



# Induction chemotherapy

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# Induction chemotherapy

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- rationale, technical aspects
- selected studies early stage NSCLC
  - Depierre trial
  - S9900 trial
  - NATCH trial
- meta-analysis induction ↔ adjuvant chemotherapy
- conclusion



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# Induction therapy followed by surgery

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- **effect :**      **downstaging locally advanced tumors**  
**eradication systemic micrometastases**  
**↓ stimulus to cancer cells by surgery**
- **advantages :**      **cytoreduction, ↑ resectability**  
**patient acceptance, compliance**  
**conservation lung parenchyma**  
**better survival**



# Induction therapy followed by surgery

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## Disadvantages

surgical treatment delayed  
technical difficulties - fibrosis

↑ morbidity, mortality

induction therapy

surgery

prolonged hospital stay

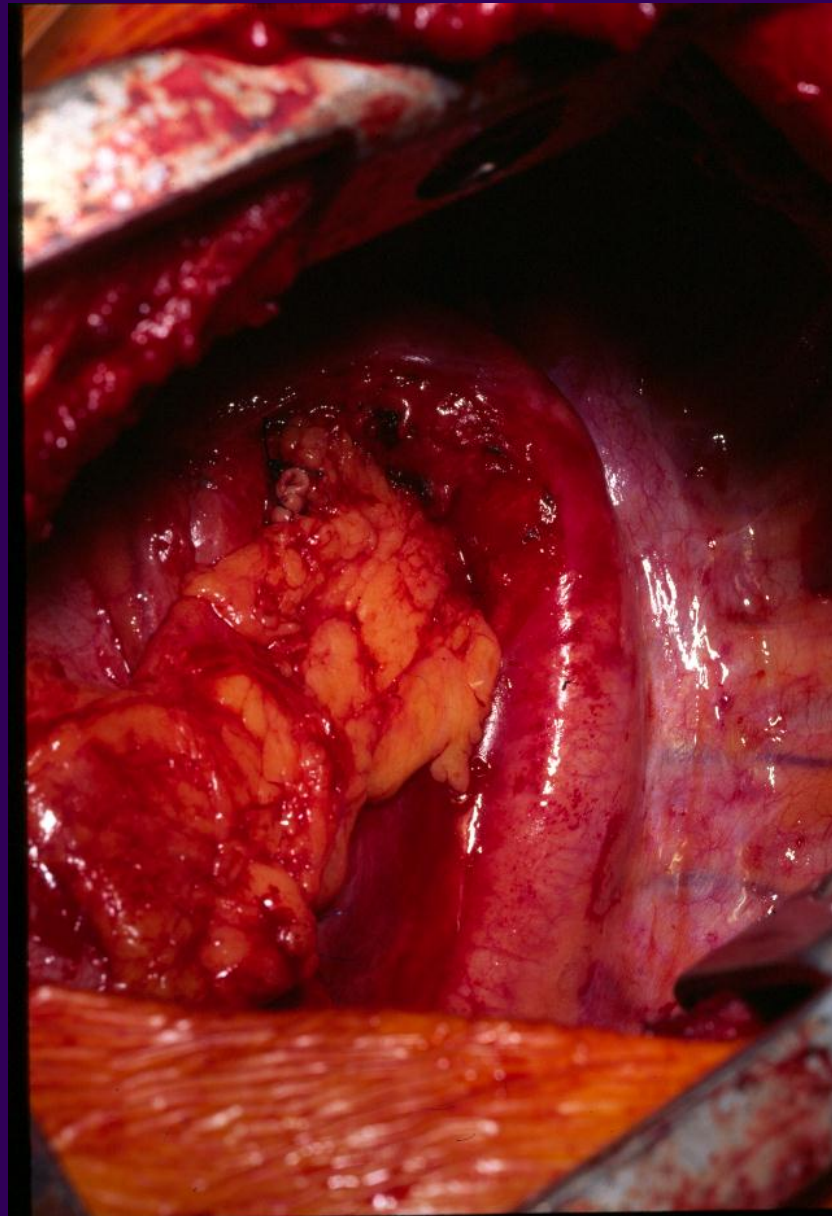
changes in immune status



# Induction therapy followed by surgery

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- no standard: “ thoracic surgery can be terribly simple or simply terrible “
- clinical staging, noninvasive response evaluation unreliable
- operative assessment: fibrosis
- intervention 3 - 6 weeks after end of induction therapy
- extent of resection ? intrapericardial control
- frozen section : helpful, but sometimes unreliable



**high – risk:  
coverage of  
bronchial stump**



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# Preoperative chemotherapy + surgery compared with surgery in resectable IB, II and IIIA NSCLC

