

Multi-modality Treatments for Lung Cancer

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Contents

- **Adjuvant therapy (Stage I, II and IIIA)**
- **Neoadjuvant therapy (Stage IIIA)**
- **Definitive therapy w/o surgery (Stage IIIA)**
- **Others**

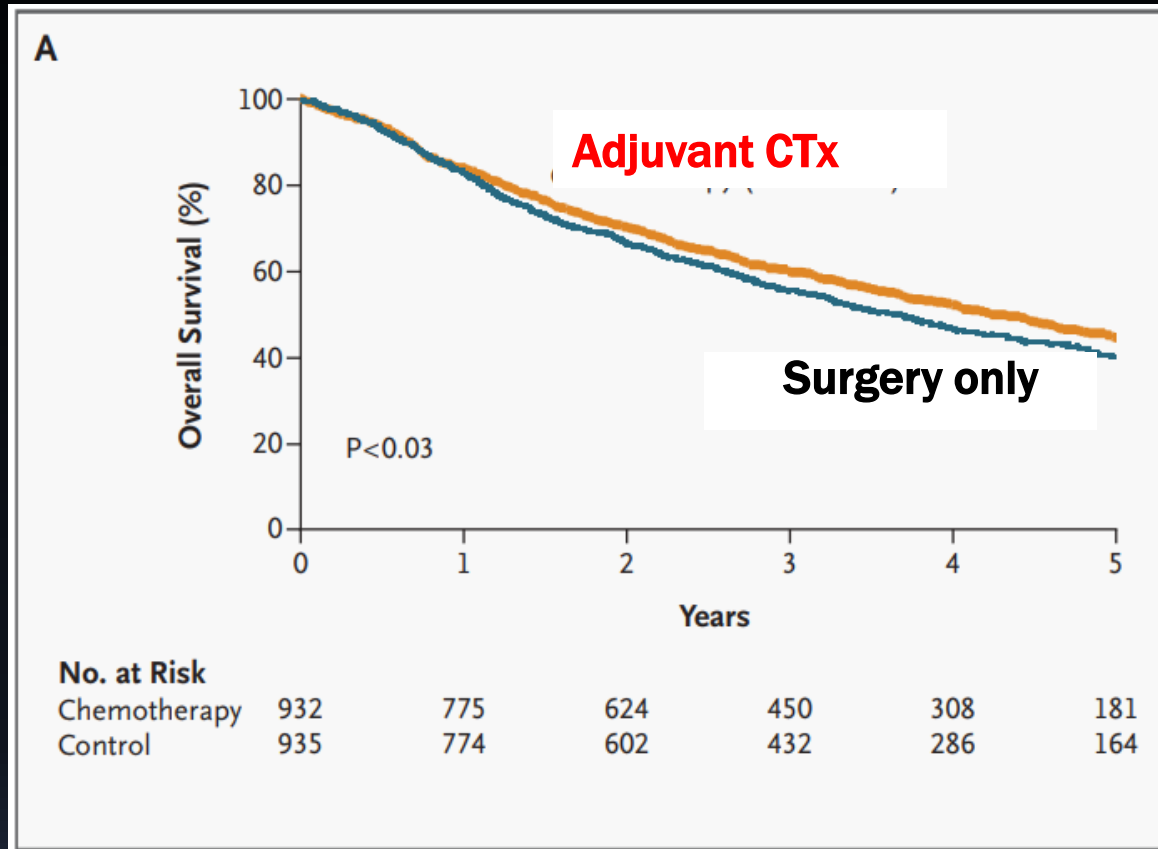
Adjuvant therapy

Adjuvant Chemotherapy

- **High postoperative relapse**
- **Most of the relapses : systemic**
(lung, bone, CNS, adrenal, etc)
- **Earlier proof of benefit : breast, colorectal ca..**

IALT trial results (2004; stages I-III)

*The International Adjuvant Lung Cancer Trial Collaborative Group; NEJM2004;350;351-60



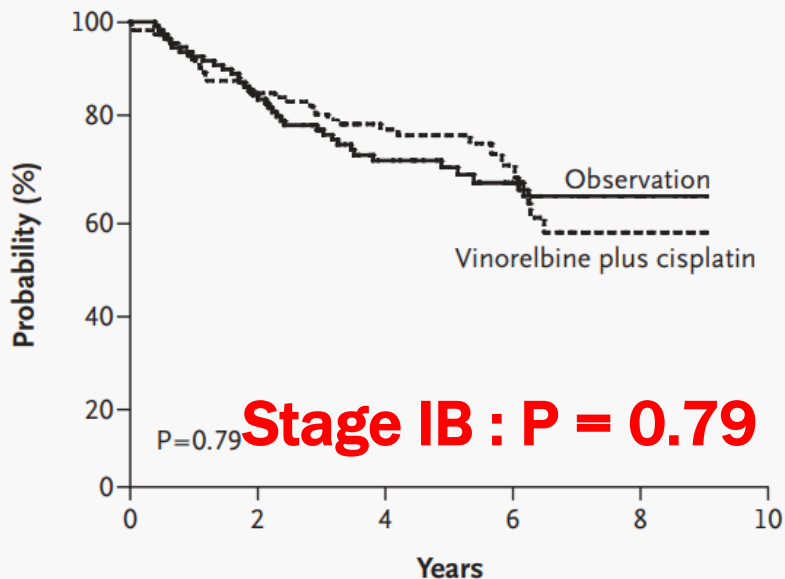
Adjuvant CTx : higher survival rate than observation

