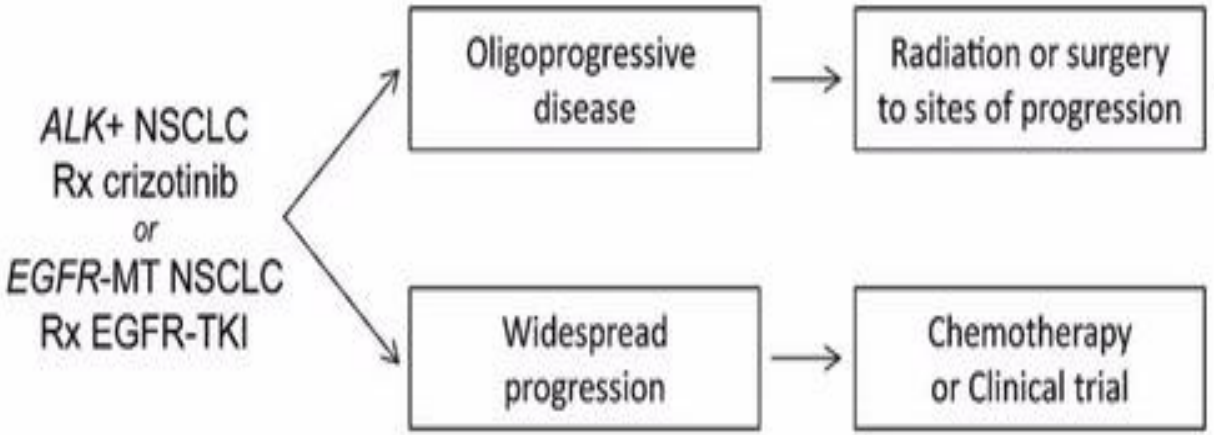
免疫治疗后进展的患者56%为寡进展（≤2个部位）

二、NSCLC寡进展的放疗

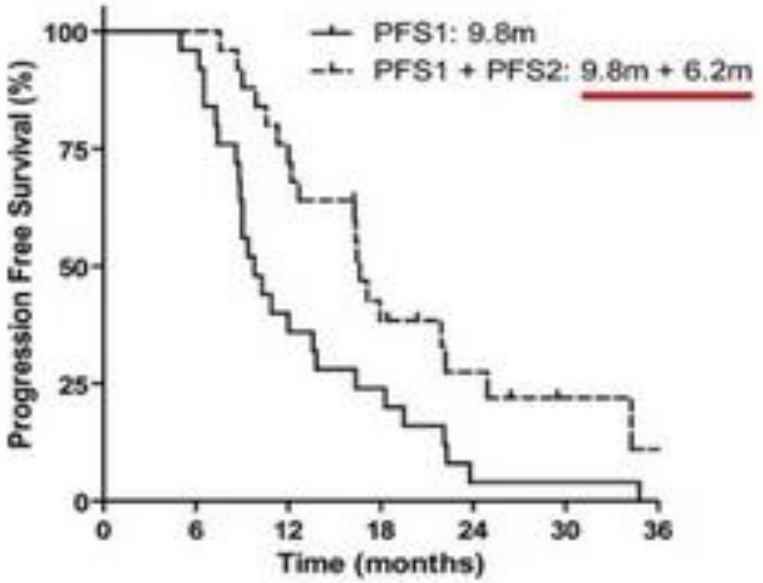
Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene addicted non-small cell lung cancer

JTO 2012

Proposed schema of therapy



(A) PFS of all patients treated with LAT and continuation of TKI therapy



EGFR敏感突变寡进展

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

J Thorac Oncol. 2013

EGFR敏感突变寡进展

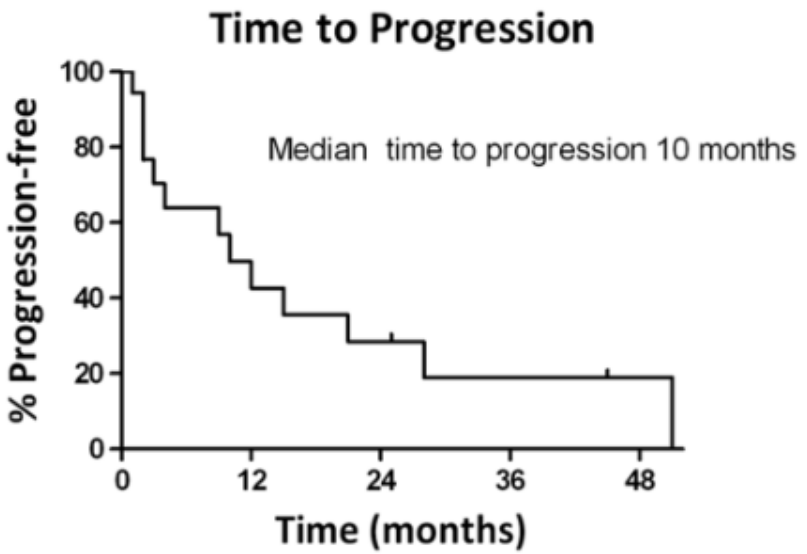


FIGURE 1. Time to progression after local therapy.

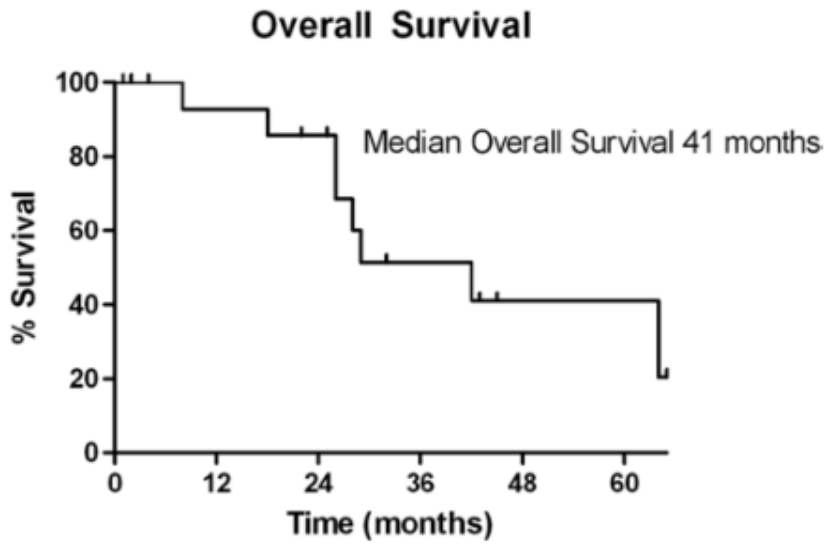


FIGURE 2. Overall survival after local therapy

TKI治疗后寡进展的患者局部治疗MST可达41月

Memorial Sloan Kettering Cancer Center

Acquired resistance to PD-1 blockade in NSCLC

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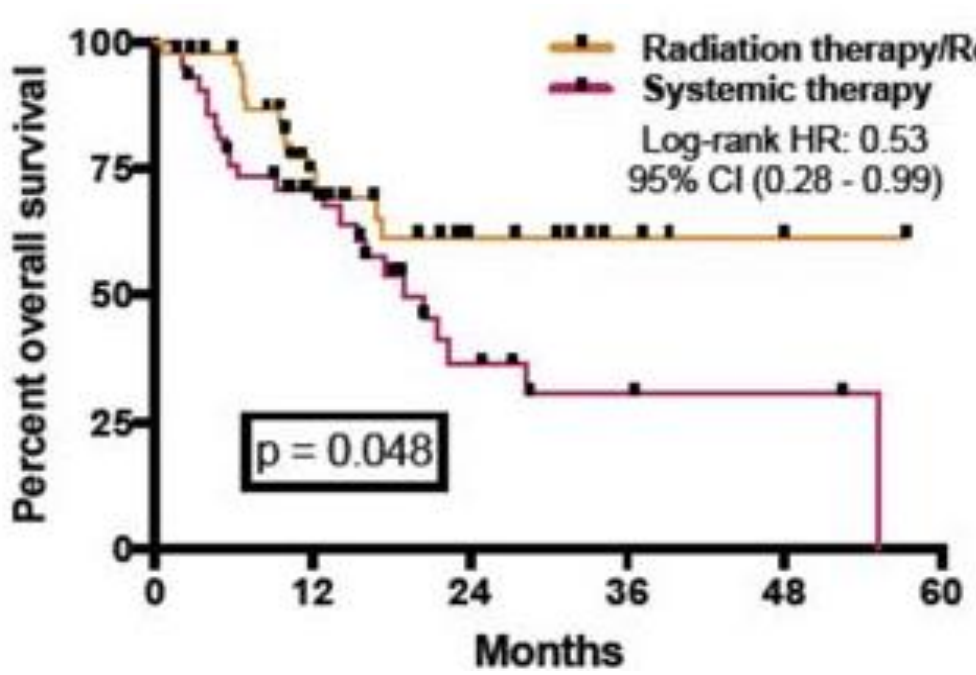

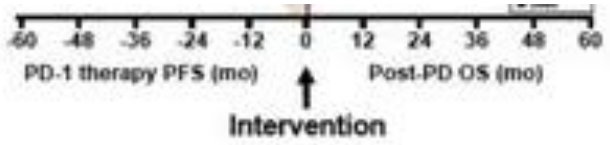

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- Differences in organ-site distribution and post-progression survival suggest distinct biology associated with acquired resistance.

免疫治疗后寡进展的患者局部治疗可改善OS

三、寡转移NSCLC放疗与药物的联合

OMD（oligometastatic disease）

All lesions should be amenable to radical intent treatment with acceptable toxicity

三、寡转移NSCLC放疗与药物的联合

3.1 免疫治疗

JAMA Oncology | Original Investigation

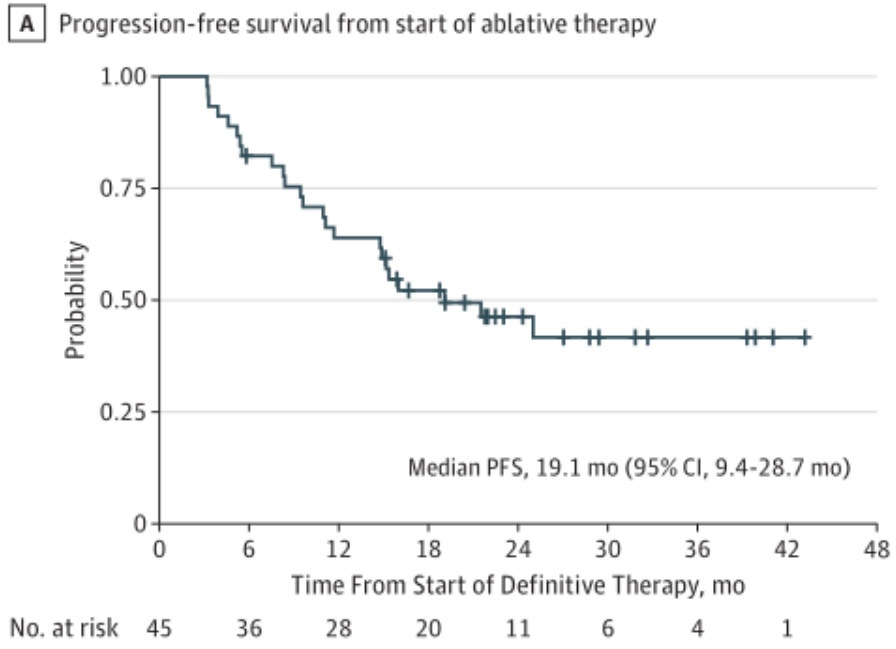
Pembrolizumab After Completion of Locally Ablative Therapy for Oligometastatic Non–Small Cell Lung Cancer A Phase 2 Trial