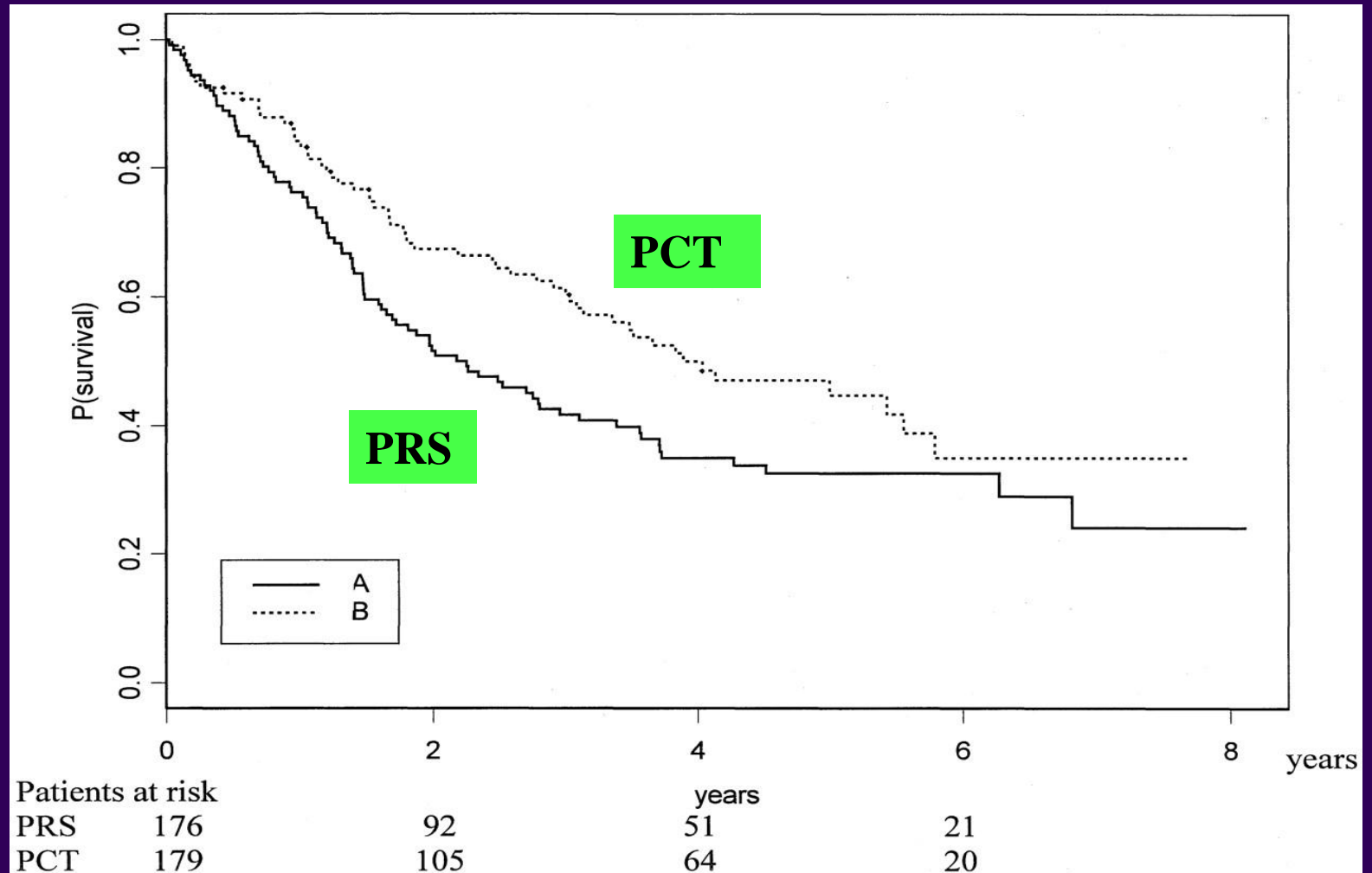
- clinical stage IB, II, IIIA randomized phase III trial :  
surgery (arm 1 n =176)  
induction chemo + surg (arm 2 n =179)
- mortality arm 1 : 4.5 % (pneumonia)  
arm 2 : 8 % (n=14)  
7 pneumonia, 6 empyema ± BPF
- non-significant excess of death preop. CT
- survival : significant  $\Delta$  stage I, II (*not IIIA*)
- effect chemotherapy on survival : after 150 days

RR death (preop. CT)	1.32	until 5 mos.
	0.74	> 5 mos.

