

# Improving stage III outcome Any perspective?



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# Improving stage III outcome

## Any perspective?

- Introduction
- Multidisciplinary discussion with upfront stratification
- N2 disease
- Pancoast and clinical T3-T4 tumours
- Volume and experience
- Conclusions

# Stage III : heterogenous

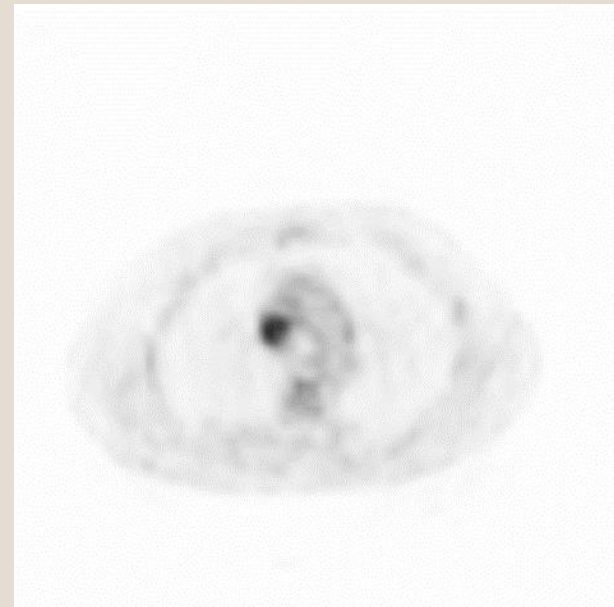
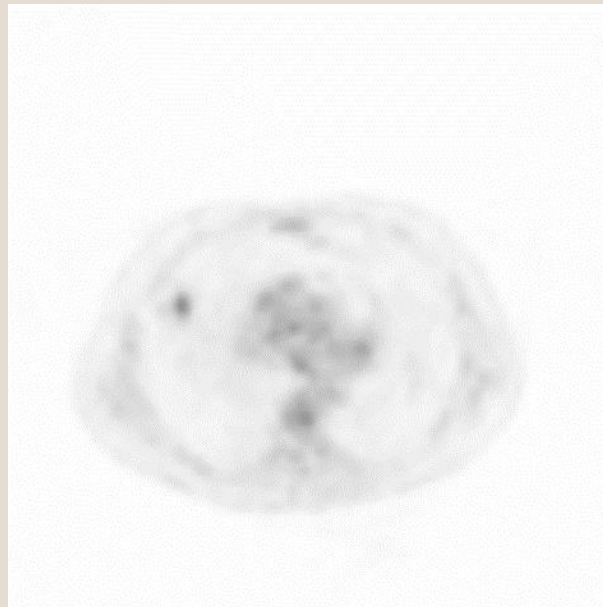
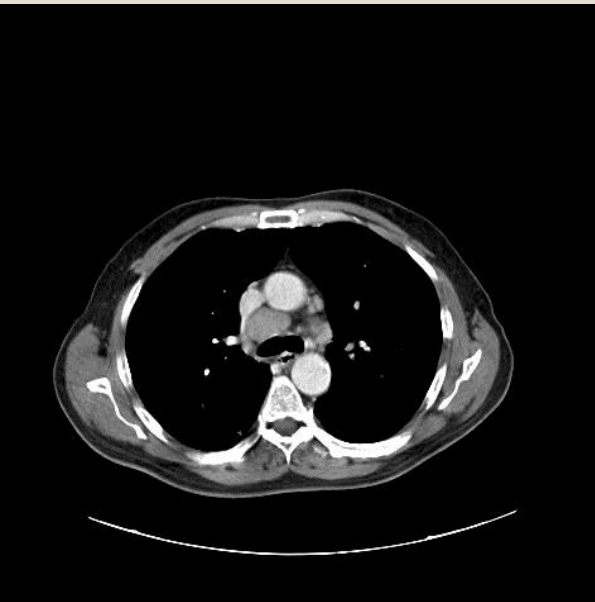
Stage grouping			
Stage IIIA	T1,T2	<b>N2</b>	M0
	T3	N1,N2	M0
	<b>T4</b>	<b>N0,N1</b>	M0
Stage IIIB	T4	N2	M0
	Any T	<b>N3</b>	M0

## Improving stage III outcome

### Any perspective?

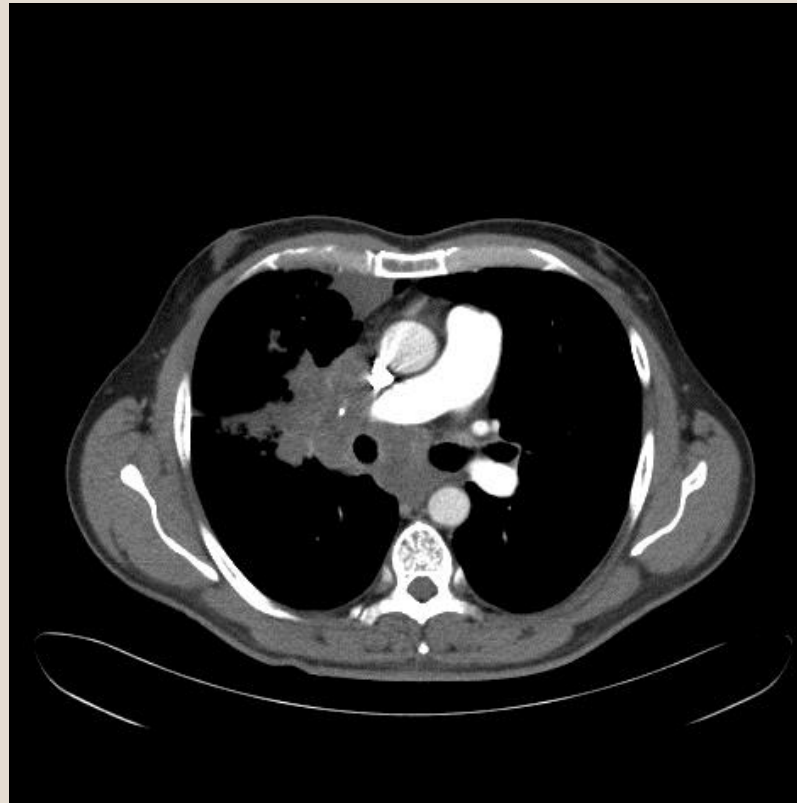
- Multidisciplinary discussion/staging and personalised treatment
- Upfront stratification
  - Baseline resectable (preoperatively proven single level N2 disease)
  - Potentially resectable with increased risk of incomplete resection (pancoast tumors, central T3-T4)
  - Unresectable
- Experience of center/volume

