


# **MANAGEMENT OF STAGE IIIA NON- SMALL CELL LUNG CANCER**

**Do we need surgery??**

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What is IIIA??

# Revised TNM Subgroups As Suggested by RPA on 17,726 “Best Stage” Cases

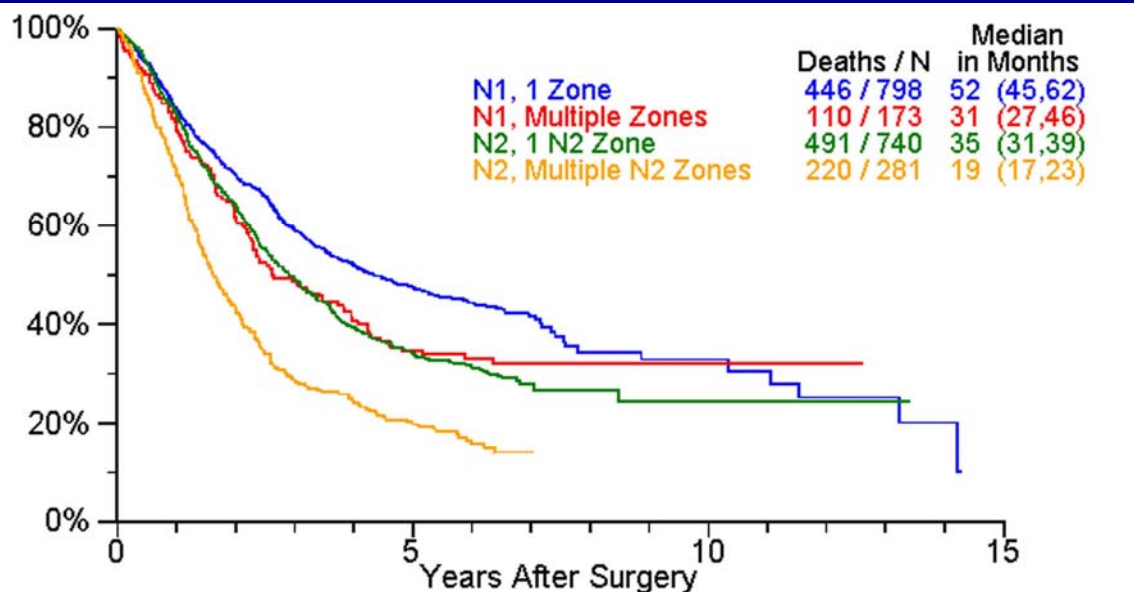
 = Change in Classification

T and M		N0	N1	N2	N3
UICC6 and Descriptor	New T/M	Stg	Stg	Stg	Stg
T1 (<=2cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2 – 3 cm)	T1b	IA	IIA	IIIA	IIIB
T2(<=5cm)	T2a	IB	IIA <b>IB</b>	IIIA	IIIB
T2 (>5-7cm)	T2b	IIA <b>IB</b>	IIIB	IIIA	IIIB
T2 (>7cm))	T3	IIIB <b>IB</b>	IIIA <b>IIIB</b>	IIIA	IIIB
T3 invasion		IIIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		IIIB <b>IIIB</b>	IIIA <b>IIIB</b>	IIIA <b>IIIB</b>	IIIB
T4 (extension)	T4	IIIA <b>IIIB</b>	IIIA <b>IIIB</b>	IIIB	IIIB
M1 (ipsilateral lung)		IIIA <b>IV</b>	IIIA <b>IV</b>	IIIB <b>IV</b>	IIIB <b>IV</b>
T4 (pleural effusion)	M1a	IV <b>IIIB</b>	IV <b>IIIB</b>	IV <b>IIIB</b>	IV <b>IIIB</b>
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