Depierre A. J Clin Oncol 2002; 20:247-53

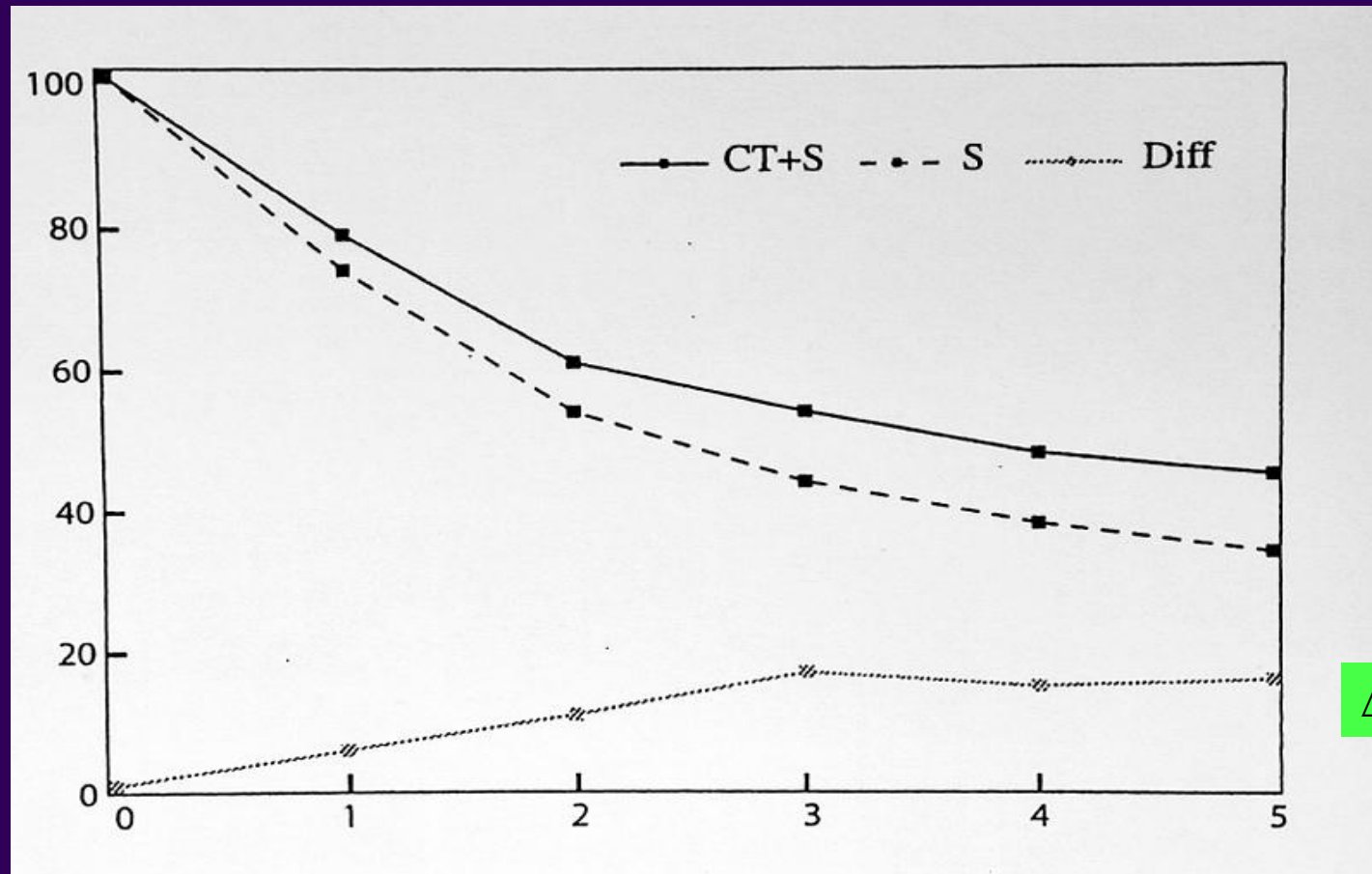
Depierre A. Lung Cancer 2003; 41 suppl 2, S62

