



N2 positive NSCLC The Surgical View

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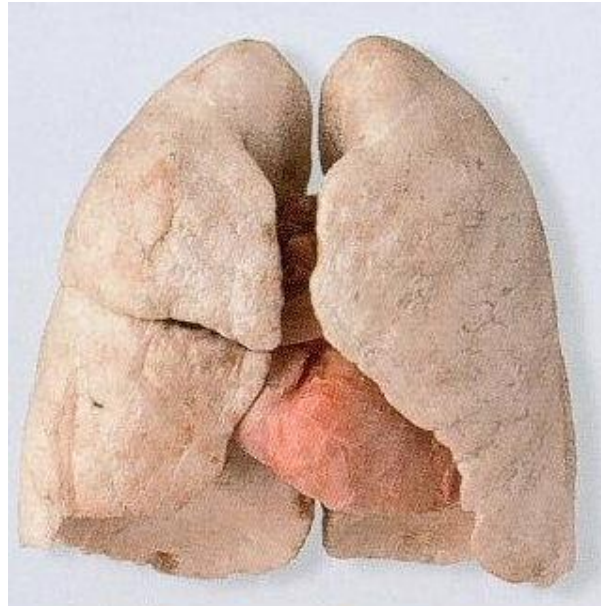
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www.meduniwien.ac.at/thoraxchirurgie



I have no conflicts of interest that relate to this presentation.



N2 NSCLC: Status quo

5-year survival:

- Stage III: 5-15% (Stage IIIA up to 24 %)
- „Standard of Care” sequential Chemotherapy

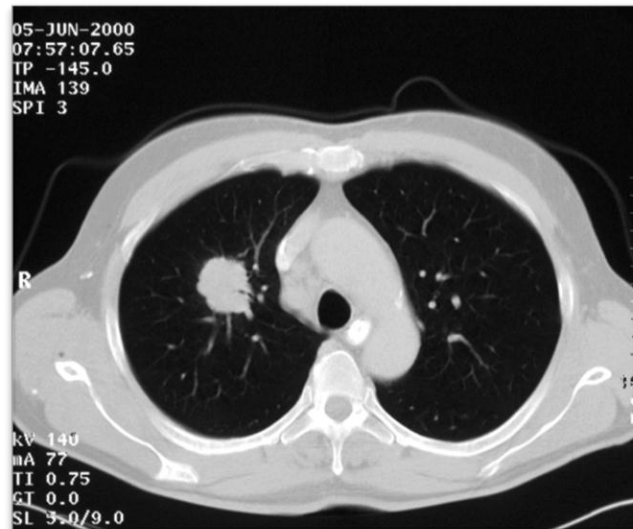
Patients with N2 NSCLC should be EXCLUDED from SURGICAL RESECTION



Patients with N2 NSCLC should be EXCLUDED

Case I

- 64 year male: no relevant comorbidity
- Solitäre mass RUL + med Lnn enlargement
- BSC: moderately differentiated Adenocarcinoma
- MSK: pos Lnn station 4R
- Stage cT2/N2 -> IIIA



Q1: What kind of treatment do YOU suggest?

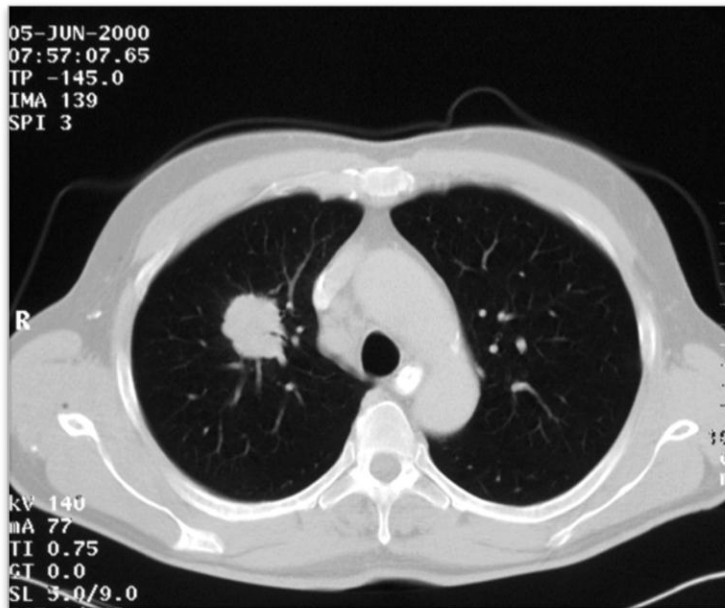
- CT
- RT
- CT/RT
- Surgery
- Surgery + adjuvant therapy
- Induction therapy followed by surgery???

Case I

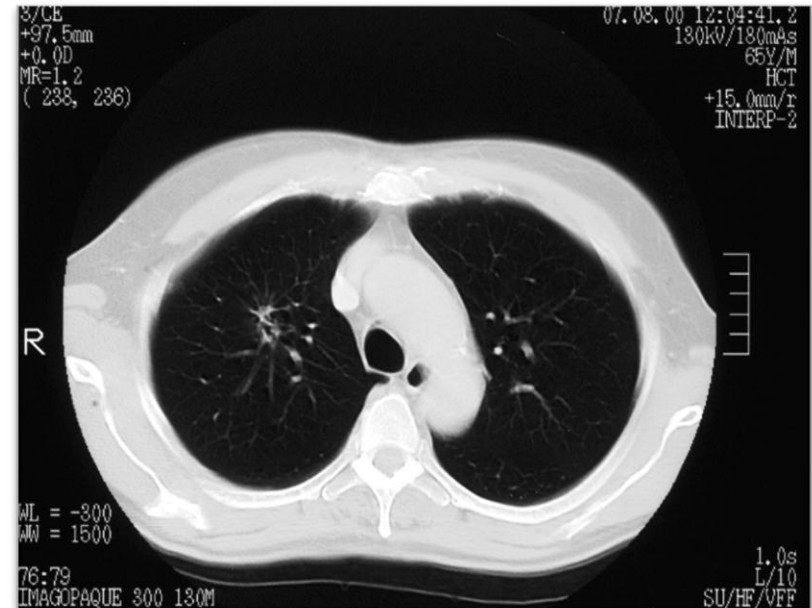
Results after induction C/RT:

- 3 cycles cisplatin based CT + 45 gray RT
 - Excellent clinical response

Pre-induction



Post-induction



Case I

- Q2: Do you still proceed to surgery?
- Q3: Do you consider mediastinal restaging necessary?

And how it turned out...

- Right upper lobe lobectomy combined with radical en block lymphadenectomy
- Pathological result: minimal residual tumor cells in primary tumor and in R4 LN: ypT1 ypN2
- Follow-up: 12 years, alive without recurrence