5y OS Adjuvant CTx: 44.5% vs Surgery only: 40.4%

HR 0.86 (95% CI, 0.76-0.98; $P < 0.03$)

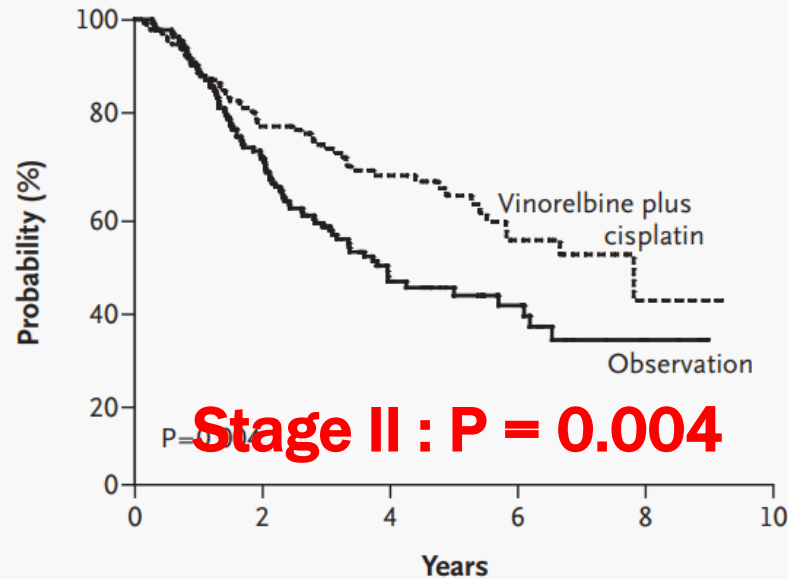
JBR.10 trial results (2005; stages 1B-II)

C Overall Survival, Patients with Stage IB Non-Small-Cell Lung Cancer



No. at Risk		0	2	4	6	8	10
Observation	108	91	57	29	8	0	0
Vinorelbine plus cisplatin	111	93	65	27	6	0	0

D Overall Survival, Patients with Stage II Non-Small-Cell Lung Cancer



No. at Risk		0	2	4	6	8	10
Observation	132	91	37	18	5	0	0
Vinorelbine plus cisplatin	131	100	56	24	4	0	0

Adjuvant CTx : higher survival rate than observation

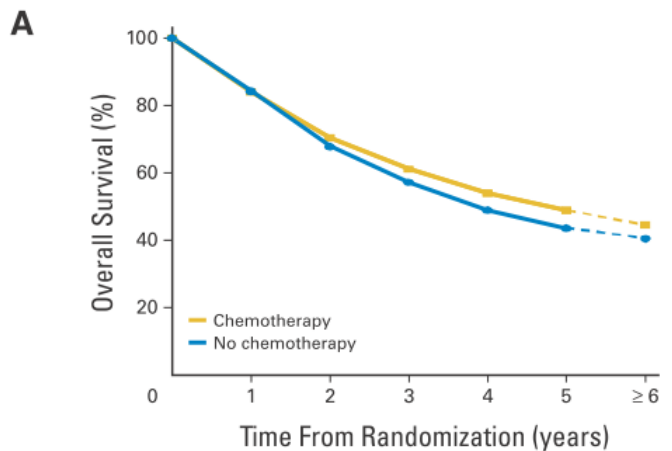
5y OS Adjuvant CTx: 69% vs Surgery only: 54% (P = 0.003)

Benefit from adjuvant CTx : Stage II or more

Meta-analysis

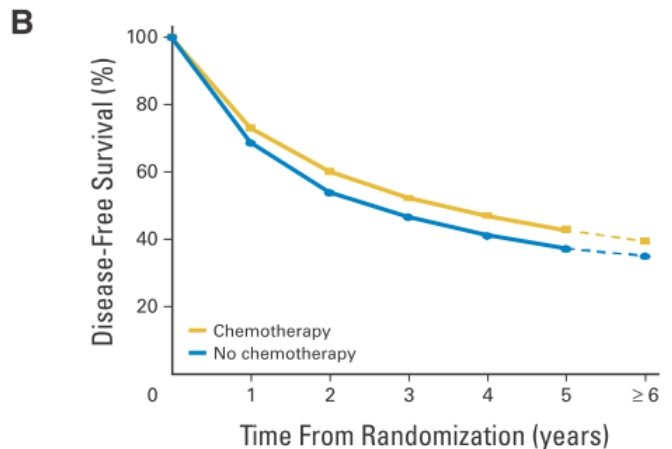
LACE Collaborative Group

J Clin Oncol 2008;26:3552-3559



Deaths / person years by period

	Years 0-3	Years 4-5	Years ≥ 6
Control	966 / 5,155	239 / 1,668	49 / 720
Chemotherapy	857 / 5,181	203 / 1,817	76 / 790