**Overall survival : arm A, PRS – primary surgery  
arm B, PCT – preop.chemotherapy + surgery**

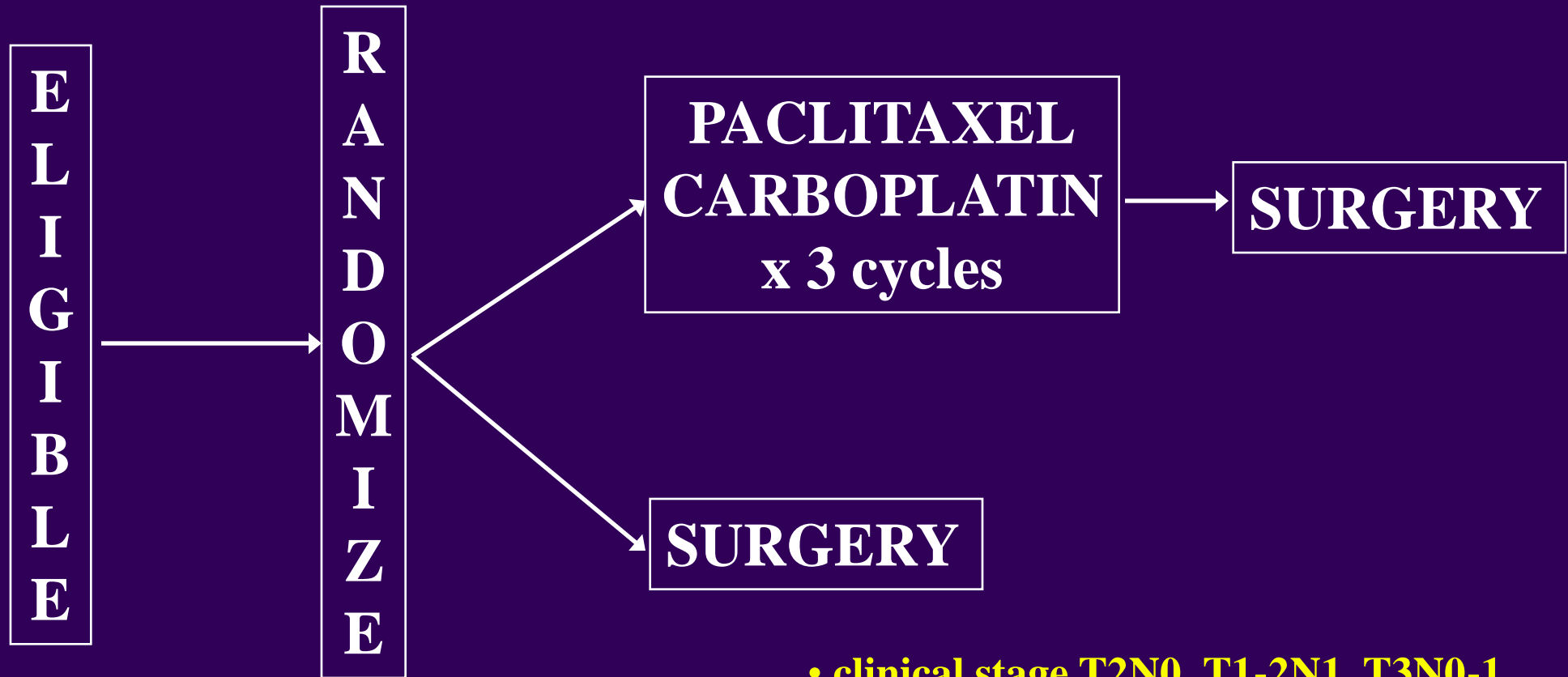


Depierre, A. et al. J Clin Oncol; 20:247-253 2002

# Preop. CT + surgery compared with surgery in resectable IB, II and IIIA NSCLC



# S9900 : phase III trial of surgery alone or surgery + preoperative chemotherapy in early stage NSCLC



- clinical stage T2N0, T1-2N1, T3N0-1
- mediastinoscopy if LN > 1 cm on CT

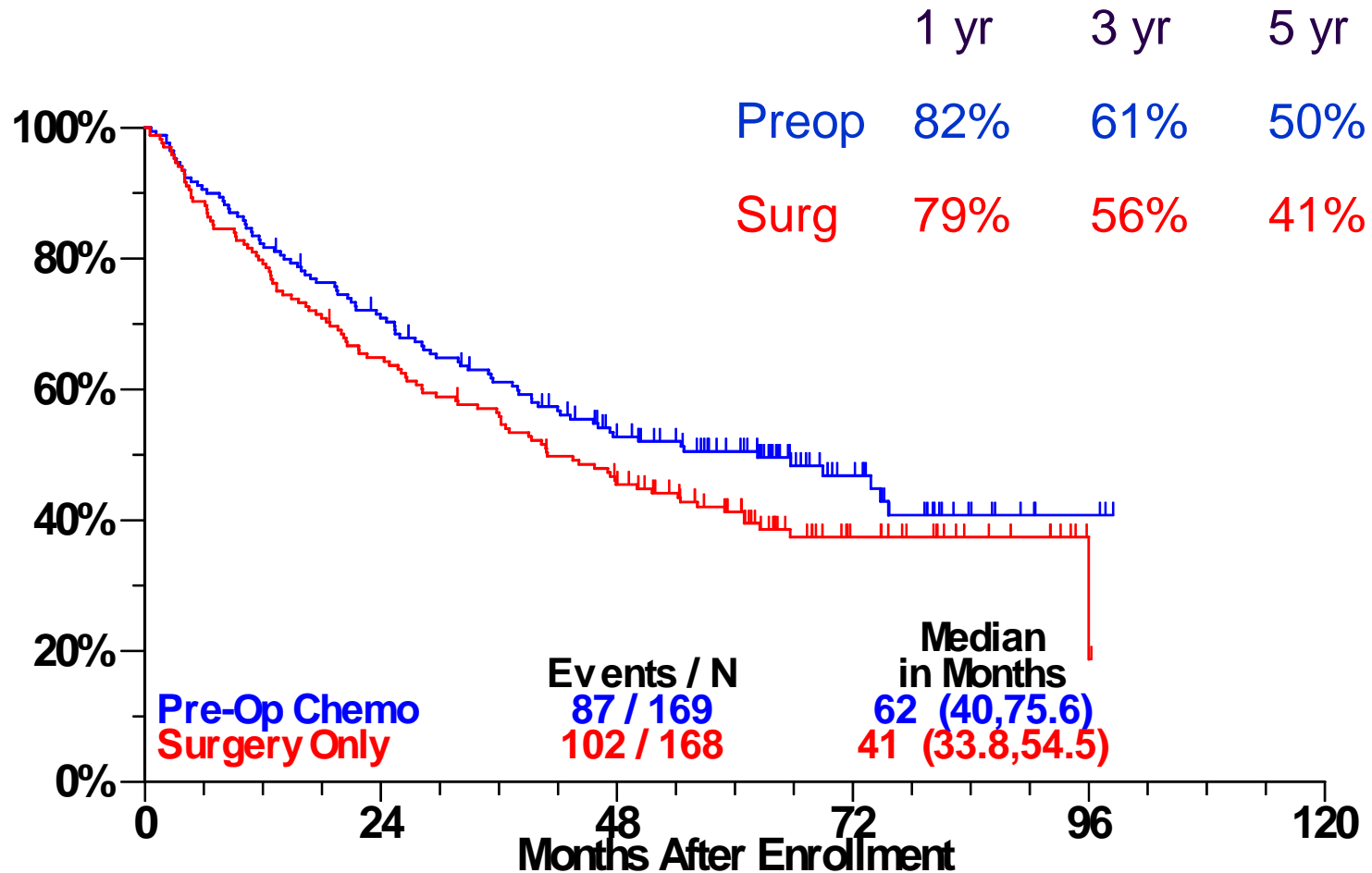
*Pisters K. JCO 2005; 23 (no. 16S) : abstract 7012*

