

Adjuvant chemotherapy after lung cancer surgery

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Thailand
Bangkok | 10-12 April



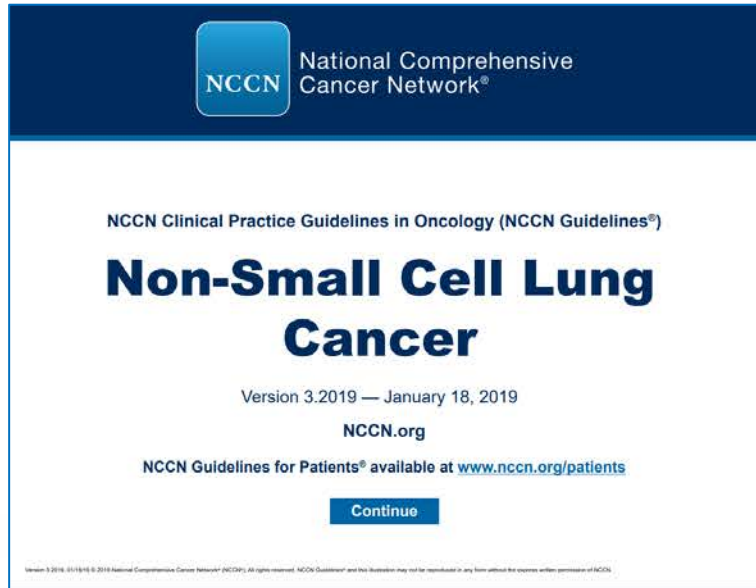
Adjuvant chemotherapy after lung cancer surgery

Outline:

- Background
- Adjuvant therapy for Stage IB and II
 - N0 vs N1 involvement
- Adjuvant therapy for Stage IIIA
 - Incidental N2 involvement
- Adjuvant therapy for Stage IA
 - Tegafur/Uracil

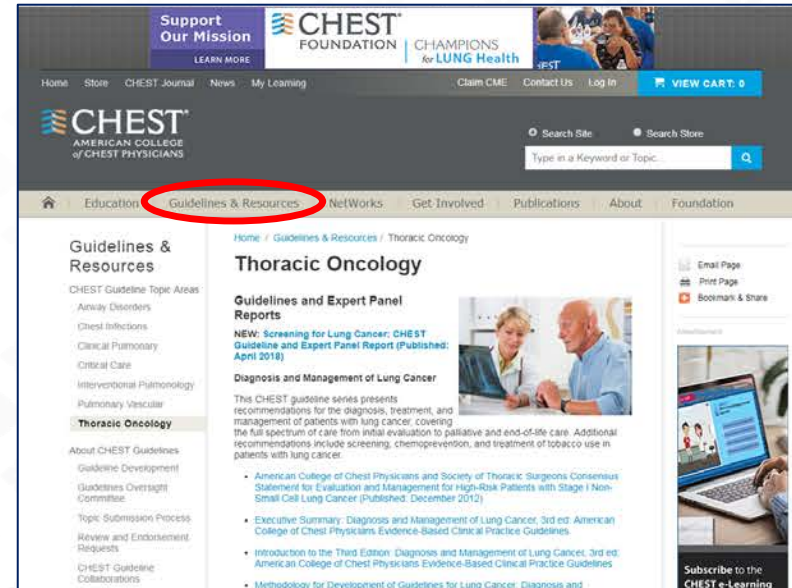
Thoracic Oncology Practice Guidelines – United States

National Comprehensive Cancer Network
<https://www.nccn.org>



Recommendations: 2A, "Based upon lower-level evidence, there is uniform NCCN consensus"

American College of Chest Physicians (CHEST)
www.chestnet.org



Recommendations are individually graded by level of evidence

Adjuvant therapy: Definition

Adjuvant therapy:

“Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.”

National Cancer Institute Dictionary of Cancer Terms

By definition, adjuvant therapy is given in the context of intent to cure

Question 1

For which of the following stages would adjuvant therapy after lung cancer surgery be recommended?

- A. T1aN1M0 (Stage IIb)
- B. T1cN1M1a (Stage IVa)
- C. T1cN3M0 (Stage IIIb)
- D. T1aN0M0, multifocal (Stage Ia, multifocal)

Question 1

For which of the following stages would adjuvant therapy after lung cancer surgery be recommended?

- A. T1aN1M0 (Stage IIb)
- B. T1cN1M1a (Stage IVa)
- C. T1cN3M0 (Stage IIIb)
- D. T1aN0M0, multifocal (Stage Ia, multifocal)

Adjuvant Chemotherapy After Lung Cancer Surgery

Clinical situations where adjuvant therapy should be given

Stage IIb	T1-2, N1, M0	Identified pre-operatively or post-operatively
Stage IIIa	T1-2, N2, M0 T3, N1, M0 T4, N0, M0	Identified pre-operatively or post-operatively

Clinical situations where adjuvant therapy could be considered (N0)

Stage IIB	T3, N0, M0	Identified pre-operatively or post-operatively, based on “high risk” features
Stage IIa	T2b ₄₋₅ , N0, M0	Identified pre-operatively, or post-operatively, based on “high risk” features
Stage Ib	T2a ₃₋₄ , N0, M0	Identified post-operatively, based on “high risk” features
Stage Ia	T1, N0, M0	In Japanese population

Evidence supporting adjuvant chemotherapy for Stage II-III NSCLC

Pignon J-P et al. Lung Adjuvant Cisplatin Evaluation: A Pooled Analysis by the LACE Collaborative Group, J Clin Oncol 2008;26:3552 (LACE Meta-analysis)

Aim: identify groups of patients who particularly benefit from postoperative chemotherapy

Eligibility:

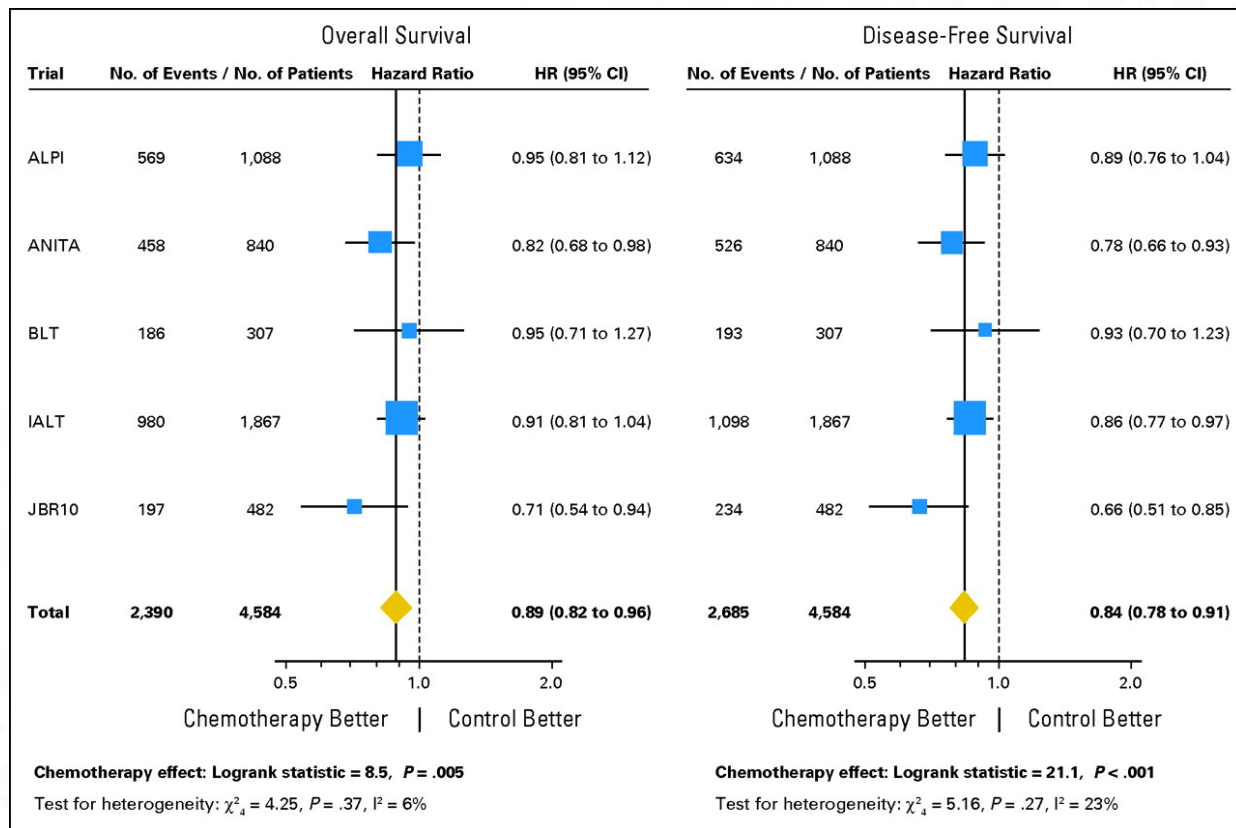
- Randomized trials with >300 patients
- Stage Ia – IIIb NSCLC
- Individual patient data available
- Primary treatment was surgery with complete resection
- Post-operative treatment with platinum-based chemotherapy vs no chemotherapy (or cisplatin-based chemotherapy plus postop RT vs post operative radiotherapy alone in patients with completely resected NSCLC)
- Primary endpoint: overall survival