## Baseline resectable N2 disease



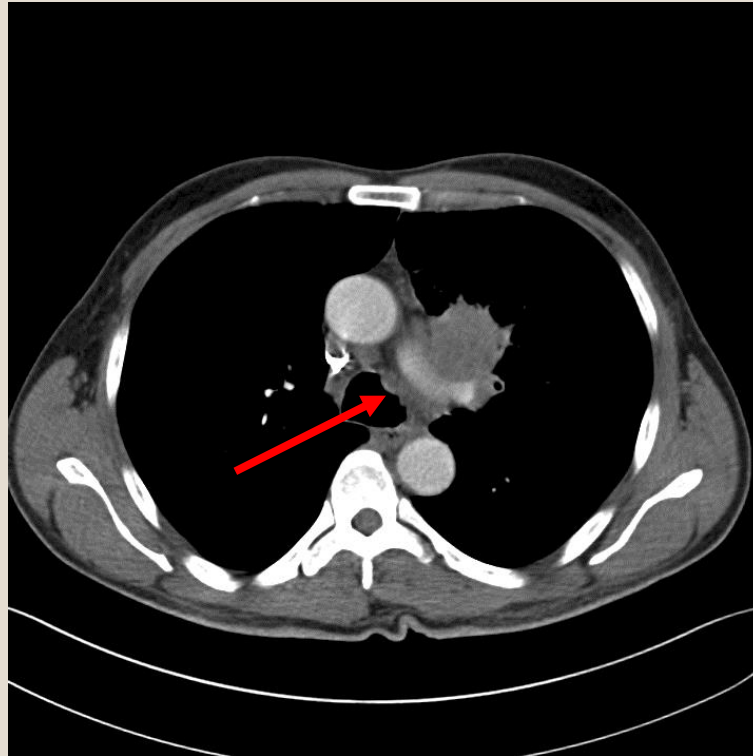
Individual LN's can be measured

## Unresectable N2 disease (no role for surgical multimodality)



Individual LN's cannot be measured

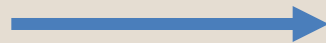
## Unresectable N2 disease (no role for surgical multimodality)



Individual LN's cannot be measured

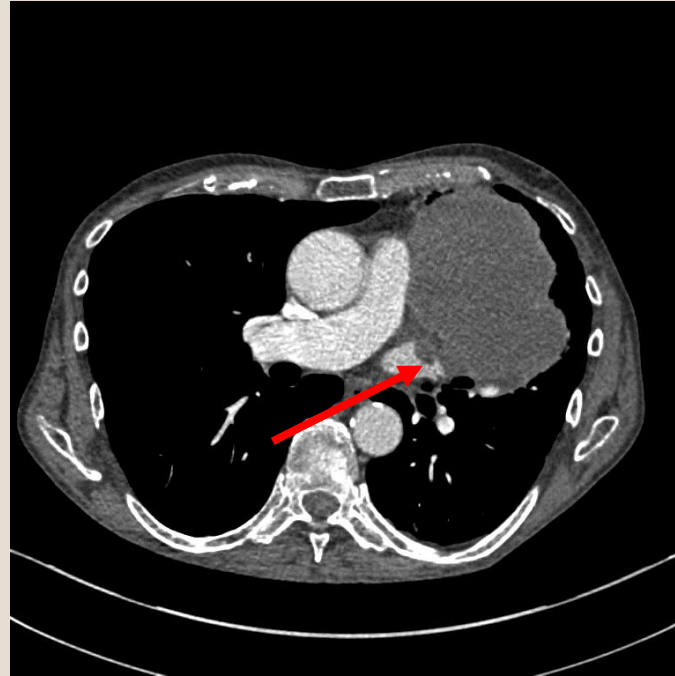
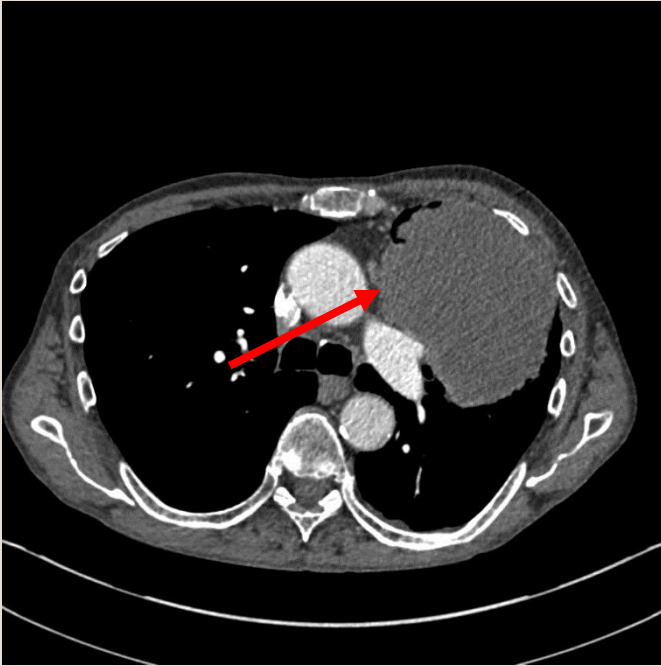