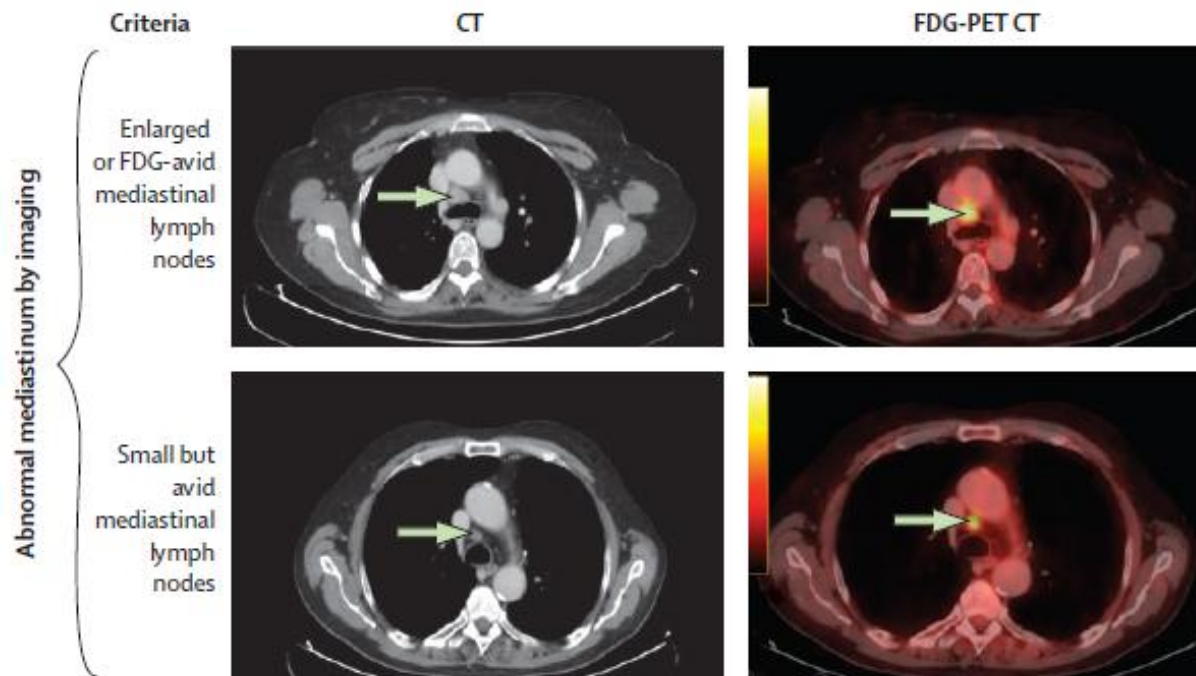
Issue Nr. 1.

DIAGNOSIS OF N2 DISEASE REQUIRES CYTOLOGICAL/HISTOLOGICAL CONFIRMATION

TISSUE IS THE ISSUE

When should we go for invasive mediastinal LN staging?

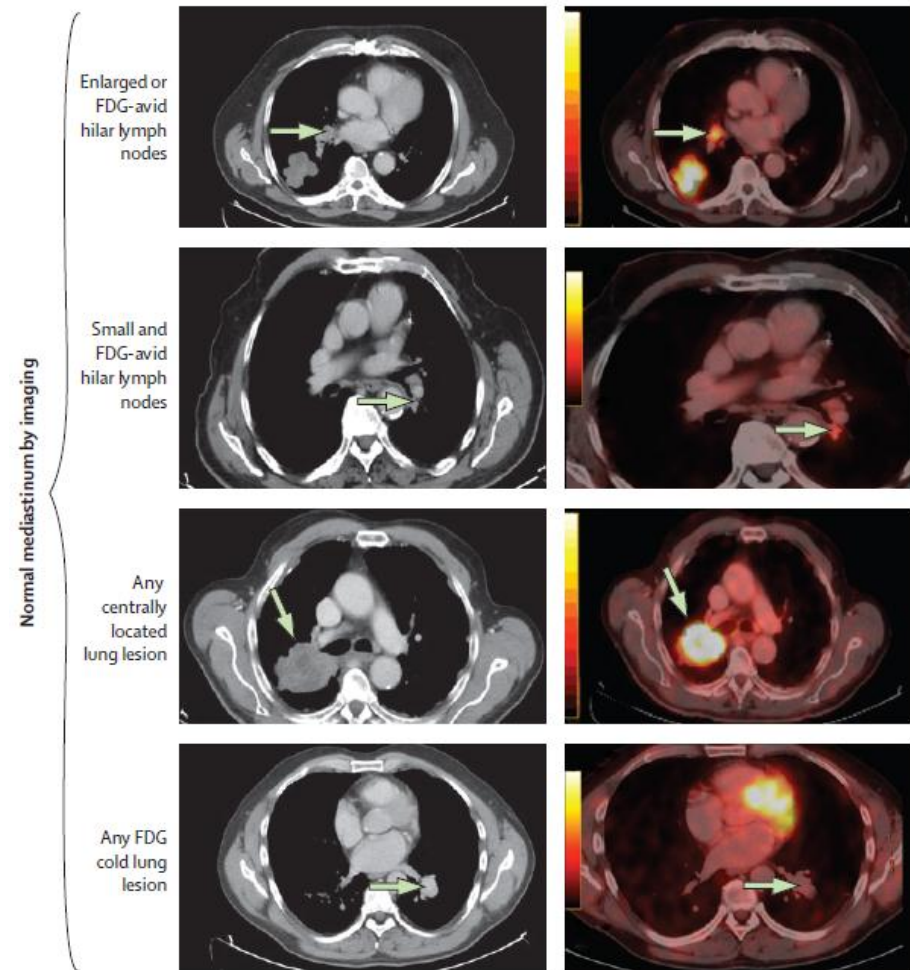
Group 1: Mediastinal lymph nodes suspected of containing metastases on the basis of either size (short axis ≥ 10 mm) or FDG uptake (abnormal mediastinum by imaging)



Tournoy et al.
Lancet Oncol 2012

Mediastinal LN Staging

Group 2: Small mediastinal LN without increased FDG uptake (normal mediastinum by imaging). Still a 6–30% prevalence of mediastinal metastases because of a centrally located primary tumour, enlarged or FDG-avid hilar lymph nodes, or a primary tumour and lymph nodes that are not FDG avid



Tournoy et al. Lancet Oncol 2012



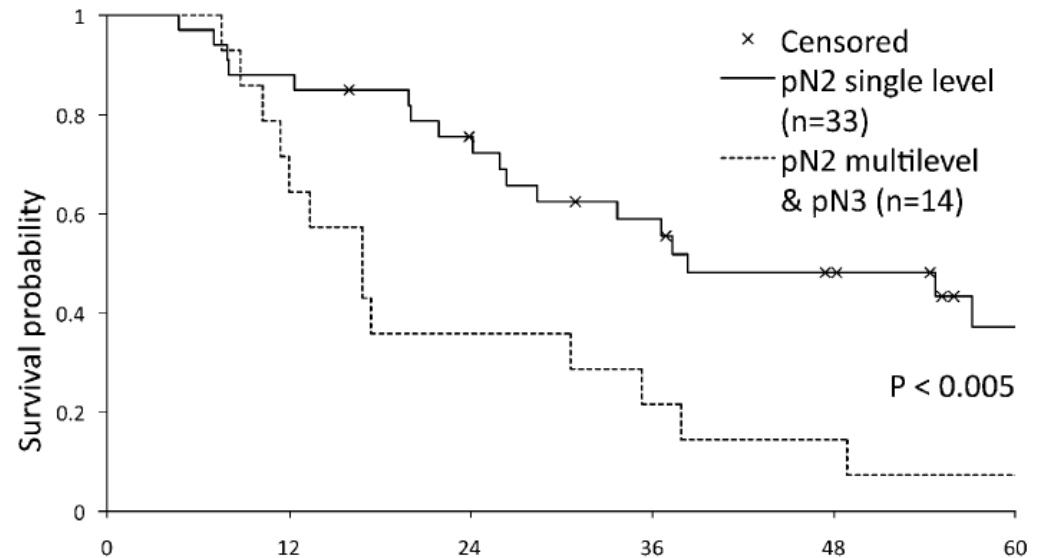
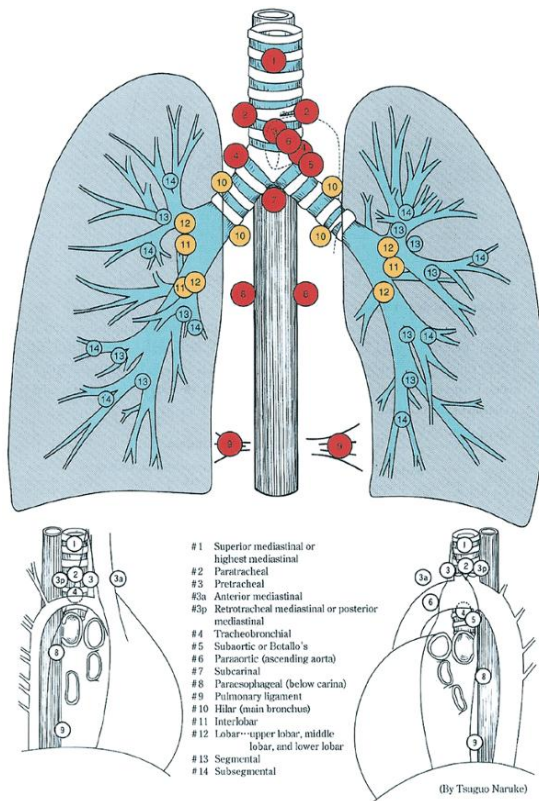
Issue Nr.2