## Series Reporting Outcomes after Resection for NSCLC with N2 Disease

<i>Authors (Year)</i>	<i>No. Pts.</i>	<i>5-yr Survival (%)</i>			
		<i>Overall</i>	<i>Single Level</i>	<i>Multi Level</i>	<i>p</i>
<b>Martini et al. (1983)</b>	<b>151</b>	<b>29</b>	<b>25</b>	<b>33</b>	<b>NR</b>
<b>Goldstraw et al. (1994)</b>	<b>149</b>	<b>20.1</b>	<b>30 (3 yr)</b>	<b>25 (3 yr)</b>	<b>0.05</b>
<b>Riquet et al. (1995)</b>	<b>237</b>	<b>18.8</b>	<b>26.3</b>	<b>8.3</b>	<b>0.0003</b>
<b>Andre et al. (2000)</b>	<b>702</b>	<b>18</b>	<b>25</b>	<b>7</b>	<b>&lt;0.0001</b>
<b>Naruke et al. (2001)</b>	<b>736</b>	<b>19.9</b>	<b>NR</b>	<b>NR</b>	<b>NR</b>
<b>Ichinose et al. (2001)</b>	<b>402</b>	<b>31</b>	<b>43</b>	<b>17</b>	<b>&lt;0.0001</b>
<b>IASLC database</b>	<b>5770</b>	<b>22</b>			

# Survival by N Status and Number of Involved N Zones



	1 Yr	5 Yrs		HR	P
<b>N1a</b>	86%	48%			
<b>N1b</b>	79%	35%	vs N1a:	1.32	<.0090
<b>N2a</b>	83%	34%	vs N1b:	1.04	0.7137
<b>N2b</b>	71%	20%	vs N2a:	1.65	<.0001

**“Bulky” N2 considered unresectable!!!**

**How large N2 is “bulky”?**

**What is “bulky”?**

# IASLC consensus report

Expert  
opinion

Chemo-radiotherapy remains the standard treatment approach for patients with advanced stage III disease and good PS

Role of surgery following **the optimal induction therapy** in the patients is not conclusively defined and evidence from randomized trials is needed

# **N2 NSCLC**

## **Surgical Multimodality vs CT+RT?**

- **Lung Intergroup Trial R0139**
- **EORTC Trial 08941**

# IIIA-N2: T1-3 N2

## Lung Intergroup Trial R0139

Potentially **resectable** T1-T2-T3 N2(mediast)

Randomised

Concurrent **low-dose** RT with cisplatin  
and etoposide X 2

Concurrent **low dose** RT with cisplatin  
and etoposide X 2

**Continue RT to 61 Gy**

**Surgery**

Consolidation  
Cisplatin and etoposide X 2

# Lung Intergroup Trial 0139 Study Design

STRATIFY



KPS 70-80 vs 90-100  
T1 vs T2 vs T3



RANDOMIZE

Induction  
CT/RT

Cisplatin, 50 mg/m<sup>2</sup> IV d1, 8, 29, 36  
Etoposide, 50 mg/m<sup>2</sup> IV d1-5, 29-33  
Thoracic RT, 45 Gy (1.8 Gy/d), begin d1

RE-EVALUATE

2-4 weeks after  
completion of RT



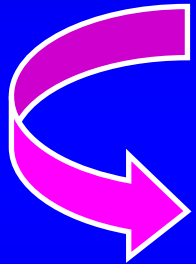
RE-EVALUATE

7 days before  
completion of RT

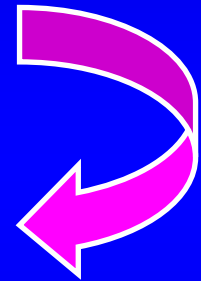
# Lung Intergroup Trial 0139 Study Design