## Extracapsular spread : baseline unresectable N2 disease



**Importance of baseline staging**

## Potentially resectable with increased risk of incomplete resection



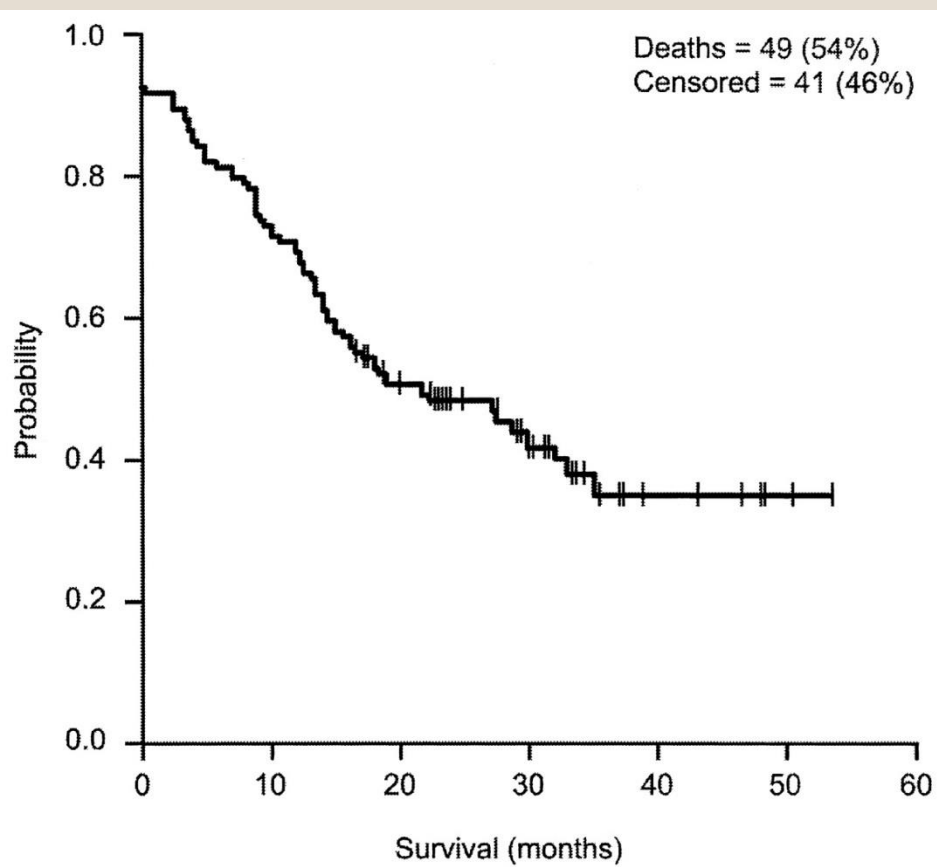
Induction chemoradiotherapy

## Potentially resectable N2 disease

- Large evidence from single center studies (good survival with acceptable morbidity/mortality in selected patients)
- One prospective randomised trial
- Downstaging of mediastinal LN is important