N2 DISEASE IS A VERY HETEROGENOUS ENTITY

Stage IIIA (N2)

- involvement of single/ multiple stations
- +/- microscopic / full thickness / transcapsular

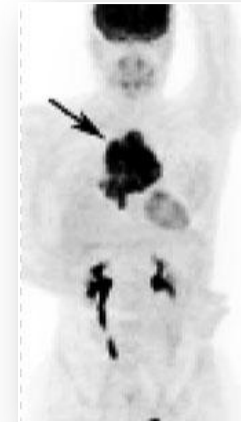


Decaluwe et al. EJCTS 2009
Induction CT (n=47)

Subsets of Stage IIIA (N2)

Robinson LA, Wagner H, Ruckdeschel JC

Treatment of Stage IIIA Non-Small Cell Lung Cancer; *Chest* 2003; 123:202-220



IIIA₁

Incidental nodal metastases found on final pathologic examination of the resection specimen

IIIA₂

Nodal (single station) metastases recognized intraoperatively

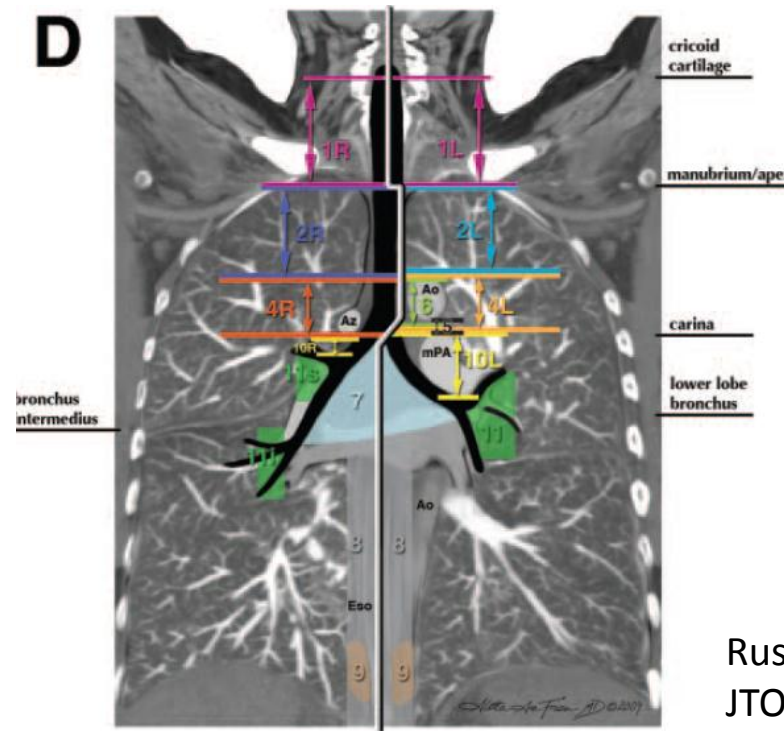
IIIA₃

Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)

IIIA₄

Bulky or fixed multistation N2 disease

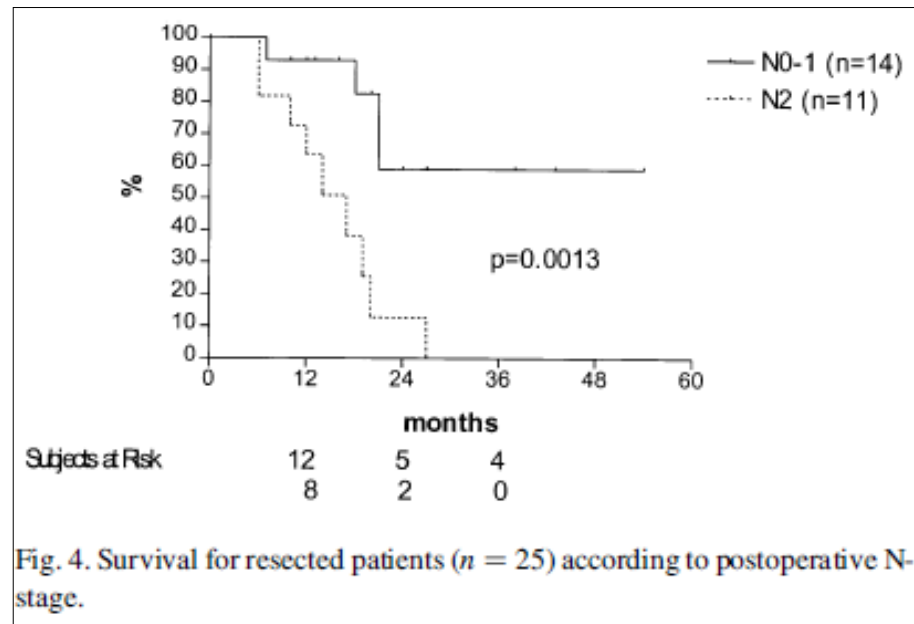
- Surgical accessibility depending from location of primary tumor: $R \ggg L \rightarrow$ Shifting of midline towards left paratracheal side in most recent IASLC classification