**No progression at  
re-evaluation**



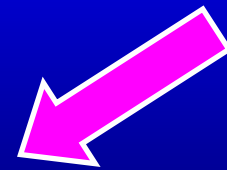
**Surgical  
Resection**



**Add 16 Gy without  
interruption**



**CONSOLIDATION  
cisplatin plus etoposide  
X 2 cycles**

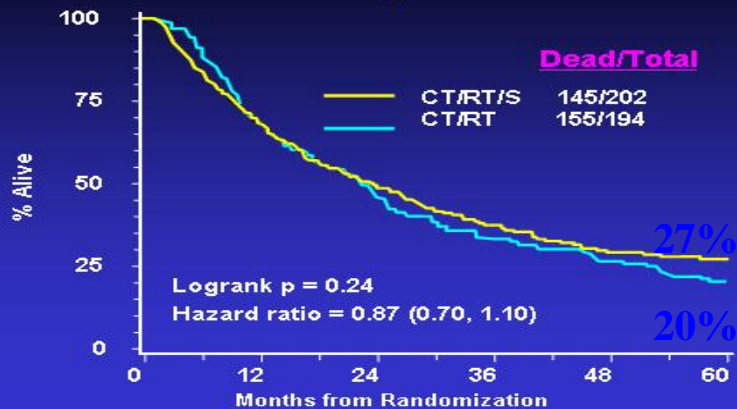


# Intergroup trial

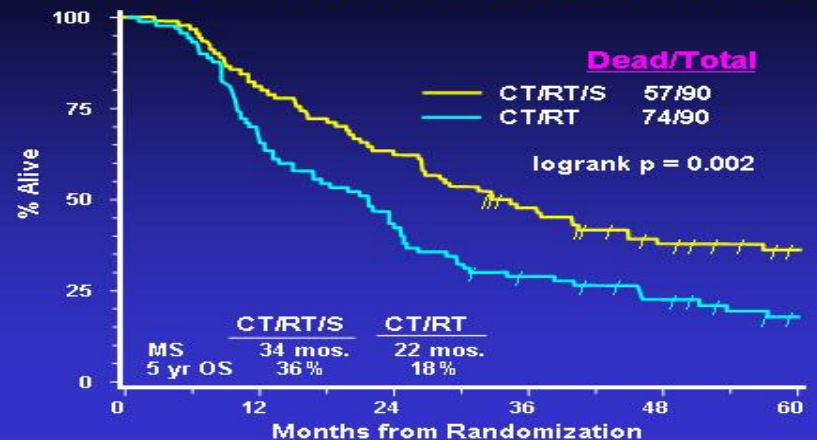
Albain et al., ASCO 2005

	CT+S	CT+ RT	
pNO	46%		
R0	88%		
Overall survival (5 year)	27%	20%	p=NS
Progression-free survival (2 year)	22%	11%	P=0.017
Treatment related mortality	7%	1.6%	
Lobectomy subset versus matched CT/RT subset (5 year survival)	36%	18%	P=0.002