*Pisters K. JCO 2007; 25 (no.18S): abstract 7520*

*Pisters K. JCO 2010; 28: 1843-9*

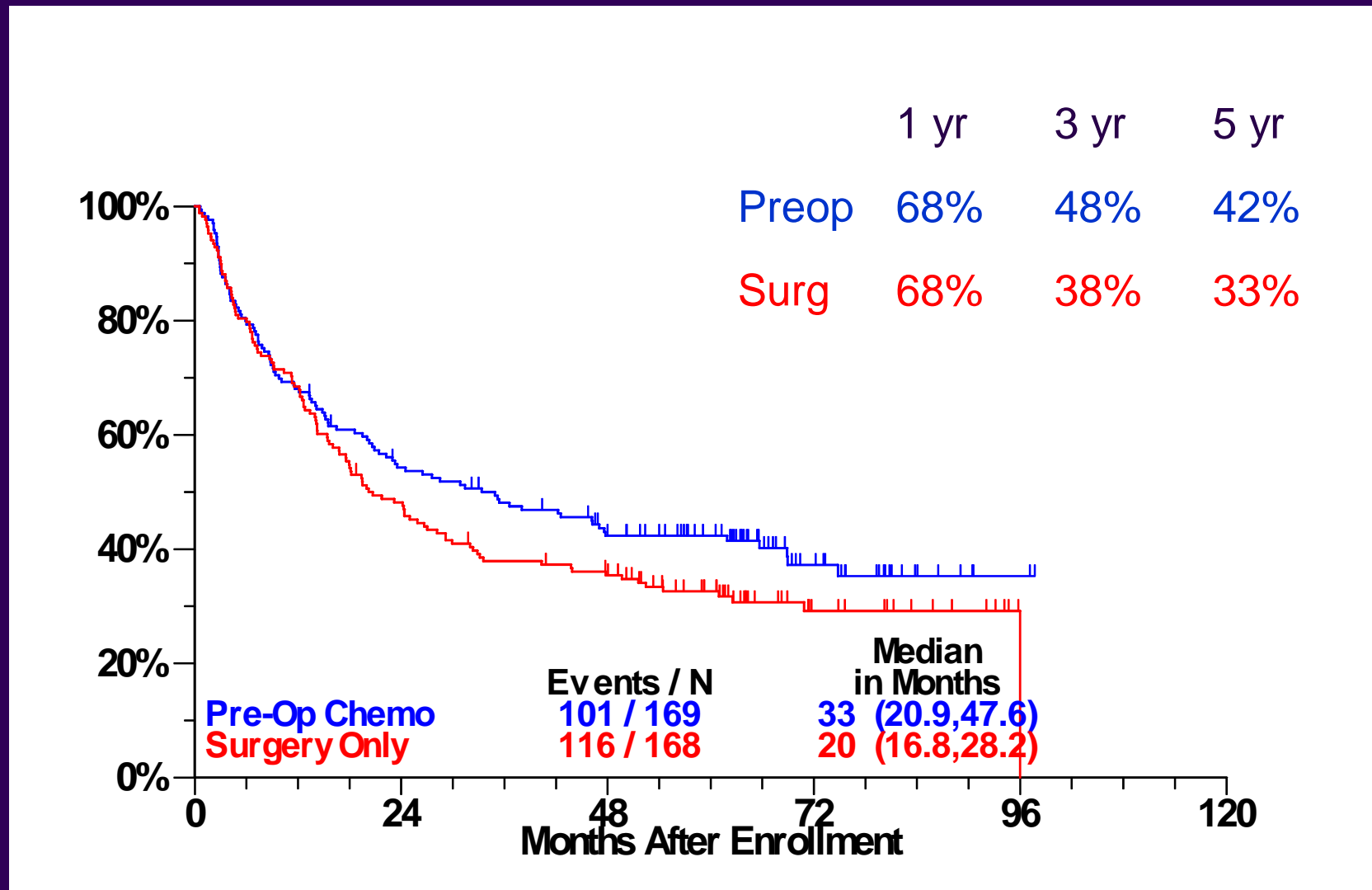


# S9900 Overall Survival, median F/U 64 mo



**HR=0.79 [0.60-1.06], p=0.11**

# S9900 Progression-Free Survival, median F/U 64 mo



**HR=0.80 [0.61-1.04], p=0.10**

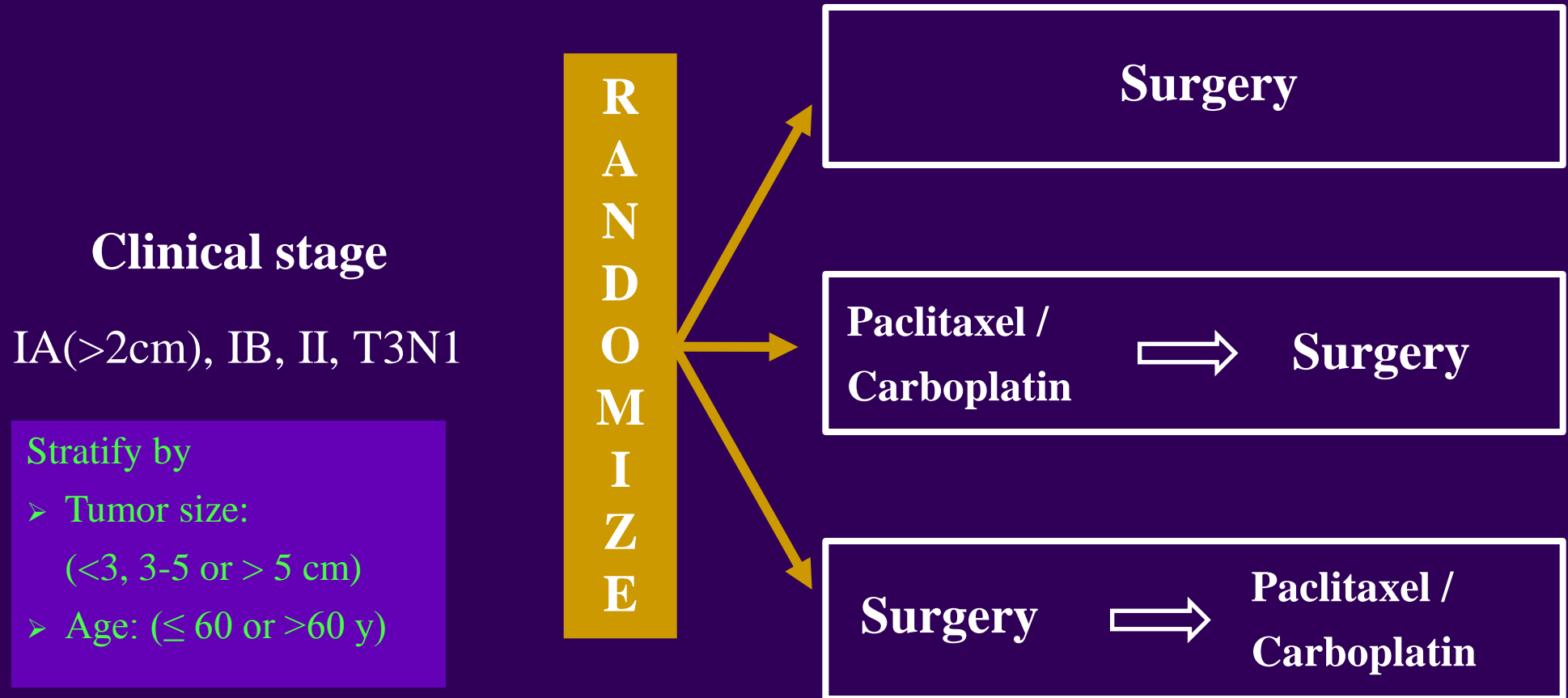
**A phase III randomized trial of surgery alone, or preoperative (PREOP) paclitaxel/carboplatin (PC) followed by surgery, or surgery followed by adjuvant (ADJ) PC in early stage non-small cell lung cancer (NSCLC): NATCH follow-up data**

E. Felip, B. Massuti, J.A. Maestre, G. Alonso, J.M.R. Paniagua, J.L. González-Larriba, C. Camps, D. Isla, T. Overbeck, E. Costas, J.J. Sánchez, R. Rosell

On behalf of the Spanish Lung Cancer Group

*13<sup>th</sup> World Conference on Lung Cancer, San Francisco, August 3, 2009*

# Study Design



- Paclitaxel 200 mg/m<sup>2</sup> /3h + Carboplatin AUC=6 q3wk for a total of 3 cycles
- Post-op thoracic RT allowed for pN2 disease

