N2 positive NSCLC
The Surgical View

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Disclosure

I have no conflicts of interest that relate to this presentation.
5-year survival:

- Stage III: 5-15% (Stage IIIA up to 24%)

- "Standard of care": concurrent or sequential Chemotherapy + Radiotherapy

Patients with N2 positive NSCLC should be EXCLUDED from SURGICAL treatment.

N2 NSCLC: Status quo
Case I

- 64 year male: no relevant comorbidity
- Solitary 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
Case I

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

And how it turned out...

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

IIIA\(_1\)  Incidental nodal metastases found on final pathologic examination of the resection specimen

IIIA\(_2\)  Nodal (single station) metastases recognized intraoperatively

IIIA\(_3\)  Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)

IIIA\(_4\)  Bulky or fixed multistation N2 disease
Issue Nr. 3: **N2 – a matter of location**

- Surgical accessibility depending from location of primary tumor: \( R \gggg L \) -> Shifting of midline towards left paratracheal side in most recent IASLC classification

Rush et al.  
JTO 2009
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
Can we do better?
N2 positive NSCLC

INCIDENTAL, UNEXPECTED N2 (IIIA_{1-2})

- In patients with NSCLC who have incidental (occult) N2 disease (IIIA$_2$) 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 (IIIA$_{1-2}$) 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 (IIIA$_{1-2}$), adjuvant postoperative radiotherapy should be considered after adjuvant chemotherapy to reduce local recurrence (2C)

- In patients with resected NSCLC who were found to have incidental (occult) N2 disease (IIIA$_{1-2}$), combined postoperative concurrent chemotherapy and radiotherapy is not recommended except as part of a clinical trial
N2 positive NSCLC

PROVEN N2 (IIIA_{3-4})
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 Caroplatin and Paclitaxel Followed by Subsequent Resection: A Singel-Center Study


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

Results

- **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
- CT
- Random.
- RT
- Surgery

Intergroup 0139 Trial
- Random.
- RT-CT
- RT-CT
- Surgery
Intergroup Trial


- 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

Overall survival
\( p = 0.24 \)

Progression free survival
\( p = 0.017 \)
RESULTS – Intergroup Trial

Exploratory analysis

Lobectomy  
\[ p = 0.002 \]

Pneumonectomy  
\[ p = \text{NS} \]
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

Stage IIIA: Based on N2

III\(\text{A}_1\):
- Surgery
  - Responders
  - Non-Responders

III\(\text{A}_2\):
- Induction chemo-/radiotherapy
  - Responders
  - Non-Responders

III\(\text{A}_3\):
- Induction chemoradiotherapy
  - Responders
  - Non-Responders

III\(\text{A}_4\):
- Induction chemoradiotherapy
  - Responders
  - Non-Responders

Adjuvant Chemo or radiotherapy

Surgery

Local radiotherapy ± Second-line chemotherapy

Surgery in highly selected cases

Local boost radiotherapy ± Second-line chemotherapy
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