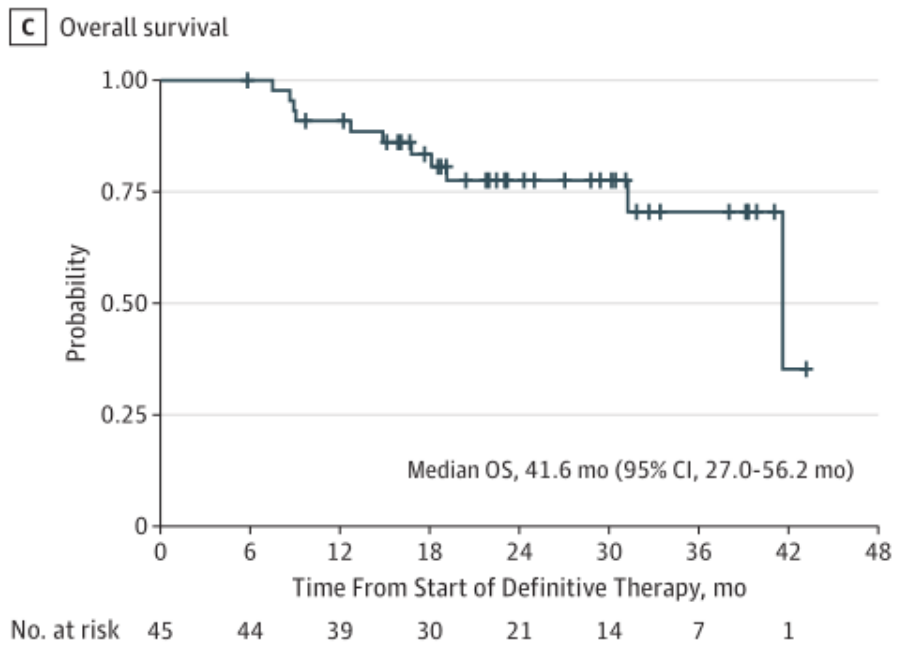
JAMA Oncol 2019

Bauml研究

oligometastatic NSCLC (≤4metastatic sites)

LAT including surgery, chemoradiotherapy, stereotactic radiotherapy





寡转移NSCLC局部治疗后K药维持治疗MST达41.6m

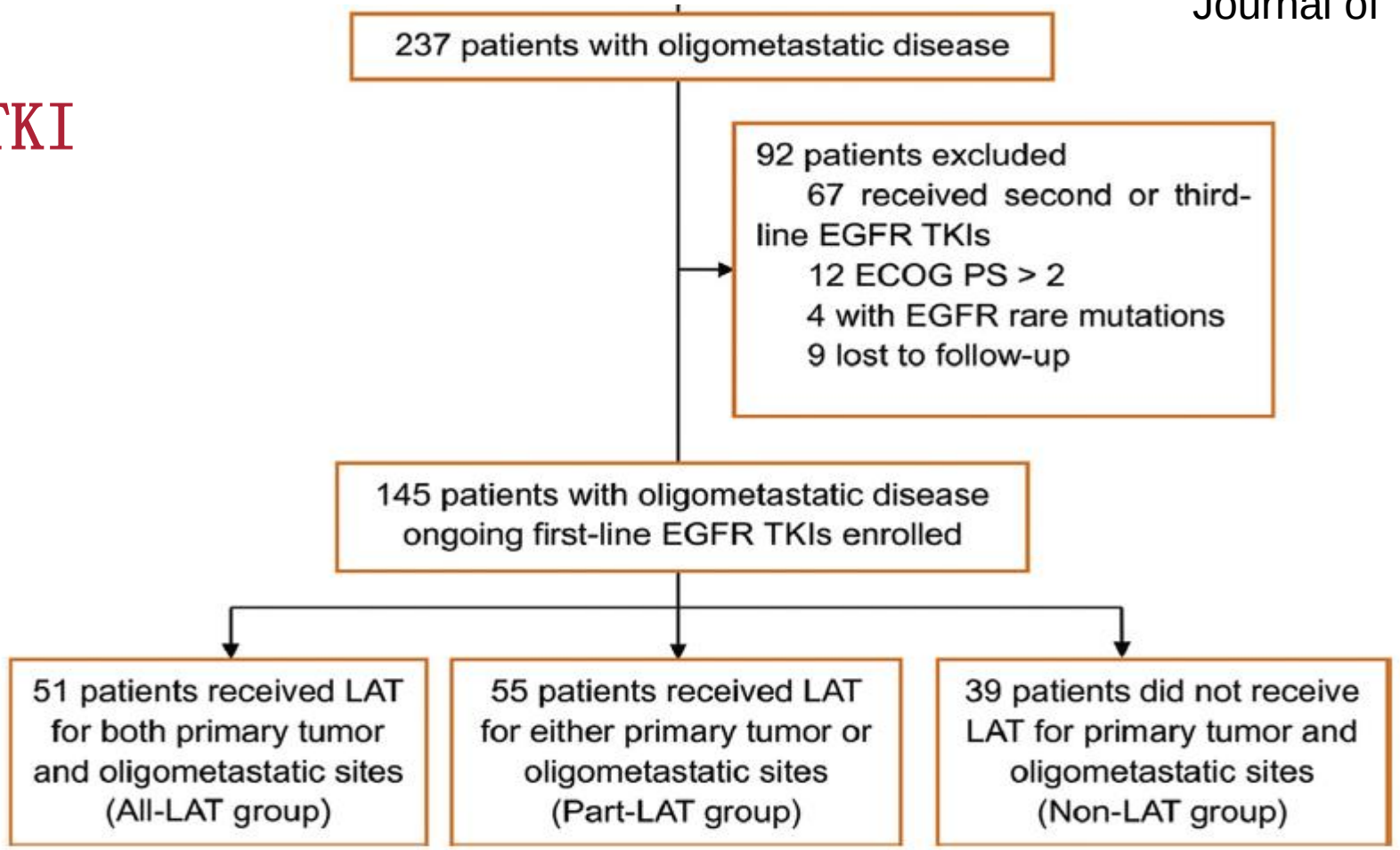
三、寡转移NSCLC放疗与药物的联合

3.2 靶向治疗

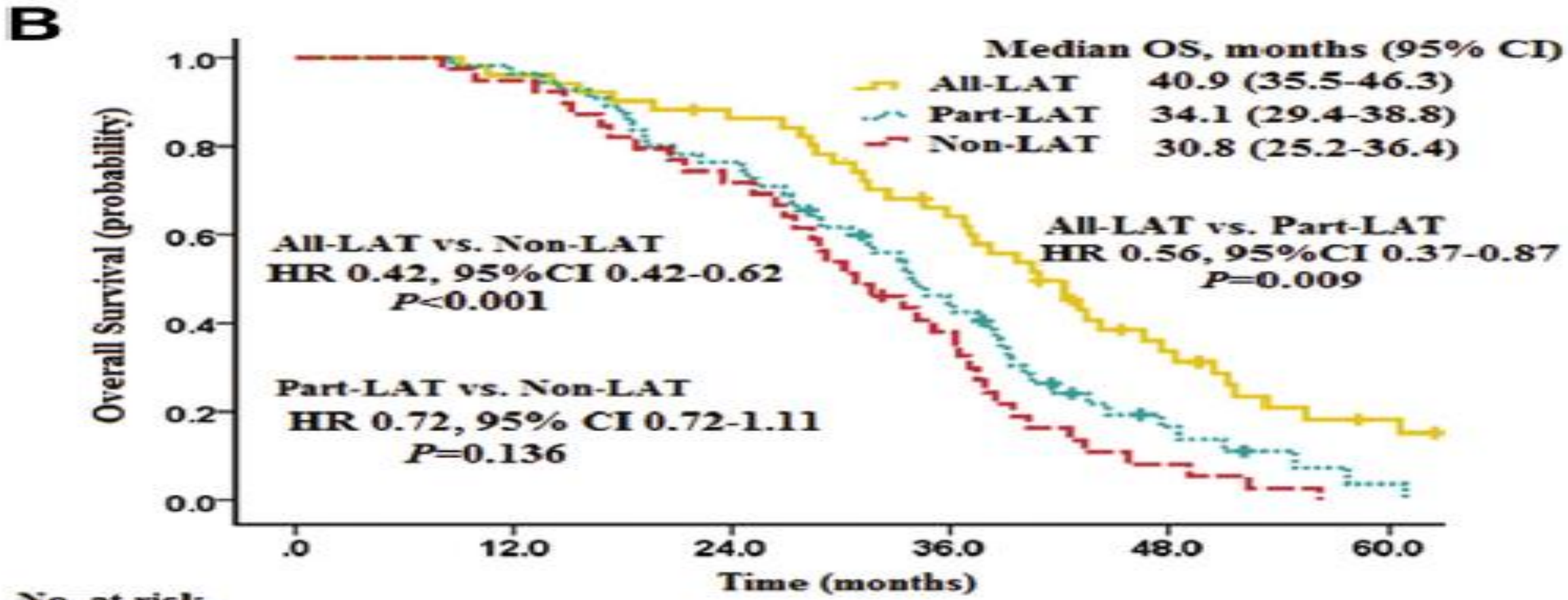
Consolidative Local Ablative Therapy Improves the Survival of Patients With Synchronous Oligometastatic NSCLC Harboring EGFR Activating Mutation Treated With First-Line EGFR-TKIs

Journal of Thoracic Oncology 2018

寡转移+TKI



原发灶和转移灶均放疗的患者OS显著延长



No. at risk						
All-LAT	51	49	43	31	14	6
Part-LAT	55	53	40	23	6	1
Non-LAT	39	37	28	14	3	0

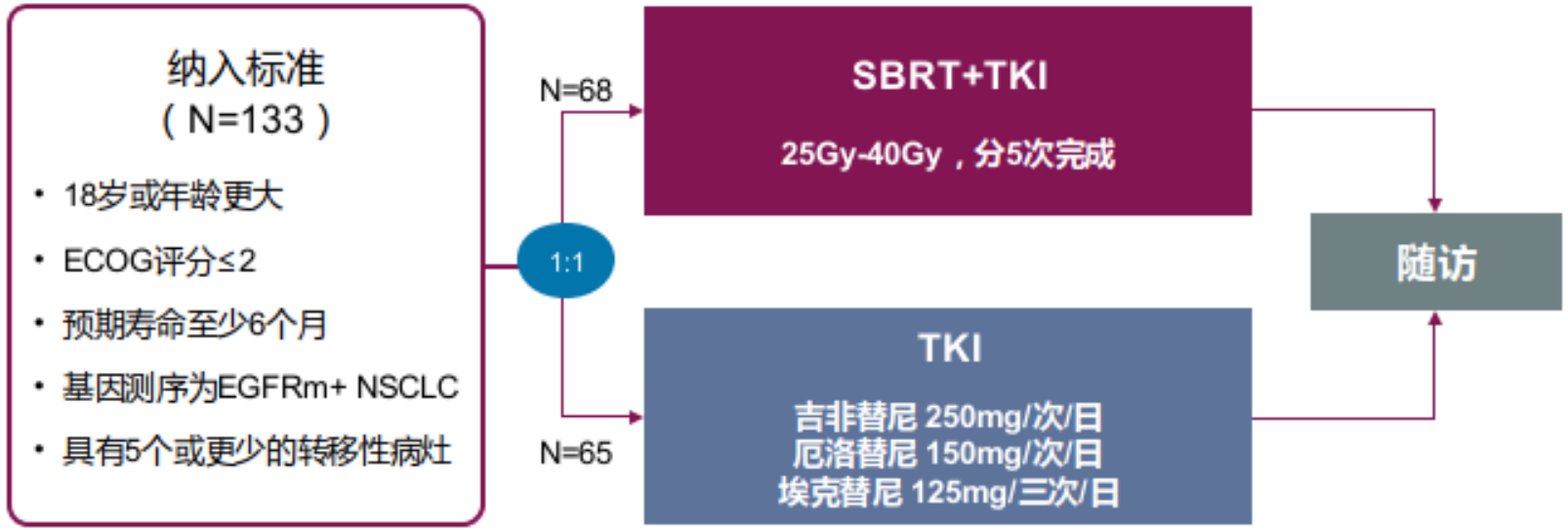
联合局部治疗死亡风险降低一半以上

Table 4. Univariable and Multivariable Analysis of Covariables Associated With OS