- stage I,II, + III (27%)
- **5yr absolute benefit : 5.4%**
- HR for stage IA = 1.40 (0.95 to 2.06)
- HR for stage IB = 0.93 (0.78 to 1.10)
- HR for stage II = 0.83 (0.73 to 0.95)
- HR for stage III = 0.83 (0.72 to 0.94)

Non-Small Cell Lung Cancer

Version 4.2018 — April 26, 2018

- Stage IA Surgery -> Observe
- Stage IB Surgery -> Observe or Chemotherapy (*high risk)
- Stage II Surgery -> Chemotherapy (category 1)
- Stage IIIA Surgery -> Chemotherapy (category 1)

***High risk:** PD tumors (ex. Neuroendocrine tumors, vascular invasion, wedge resection, tumors > 4 cm, VPI (+), Nx, etc

Multi-modality for N2 NSCLC

; Neoadjuvant treatment

; Definitive CCRT

N2 NSCLC

- Heterogeneity of N2 disease

Subset	Description
	➔ Resectable
	➔ Potentially resectable
	➔ Unresectable

Surgery

- No role for single modality treatment
- IIIA₁, IIIA₂ : resectable → Surgery + adjuvant therapy
- IIIA₃ : potentially resectable → Surgery ?
- IIIA₄ : unresectable → No surgery

NCCN guideline

IIIA₁, A₂

Surgical exploration and resection^k + mediastinal lymph node dissection or systematic lymph node sampling^l

Stage IIIA
(T1-3, N2;
T3, N1)

Margins negative
(R0)^m

Chemotherapy^p (category 1) + RTⁱ

Margins positive
(R1, R2)^{m,n}

Chemoradiation^{i,j,n} + chemotherapy^{j,p}

IIIA₃

T1-2, T3
(other than
invasive),
N2 nodes
positive, M0

Definitive concurrent
chemoradiation^{l,q} (category 1)

Durvalumab^q

[Surveillance \(NSCL-15\)](#)

Induction
chemotherapy^{o,w} ± RT^l

No apparent
progression

Surgery^k ± chemotherapy^o (category 2B)
± RT^l (if not given)

Progression

Local → RT^l (if not given) ± chemotherapy^o

Systemic → [See Treatment for Metastasis limited sites \(NSCL-13\) or distant disease \(NSCL-16\)](#)

How can we select the surgical candidates?

Mediastinal LN staging

Chest CT

- **>1 cm short axis diameter with standard CT scan**
- **sensitivity 57%, specificity 82%**

Chest 2003;123:137S

PET

- **meta-analysis**
15%~26% PET (-) & pathologic N2 (+)
- **recent single institutional study**
6%~16% PET (-) & pathologic N2 (+)

Ann Intern Med 2003;139:879

EBUS + EUS

- **sensitivity 91.1%, specificity 100%**

Chest 2010;138:795

Prognostic factor

- **Single-station** > multi-station
- **Clinical N factor**
 - unsuspected N2 (cN0-1) > known cN2
- **Complete resection** > incomplete
- **Anatomic site of N2**
 - Level 7,8, and 9 < all other levels
- Lower T stage
- Skip metastasis > pN1+
- Mediastinal dissection vs sampling?
 -
 -
 -