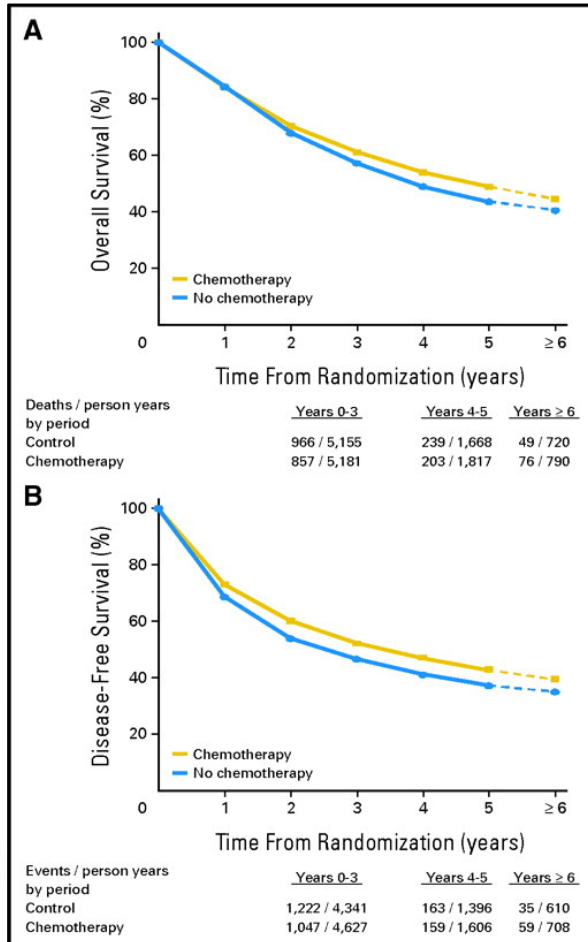
LACE meta-analysis

Included 5 large trials

- Adjuvant Lung Cancer Project (ALPI)
- Adjuvant Navelbine International Trialist Association (ANITA)
- Big Lung Trial (BLT)
- International Adjuvant Lung Cancer Trial Collaborative Group (IALT)
- North American Intergroup (JBR10)

4584 patients
Stage Ia-IIIb





LACE meta-analysis

For the entire pooled population at 5 year follow-up:

- 5.4% absolute benefit in overall survival
- 5.8% absolute benefit in disease free survival
- 6.9% decrease in lung cancer deaths

Pignon, J-P et al. Journal of Clinical Oncology 2008;26:3552

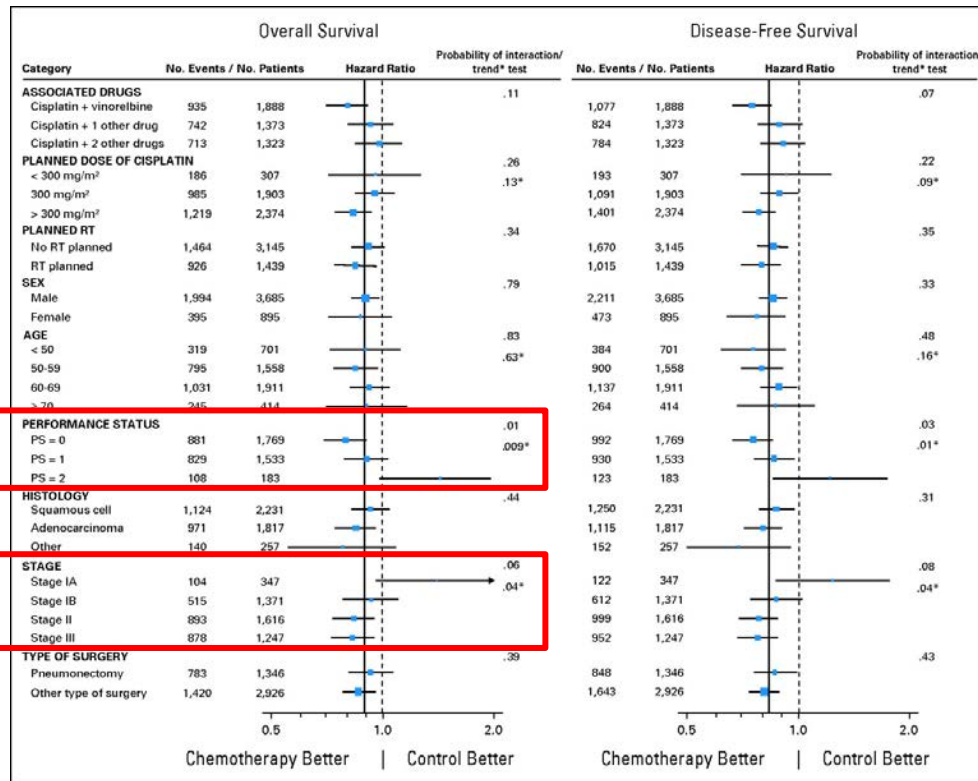


Fig 3. (A) Overall survival (OS): hazard ratio (HR) of death with chemotherapy versus control (no chemotherapy) by trial or baseline patient characteristic. (B) Disease-free survival (DFS): HR of recurrence or death with chemotherapy versus control by trial or baseline patient characteristic. RT, radiotherapy; PS, performance status.