Rush et al.
JTO 2009

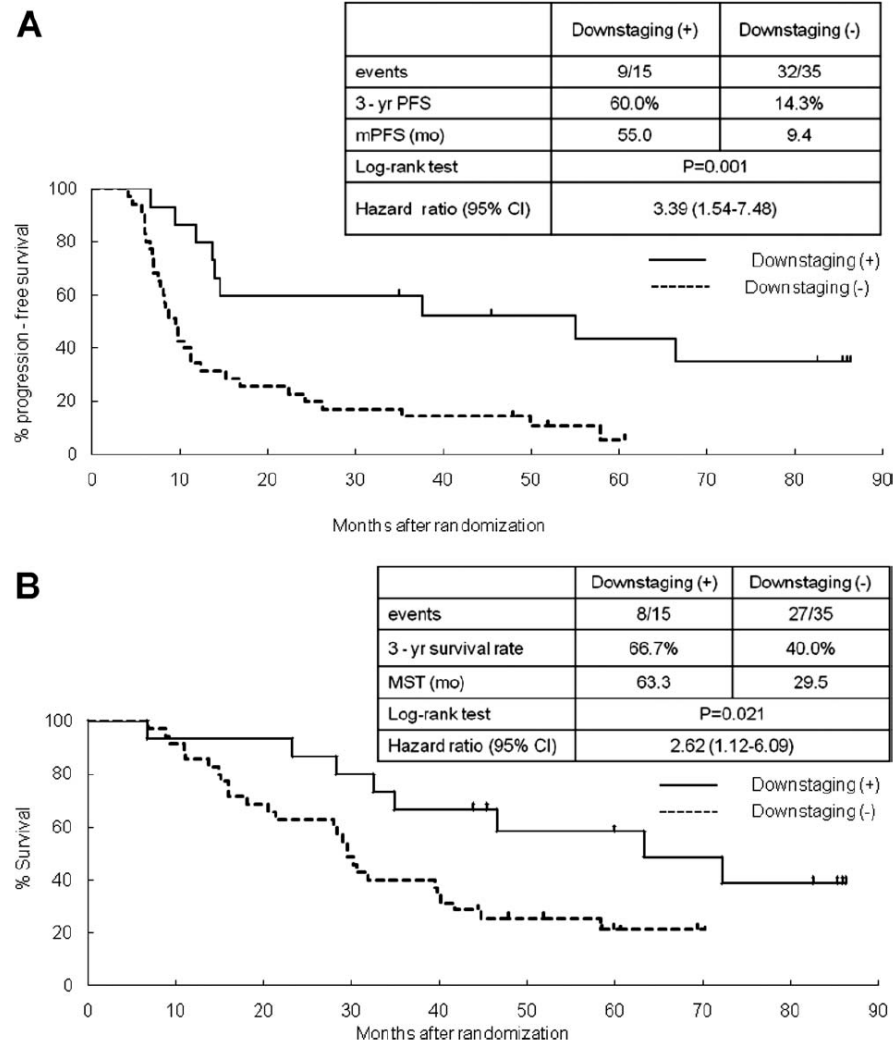
Issue Nr.4 : Impact of response

Response to induction therapy is an important parameter



Voltolini et al.
EJCTS 2001

Impact of response



Katakami et al.
Cancer 2012
Induction CT or CRT (n=60)

Recent literature

Uy et al. JTCVS 2007 (n=40)

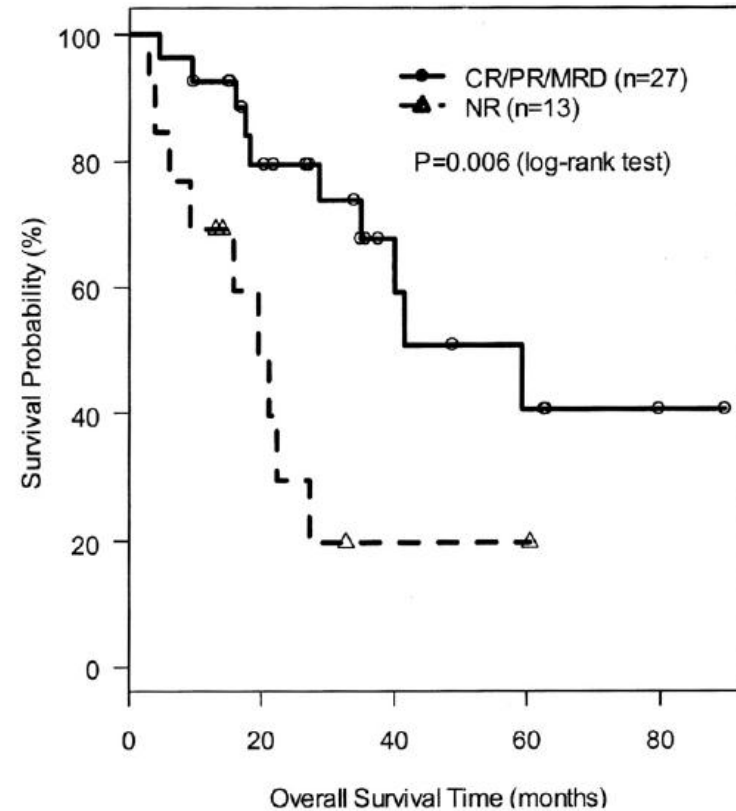
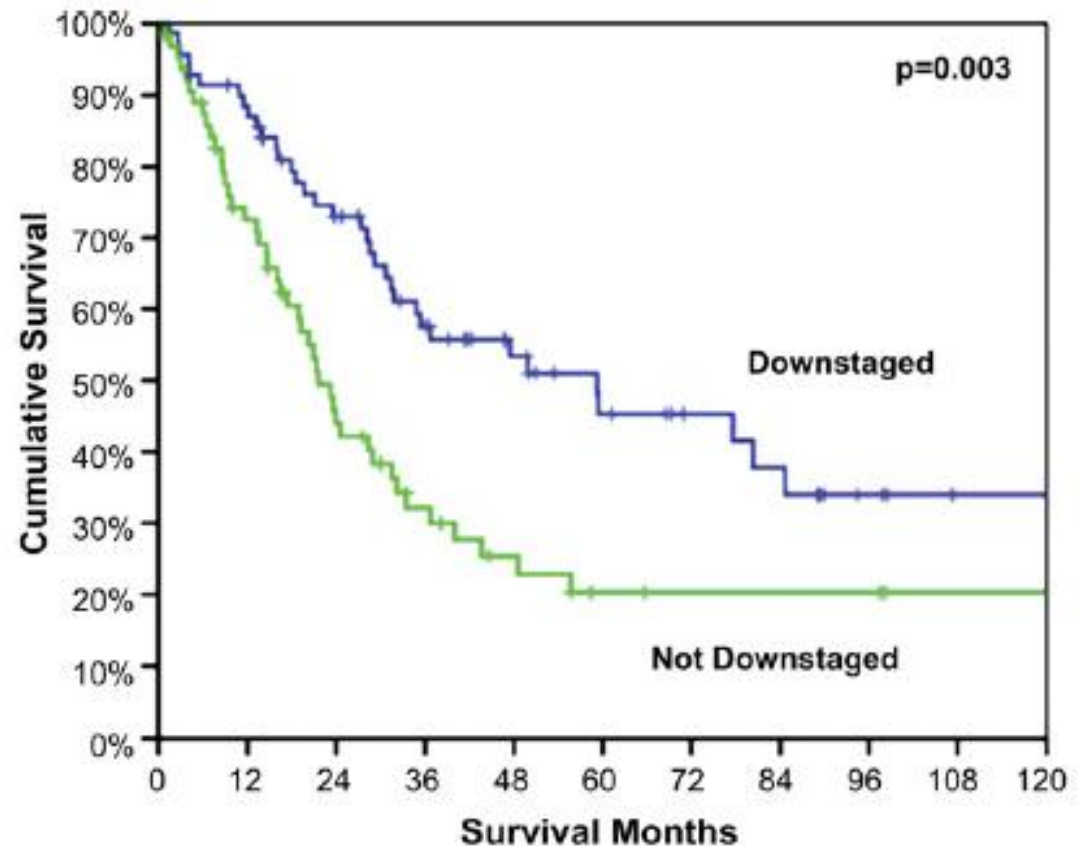


Figure 3. Overall survival by pathologic response. *CR*, Complete pathological response; *PR*, partial pathological response; *MRD*, minimum residual disease defined as less than 10% viable tumor cells; *NR*, no response.