Detterbeck, J Thorac Oncol. 2008;3:289

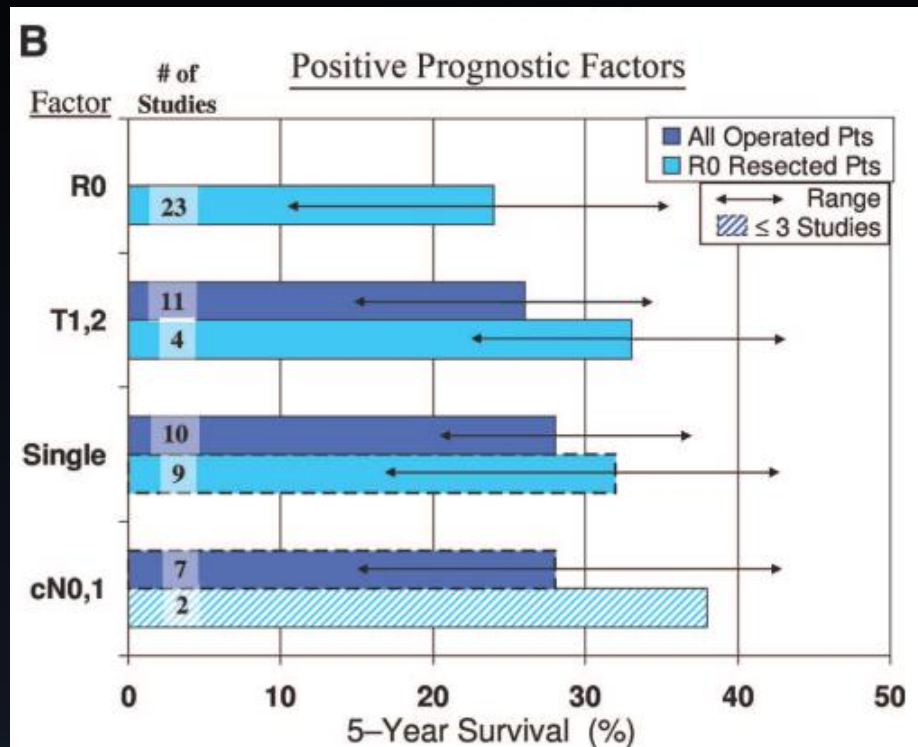
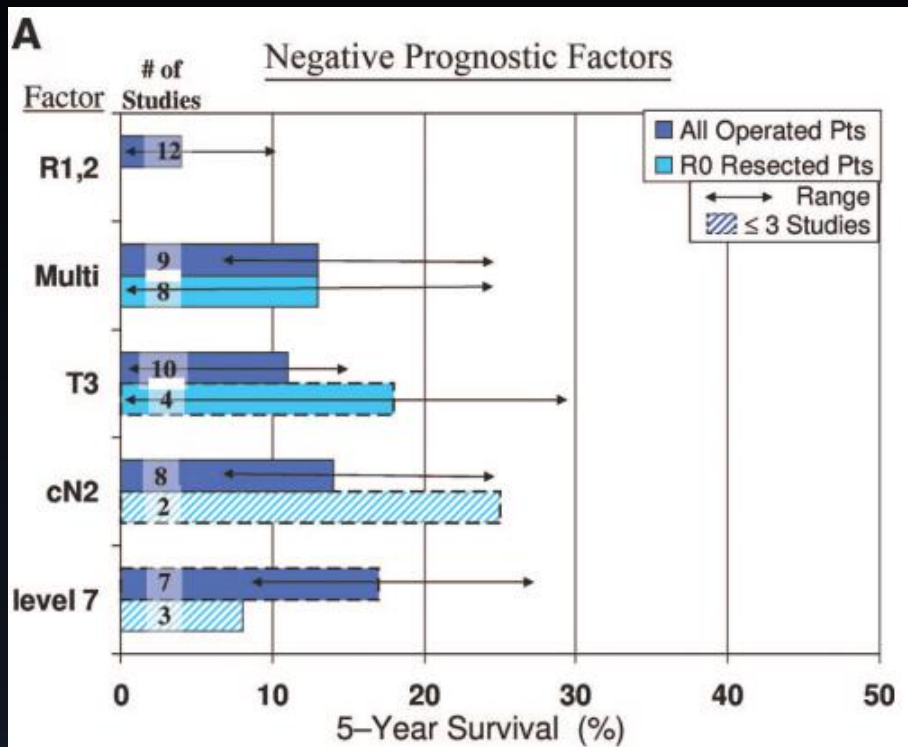
Prognostic factor

TABLE 2. Multivariate Analyses of Factors Predicting Poor Survival in pN2 Patients^a

Study	n	Multilevel	Node Level						T3,4	Larger Size	Lower Lobe	Pneum	Adeno/Large	Older Age
			cN2	R1,2	N1+	7	5	1,2						
Andre et al. ²⁹	702	<0.0001	<0.0001	NS	—	—	—	—	<0.0001	—	—	—	NS	—
Ichinose et al. ⁴⁶	406	<0.0001	NS	—	<0.03	—	—	—	<0.05 ^b	—	—	NS	NS	0.02
Riquet et al. ³¹	237	<0.05	—	<0.05	NS	NS	NS	NS	NS	NS	NS	NS	NS	—
Suzuki et al. ²⁴	222	<0.001	<0.001	0.02	—	—	—	—	NS	0.001	—	NS	NS	NS
Miller et al. ²⁸	167	<0.05	—	NS	—	<0.05	NS	(NS) ^c	NS	—	—	<0.05	NS	<0.05
Thomas et al. ³³	163	<0.02	—	—	—	NS	—	NS	NS	—	—	—	NS	—
Tanaka et al. ³⁴	155	NS	NS	0.001	—	—	—	—	0.03	—	—	—	NS	NS
Inoue et al. ⁹¹	154	0.005	<0.001	—	—	—	—	—	NS	—	<0.04	—	0.002	0.007
Iwasaki et al. ⁹³	142	NS	—	—	NS	0.002	—	—	NS	—	—	NS	NS	NS
Vansteenkiste et al. ²⁷	140	0.03	0.04	NS	—	NS	NS	(NS) ^c	0.003	—	NS	NS	0.03	NS
Tanaka et al. ⁹⁶	99	0.01	<0.04	—	—	—	—	—	NS	—	—	—	NS	NS
Ohta et al. ⁹⁷	94	—	NS	—	0.03	<0.001	—	NS	<0.001	NS	NS	—	NS	NS
Prognostic value^d		High	Mod	Mod	Mod	Mod	—	—	Low	Low	Low	—	—	Low