	Univariable Analysis			Multivariable Analysis		
Variable	HR	95% CI	*p*	HR	95% CI	*p*
Age						
<65 vs. ≥65	0.83	0.58-1.19	0.30			
Gender						
Male vs. Female	1.58	1.11-2.25	0.011	0.97	0.62-1.51	0.899
ECOG performance status						
0-1 vs. 2	0.77	0.57-1-1.15	0.20	0.91	0.59-1.40	0.676
Histology						
Adenocarcinoma vs. nonadenocarcinoma	0.49	0.31-0.76	0.001	0.46	0.29-0.73	0.001
Smoking status						
Nonsmoker vs. current or former smoker	0.66	0.46-0.94	0.021	0.60	0.37-0.96	0.034
T stage						
T1-2 vs. T3-4	0.90	0.63-1.28	0.554			
N stage						
N0-1 vs. N2-3	0.68	0.48-0.97	0.031	0.66	0.45-0.95	0.027
EGFR mutation						
Exon 19 deletion vs. Exon 21 L858R	0.52	0.36-0.74	<0.001	0.50	0.34-0.74	<0.001
Metastases number						
1 vs. >1	0.56	0.39-0.80	0.002	0.51	0.35-0.76	0.001
LAT for primary tumor						
Yes vs. No	0.49	0.34-0.70	<0.001	0.45	0.30-0.66	<0.001
Subsequent treatment						
Yes vs. No	0.58	0.38-0.88	0.01	0.49	0.32-0.76	0.002

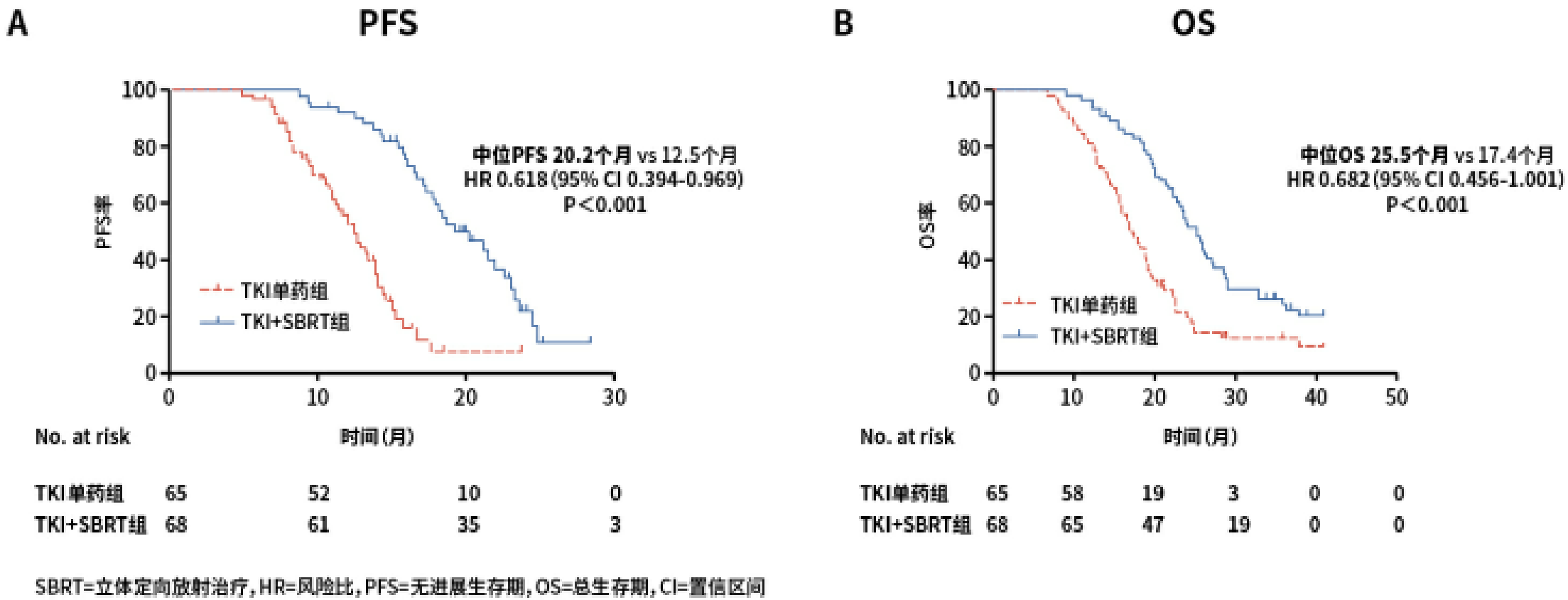
一项随机、III期、开放性临床试验（SINDAS）的中期结果：
EGFRm+寡转移NSCLC患者一线EGFR-TKI±积极早期局部放疗

First-Line Tyrosine Kinase Inhibitor With or Without Aggressive Upfront Local Radiation Therapy In Patients With EGFRm Oligometastatic Non-Small-Cell Lung Cancer:Interim Results of A Randomized Phase Ⅲ，Open-Label ClinicalTrial (SINDAS) (NCT02893332)



主要终点：PFS
次要终点：OS，安全性

TKI+放疗组显著延长中位PFS和OS



SBRT=立体定向放射治疗，HR=风险比，PFS=无进展生存期，OS=总生存期，CI=置信区间

TKI+放疗：晚期NSCLC放疗介入的时机

Lung Cancer 140 (2020) 65–70

Timing in combination with radiotherapy and patterns of disease progression in non-small cell lung cancer treated with EGFR-TKI

Yi Tang[a,b], Bing Xia[b], Xiao Xu[b], Minna Zhang[b], Kan Wu[b], Bing Wang[b], Shenglin Ma[a,b,*]

TKI有效的患者：中位起效时间2月（1.08-2.92月）
SD的患者：肿瘤最大退缩时间2月（1.42-2.58月）

TKI同时放疗 vs TKI先用2月后再行放疗

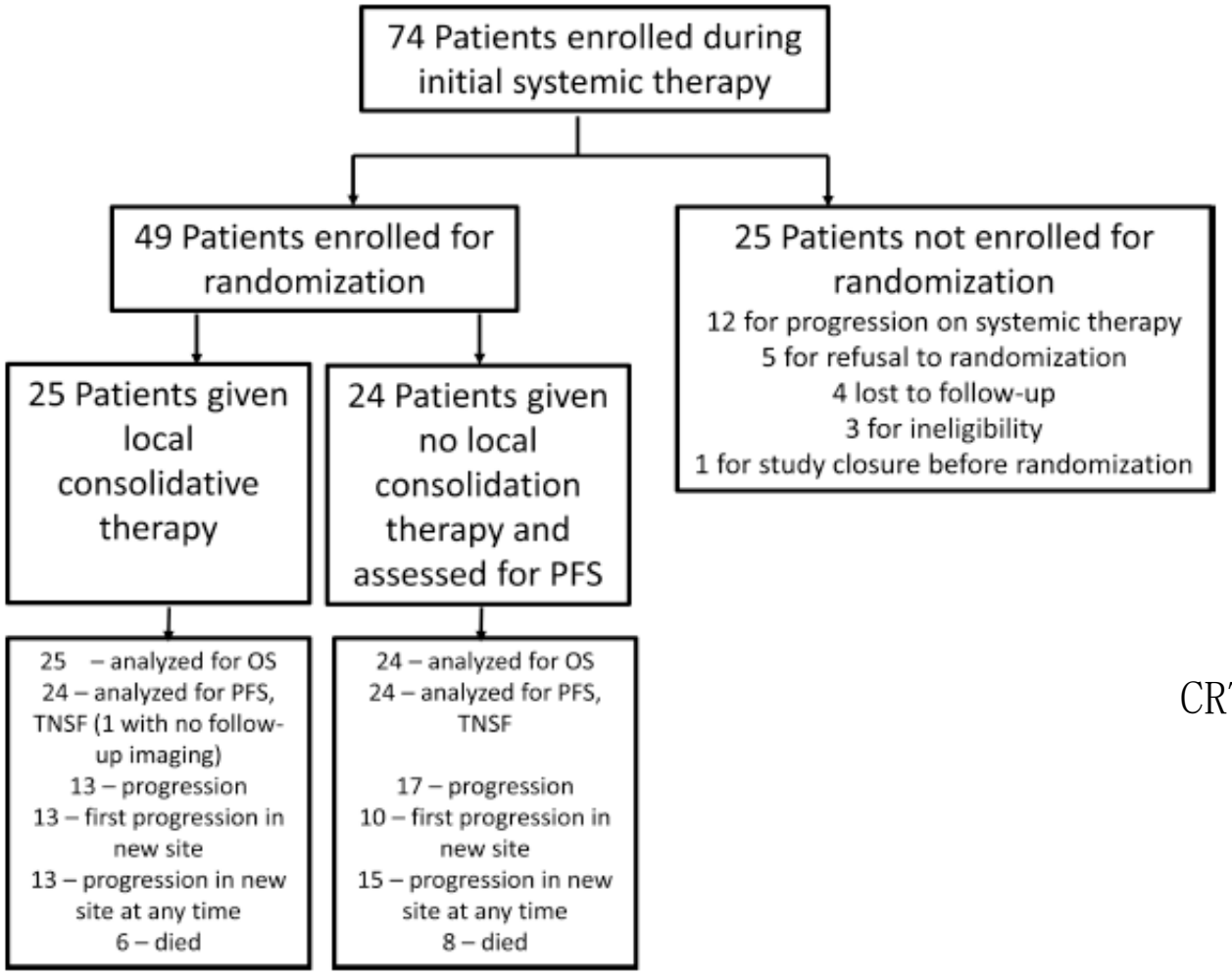
三、寡转移NSCLC放疗与药物的联合

3.3 化学治疗

Local Consolidative Therapy versus Maintenance Therapy/ Observation for Patients with Oligometastatic Non-Small Cell Lung Cancer without Progression after Front-Line Systemic Therapy: Results of a Multi-Institutional Phase II Randomized Study