Impact of response



Paul et al. JTCVS 2011
Induction CT or CRT (n=136)

Clinical response to induction therapy

Morphological: Decrease in diameters at CT

Biological: Decrease in SUV uptake at PET

TuMarkers: decrease in level

- Large tumors sometimes do not significantly decrease in size, yet there can be a high percentage of necrosis
- Good clinical response does not necessarily exclude presence of residual tumor cells

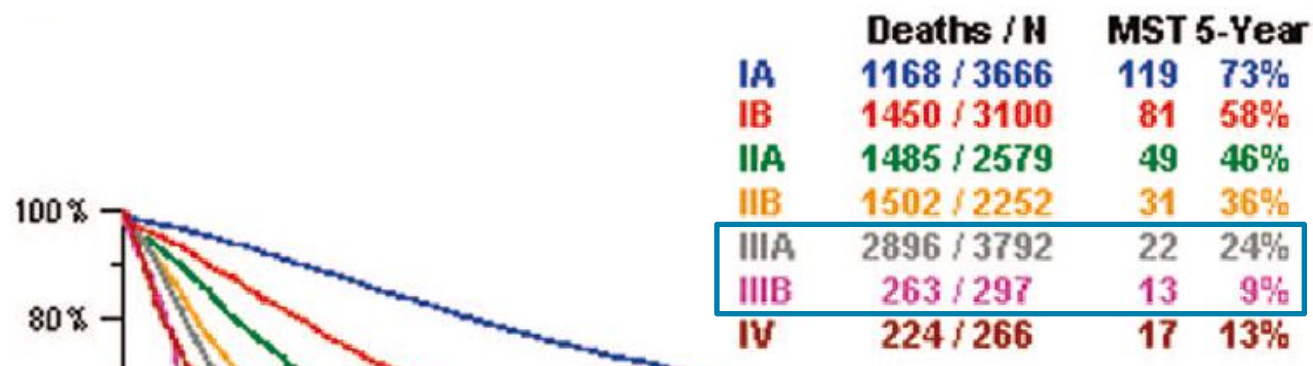
..... sometimes remains difficult to be determined



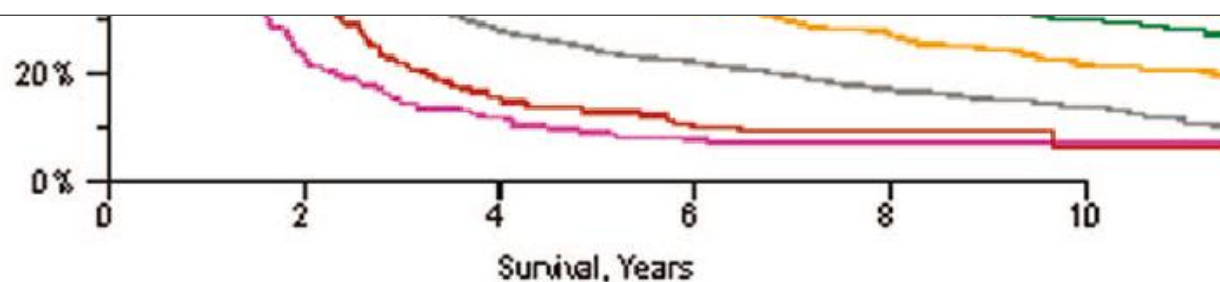
The FACTS

SURGERY IN N2 DISEASE

The IASLC Staging Project



Can we do better?





N2 positive NSCLC

INCIDENTAL, UNEXPECTED N2 (IIIA₁₋₂)

Robinson, Wagner. Chest 2007;132:243-265

- In patients with NSCLC who have **incidental (occult) N2 disease (IIIA₂)** found at surgical resection and in whom complete resection of the lymph nodes and primary tumor is technically possible, **completion of the planned lung resection and mediastinal lymphadenectomy** is recommended (2C)
- In patients with resected NSCLC who were found to have **incidental (occult) N2 disease (IIIA₁₋₂)** and who have good performance status, **adjuvant platinum-based chemotherapy** is recommended (1A)
- In patients with resected NSCLC who were found to have **incidental (occult) N2 disease (IIIA₁₋₂)**, adjuvant postoperative radiotherapy should be considered after adjuvant chemotherapy to reduce local recurrence (2C)

Robinson, Wagner. Chest 2007;132:243-265

- In patients with resected NSCLC who were found to have **incidental (occult) N2 disease (IIIA₁₋₂)**, combined **postoperative concurrent chemotherapy and radiotherapy is not recommended** except as part of a clinical trial

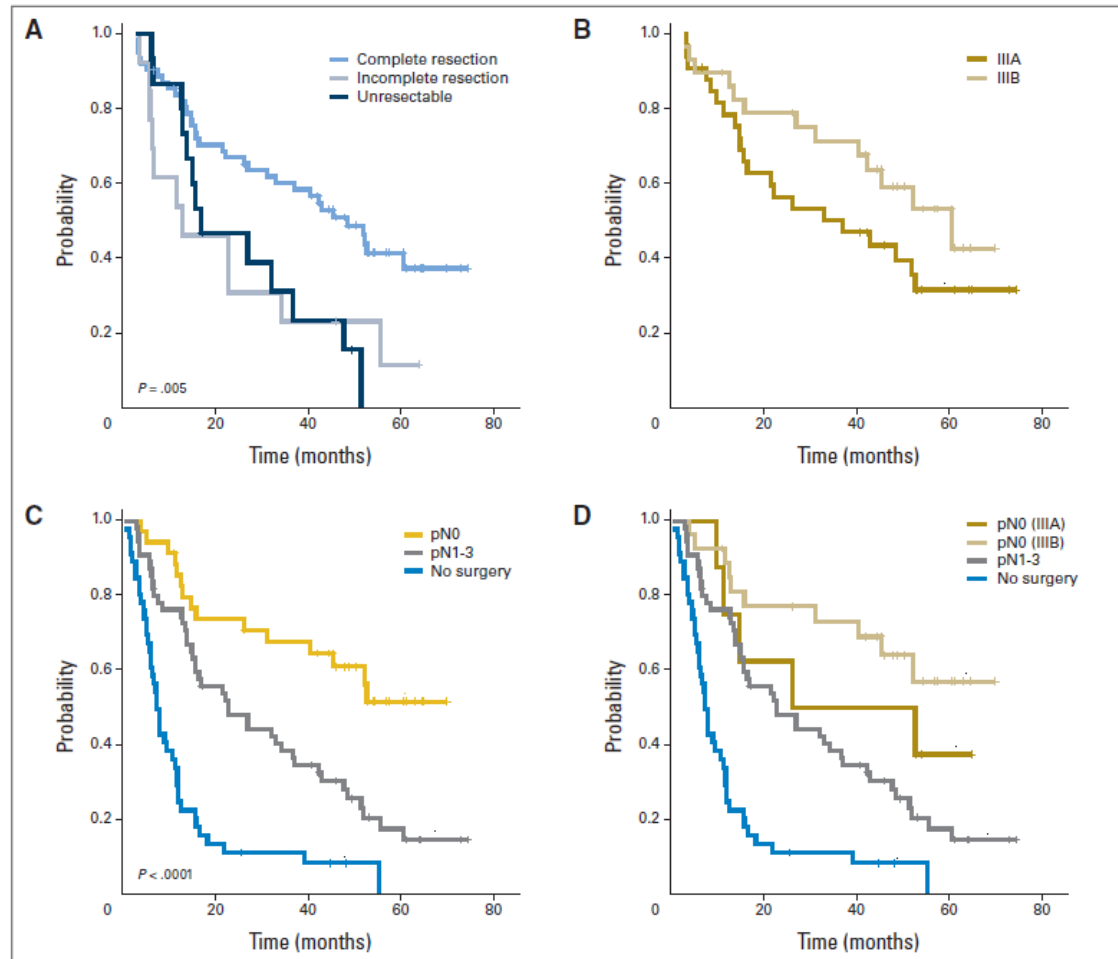


N2 positive NSCLC

PROVEN N2 (IIIA₃₋₄)