Detterbeck, J Thorac Oncol. 2008;3:289

Survival



Detterbeck, J Thorac Oncol. 2008;3:2892

Unsuspected N₂ (III A₁, III A₂)

Adjuvant chemotherapy

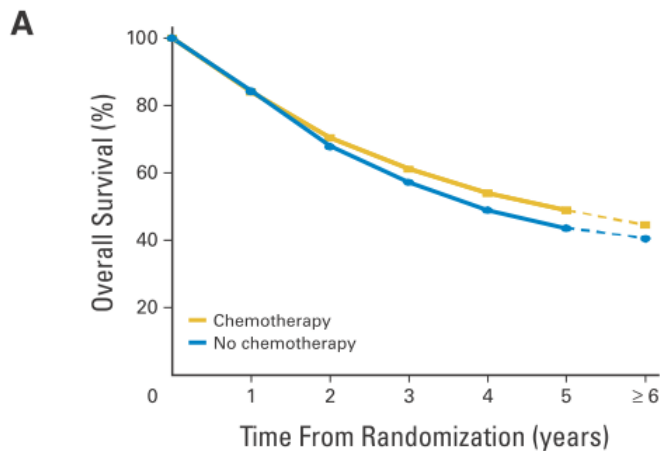
Resectable N2 (IIIA₁/IIIA₂)

- Complete resection + **adjuvant chemotherapy**
- **Level of evidence (NCCN): category 1**
- Several meta-analyses & RCTs (stage I, II, and IIIA)
- No large RCT designed to include only N2 disease

Meta-analysis

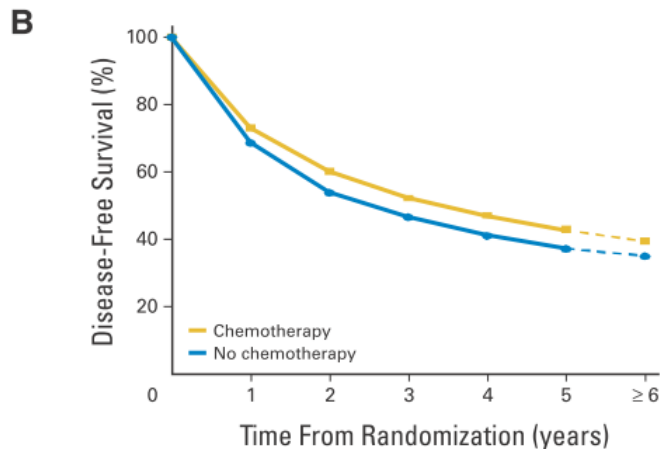
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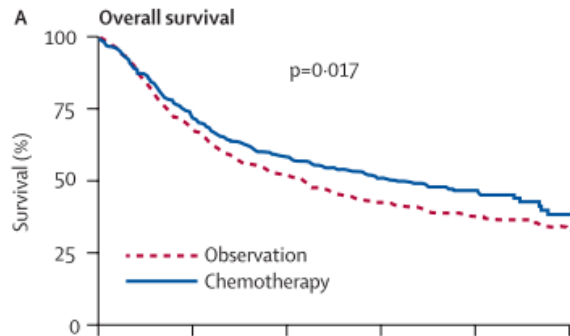
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- **HR for stage III = 0.83 (0.72 to 0.94)**