Lancet Oncol. 2016

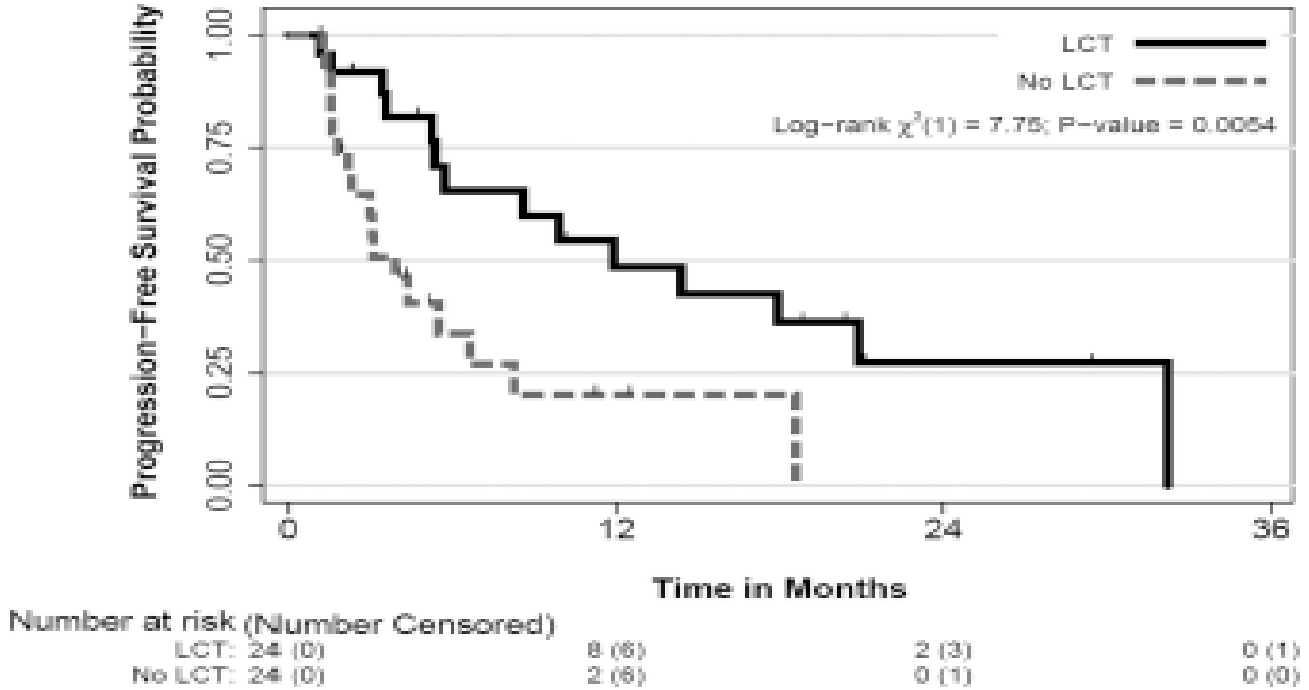
寡转移



CRT or S

结果

PFS　11.9 vs 3.9m



疗效差距显著
研究提前终止

original report

Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non–Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study

J Clin Oncol 2019

PFS 14.4 vs 4.4m

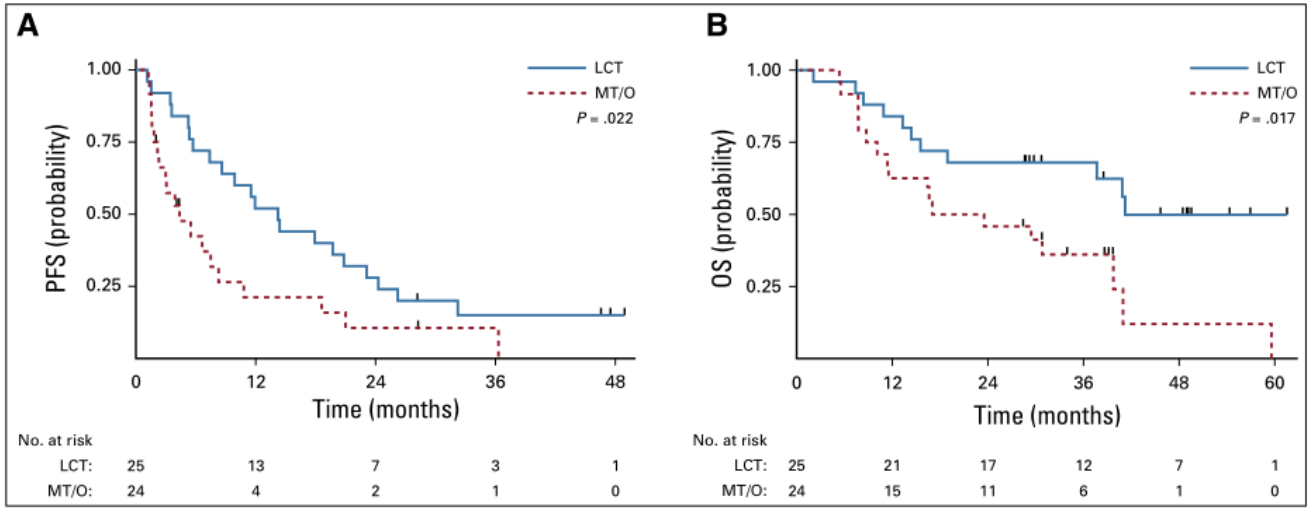


FIG 1. (A) Progression-free survival (PFS) and (B) overall survival (OS) in patients given local consolidative therapy (LCT) or maintenance therapy or observation (MT/O) for oligometastatic non–small-cell lung cancer.

OS 41.2 vs 17m

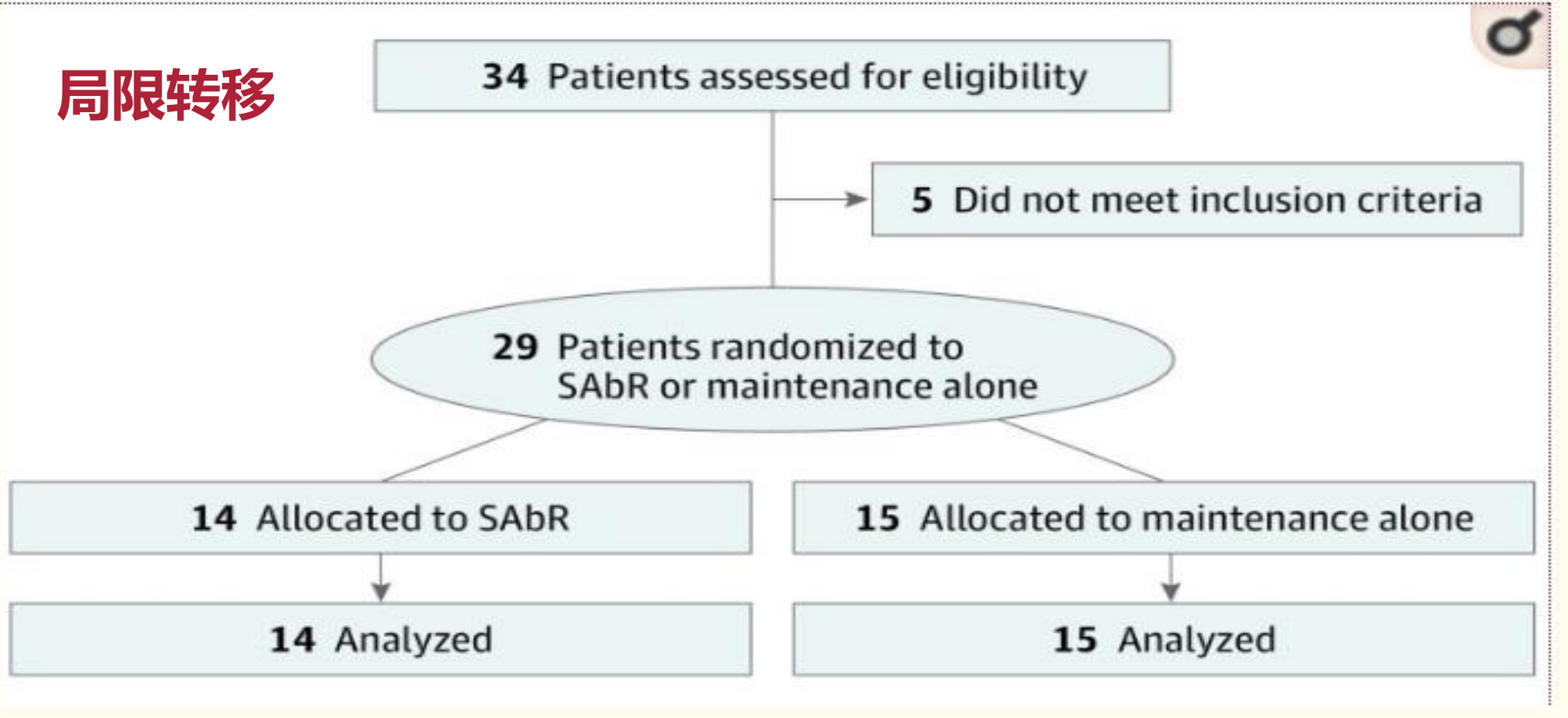
寡转移NSCLC化疗后局部治疗显著延长PFS和OS

Consolidative Radiotherapy for Limited Metastatic NSCLC

A Phase 2 Randomized Clinical Trial

JAMA Oncol. 2018

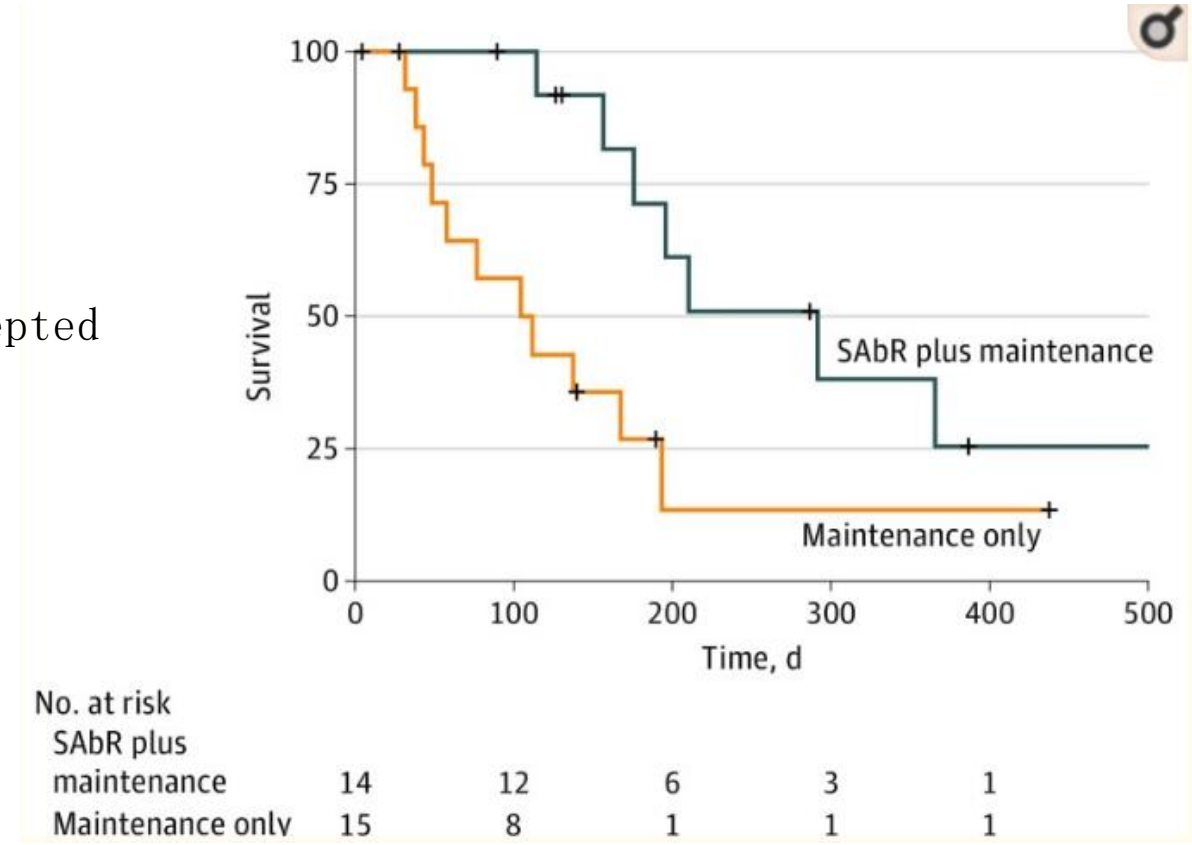
局限转移



RESULTS

PFS 9.7 vs 3.5m

45Gy/15f was accepted



疗效好研究提前终止

Curing Metastatic Disease with Radiation Therapy: Myth or Reality?—Arguing for Reality