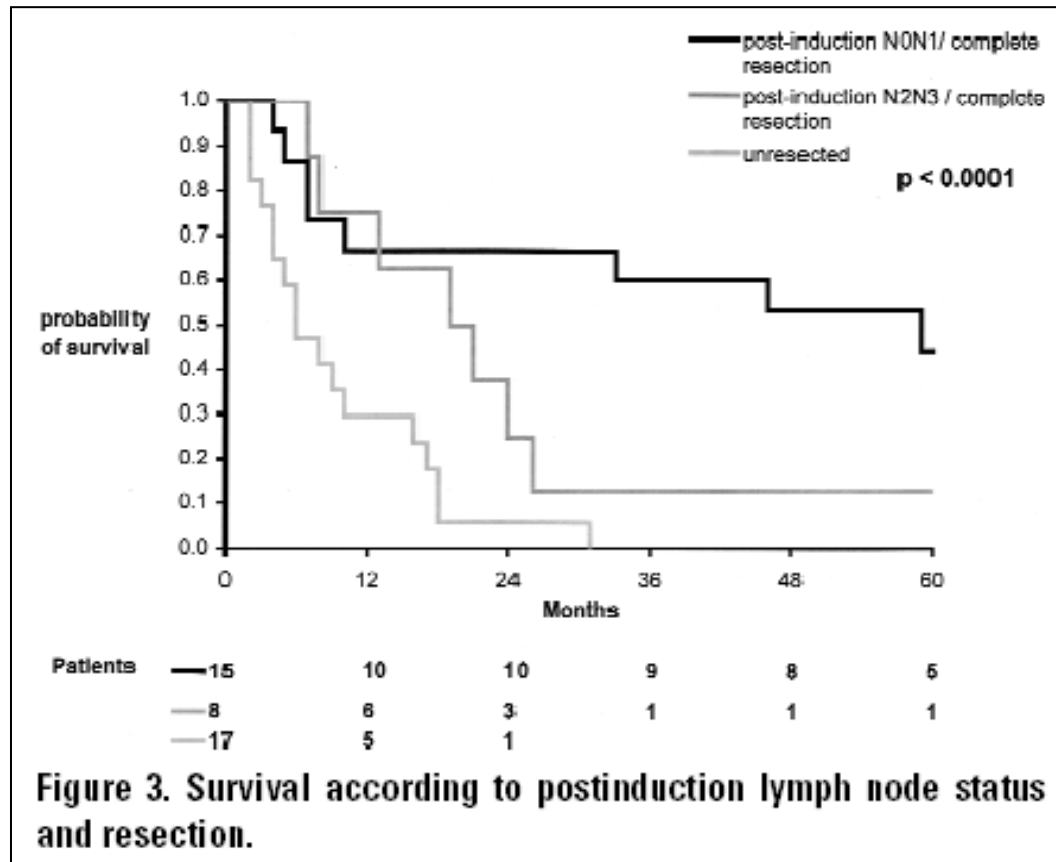
Recent literature

Garrido et al. JCO 2007 (n=136)



Surgery in Stage IIIB?

Benefit of Surgery after Chemoradiotherapy in Stage IIIB (T4 and/or N3) Non-small Cell Lung Cancer



Grunenwald et al.
JTCVS 2001

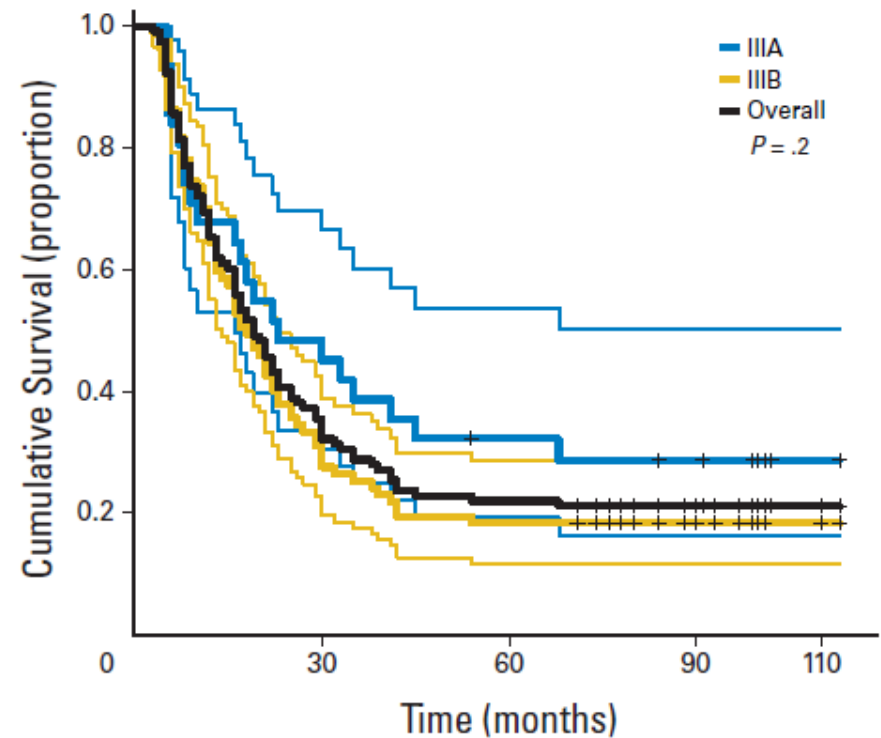
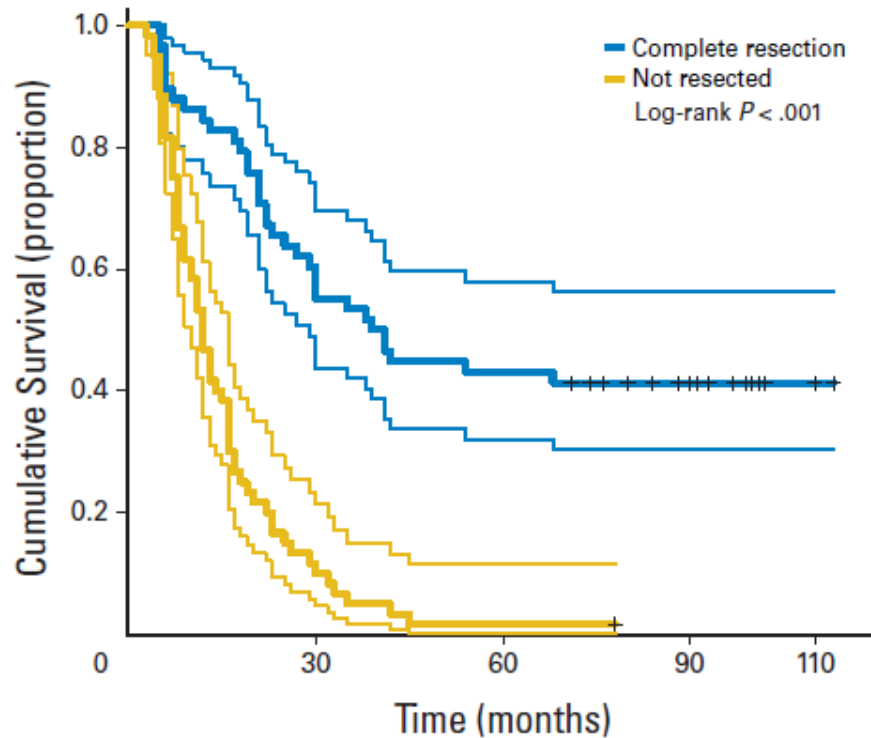
Another argument for surgery

Phase II Trial of a Trimodality Regimen for Stage III NSCLC using Chemotherapy as Induction Treatment with Concurrent Hyperfractionated Chemoradiation with Carboplatin and Paclitaxel Followed by Subsequent Resection: A Singel-Center Study

Friedel G. et al. J Clin Oncol 2010. Jan 25.