# N2 NSCLC

## Swiss experience



**N= 90**

**Resectability : 83% (75)**

**Complete resection (R0) : 70% (63)**

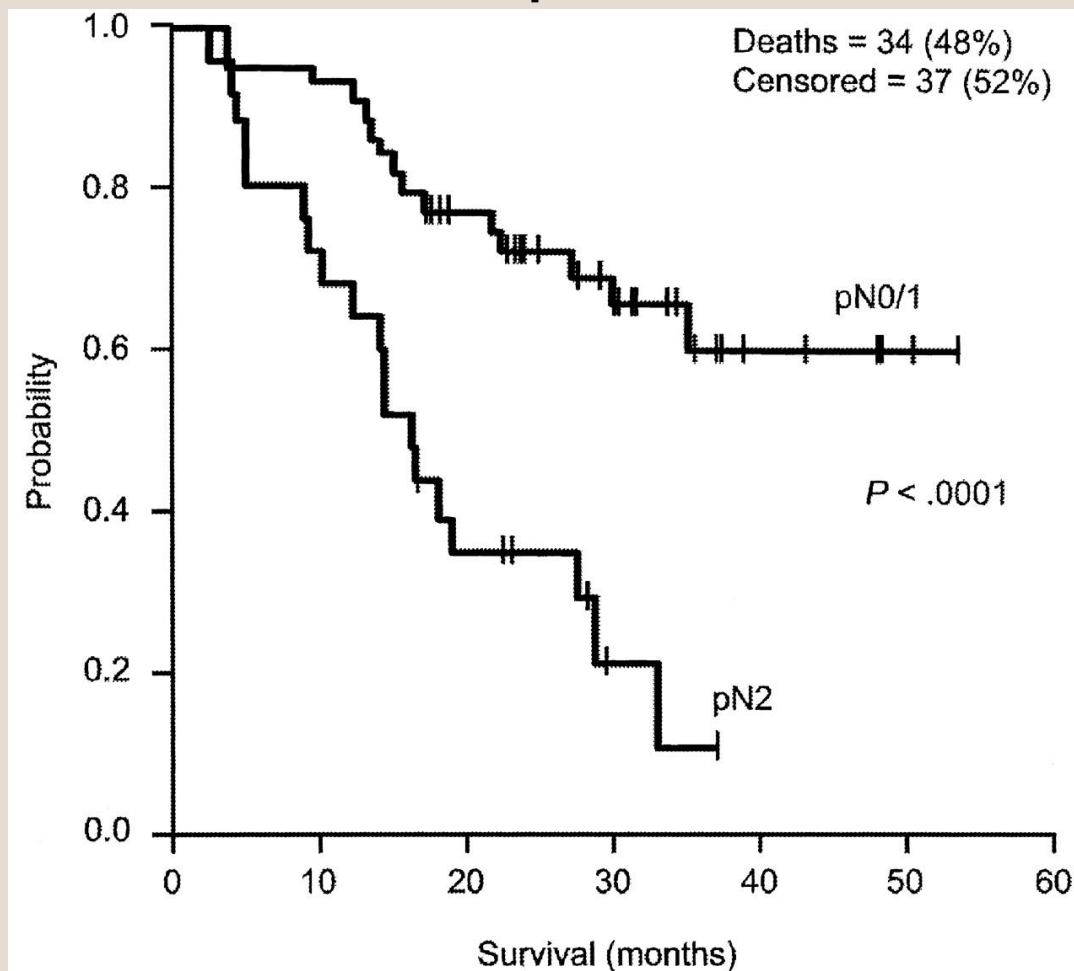
**Operative mortality : 3%**

**Median overall survival : 35 m**

**36% of operated patients  
are alive and tumor-free  
(3 years after diagnosis)**

# N2 NSCLC

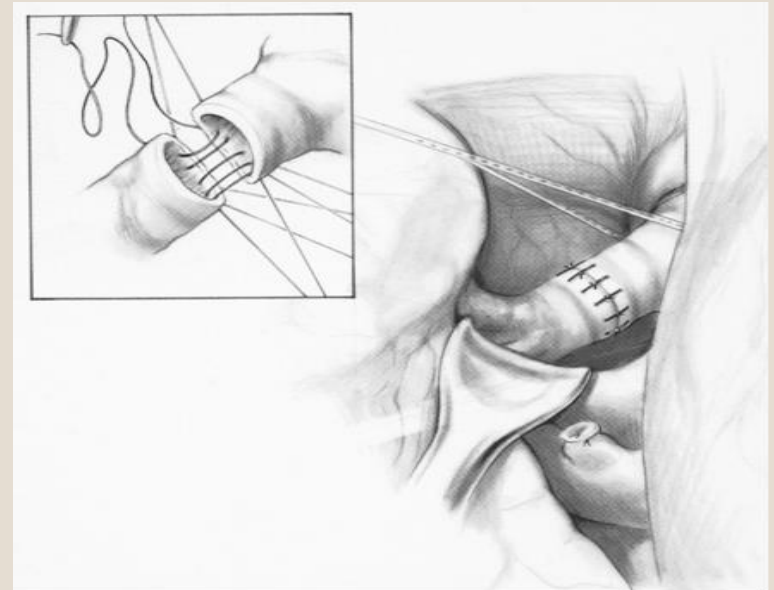
## Swiss experience



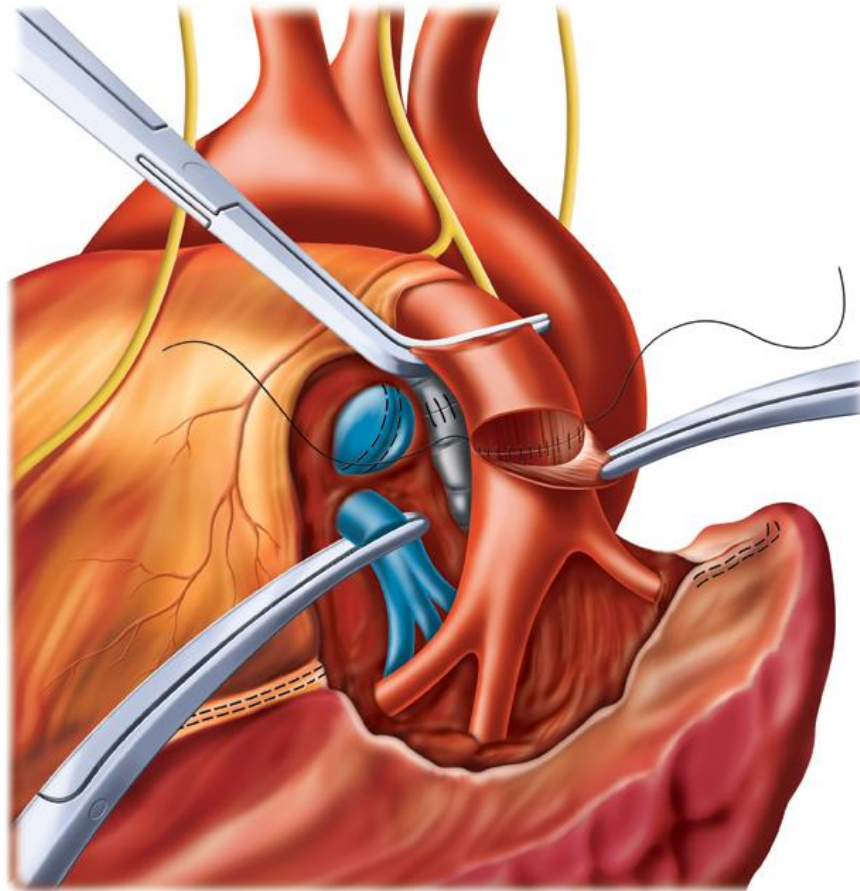
# UZ Leuven Data 2000-2006

## Surgical multimodality treatment for IIIA N2 NSCLC

- Prospective consecutive surgical database (2000-2006) N=92
- Histologically proven N2 disease (potentially resectable)
- Response or stable disease after induction chemotherapy
- Surgical exploration
- R0 resection : **63%**
  - Pneumonectomy : **24%**
  - Sleeve resection : **13%**
- Hospital mortality : **2.3%**



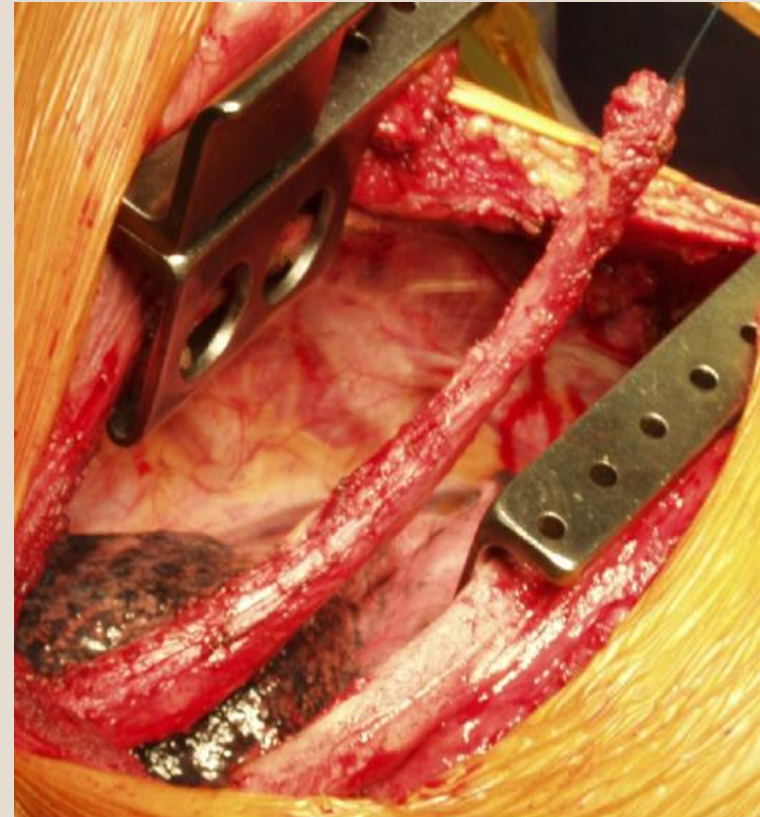
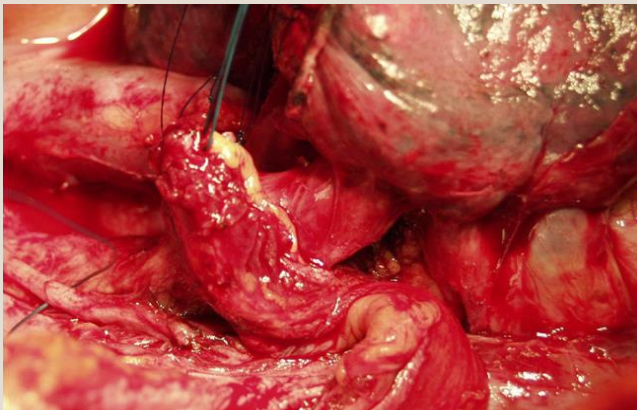
# Arterial sleeve resection