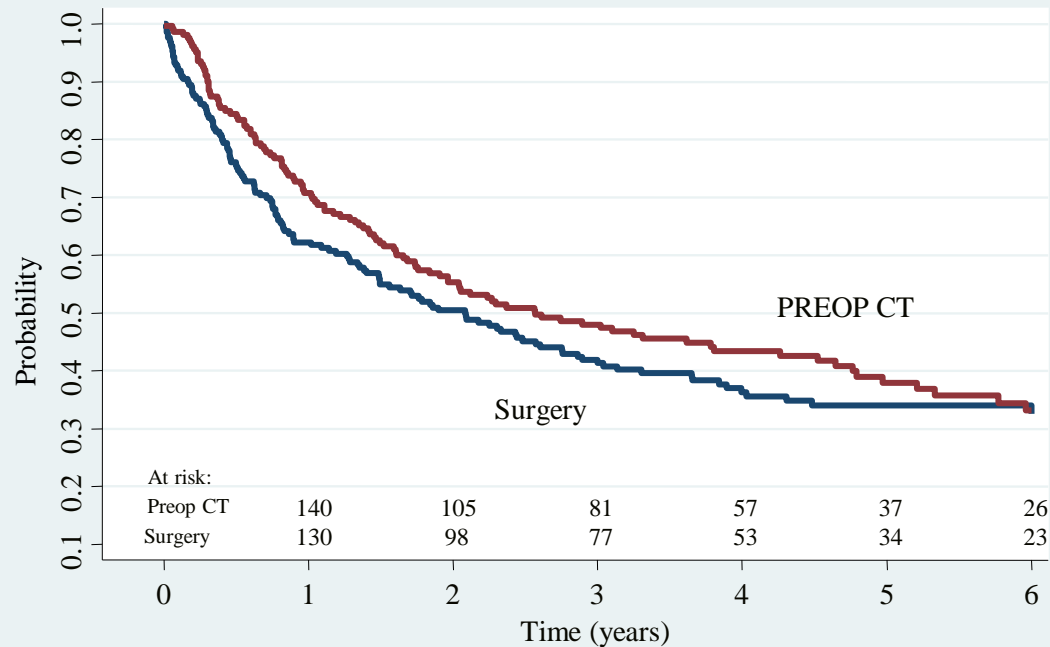
# Patients' Characteristics

Characteristic	Surgery alone (N=210)	ADJ CT (N=210)	PREOP CT (N=199)
<b>Age (yr)</b>			
Median, range	64 (36-89)	64 (33-81)	65 (35-80)
<b>Histologic features</b>			
SCC	105 (50%)	103 (49%)	107 (54%)
ADC	71 (34%)	69 (33%)	57 (29%)
Large-cell	21 (10%)	24 (11%)	21 (10%)
Other	13 (6%)	14 (7%)	14 (7%)
<b>Clinical stage</b>			
T1N0	20 (10%)	30 (14%)	16 (8%)
T2N0	134 (64%)	133 (63%)	132 (66%)
T1N1	1 (0.5%)	3 (1%)	4 (2%)
T2N1	25 (12%)	25 (12%)	24 (12%)
T3N0	26 (12%)	18 (9%)	18 (9%)
T3N1	4 (2%)	1 (0.5%)	4 (2%)
T4N0*	-	-	1 (0.5%)

\* Ineligible pt

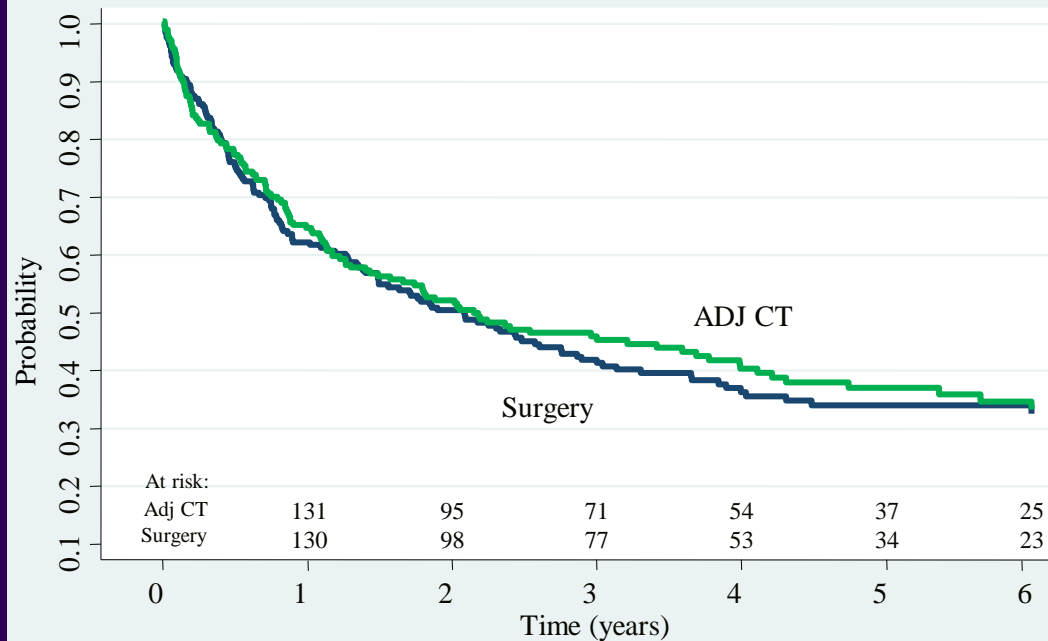
# Disease-Free Survival by Arm

## PREOP CT Arm vs Surgery Arm



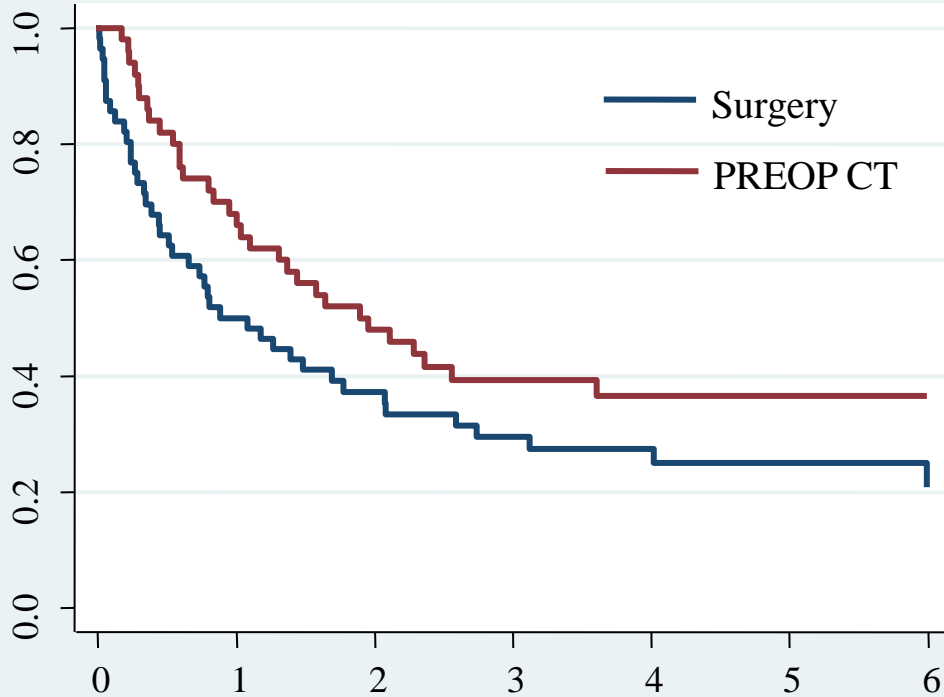
	Surgery (N=210)	PREOP CT (N=199)
Events	132	117
Median DFS (mo)	25.1	31.5
3-year DFS	41.9%	48.4%
5-year DFS	34.1%	38.3%
HR = 0.92; 95% CI (0.81 to 1.04); P = 0.176		