RCT

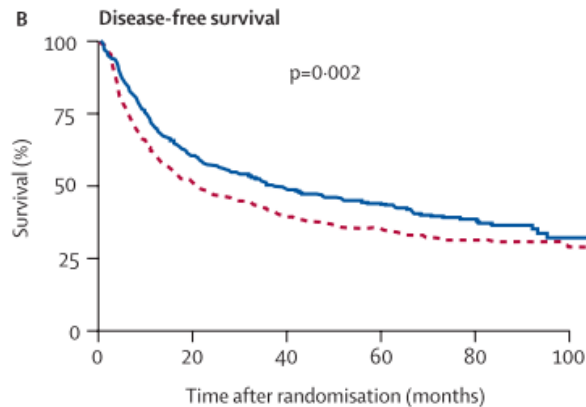
ANITA trial

Lancet Oncol 2006;7:719-27

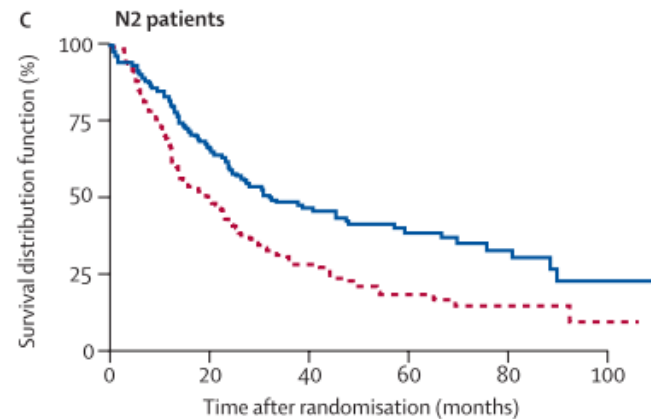
- stage IB,II, + IIIA (39%)
- vinorelbine+cisplatin vs observation
- **5yr overall survival benefit : 8.6%**
- **HR for N2 = 0.60 (0.44-0.82)**



Number at risk	0	20	40	60	80	100
Observation	433	293	211	119	65	17
Chemotherapy	407	288	228	144	63	18



Number at risk	0	20	40	60	80	100
Observation	433	217	160	95	50	15
Chemotherapy	407	239	191	130	57	16



Number at risk	0	20	40	60	80	100
Chemotherapy	118	77	53	29	13	2
Observation	106	52	27	13	7	1

Adjuvant radiation

Potential benefit

- Reduce the risk of loco-regional recurrence
- Overall survival ?

Indication

- Close or positive surgical margin
- Involvement of multiple nodal stations
- Extracapsular tumor spread

Adjuvant radiation

PORT Meta-analysis Trialists Group

Cochrane Database Syst Rev. 2005

- PORT vs surgery alone, 10 RCTs
- N0-1 subset : increased mortality
- N2 subset : no difference in overall survival

SEER database

J Clin Oncol 2006;24;2998

- Retrospective study
- N2 subset : superior survival rate HR = 0.86 (0.76-0.96)

Adjuvant radiation

From ANITA trial

*Int. J. Radiation Oncology
Biol. Phys 2008;3:695*

- Non-randomized sub-analysis of ANITA trial

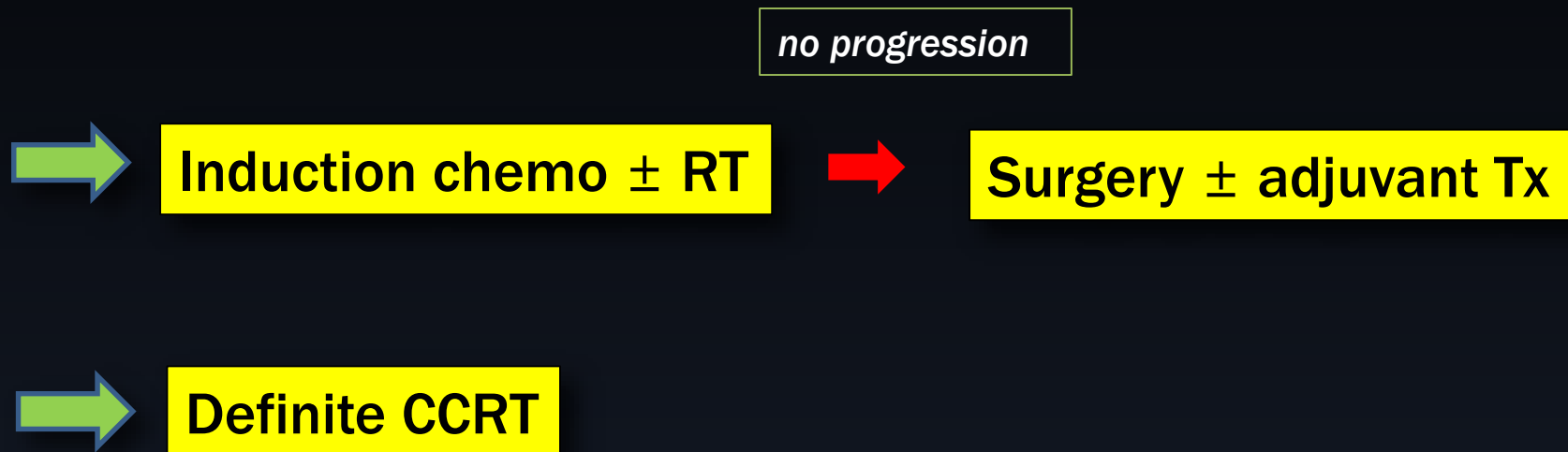
Treatment group	pN0	pN1	pN2
Observation (%)	62.3	31.4	16.6
Observation + PORT (%)	43.8	42.6	21.3
Chemotherapy* (%)	59.7	56.3	34.0
Chemotherapy* + PORT (%)	44.4	40.0	47.4

preferably after completion of adjuvant chemotherapy !