**Intergroup 0139/RTOG 9309  
Overall Survival by Treatment Arms**

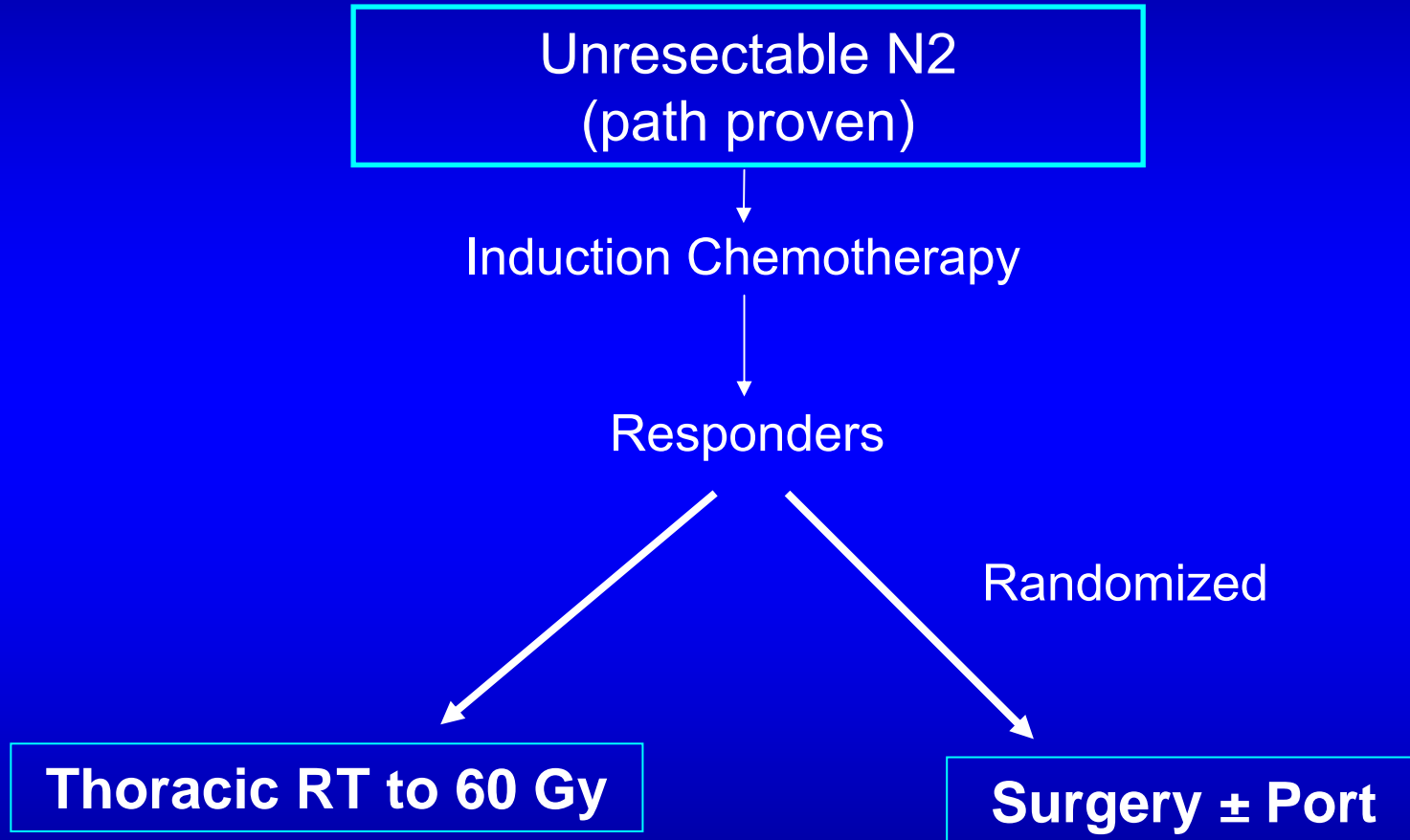


**INT0139 Overall Survival of the Lobectomy Subset versus Matched CT/RT Subset**



# IIIA-N2: T1-3 N2

## EORTC 08941



# EORTC 08941

	CT+S ( ± Port)	CT+ RT	
<b>pNO</b>	<b>42%</b>		
<b>R0</b>	<b>50%</b>		
<b>Overall survival (5 year)</b>	<b>16%</b>	<b>14%</b>	<b>p=NS</b>
<b>Progression-free survival (2 year)</b>	<b>26.5%</b>	<b>24.2%</b>	<b>P=NS</b>
<b>Treatment related mortality</b>	<b>6%</b>	<b>NA</b>	