# Bronchusprotection

Bronchusprotection	78
– Intercostal muscle	60
– Pericard fat	11
– Pleura	7





# UZ Leuven Data 2000-2006

## Surgical multimodality treatment for IIIA N2 NSCLC

In-hospital mortality

2.3%

	5 Yrs Survival
Overall survival after resection	37%
R0	43%
pT0-1	65%
Single level positive at initial mediastinoscopy	43%
pN0-1	49%
pN2	27%

**Potentially resectable N2 NSCLC  
CT-RT vs surgical multimodality Tx?  
one prospective randomized trials**

**Lung Intergroup trial R0139**

# Lung Intergroup Trial R0139

Potentially resectable T1-T3 N2(mediast)

Randomised

Concurrent RT with cisplatin  
and etoposide X 2

Concurrent RT with cisplatin  
and etoposide X 2

**Continue RT to 61 Gy**

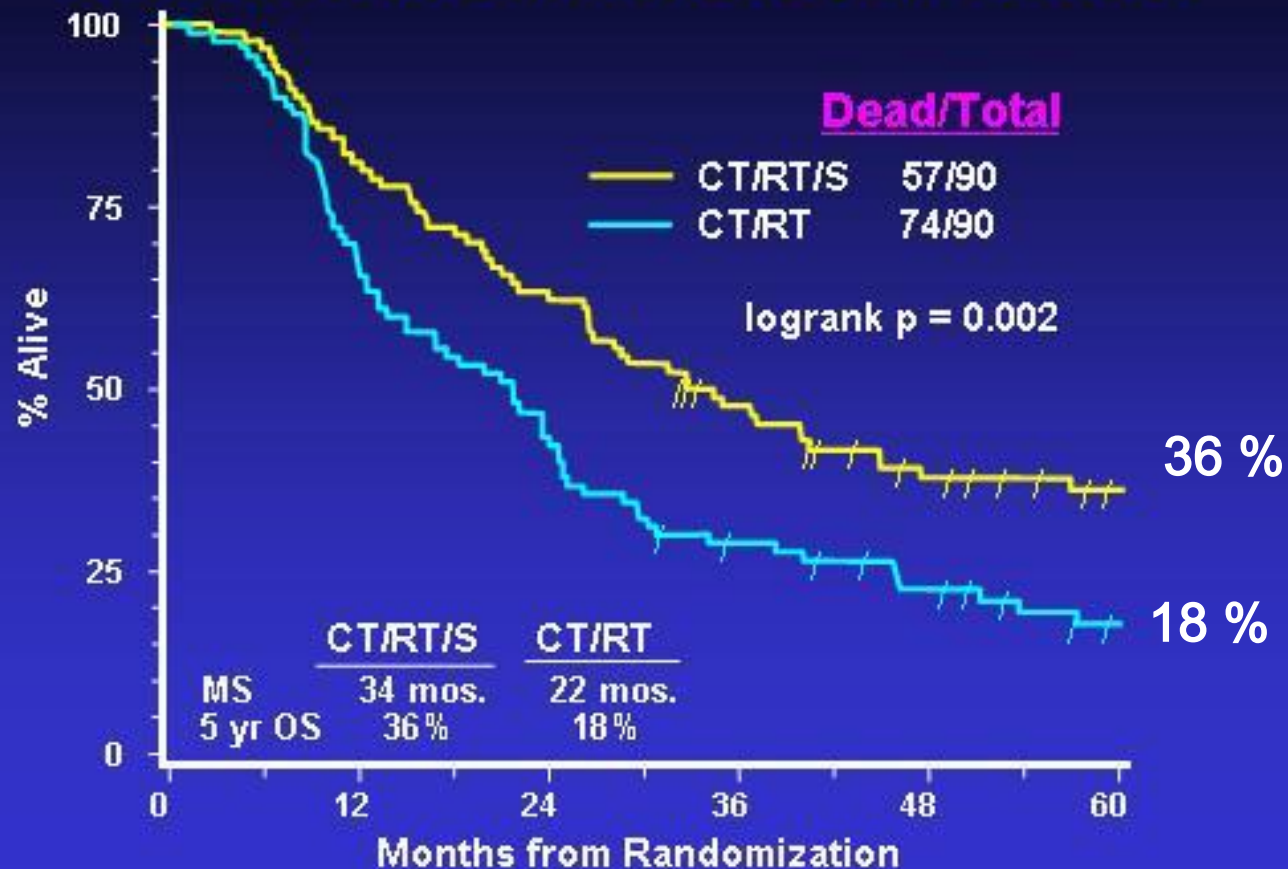
**Surgery**

Consolidation  
Cisplatin and etoposide X 2

## Intergroup trial

	<b>CT+S</b>	<b>CT+ RT</b>	
<b>pNO</b>	<b>46%</b>		
<b>R0</b>	<b>88%</b>		
<b>Overall survival (5 year)</b>	<b>27%</b>	<b>20%</b>	<b>p=NS</b>
<b>progression-free survival (2 year)</b>	<b>22%</b>	<b>11%</b>	<b>P=0.017</b>
<b>Treatment related Mortality (30 day)</b>	<b>7%</b> <b>Lobect : 1%</b> <b>Pneum : 26%</b> <b>R Pneum : 38%</b>	<b>1.6%</b>	