Clinical N2 (III A₃)

Surgical multimodality vs CCRT (definite)

- IIIA₃ (potentially resectable)



Neoadjuvant chemotherapy

Proposed benefits

- A reduction in tumor size → resectability ↑
- Early eradication of micrometastases
- Down-staging of mediastinal LN's
- In vivo test of chemosensitivity
- Better tolerability (> adjuvant chemo)

Response rate : 50~70%

Complete resectability : 50~90%

Median 5yr survival : 20%~30%

Neoadjuvant chemotherapy

Disadvantages

- **Increased morbidity and mortality**
- **Ineffective induction regimen**
- **Progression of resectable disease**

Neoadjuvant chemotherapy

Meta-analysis

J Thorac Oncol. 2010;5:510

• Neoadjuvant CTX + Surgery Vs Surgery alone

Study or Subgroup	NC		SUR		O-E	Variance	Weight	Hazard Ratio		Year	Hazard Ratio	
	Events	Total	Events	Total				Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI			
Roth	19	28	27	32	-6.38	11.15	4.1%	0.56	[0.31, 1.01]	1998		
Rosell	25	30	30	30	-9.38	13.64	5.0%	0.50	[0.30, 0.85]	1999		
Zhou	206	314	235	310	-12.24	89.77	33.0%	0.87	[0.71, 1.07]	2001		
Depierre	51	72	40	50	0.89	22.42	8.2%	1.04	[0.69, 1.57]	2002		
JCOG	28	31	24	31	2.26	12.92	4.7%	1.19	[0.69, 2.05]	2003		
Liao	32	37	24	28	4.144	15.31	5.6%	1.31	[0.79, 2.16]	2003		
Li	59	77	47	60	-10.03	26.2	9.6%	0.68	[0.46, 1.00]	2003		
Yao	154	234	171	222	-15.19	81.03	29.7%	0.83	[0.67, 1.03]	2004		
Total (95% CI)		823		763			100.0%	0.84	[0.75, 0.95]			
Total events	574		598									
Heterogeneity: Chi ² = 12.27, df = 7 (P = 0.09); I ² = 43%												
Test for overall effect: Z = 2.78 (P = 0.005)												

• Stage III; combined HR=0.84 (0.75 to 0.95)

• No large RCT designed to include only N2 disease

Surgical multimodality vs Chemoradiation

EORTC 08941

**Histologic proven,
unresectable IIIA-N2**

J Natl Cancer Inst 2007;99:442

**Platinum based (x3)
Induction CTX**

Responder

Randomized

**RT (60 Gy)
N= 165**

**Surgery ± RT
N= 167**

EORTC 08941

	RT arm (N = 165)	Surgery arm (N = 167)	<i>P</i>
R0 resection		50%	
Down staging		41%	
pathologic CR		5%	
Treatment related mortality	0.7%	4%	
pneumonectomy		7%	
2yr progression-free survival (%)	24 (18 to 31)	27 (20 to 33)	NS
5yr survival (%)	14. (9 to 20)	15.7 (10 to 22)	NS

EORTC 08941

	RT arm (N = 165)	Surgery arm (N = 167)	<i>P</i>
R0 resection		50%	
Down staging		41%	
pathologic CR		5%	
Treatment related mortality	0.7%	4%	
pneumonectomy		7%	
2yr progression-free survival (%)	24 (18 to 31) ≈	27 (20 to 33)	NS
5yr survival (%)	14. (9 to 20) ≈	15.7 (10 to 22)	NS

Intergroup 0139

**Histologic proven N2
Technically resectable**

Lancet 2009;374:379

Randomized

**Concurrent
CTx/RT**

**Concurrent
CTx/RT**

Surgery

RT (60 Gy)

**Consolidation
Cisplatin/Etoposide #2**

Intergroup 0139

	CT/RT/S (N = 202)	CT/RT (N = 194)	<i>P</i>
R0 resection	71%		
Down staging	38%		
pathologic CR	12%		
Treatment related mortality	8%	2%	
lobectomy	1%		
pneumonectomy	26%		
5yr progression-free survival (%)	22.4	11.1	0.017
5yr survival (%)	27.2	20.3	NS
5yr survival (% , lobectomy matched)	36	18	0.002