## ADJ CT Arm vs Surgery Arm



	Surgery (N=210)	ADJ CT (N=210)
Events	132	125
Median DFS (mo)	25.1	26.0
3-year DFS	41.9%	44.9%
5-year DFS	34.1%	36.6%
HR = 0.96; 95% CI (0.75 to 1.22); P = 0.73		

# DFS in Clinical Stage II-T3N1

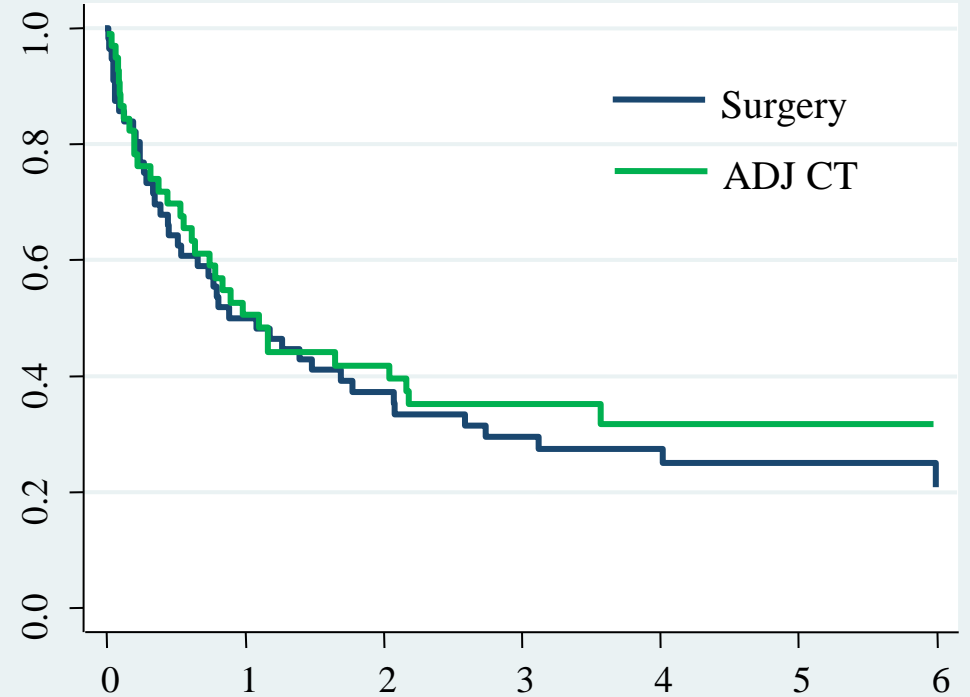


At risk

Surgery	56	28	19	15	11	7	6
PREOP CT	51	34	24	17	11	7	5

**5 year DFS 36.6% in PREOP CT vs 25% in Surgery alone**

**HR=0.81 (0.64-1.02); P=0.07**



At risk

Surgery	56	28	19	15	11	7	6
ADJ CT	47	23	18	11	9	8	5

**5 year DFS 31% in ADJ CT vs 25% in Surgery alone**

**HR=0.87 (0.54-1.38); P=0.54**

# NATCH trial

- preop & adj CT well tolerated
- ↑ pt compliance with preop CT vs adj CT (97% vs 66%)
- surgical procedures and post-operative † = across arms
- preop CT: a non-significant trend towards ↑ DFS when compared to surgery (4.2% absolute ↑ in 5-year DFS)
- exploratory analysis showed ↑ CT effect in clinical stages II-T3N1
- *but: most pts stage I, adequately powered?, choice of chemotherapy?*



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# Induction ↔ adjuvant chemotherapy

*ongoing discussion*

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➤ *induction pro*    ↑ compliance, evaluation tumor response  
                              ↓ extent of resection  
                              control micrometastases

*con*    delays effective treatment  
          ↑ morbidity, †

➤ future: pharmacogenomic approach → ERCC1, RRM1, BRCA1



# Induction ↔ adjuvant chemotherapy *meta-analysis*

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- systematic review, meta-analysis randomized trials
- 32 randomized trials > 10 000 patients: 22 postop. 10 preop.
- *overall survival* HR postop. CT 0.80 preop. 0.81  
p < .001 p = 0.024  
relative hazard postop. vs preop. 0.99 p = 0.91
- *disease-free survival* HR postop. CT 0.76 preop. 0.79  
p < .001 p = 0.05  
relative hazard postop. vs preop. 0.96 p = 0.70
- no Δ OS and DFS between postop. and preop. chemotherapy



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## Conclusions

- rationale:     downstaging, evaluation response  
                  conservation pulmonary parenchyma  
                  control micrometastases  
                  patient acceptance, compliance
- disadvantages:  surgery delayed, ↑ technical difficulties  
                          ↑ morbidity, mortality (extensive procedures)
- meta-analysis: no  $\Delta$  OS and DFS between postop. and preop. chemotherapy

*the issue has not been settled yet !*