- Variation of chemotherapy effect according to stage, related mainly to patients with stage IA disease.
- Worse outcomes with adjuvant chemotherapy associated with:
 - Stage IA
 - Poor performance status

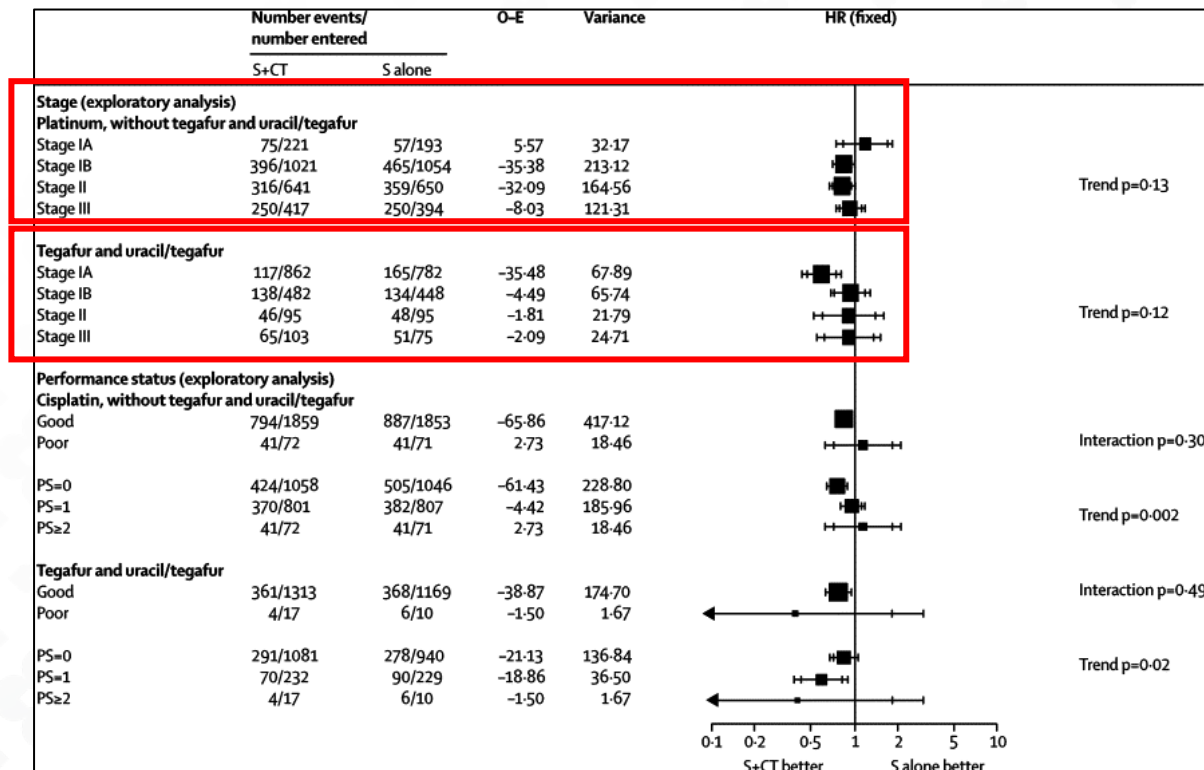
Conclusion:

Adjuvant cisplatin-based chemotherapy is of benefit in completed resected Stage Ib – III NSCLC with good performance status

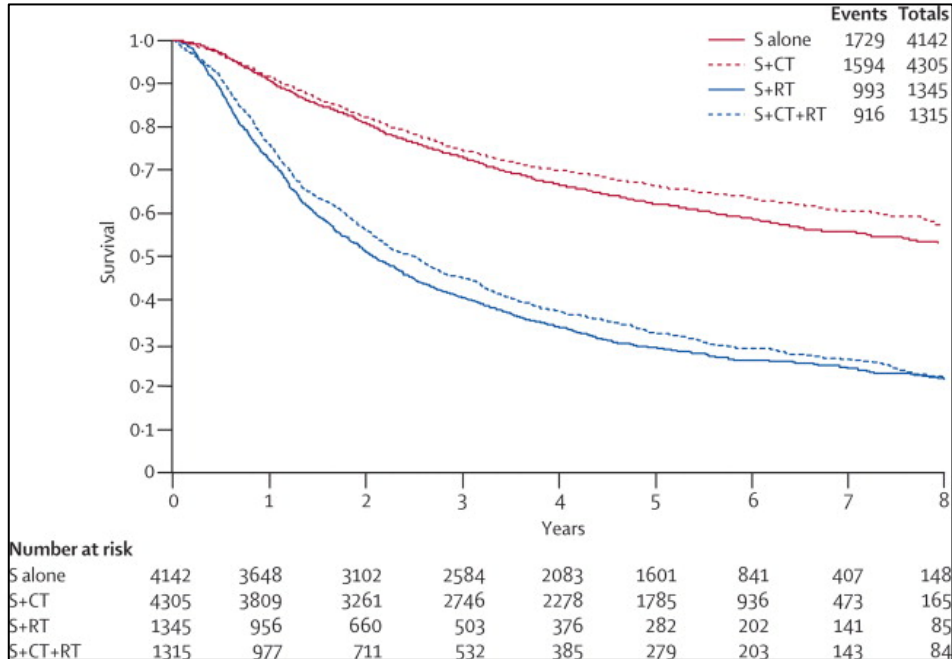
NSCLC Meta-analyses Collaborative Group. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010; 375:1267-77

- 34 randomized trials
- Stage I – III NSCLC
- Complete surgical resection
- Surgery alone vs surgery plus adjuvant chemotherapy (or surgery alone vs surgery plus adjuvant radiotherapy and chemotherapy vs surgery plus adjuvant radiotherapy)
- Included studies from North America, Europe, Asia (Japan)

8447 patients (3323 deaths)



NSCLC Meta-analysis: Surgery (S) alone vs Surgery and Chemotherapy (CT) or Surgery and Chemotherapy and Radiotherapy (RT) vs Surgery and Radiotherapy



NSCLC Meta-analyses Collaborative Group. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. *Lancet* 2010; 375:1267-77

Conclusions:

- Evidence for survival benefit with adjuvant chemotherapy after surgery (HR 0.86, 95% CI 0.81-0.92, $p < 0.0001$)
- Absolute increase in 5 year survival = 4% (95% CI 3-6) (increased to 64% from 60%)
- In patients at high risk of recurrence (ie. Stage IB,II,III) and medically fit for chemotherapy, adjuvant platinum-based chemotherapy should be considered

Adjuvant Therapy for NSCLC

LACE and NSCLC Collaborative Group:

- Adjuvant platinum-based chemotherapy is beneficial for patients with Stage IB, II, III NSCLC

Decisions about adjuvant therapy should consider:

- Heterogeneity between stages
- Heterogeneity within stages

8th Edition NSCLC Staging Classification

T/M	Label	N0	N1	N2	N3
T1	T1a ≤ 1	IA1	IIB	IIIA	IIIB
	T1b $>1-2$	IA2	IIB	IIIA	IIIB
	T1c $>2-3$	IA3	IIB	IIIA	IIIB
T2	T2a <i>Cent, Yisc Pl</i>	IB	IIB	IIIA	IIIB
	T2a $>3-4$	IB	IIB	IIIA	IIIB
	T2b $>4-5$	IIA	IIB	IIIA	IIIB
T3	T3 $>5-7$	IIB	IIIA	IIIB	IIIC
	T3 <i>Inv</i>	IIB	IIIA	IIIB	IIIC
	T3 <i>Satell</i>	IIB	IIIA	IIIB	IIIC
T4	T4 >7	IIIA	IIIA	IIIB	IIIC
	T4 <i>Inv</i>	IIIA	IIIA	IIIB	IIIC
	T4 <i>Ipsi Nod</i>	IIIA	IIIA	IIIB	IIIC
M1	M1a <i>Contr Nod</i>	IVA	IVA	IVA	IVA
	M1a <i>Pl Dissem</i>	IVA	IVA	IVA	IVA
	M1b <i>Single</i>	IVA	IVA	IVA	IVA
	M1c <i>Multi</i>	IVB	IVB	IVB	IVB

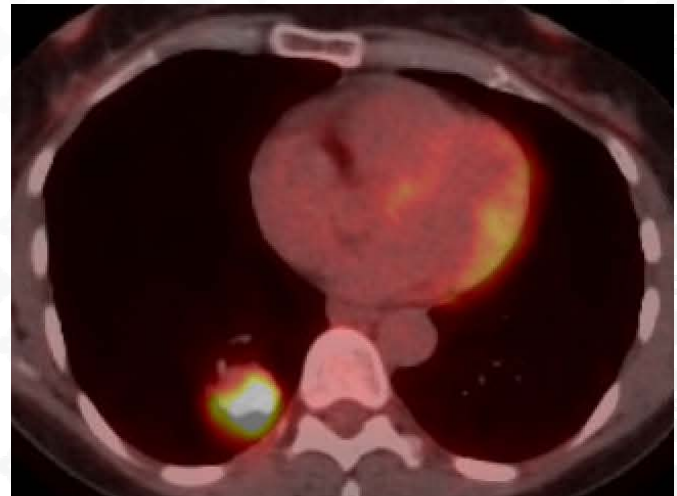
Adjuvant therapy for Stage IB?