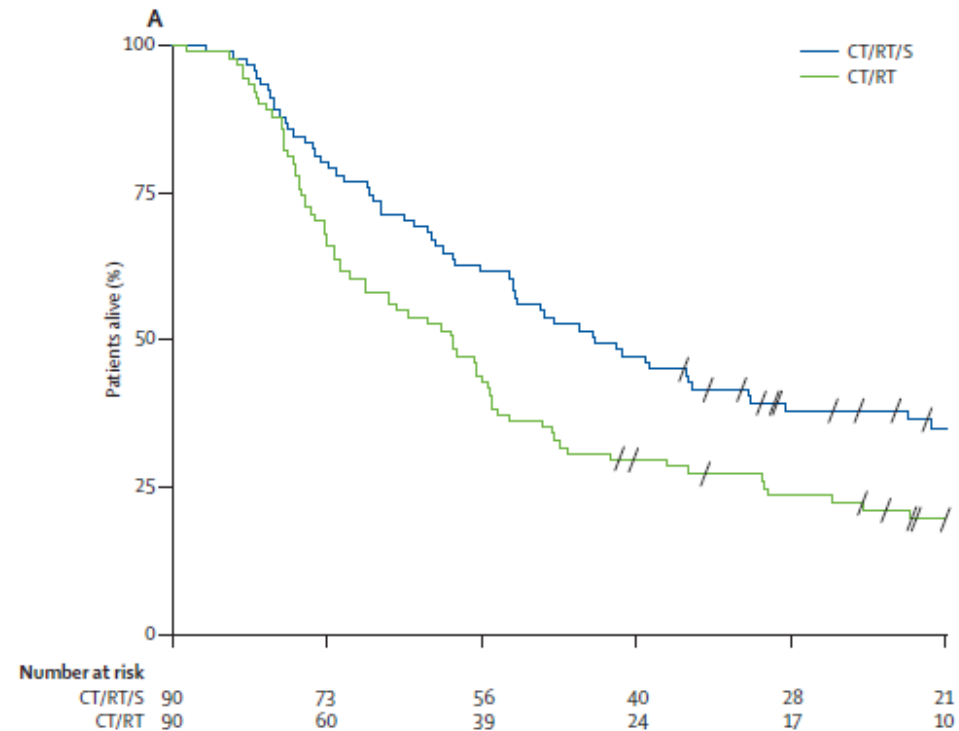
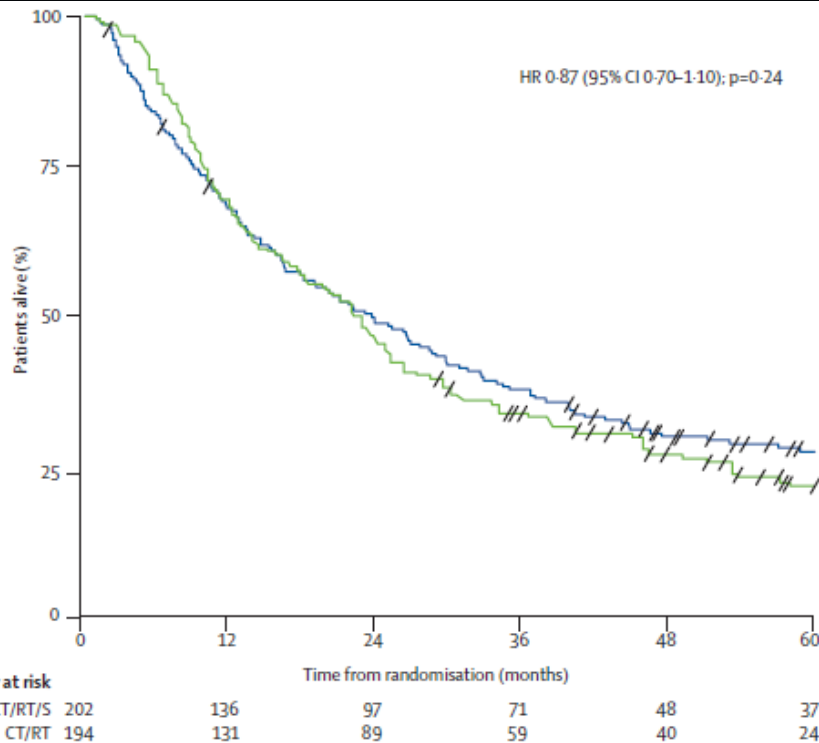
Intergroup 0139

	<u>CT/RT/S</u> (N = 202)		CT/RT (N = 194)	P
R0 resection	71%			
Down staging	38%			
pathologic CR	12%			
Treatment related mortality	8%		2%	
lobectomy	1%			
pneumonectomy	26%			
5yr progression-free survival (%)	22.4	>	11.1	0.017
5yr survival (%)	27.2	NS	20.3	NS
5yr survival (%, lobectomy matched)	36	>	18	0.002

Intergroup 0139

OS by treatment arm

OS by matched lobectomy subset



CTx + RT with or without resection (preferably lobectomy)



Treatment options for N2 disease.

Conclusions

- **Multidisciplinary evaluation (which includes a thoracic surgeon) is recommended before embarking on definitive treatment.**
- **Surgery alone is not enough to cure the majority of patients even with resectable disease.**
- **Need of multimodality approach to the treatment.**