Asal Rahimi, MD, MS, and Robert Timmerman, MD

*Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, Texas; Harold C. Simmons Comprehensive Cancer Center, Dallas, Texas

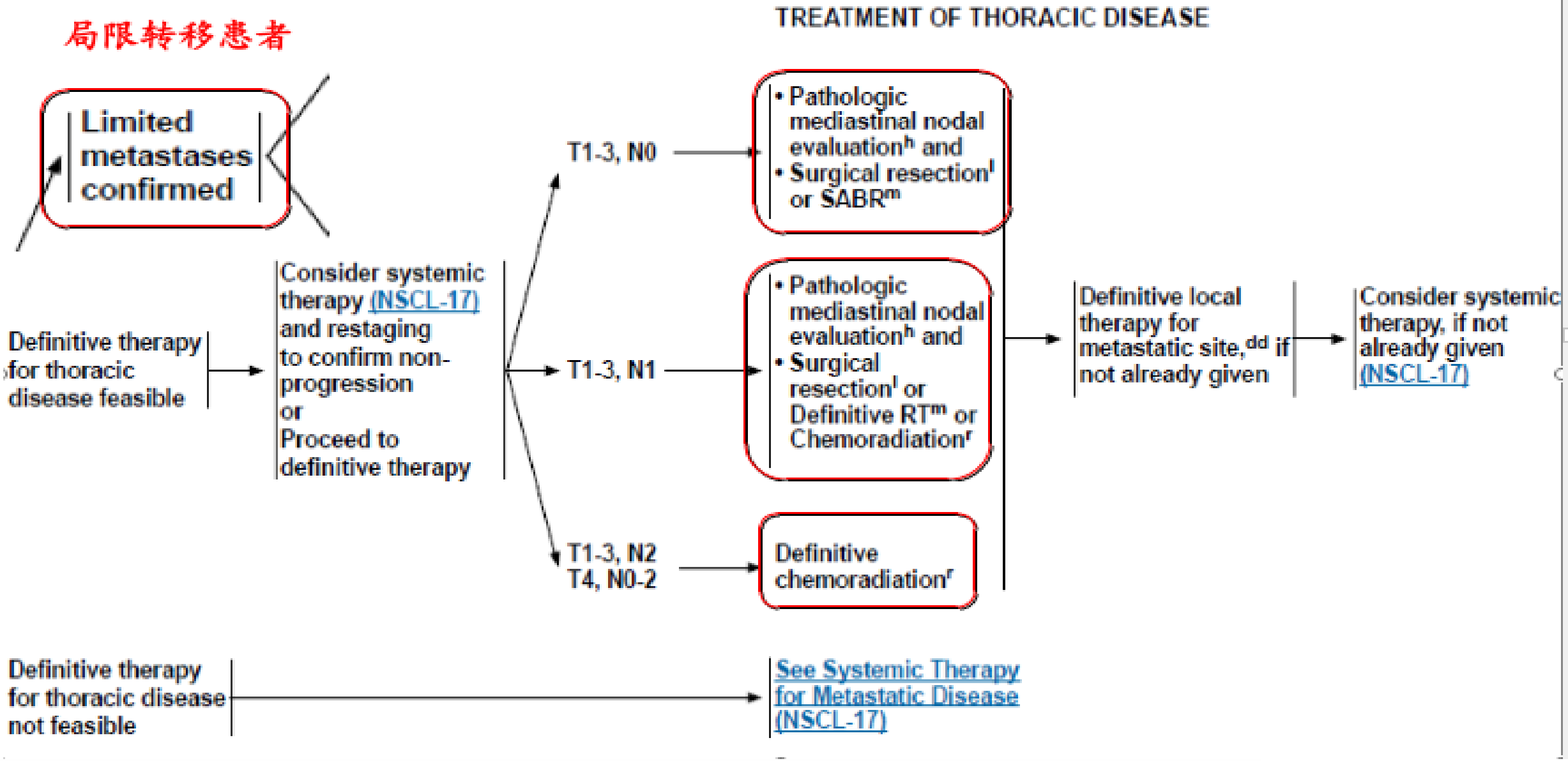
Received Jan 16, 2020. Accepted for publication Mar 11, 2020.

Can SABR cure or prolong the lives of patients with metastatic disease?

Obviously, the answer is yes

NCCN指南

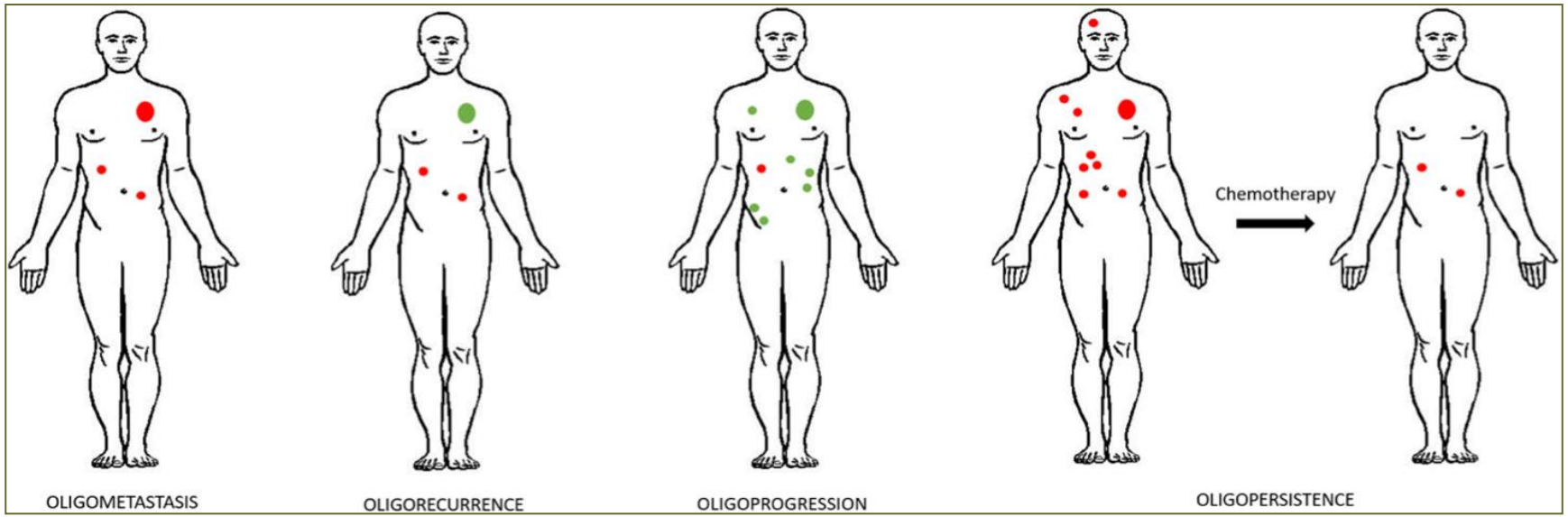
局限转移患者



EGFR 突变非小细胞肺癌的治疗

分期	分层	Ⅰ级推荐	Ⅱ级推荐	Ⅲ级推荐
Ⅳ期 EGFR 突变 NSCLC 一线治疗[a,b,c]		吉非替尼（1A 类证据）、厄洛替尼（1A 类证据）、埃克替尼（1A 类证据）、阿法替尼（1A 类证据）、达克替尼（1A 类证据）、奥希替尼（1A 类证据）[1-6]；（脑转移病灶≥3 个：EGFR-TKI 治疗（1B 类证据）[7]）	吉非替尼或厄洛替尼+化疗（PS=0~1）[9]；厄洛替尼＋贝伐珠单抗[14]；含铂双药化疗或含铂双药化疗＋贝伐珠单抗（非鳞癌）[d]	
Ⅳ期 EGFR 突变 NSCLC 耐药后治疗[e]	寡进展或 CNS 进展	继续原 EGFR-TKI 治疗+局部治疗[10]	再次活检明确耐药机制	