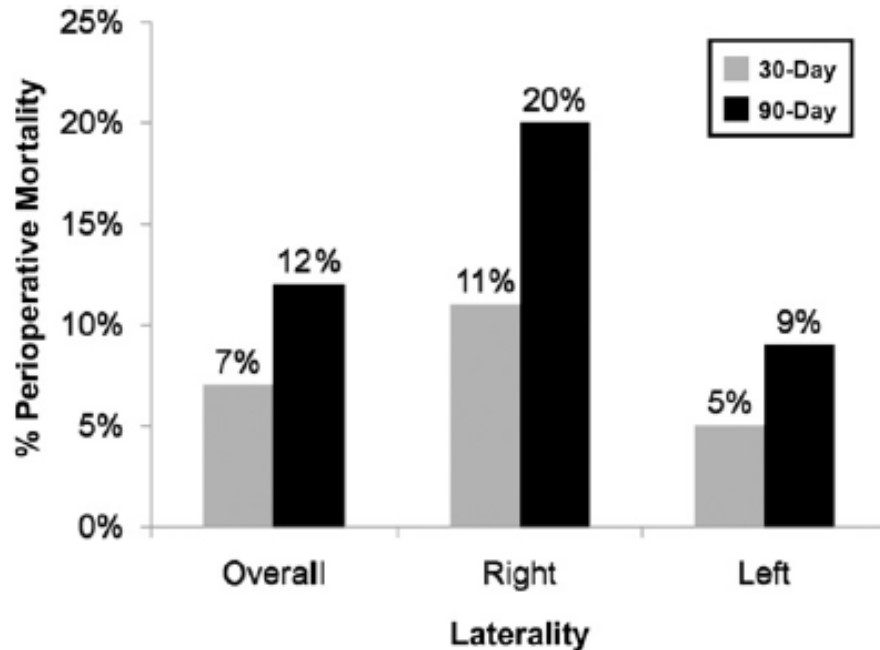
# INT0139 Overall Survival of the Lobectomy Subset versus Matched CT/RT Subset



# Perioperative mortality after neoadjuvant therapy and pneumonectomy for NSCLC

- Meta-analysis (1990-2010)
- Postoperative mortality after neoadjuvant therapy and pneumonectomy
- N = 27 studies (including intergroup trial)
- 30-day mortality 7%
- 90-day mortality 12%

# Perioperative mortality after neoadjuvant therapy and pneumonectomy for NSCLC



**FIGURE 3.** Perioperative mortality. Perioperative mortality represented according to overall, right, and left pneumonectomies for all 27 studies.

Lower than mortality intergroup trial  
Pneumonectomy : 12% vs 26%  
Right pneumonectomy : 20 % vs 38%

# Effect of preoperative chemoradiation in addition to preoperative chemotherapy in stage III NSCLC

## Mortality after surgery

	Chemoradiation (142)	Chemotherapy (154)
Overall	9%	5%
Lobectomy or bilobectomy	7.5%	2.3%
Pneumonectomy	14%	6%



# Effect of preoperative chemoradiation in addition to preoperative chemotherapy in stage III NSCLC

## Mortality after surgery

	Chemoradiation (13) 9%	Chemotherapy (6) 5%
Pneumonia	4	3
Empyema	1	0
Stump insufficiency	5	1
Pulmonary haemorrhage	2	0
Pulmonary embolism	1	0
Heart failure	0	1
Apoplectic stroke	0	1

# Baseline unresectable N2 disease

**EORTC 8947**

unresectable N2(path proven)

↓  
Induction chemotherapy

↓  
Responders

Randomized

↙  
Thoracic RT to 60 Gy

↘  
Surgery ± Port

# EORTC 08941

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

**Potentially resectable with increased risk of incomplete resection : Pancoast tumor**

**Major challenge : control of locoregional disease**



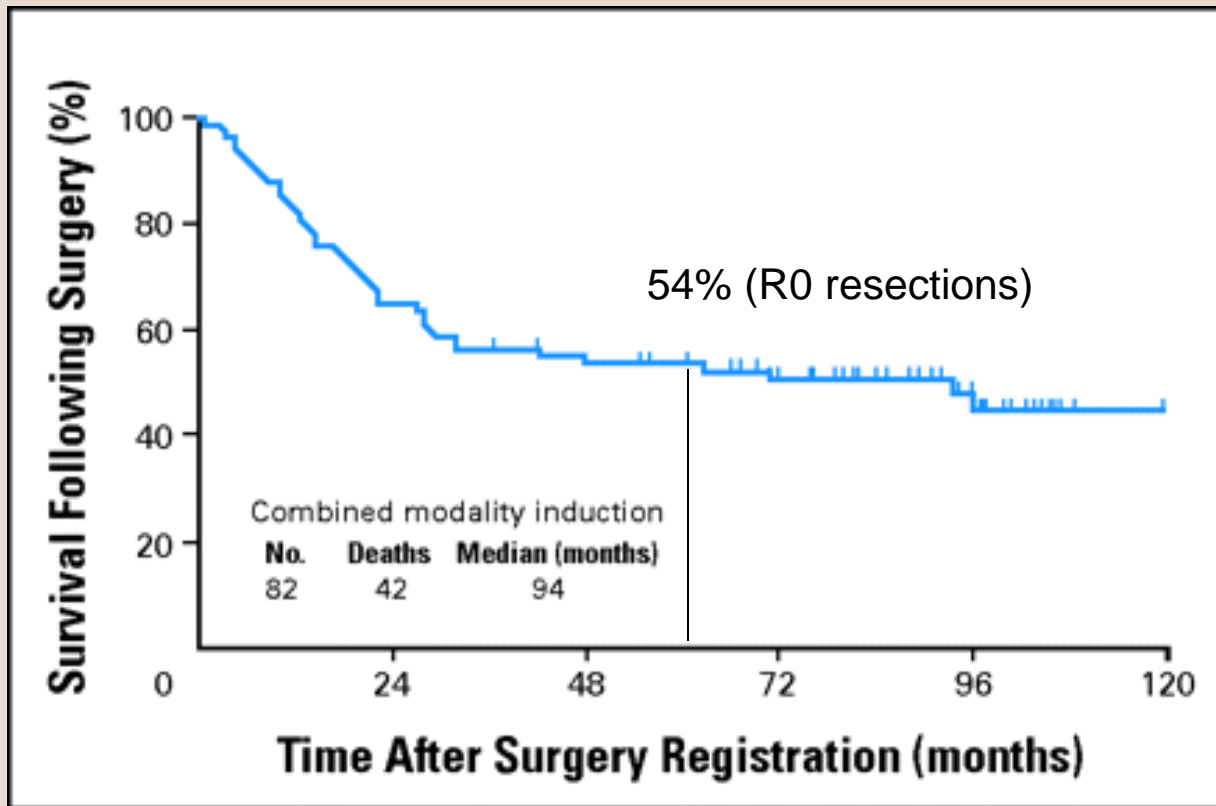
# Induction chemoradiotherapy for pancoast (SWOG 9416)