61 year old Caucasian woman, in good health. She has a 15 pack-year smoking history, discontinued 25 years ago. CXR performed for cough showed a right lower lobe mass.

- Chest CT: 3.2 cm right lower lobe mass, no mediastinal adenopathy or other abnormalities, centrally located
- PET-CT: RLL mass SUV 7.8. No other sites of FDG avidity.
- PFT: normal

She underwent right lower lobectomy with complete lymphadenectomy

- Pathology: T2aN0M0 large cell carcinoma, poorly differentiated with neuroendocrine features. Stage IB



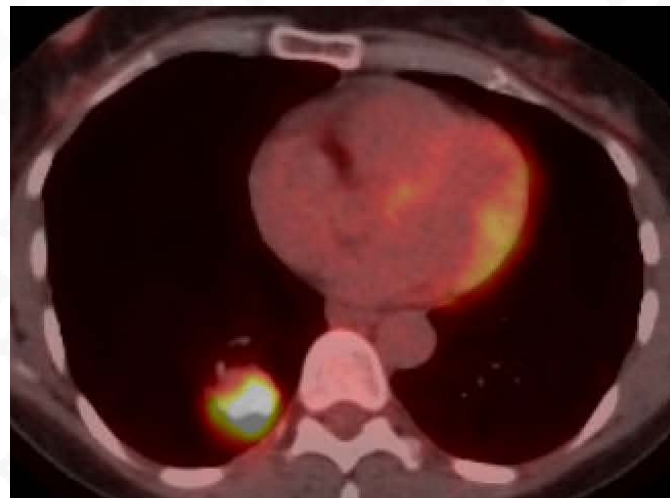
Question 2

61 year old Caucasian woman, PS 0.

- s/p right lower lobectomy
- T2aN0M0 large cell carcinoma, poorly differentiated with neuroendocrine features. Stage IB

Would you recommend adjuvant platinum-based chemotherapy to this patient?

- A. Yes
- B. No



Question 2

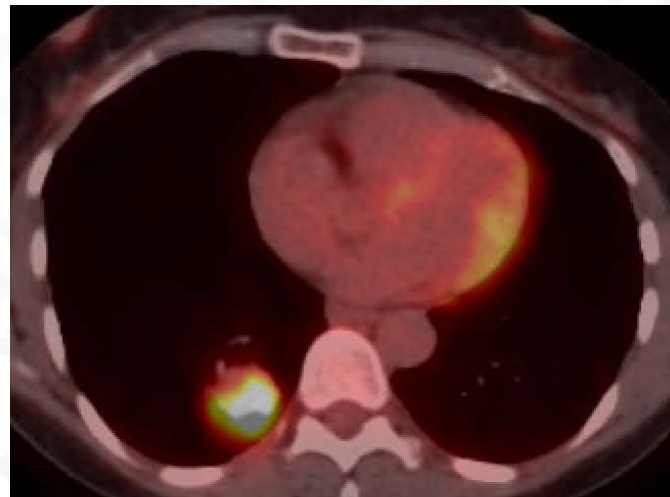
61 year old Caucasian woman, PS 0.

- s/p right lower lobectomy
- T2aN0M0 large cell carcinoma, poorly differentiated with neuroendocrine features. Stage IB

Would you recommend adjuvant platinum-based chemotherapy to this patient?

A. Yes

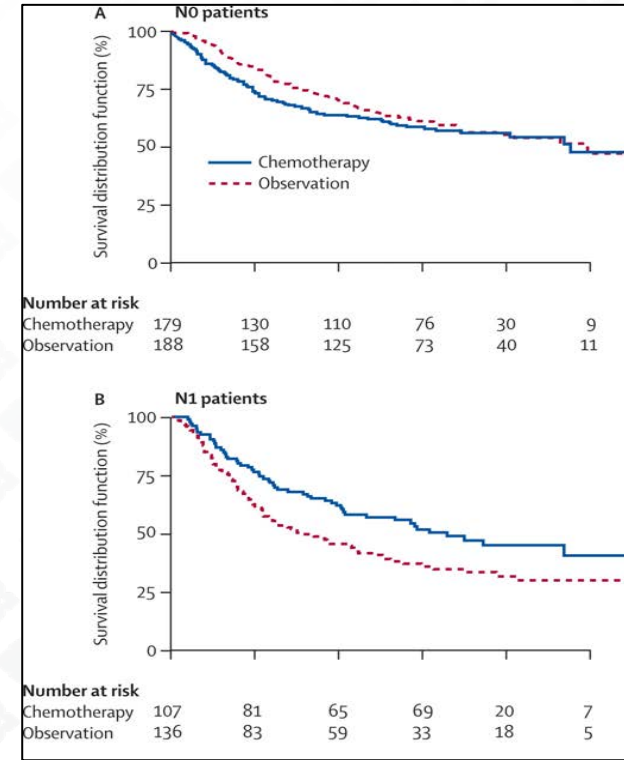
B. No



Adjuvant Therapy for Stage IB and Stage II

Douillard J-Y et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell-lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomized controlled trial. Lancet Oncology 2006;7:719

- 840 patients with stage IB-IIIA NSCLC randomized to cisplatin/vinorelbine vs observation
 - Median disease-free survival for chemotherapy vs observation: 36.3 months vs 20.7 months (HR 0.76, 95% CI 0.64-0.91)
- N0 involvement: 367 patients
 - 5 year-survival for chemotherapy vs observation: 58% vs 61% (HR death 1.14, 95% CI 0.83-1.57)
- N1 involvement: 243 patients
 - 5 year-survival for chemotherapy vs observation: 52% vs 36% (HR death 0.67, 95% CI 0.47-0.94)

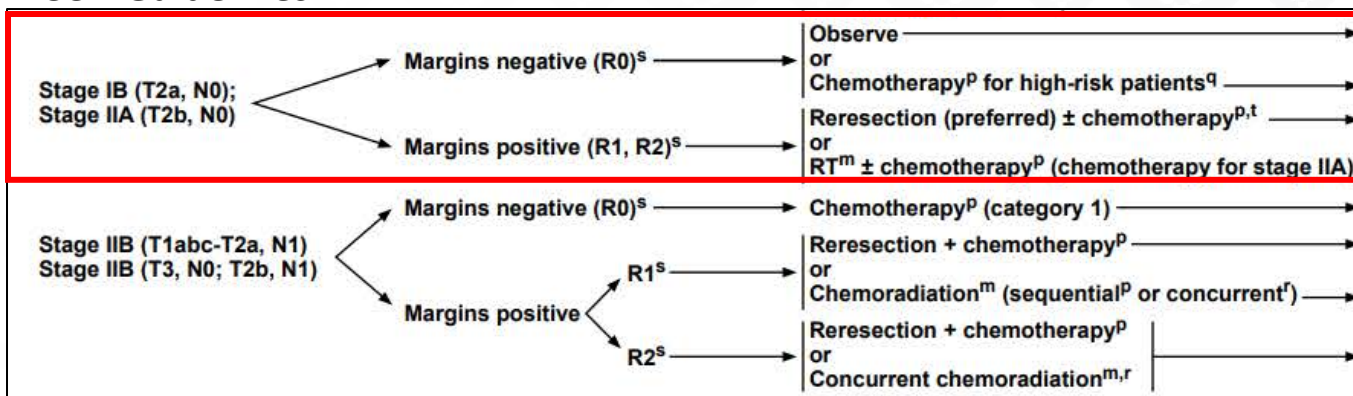


Adjuvant therapy for Stage IB – IIA NSCLC

ACCP Guidelines:

- **6.1.5.2. For patients with completely resected pathologic stage IIA,B (N1) NSCLC and good PS, postoperative platinum-based chemotherapy is recommended (Grade 1A).**
- *Remark:* No clear recommendation is possible regarding adjuvant chemotherapy for larger tumors without lymph node involvement. [ie. no recommendation for or against adjuvant chemotherapy for Stage IB or IIA (N0)]

NCCN Guidelines:



“high-risk” factors: poorly differentiated, vascular invasion, wedge resection, >4 cm, visceral pleural involvement

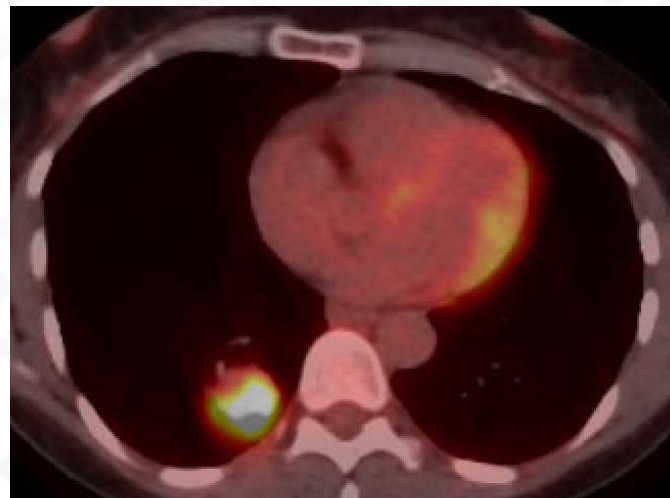
Question 2

61 year old Caucasian woman, PS 0.

- s/p right lower lobectomy
- T2aN0M0 large cell carcinoma, poorly differentiated with neuroendocrine features. Stage IB

Would you recommend adjuvant platinum-based chemotherapy to this patient?

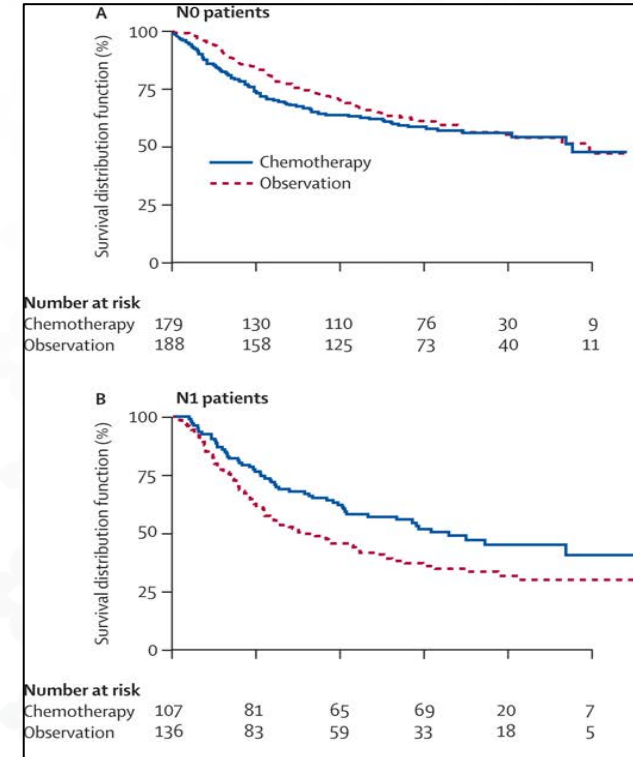
- A. Yes
- B. No



Adjuvant Therapy for Stage IB and II

T/M	Label	N0	N1	N2	N3
T1	T1a ≤ 1	IA1	IIB	IIIA	IIIB
	T1b $>1-2$	IA2	IIB	IIIA	IIIB
	T1c $>2-3$	IA3	IIB	IIIA	IIIB
T2	T2a <i>Cent, Yisc Pl</i>	IB	IIB	IIIA	IIIB
	T2a $>3-4$	IB	IIB	IIIA	IIIB
	T2b $>4-5$	IIA	IIB	IIIA	IIIB
T3	T3 $>5-7$	IIB	IIIA	IIIB	IIIC
	T3 <i>Inv</i>	IIB	IIIA	IIIB	IIIC
	T3 <i>Satell</i>	IIB	IIIA	IIIB	IIIC
T4	T4 >7	IIIA	IIIA	IIIB	IIIC
	T4 <i>Inv</i>	IIIA	IIIA	IIIB	IIIC
	T4 <i>Ipsi Nod</i>	IIIA	IIIA	IIIB	IIIC
M1	M1a <i>Contr Nod</i>	IVA	IVA	IVA	IVA
	M1a <i>PI Dissem</i>	IVA	IVA	IVA	IVA
	M1b <i>Single</i>	IVA	IVA	IVA	IVA
	M1c <i>Multi</i>	IVB	IVB	IVB	IVB

ANITA trial. *Lancet Oncology* 2006;7:719

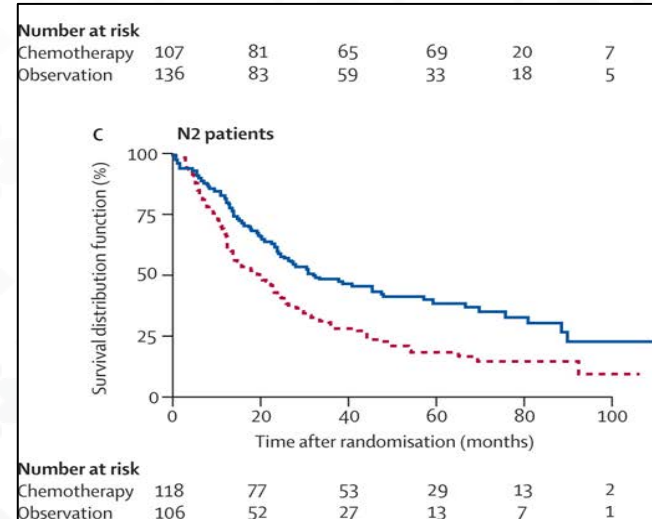


- Acknowledge heterogeneity within stage
- Consider individual tumor risk factors as well as patient risk factors for treatment

Adjuvant Therapy for Stage IIIA

Douillard J-Y et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non-small-cell-lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomized controlled trial. Lancet Oncology 2006;7:719

- 840 patients with stage IB-IIIa NSCLC randomized to cisplatin/vinorelbine vs observation
 - Median disease-free survival for chemotherapy vs observation: 36.3 months vs 20.7 months (HR 0.76, 95% CI 0.64-0.91)
- N2 involvement: 243 patients
 - 5 year-survival for chemotherapy vs observation: 40% vs 19% (HR death 0.60, 95% CI 0.44-0.82)



Treatment for Stage IIIA NSCLC

ACCP Guidelines:

- **3.5.2 In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), either definitive chemoradiation therapy or induction therapy followed by surgery is recommended** over either surgery or radiation alone (Grade 1A)
- 3.5.3 In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), **primary surgical resection followed by adjuvant therapy is not recommended** (except as part of a clinical trial) (Grade 1C)
- **4.5.3 In patients with resected NSCLC (R0) who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and who have good performance status, adjuvant platinum-based chemotherapy is recommended** (Grade 1A)