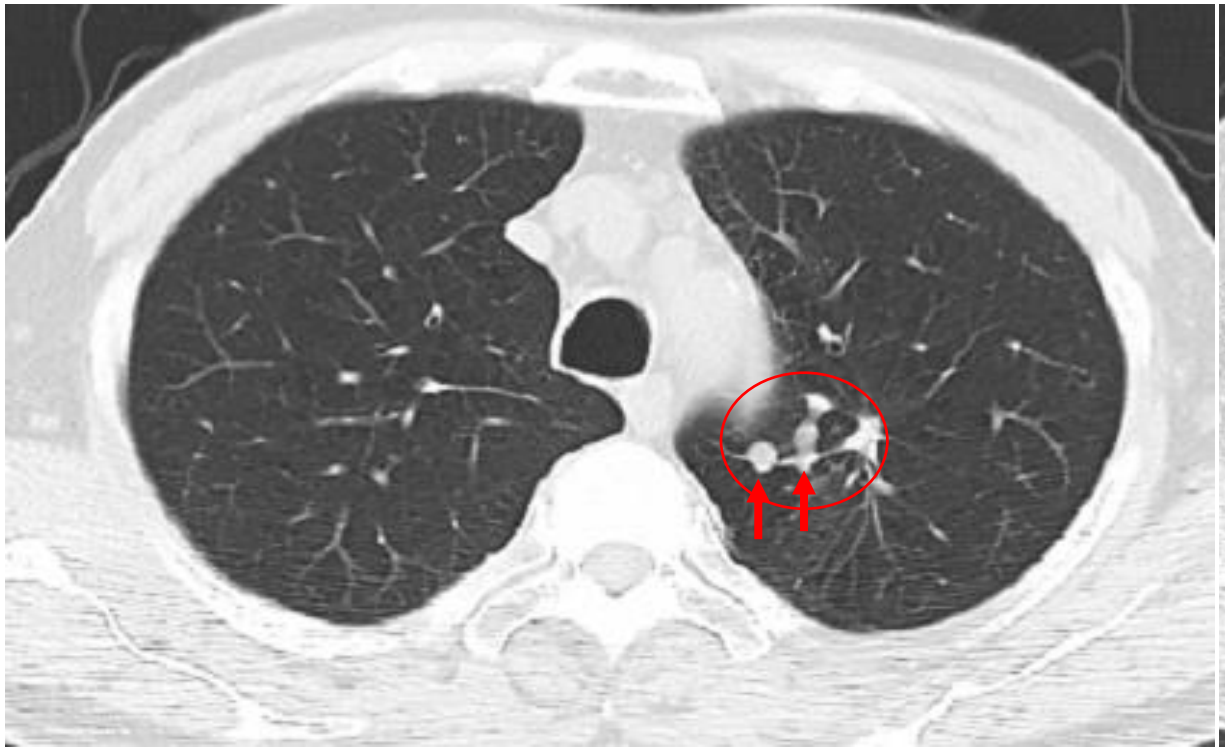
小结



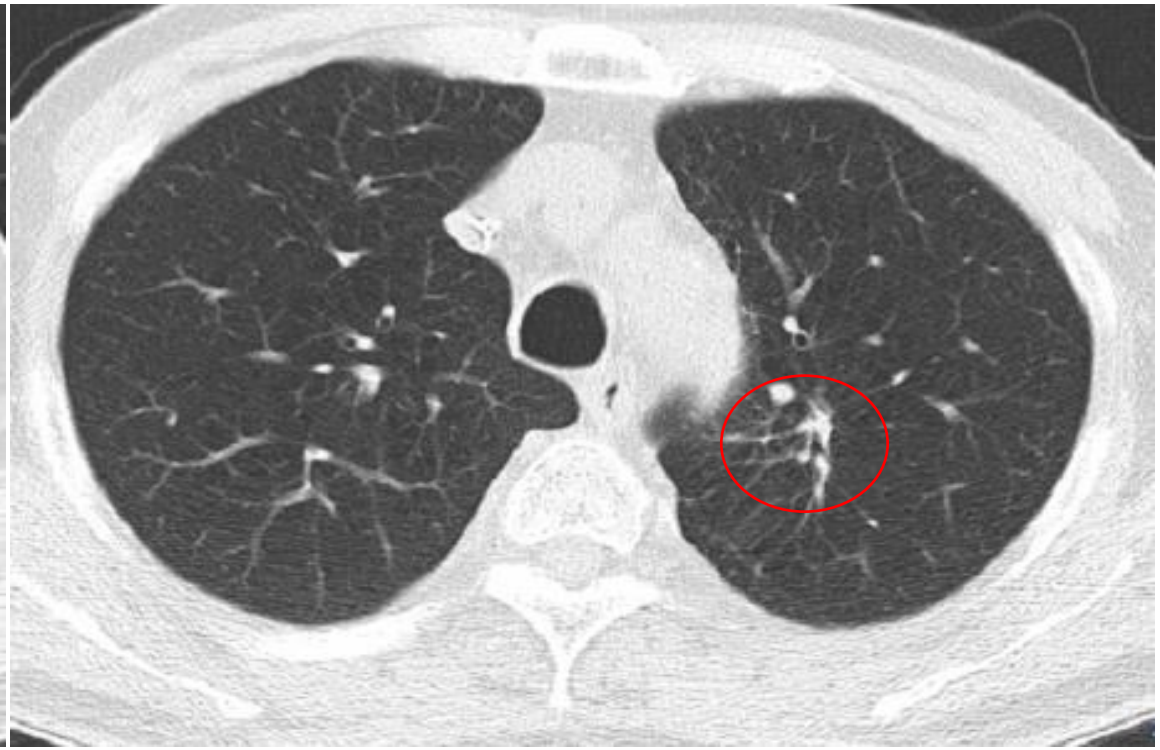
NSCLC寡转移/寡复发/寡进展局部治疗效果确切
放疗与靶向治疗/免疫治疗是研究方向

SCLC化疗联合免疫治疗后寡进展，所有可见病灶接受了再程放疗，大部分病灶消失

2021.03.29



2021.06.28

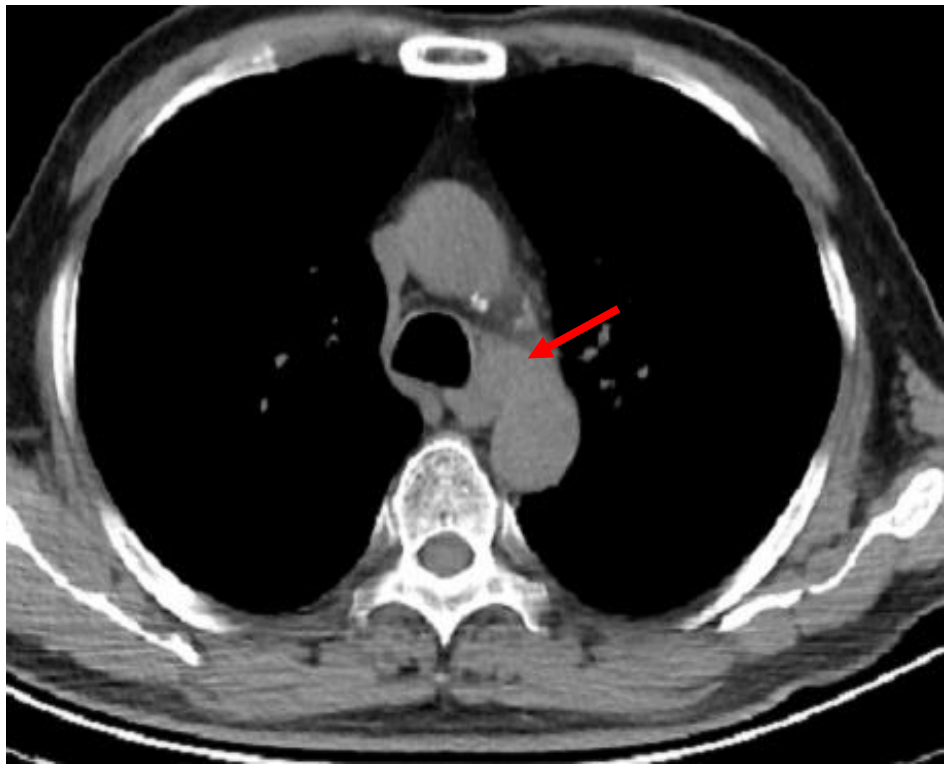


左图红色箭头所指为转移瘤，右图放疗后消失

化疗+免疫治疗后寡进展的患者经放疗联合化疗免疫治疗可望获得更佳疗效

再程低剂量放疗后病灶明显缩小

2021.03.29



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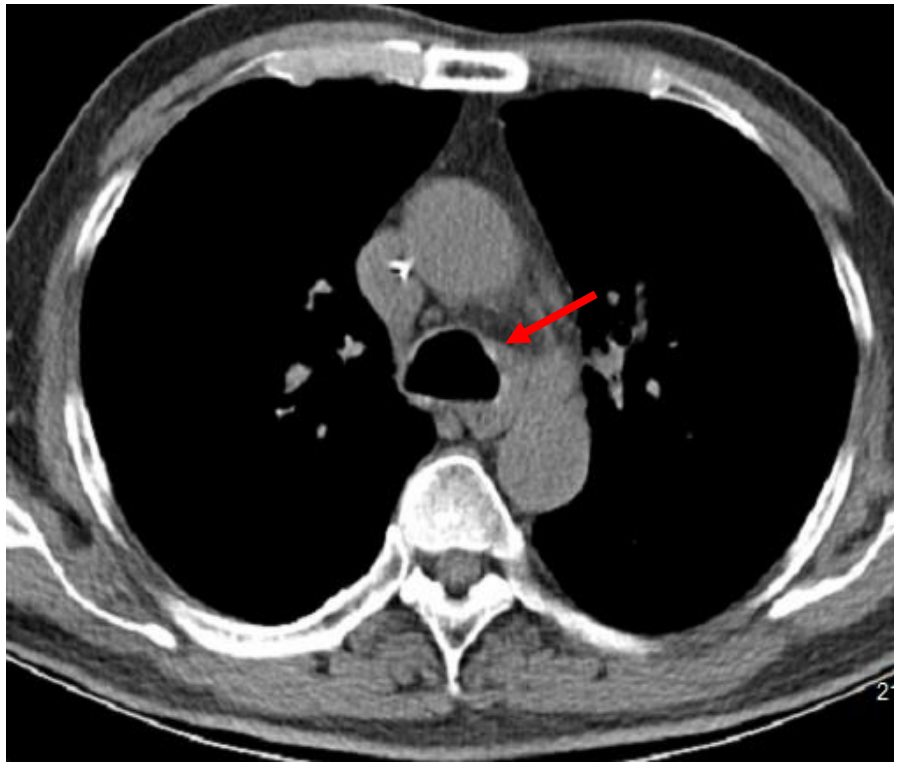
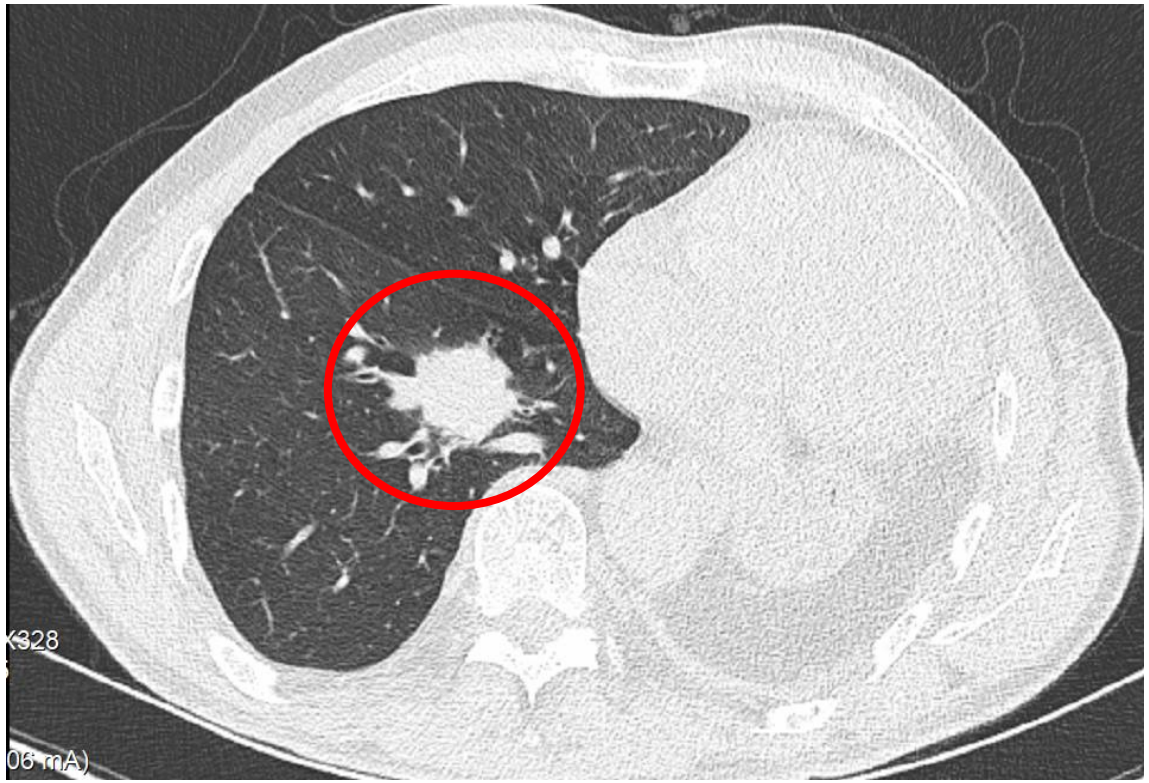