- Inclusion : cT3-T4NO (mediast : neg) n=110
- Concurrent chemoradiotherapy (cis, etoposide; 45 gy)
- Surgery in responders and stable disease

# Induction chemoradiotherapy for pancoast (SWOG 9416)

- **Complete resectability : 75%**
- **Pathological complete response or minimal microscopic disease : 65%**
  - **Overall survival (5-yr) : 44%**
  - **Survival in R0 resections (5-yr) : 54%**

# Induction chemoradiotherapy for pancoast (SWOG 9416)



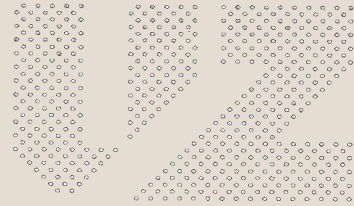
# Induction chemoradiotherapy for pancoast (SWOG 9416)

- **Pathological complete response : 32 (36%)**
  - 17 response on CT scan
  - 15 stable disease on CT scan
- **Both patients with response and stable disease should be explored. Pain is important prognostic sign**
- **Induction chemoradiotherapy is standard of care in patients with pancoast tumors. Experience of team**





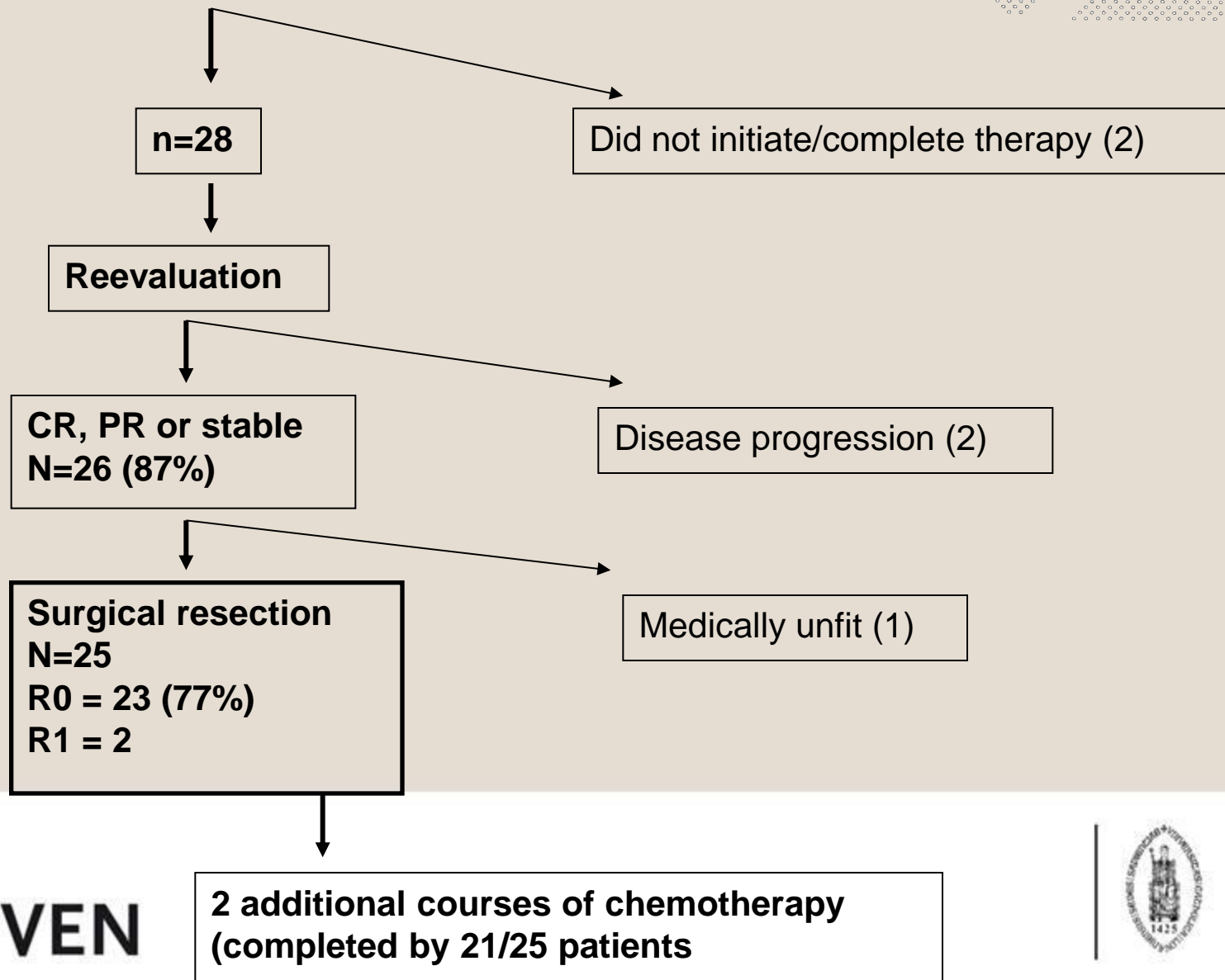
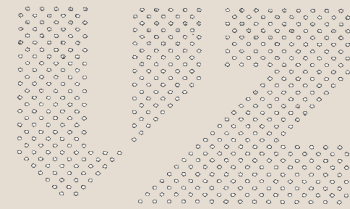
# Induction chemoradiotherapy for pancoast and cT4 tumors