# EORTC Trial 1994 – 2002

## Experience of center and thoracic surgeon?

41 centers randomised 331 patients in 8 years

13 centers randomised  $\geq 10$  patients

5 centers randomised 4 – 9 patients

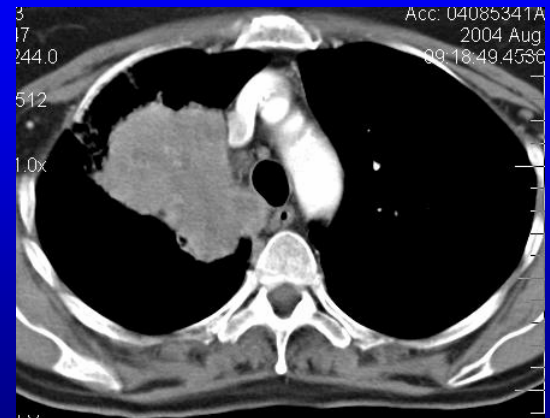
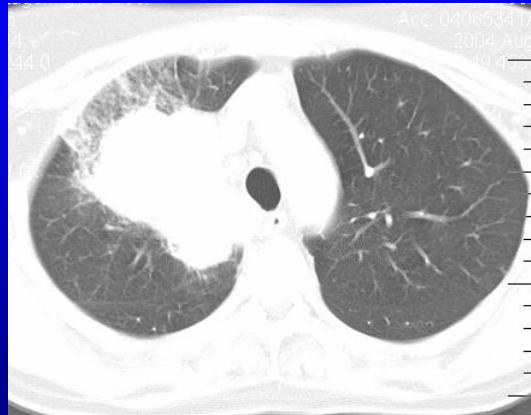
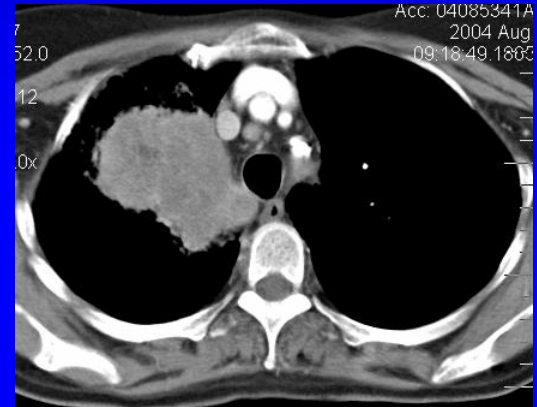
23 centers randomised  $\leq 3$  patients

**Any reason to believe that it is different  
for radiotherapy?**

**No!**

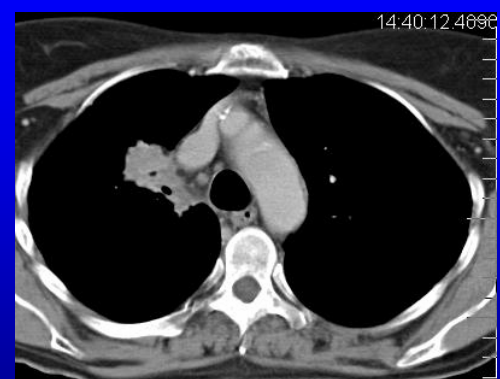
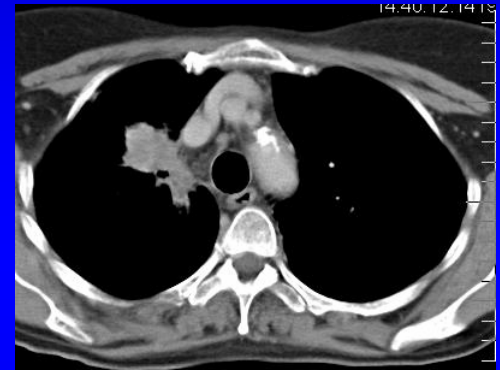
# Repopulation after chemotherapy (1)