- Patients (n=120) with stage III NSCLC
- Treated with neoadjuvant chemoradiotherapy
- If resectable, patients underwent surgery, if not definitive chemoradiotherapy

Another argument for surgery



Friedel G. et al. J Clin Oncol 2010. Jan 25.

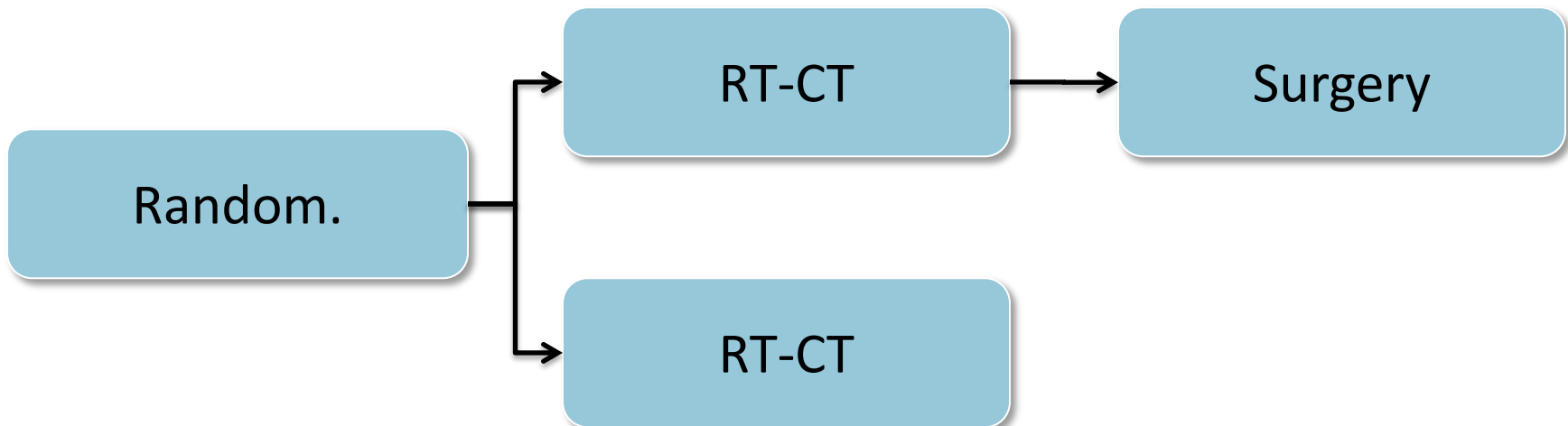
- **Complete resection** resulted in **5-y survival = 45%, median survival 39 mo**
- No resection 5-y survival = 0%; MS 12 mo; $p < 0,001$)
- Negative mediastinal lymph nodes were NO major prognostic factor: no significant difference between 5-y survival of ypN0 (57%), ypN1 (36%), ypN2 (38%)
- Only persisting ypN3 had significantly worse outcome

RCTs - Stage III (N2) NSCLC

EORTC 08941 Trial



Intergroup 0139 Trial



Intergroup Trial

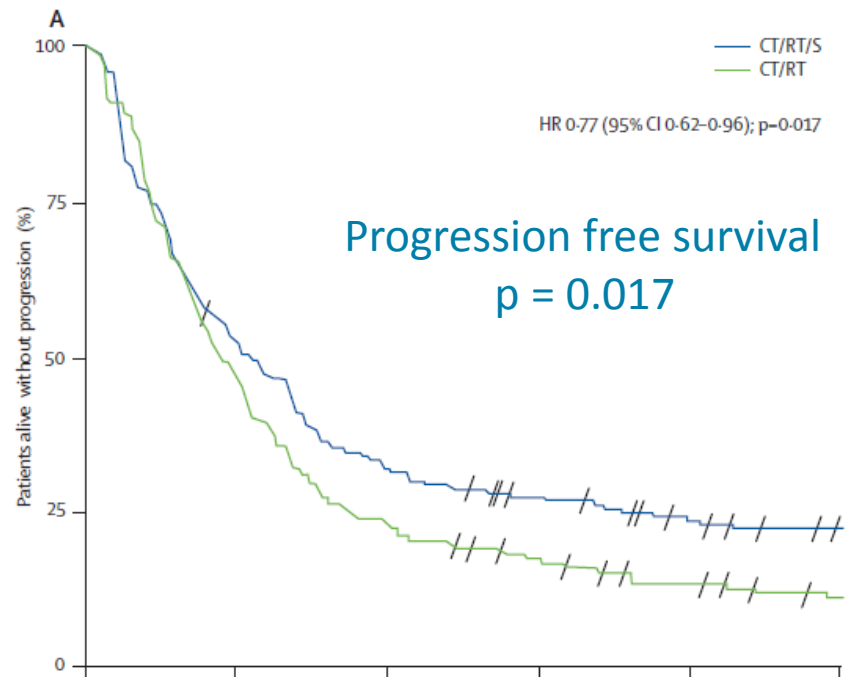
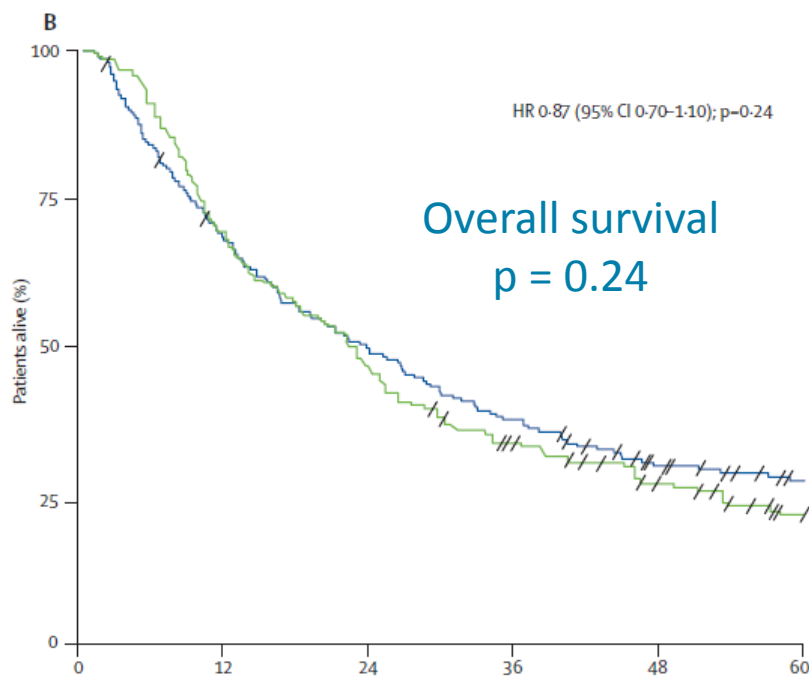
Albain et al. Lancet 2009;374:379-86

- Prospective Phase III RCT
- 396 Pat. (1994-2001)
- Stage IIIA(pN2) NSCLC
- 2 groups:
 - Group 1:** induction chemotherapy (cis/etoposide) and radiotherapy + surgery (n=202)
 - Group 2:** induction chemotherapy (cis/etoposide) and radiotherapy + definitive dose radiotherapy (n=194)