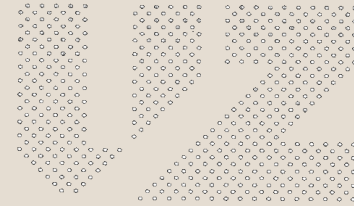
- 2003 – october 2007
- 30 patients (prospective, consecutive)
- cT4 tumor (50%) – Pancoast (cT3-4) (50%)
  - Pulmonary artery
  - Atrium
  - Caval vein
  - Vertebra
  - Esophagus
  - Carina : not included!
- N0 – M0 (PET of CT/PET and mediastinoscopy)



**Induction chemoradiotherapy pancoast and  
CT4N0/1M0 disease  
n=30**

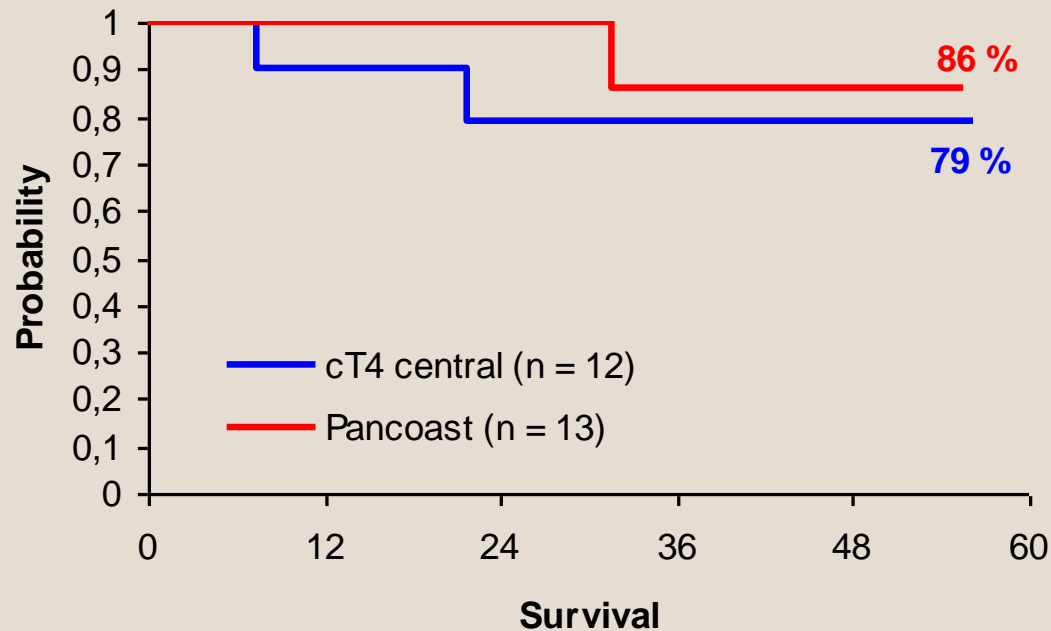


# Results



- Survival

## Resected patients (n=25)



# Influence of hospital volume on survival after resection for lung cancer

Postoperative complications and survival in 76 hospitals in United States

2118 resections for lung cancer (1985-1996)

	1-8 (n=34)	9-14 (n=14)	15-19 (n=10)	20-66 (n=16)	67-100 (n=2)	P value
% of all hospitals	45%	18%	13%	21%	3%	
Postoperative complications	44%	28%	35%	32%	20%	<0.001
Overall 5-Yr survival	33%	36%	39%	40%	44%	<0.001

## High procedure volume is strongly associated with improved survival after lung cancer surgery

- Analysis of 134.293 NSCLC in England (2004-2008)
- 12.862 (9,6%) surgical resection
- Analysis of relation between hospital volume and survival

# High procedure volume is strongly associated with improved survival after lung cancer surgery

- Increasing volume  $\approx$  increasing survival
- Increasing volume  $\approx$  increasing resection rate
- Increasing volume  $\approx$  increasing percentage of resections in patients with higher comorbidity

# High procedure volume is strongly associated with improved survival after lung cancer surgery

**Table 3.** HRs and 95% CIs According to Hospital Volume Among Patients With NSCLC by Period of Follow-Up

	0 to 30 Days		31 to 365 Days		> 365 Days	
Hospital Volume (No. of procedures per year)	HR	95% CI	HR	95% CI	HR	95% CI
< 70	1.00	—	1.00	—	1.00	—
70 to 99	0.81	0.58 to 1.13	0.82	0.70 to 0.96	0.95	0.83 to 1.09
100 to 129	0.75	0.52 to 1.08	0.92	0.78 to 1.09	0.94	0.81 to 1.08
130 to 149	0.91	0.64 to 1.31	0.78	0.66 to 0.93	0.97	0.84 to 1.13
≥ 150	0.58	0.38 to 0.89	0.80	0.67 to 0.95	0.84	0.71 to 0.99
$\chi^2$ *	3.24		5.93		2.67	
P	.07		.01		.10	

NOTE. Based on shared-frailty model adjusted for age, sex, socioeconomic deprivation, Charlson comorbidity score, resection quintile, and hospital (random effect). Abbreviations: HR, hazard ratio; NSCLC, non-small-cell lung cancer.

\*1 df.

# Conclusions

- **Marked heterogeneity in stage III disease**
- **Patients should be multidisciplinary discussed (both baseline and after induction treatment) by experienced pneumologist/oncologist, radiation oncologist, thoracic surgeon**
- **Upfront stratification**
  - Baseline resectable (single level N2 disease, non-bulky)
  - Potentially resectable with increased risk of incomplete resection (pancoast tumors, central T3-T4)
  - Unresectable



# Conclusions

- **Therapy for stage III must be individualised**
- **Surgical multimodality treatment for resectable pancoast tumor and in selected patients with N2 disease. For N2 disease no survival benefit of induction chemoradiotherapy compared to induction chemotherapy**
- **Right pneumonectomy only in selected patients**
- **Experience of center is important. Need for centralisation**



***Thank you!***

**K.U. Leuven, Belgium**  
**University Hospital Gasthuisberg**  
**Leuven Lung Cancer Group ([www.LLCG.be](http://www.LLCG.be))**