Pre-chemo



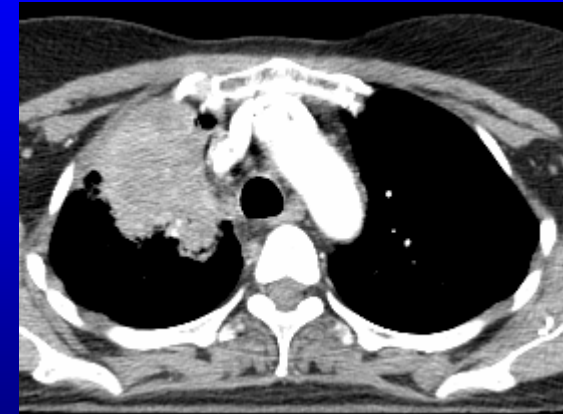
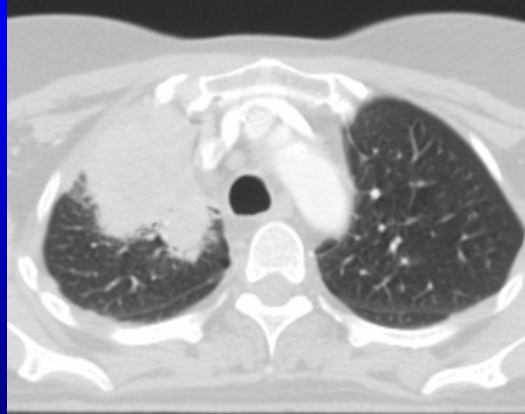
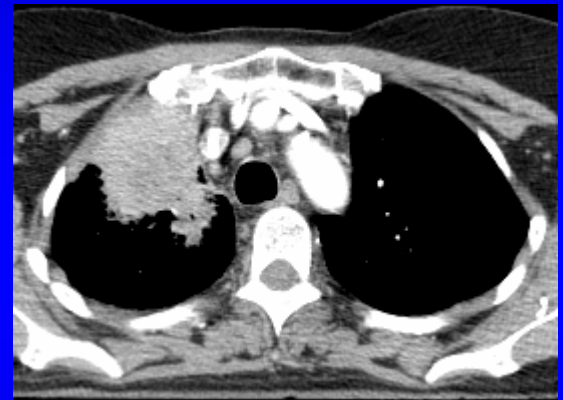
# Repopulation after chemotherapy (2)

Post-chemo



# Repopulation after chemotherapy (3)

Planning scan 7  
wks after last  
chemo.



# Accelerated repopulation after chemotherapy



**PRECLINICAL DATA:** Time factor in chemotherapy.  
Davis & Tannock, Lancet Oncol 2000

**CLINICAL DATA:** El Sharouni *et al*, BJC 2003  
41% of potentially curable patients became 'incurable'  
Tumour doubling times ranged from 8.3 to 171 days

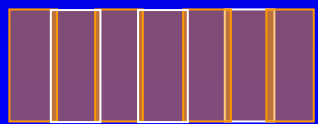
**EORTC 08941 study:** 10 weeks allowed between end of chemotherapy and start of radiotherapy; 249/582 patients went off-study

# Stage III-N2: EORTC 08941 vs INT 0139

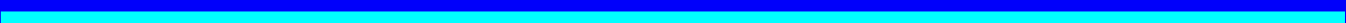
**Chemo-RT completed in 33 days**



INT 0139



**Chemo-radiotherapy completed in 137 days #**



EORTC  
08941

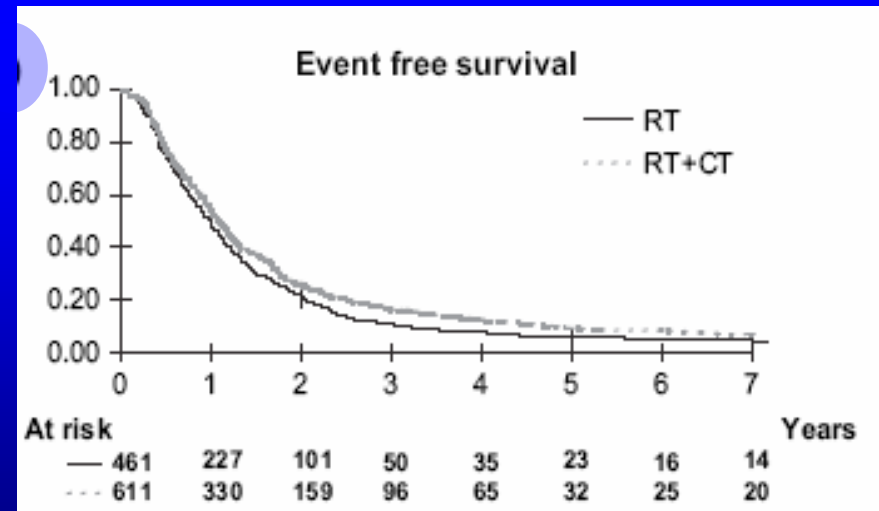
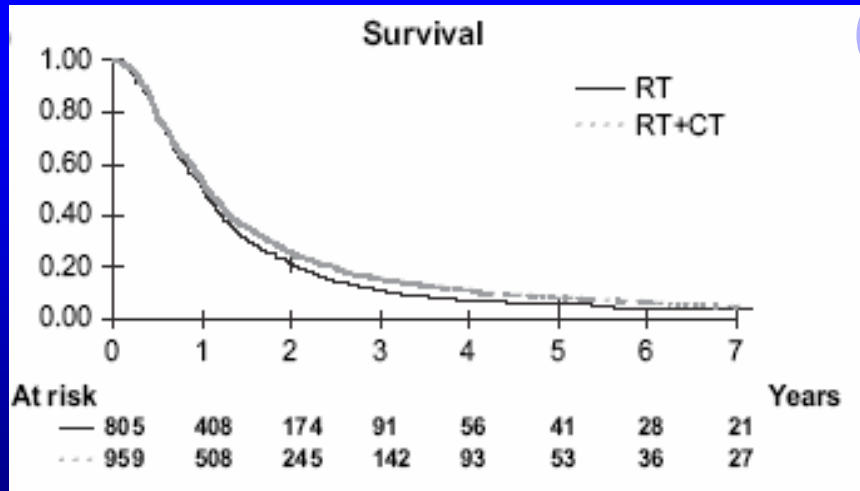