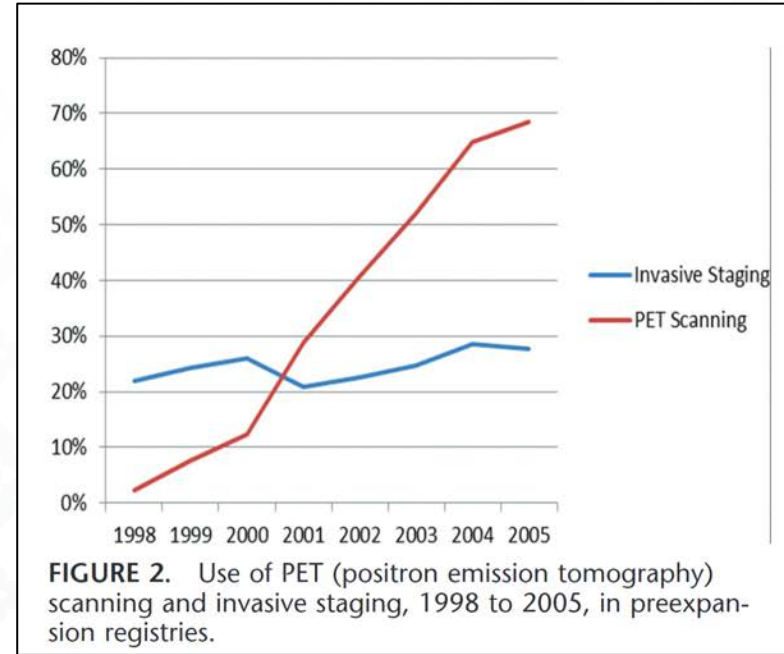
Treatment for Stage IIIA NSCLC

ACCP Guidelines:

- **3.5.2 In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), either definitive chemoradiation therapy or induction therapy followed by surgery is recommended** over either surgery or radiation alone (Grade 1A)
- **3.5.3 In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), primary surgical resection followed by adjuvant therapy is not recommended** (except as part of a clinical trial) (Grade 1C). **ie. First-line therapy for Stage IIIA (N2): combined chemoradiation or neoadjuvant chemotherapy/radiation therapy followed by surgery. Surgery should not be the primary approach.**
- **4.5.3 In patients with resected NSCLC (R0) who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging and who have good performance status, adjuvant platinum-based chemotherapy is recommended** (Grade 1A). **i.e. Adjuvant therapy is recommended for incidental (“surprise”) N2 disease found at surgery.**

Incidental (“surprise”) N2 disease

- Thorough evaluation of the mediastinum is a critical part of staging of all patients thought to have Stage IIIA disease
- Nodal disease clinically suspected by CT or PET-CT should be confirmed/excluded prior to a definitive surgical resection
- Conditions that increase likelihood of N2 involvement, even with negative CT/PET:
 - Central tumor location
 - N1 disease
 - 25% likelihood of N2 disease
- True, unsuspected N2 disease (ie. even with invasive staging) occurs in approximately 10% (5%-16%) of patients.



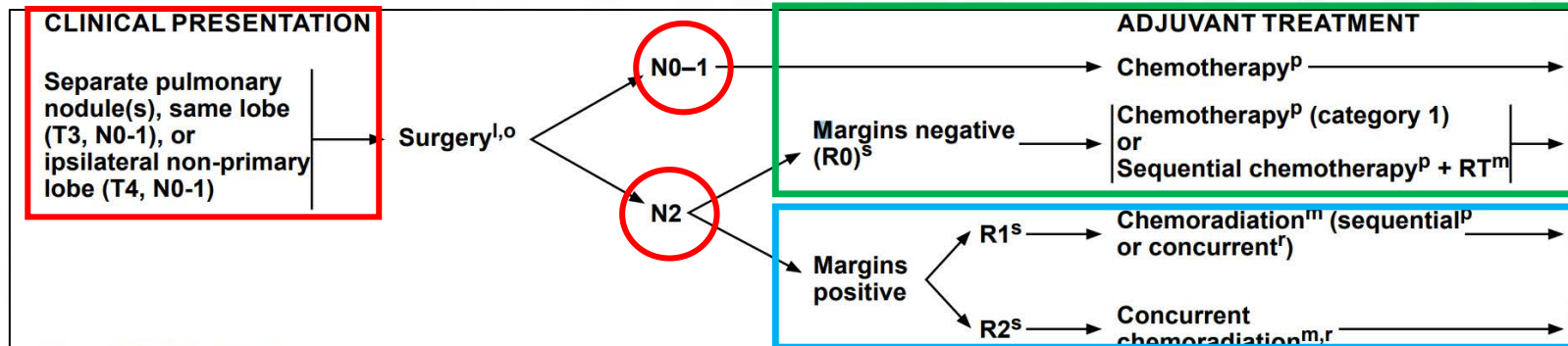
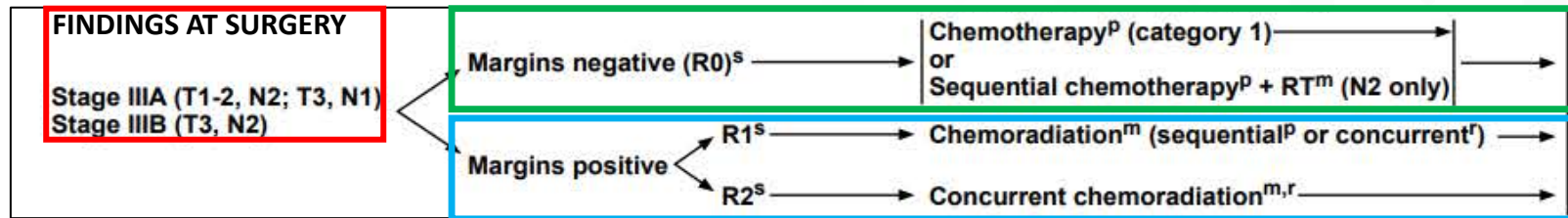
Vest M et al. Thoroughness of Mediastinal Staging in Stage IIIA NSCLC. JTO 2012;7:188.

Of 7583 stage IIIA NSCLC patients (SEER-Medicare database), 1678 (22%) underwent invasive mediastinal staging

Treatment for Stage IIIA NSCLC

NCCN Guidelines:

"Incidental N2"



Adjuvant Chemotherapy After Lung Cancer Surgery

Clinical situations where adjuvant therapy should be given

Stage IIb	T1-2, N1, M0	Identified pre-operatively or post-operatively
Stage IIIa	T1-2, N2, M0 T3, N1, M0 T4, N0, M0	Identified pre-operatively or post-operatively

Clinical situations where adjuvant therapy could be considered (N0)

Stage IIB	T3, N0, M0	Identified pre-operatively or post-operatively, based on “high risk” features
Stage IIa	T2b ₄₋₅ , N0, M0	Identified pre-operatively, or post-operatively, based on “high risk” features
Stage Ib	T2a ₃₋₄ , N0, M0	Identified post-operatively, based on “high risk” features
Stage Ia	T1, N0, M0	In Japanese population

Question 3

DH is a 72 year old Caucasian man with severe COPD (FEV1 40% predicted, DLCO 40% predicted) and current smoker of 1 pack/day x 55 years. He had a CXR performed because of cough, which suggested a left lower lobe lung nodule. An 11 mm nodule was confirmed on chest CT scan. PET-CT scan demonstrated FDG avidity in the nodule (SUV 4.8) but no FDG uptake at any other site.



Question 3

DH underwent a superior segment-sparing left lower lobectomy.

Pathologic stage: T1bN0M0 Stage IA adenocarcinoma

What further therapy, if any, would you recommend?

- A. Platinum-based adjuvant chemotherapy
- B. Tegafur-uracil adjuvant chemotherapy
- C. Nivolumab adjuvant therapy
- D. No adjuvant therapy



Question 3

DH underwent a superior segment-sparing left lower lobectomy.

Pathologic stage: T1bN0M0 Stage IA

What further therapy, if any, would you recommend?