Endpoints

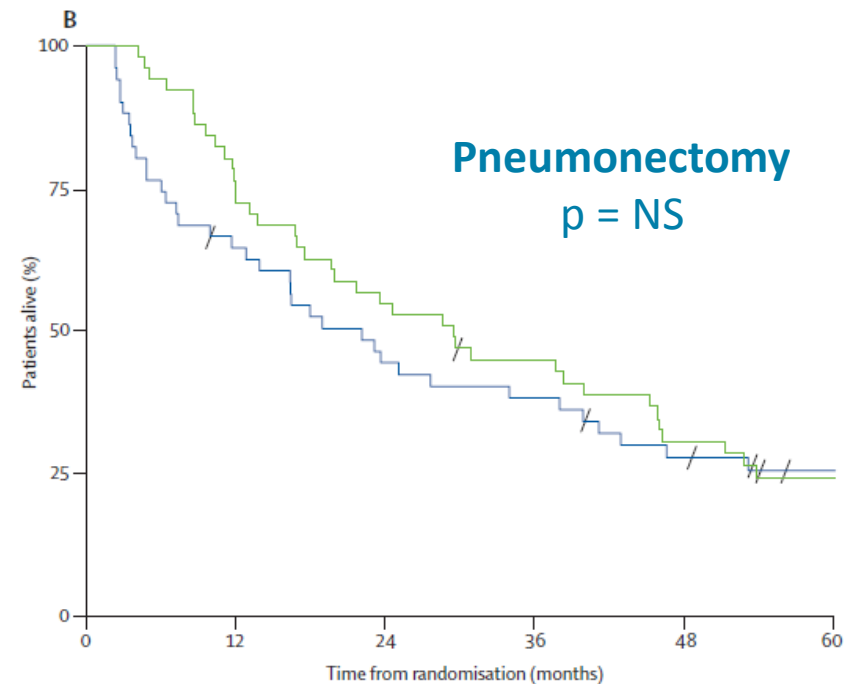
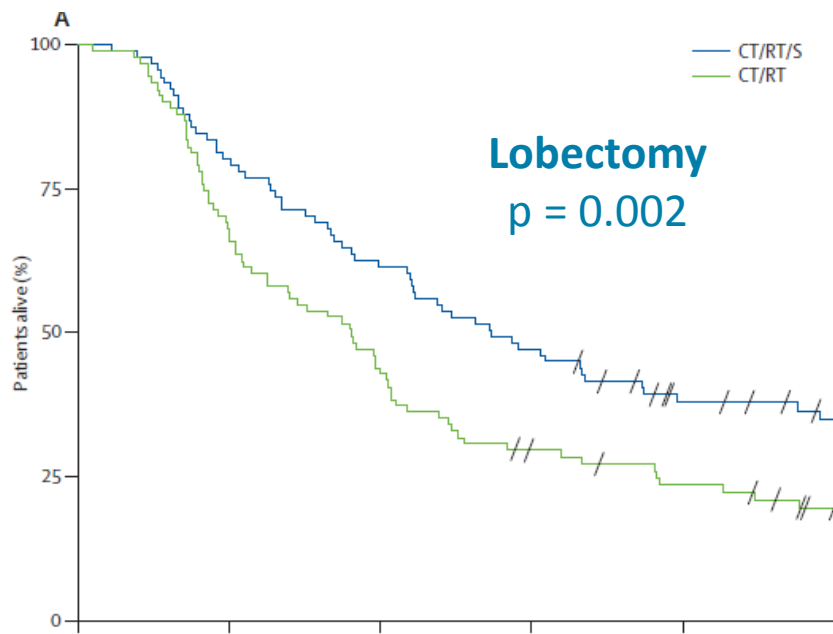
- **Primary Endpoint:**
 - overall survival (OF)
- **Secondary Endpoints:**
 - progression-free survival (PFS)
 - safety/toxicity
 - patterns of local and distant disease recurrence

RESULTS – Intergroup Trial



RESULTS – Intergroup Trial

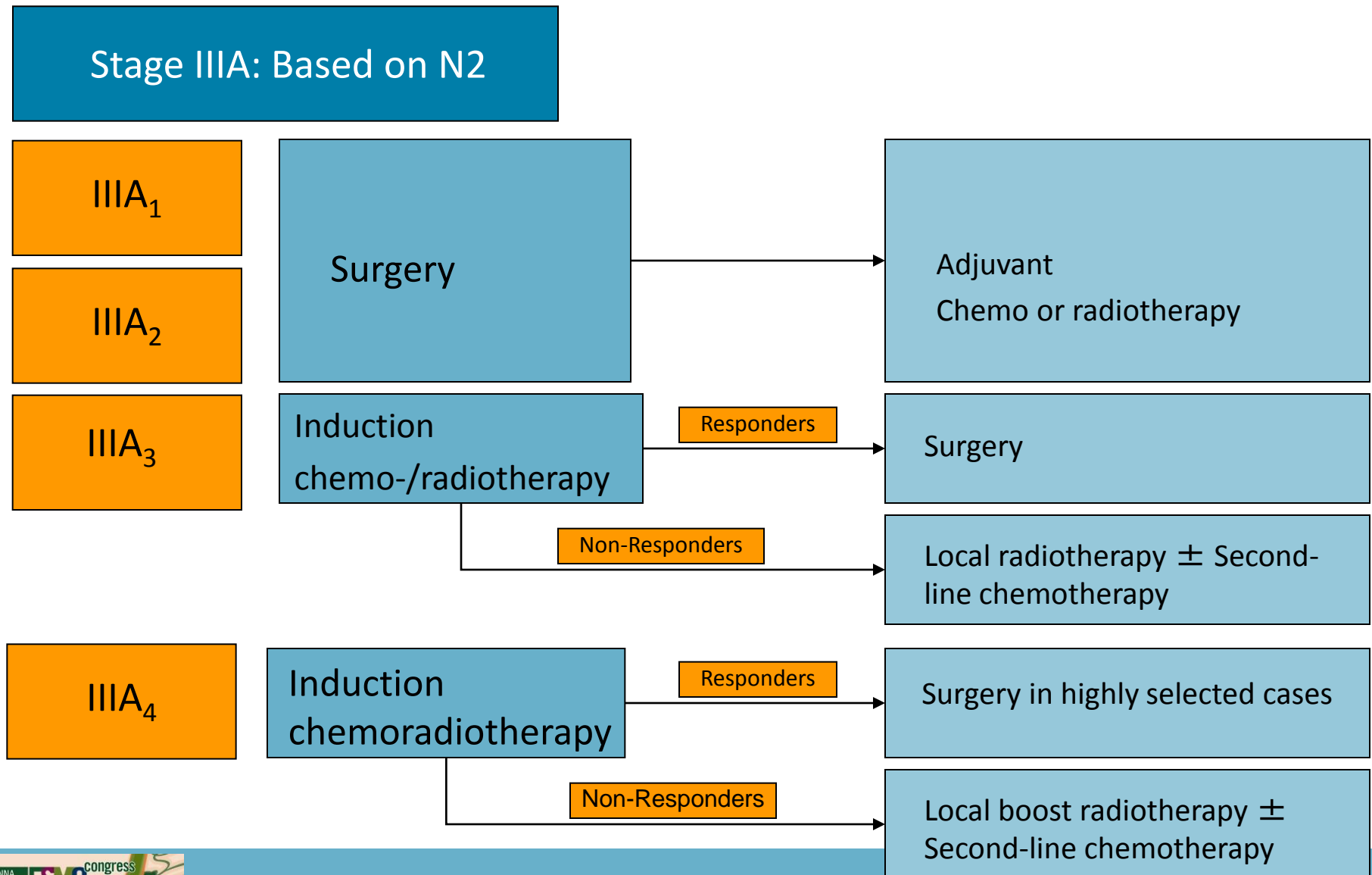
Exploratory analysis



RESULTS – Intergroup Trial

- **OS was improved in the surgical lobectomy group (33,6 vs. 21,7 months; $p=0,002$)**
- **OS was non significantly worse in surgical pneumonectomy group**
- **However: reported mortality of 26% for pneumonectomy was unacceptably high and does not compare to results from several other studies.**

Surgery for N2 positive NSCLC



Patients with N2 positive NSCLC should be EXCLUDED from SURGICAL treatment