# Median interval chemo-surgery = **49 days** (22-86)

# Meta-analysis of CT-RT vs RT alone

Auperin A, Ann Oncol 2006

- Individual patient data from 9 trials (1764 pts)
- Absolute benefit of chemotherapy was 4% at 2 yrs
- Evidence of heterogeneity among trials.
- Platin and etoposide seemed more effective than platin alone.



# Stage III NSCLC: Overview of randomised trials of sequential vs concurrent CT-RT

		Furuse	RTOG 94-10	Mornex <sup>•</sup>
Median survival	Seq.	13.3 mo	14.6 mo	14.1 mo
	Concur.	16.5 mo	17 mo	15.8 mo
2-year survival	Seq.	27.4 %	31 %	27 %
	Concur.	34.6 %	39 %	38 %
Grd 3-4 esophagitis	Seq.	3 %	4 %	6%
	Concur.	4 %	25 %	31%

Seq. = sequential; concur. = concurrent; <sup>•</sup> Statistically not significant

# Effect of Preoperative Chemoradiation in Addition to Preoperative Chemotherapy in Stage III NSCLC

Prospective randomised trial

German Lung Cancer Cooperative Group (26 institutions)

October 1995 – July 2003

Effect of induction chemoradiotherapy compared with induction chemotherapy

Inclusion : Stage III NSCLC (marginally resectable and unresectable)  
67% had IIIB  
22% had pathological confirmed N3 nodes

# Effect of Preoperative Chemoradiation in Addition to Preoperative Chemotherapy in Stage III NSCLC

	Interventional group (264)	Control group (260)
Surgery (%)	142 (54%)	154 (59%)
Complete resection	98 (37%)	84 (32%)*
% nodal downstaging (pN0-1) after complete resection	<b>45 (46%)</b>	<b>24 (29%)*</b>
5-yr overall survival	21%	18%
5-year PFS	16%	14%

\* : < 0;05

# Effect of Preoperative Chemoradiation in Addition to Preoperative Chemotherapy in Stage III NSCLC

## Mortality After Surgery

	Interventional group (142)	Control group (154)
Overall	9%*	5%
Lobectomy or bilobectomy	7.5%	2.3%
Pneumonectomy	14%	6%

\* 40% : BP fistulae

# conclusions

- There is sufficient evidence that CT-RT is better than CT
- There is evidence that concurrent CT-RT is better than sequential
- There is evidence that surgery even after insufficient dosed RT **harms** (INT)
- “lousy” surgery is not better than “lousy” radiotherapy (EORTC)
- If surgery plays a role, it will only be in a small subset of IIIA N2.
- The appropriate trial to prove that has not been done so far