- A. Platinum-based adjuvant chemotherapy
- B. Tegafur-uracil adjuvant chemotherapy
- C. Nivolumab adjuvant therapy
- D. No adjuvant therapy



Adjuvant Chemotherapy for Stage IA NSCLC

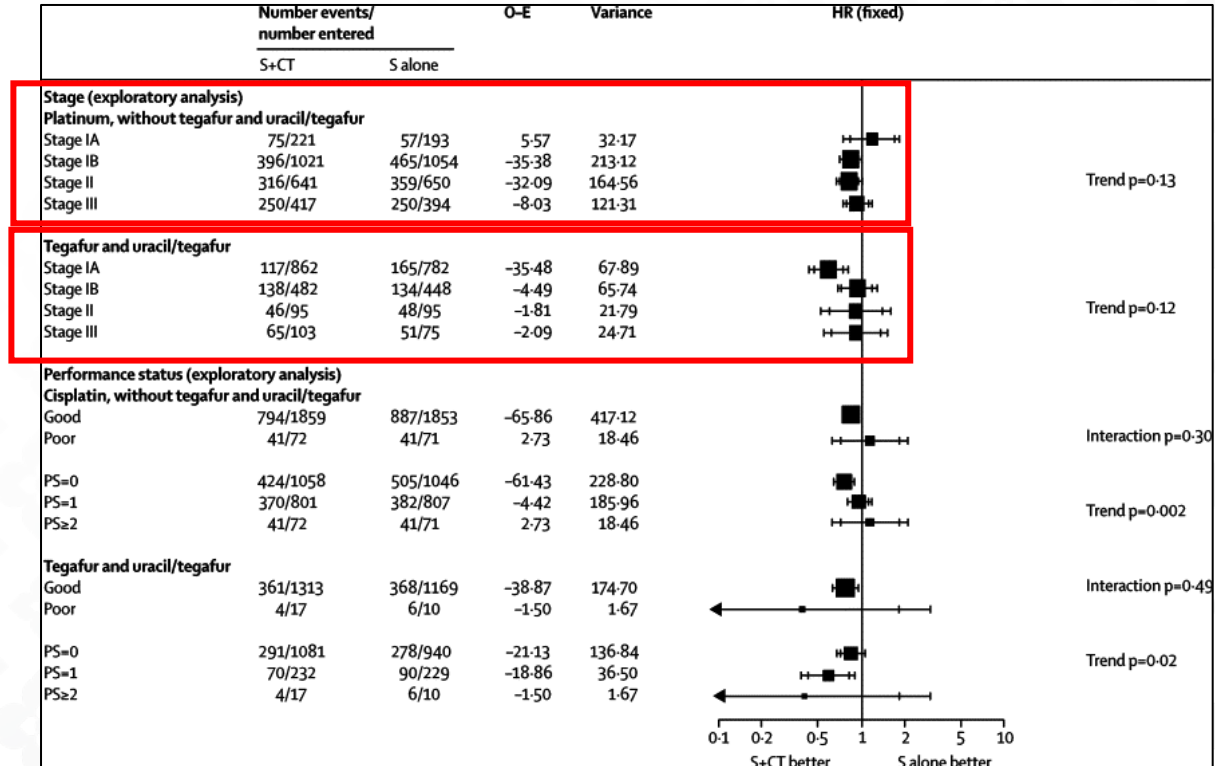
*NSCLC Meta-analyses
Collaborative Group. Lancet
2010; 375:1267-77*

Tegafur-uracil (UFT)

- Tegafur = Fluorouracil (FU) prodrug
- Uracil: inhibits FU degradation

Widely used in Japan for postoperative adjuvant therapy

- Low toxicity profile



Adjuvant Chemotherapy for Stage IA NSCLC: Tegafur-uracil

Hamada C et al. Meta-Analysis of Postoperative Adjuvant Chemotherapy With Tegafur-Uracil in Non–Small-Cell Lung Cancer. J Clin Oncol 2005;23:4999

- Meta-analysis of 6 trials in Japan comparing surgery alone vs. surgery plus UFT
- 2003 eligible patients
 - T1 (65.3%)
 - N0 (96%)
 - Median follow up 6.4 years

Table 2. Clinical Characteristics of Patients

	Surgery Alone (n = 1,002)	Surgery + UFT (n = 1,001)	P
Age, years			
Mean	62.3	62.0	.37*
SD	7.8	8.3	
< 70	794	792	.95†
≥ 70	208	209	
Sex			
Male	561	552	.70†
Female	441	449	
Histologic type			
Adenocarcinoma	837	842	.93†
Squamous cell carcinoma	152	147	
Others	13	12	
Pathological T			
T1	648	660	.50†
T2	341	333	
Others	13	8	
Pathological N			
N0	963	960	.21†
N1	30	24	
Others	9	17	

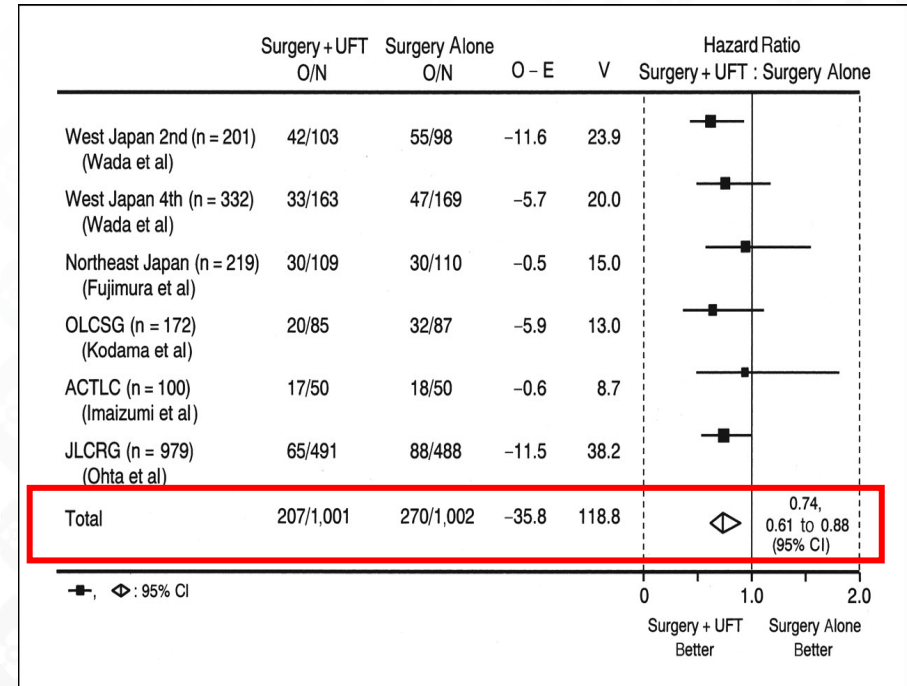
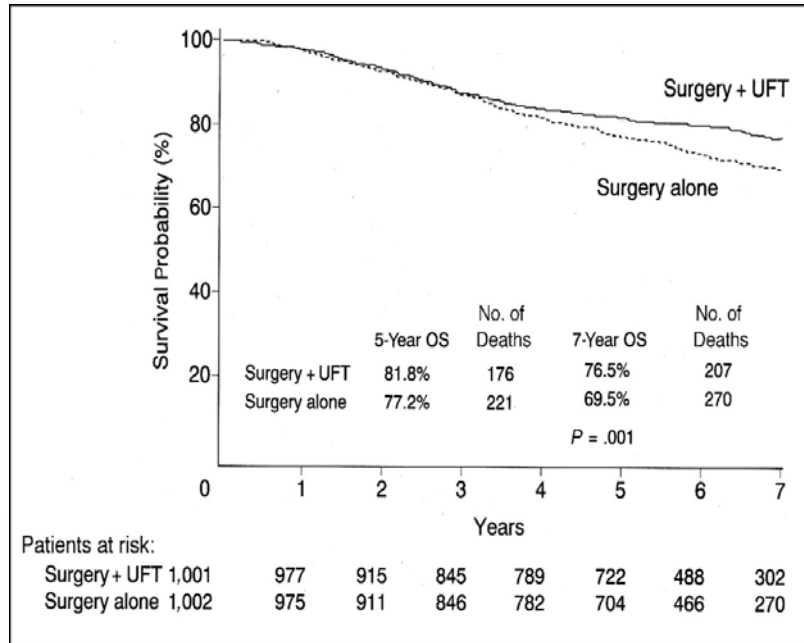
Abbreviation: UFT, tegafur-uracil.