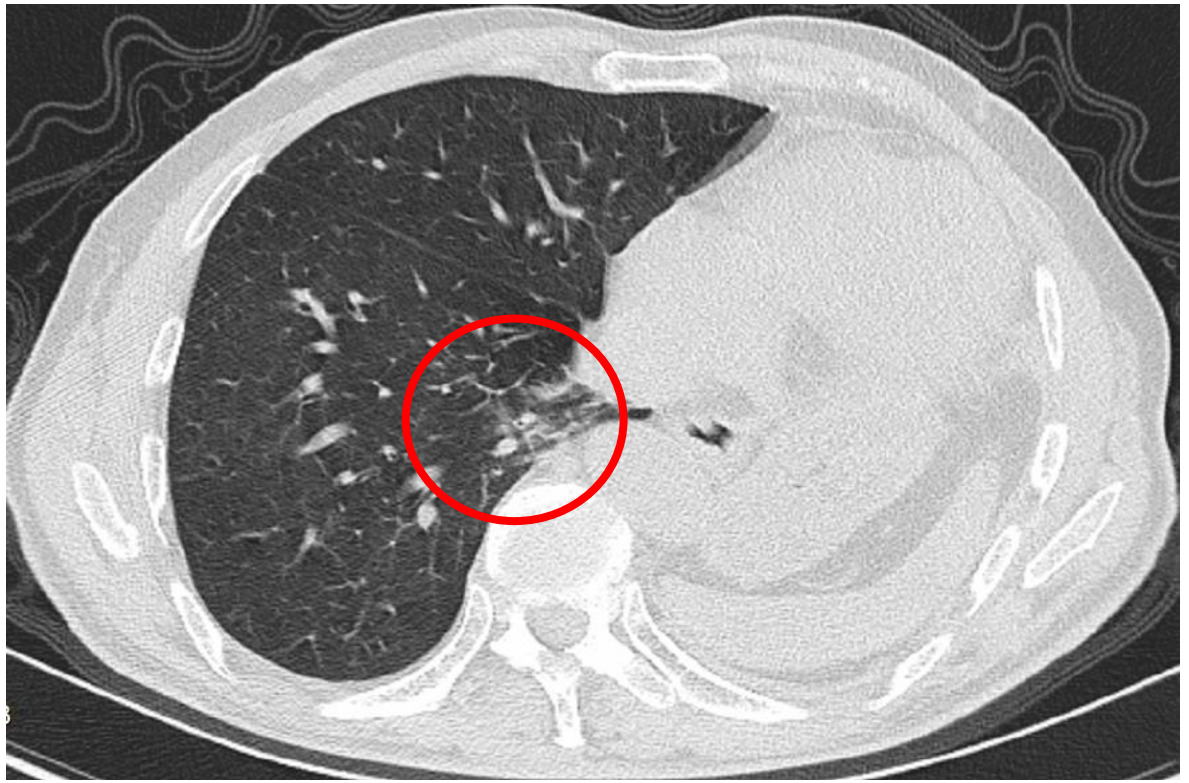
左图红色箭头所指为区域淋巴结复发，右图放疗后病灶明显缩小

化疗+免疫治疗后寡进展的患者经放疗联合化疗免疫治疗可望获得更佳疗效

71岁，左肺癌全切术后，右肺寡转移SBRT治疗



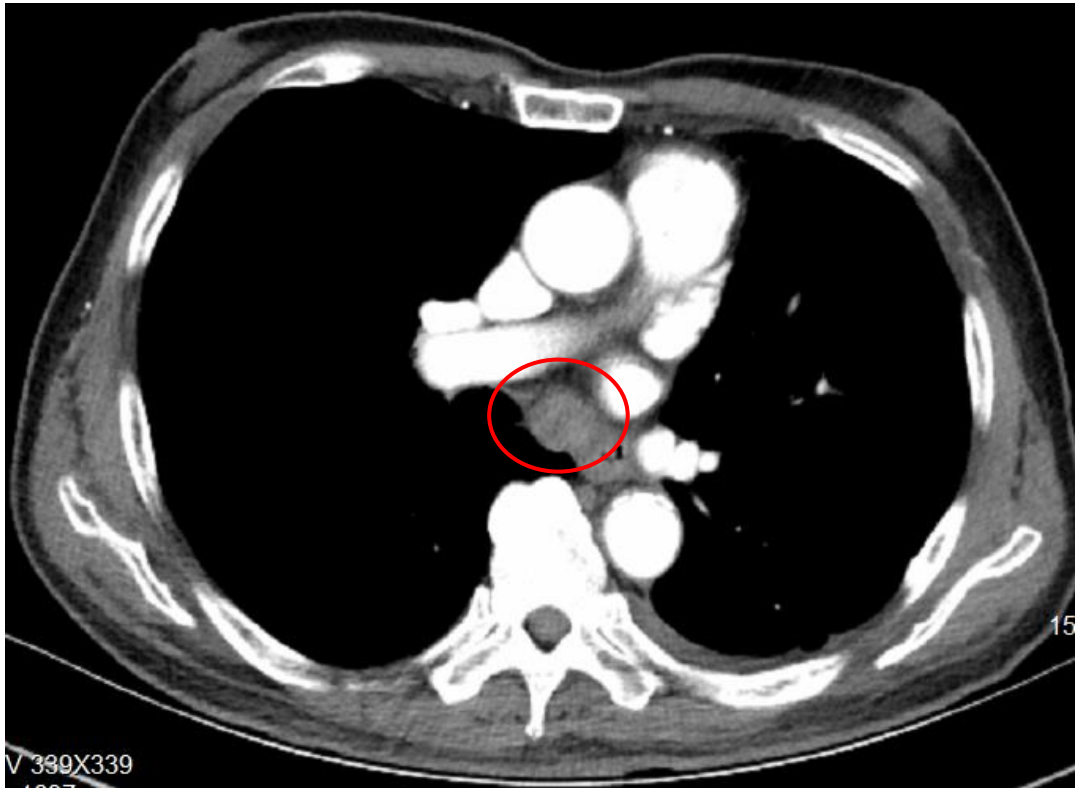
放疗前



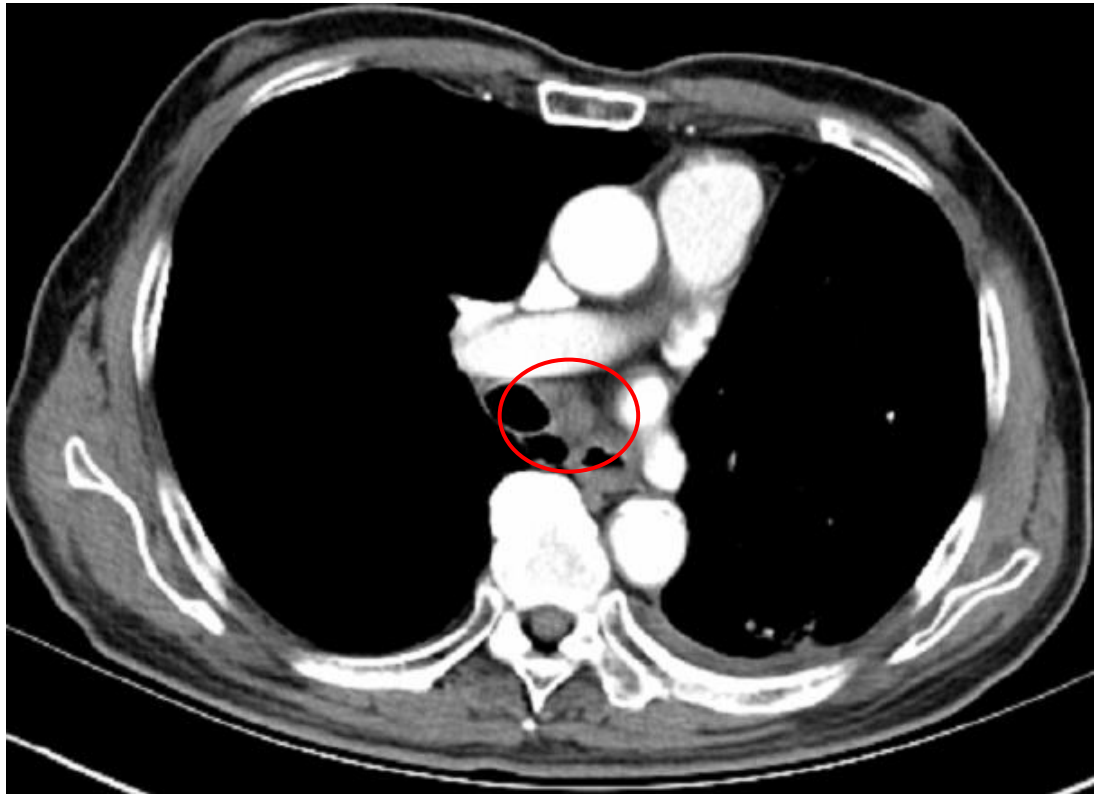
放疗后

Case3 左上肺癌术后1年余区域复发

放疗前



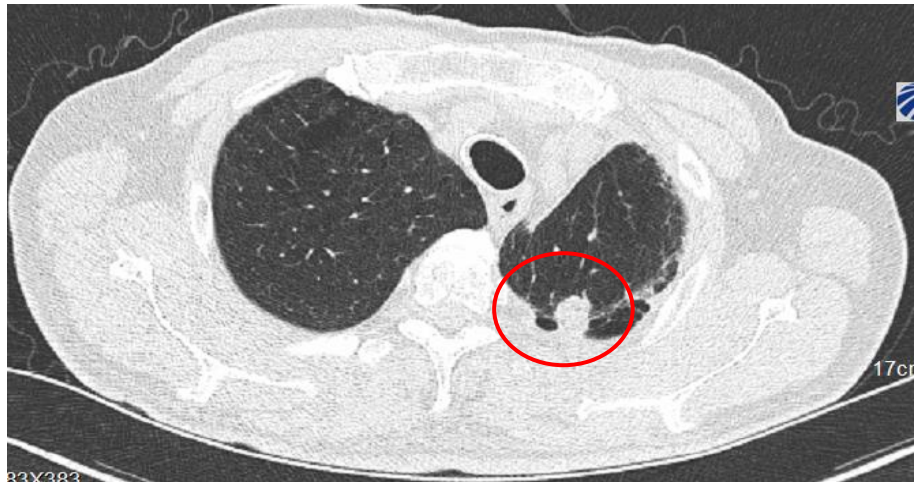
放疗后

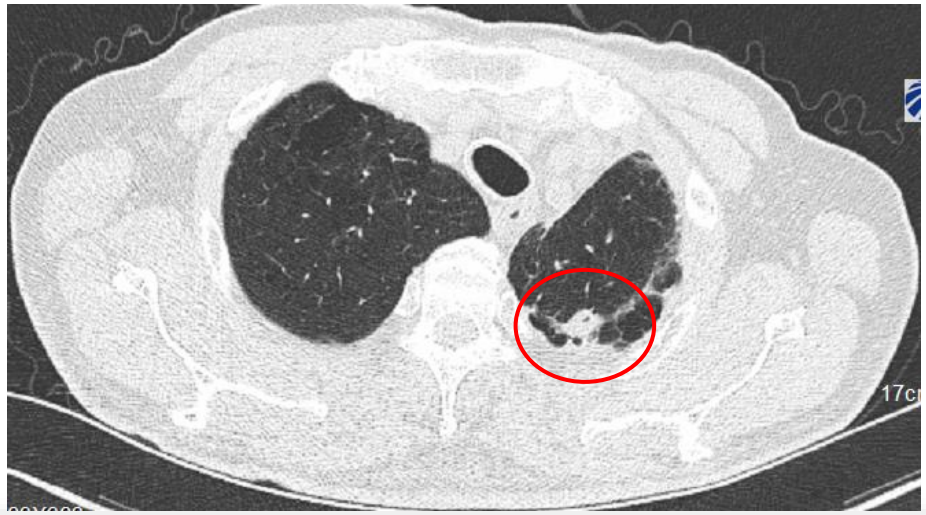


2019.10.31因纵隔淋巴结转移，诊断肺癌术后区域复发，
行根治性放化疗，DT 6000cGy/30fx/6w

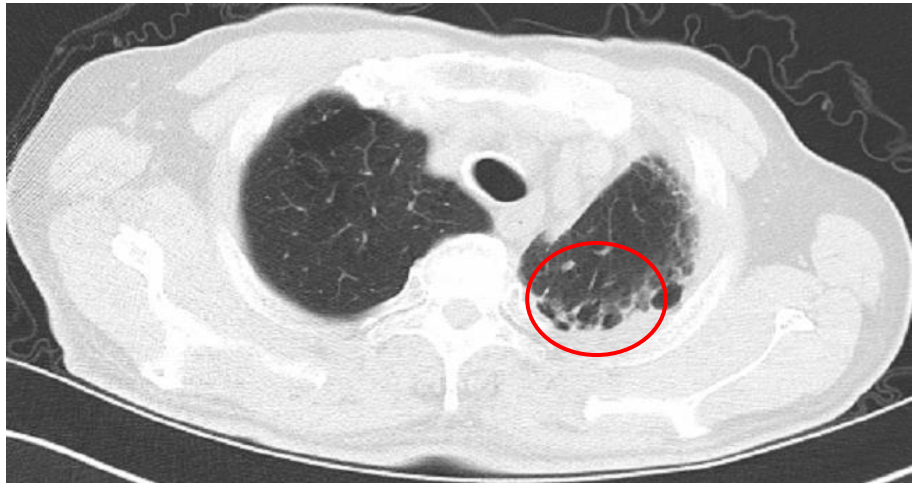
Case3 再次出现肺内复发

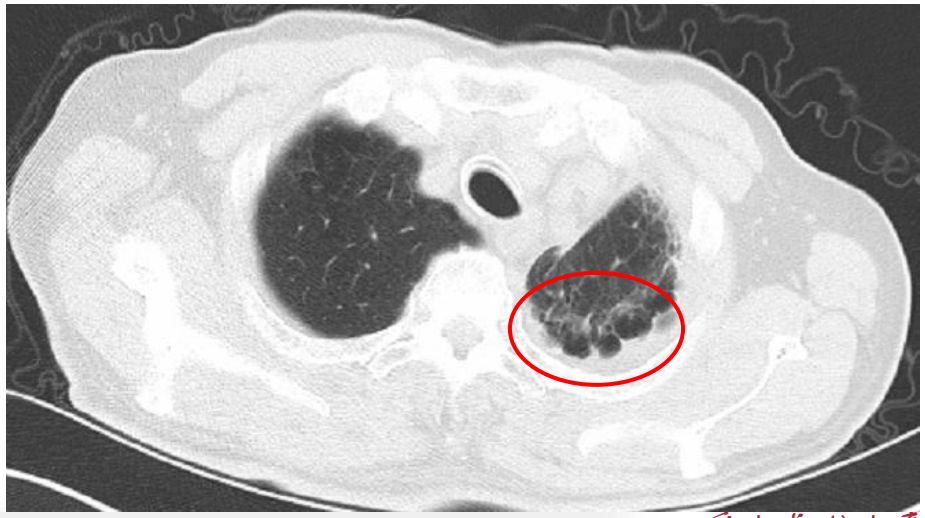
放疗前



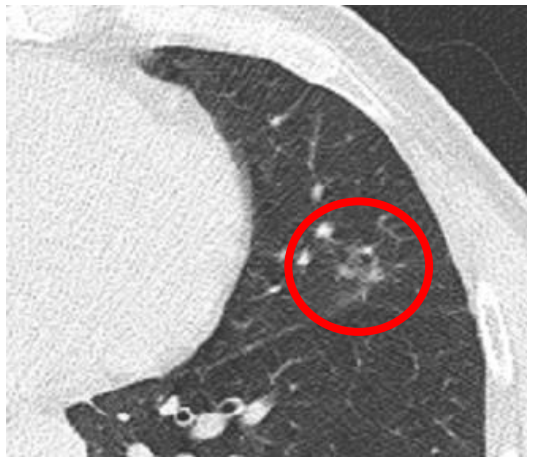
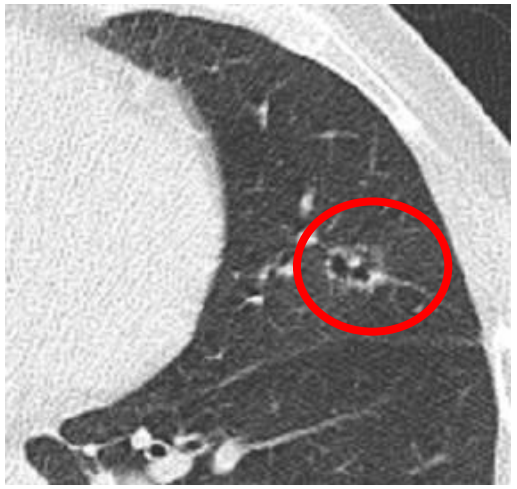
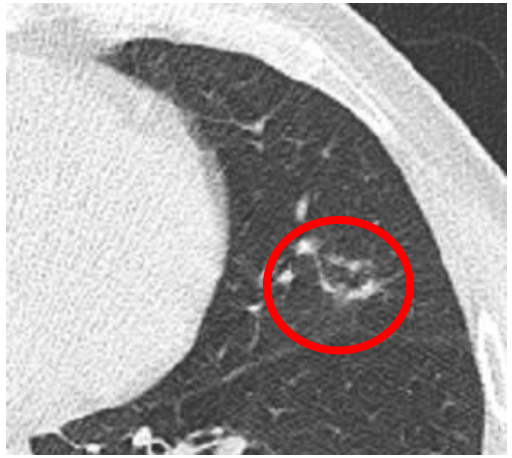
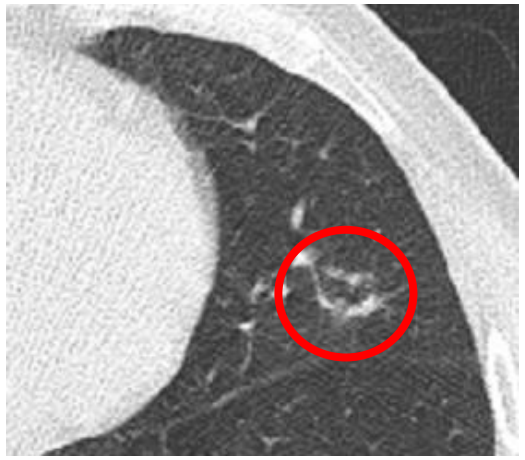


放疗后

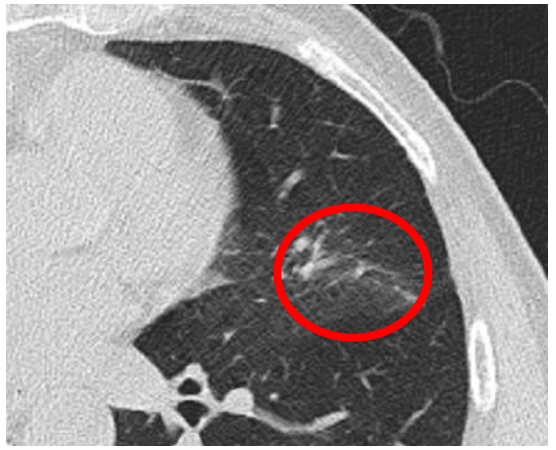
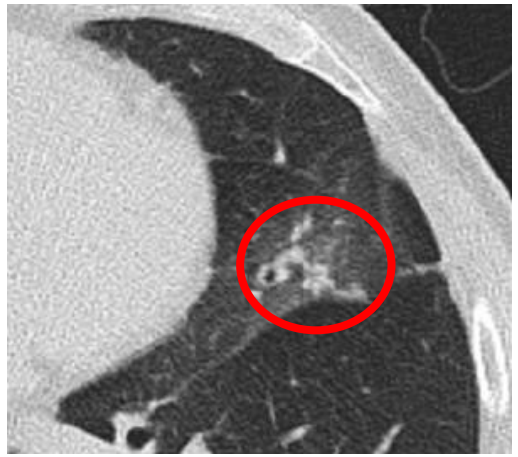
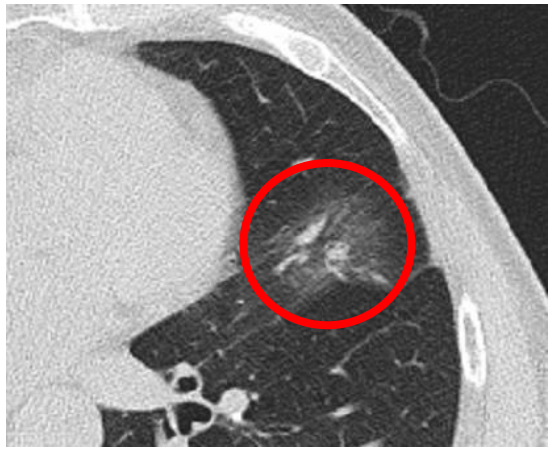
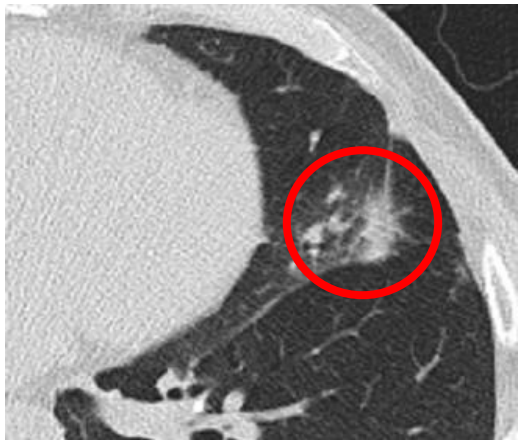




case4男性，72岁，左肺癌术后复发SBRT治疗

放疗前

放疗后

放疗联合药物治疗小结

- 肺癌药物治疗后进展多数先发生在原有病灶
- 寡转移/寡进展肺癌药物联合局部放疗效果显著
- 放疗+系统治疗：靶向（驱动基因阳性）
  免疫（驱动基因阴性）

谢谢聆听

THANK YOU FOR YOUR ATTENTION

浙江省人民医院
ZHEJIANG PROVINCIAL PEOPLE'S HOSPITAL
杭州医学院附属人民医院
PEOPLE'S HOSPITAL OF HANGZHOU MEDICAL COLLEGE

仁爱 | 卓越 | 奉献 | 创新