*t test.

† χ^2 test.

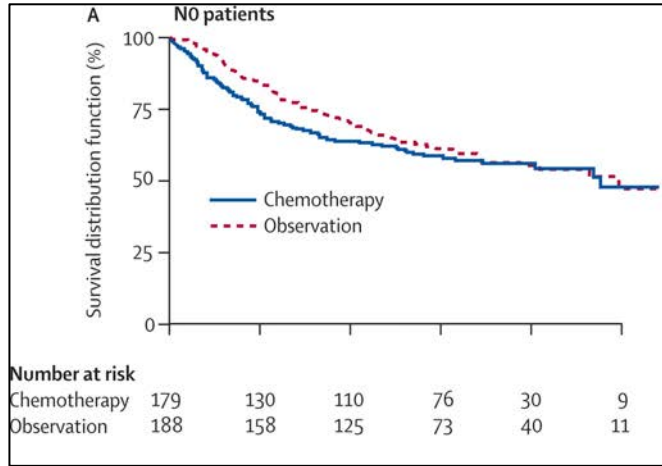
Adjuvant Chemotherapy for Stage IA NSCLC: Tegafur-uracil

Overall Survival

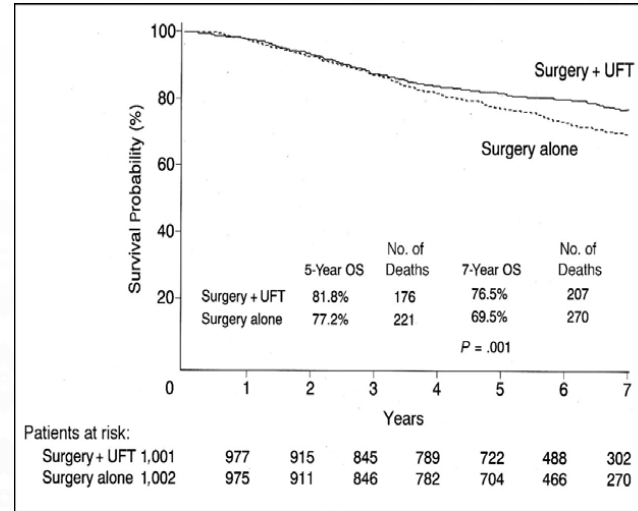


Hamada C et al. J Clin Oncol 2005;23:4999

Adjuvant Therapy for Stage IA NSCLC



ANITA trial. Lancet Oncology 2006;7:719



UFT Meta-Analysis. J Clin Oncol 2005;23:4999

Conclusions:

- For Japanese population with completely resected Stage IA NSCLC, adjuvant therapy with UFT improves long term survival
- For Caucasian population with completely resected Stage IA NSCLC, there is no evidence that adjuvant therapy with platinum-based chemotherapy improves survival

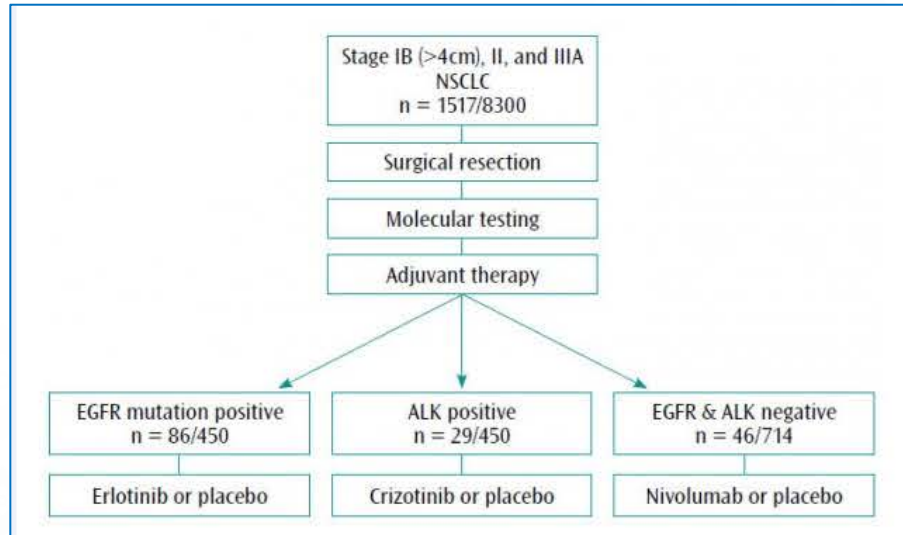
Limitations to trials evaluating adjuvant chemotherapy after lung cancer surgery

- Challenges of accruing patients with specific T and N status
 - Meta-analyses compiling individual patient data from trials
- Difficult for patients to complete adjuvant therapy in clinical trials
 - 30% dropout rate
- Increasing recognition that population differences (ethnicities, gender, etc.) make generalization problematic
 - Genetic differences in response to treatment
 - Tumor sensitivity to drug
 - Drug metabolism
 - Drug toxicities

Future Directions: Clinical trials evaluating adjuvant therapy after curative intent lung cancer surgery – Targeted therapies and Immunotherapy

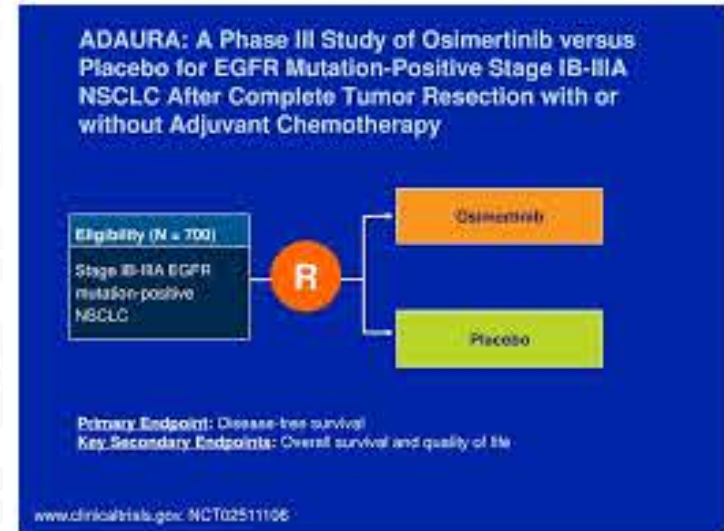
ALCHEMIST

- Stage IB (>4 cm) – IIIA NSCLC
- Complete surgical resection



ADAURA

- Stage IB – IIIA NSCLC
- Complete surgical resection



Adjuvant Chemotherapy After Lung Cancer Surgery

Clinical situations where adjuvant therapy should be given

Stage IIb	T1-2, N1, M0	Identified pre-operatively or post-operatively
Stage IIIa	T1-2, N2, M0 T3, N1, M0 T4, N0, M0	Identified pre-operatively or post-operatively

Clinical situations where adjuvant therapy could be considered (N0)

Stage IIB	T3, N0, M0	Identified pre-operatively or post-operatively, based on “high risk” features
Stage IIa	T2b ₄₋₅ , N0, M0	Identified pre-operatively, or post-operatively, based on “high risk” features
Stage Ib	T2a ₃₋₄ , N0, M0	Identified post-operatively, based on “high risk” features
Stage Ia	T1, N0, M0	In Japanese population

Future Directions: Adjuvant therapy for Stage I-IIIa tumors with targetable mutations or responsive to immunotherapy