

The impact of lymph nodes down staging on survival after induction chemotherapy for pN2 non small cell lung cancer

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BACKGROUND

- Patients with stage IIIA-N2 tumors represent a **heterogeneous group** with different clinical presentation, and both prognosis and treatment strategies based on the extension of the disease to the mediastinum
- Numerous **non-randomized phase II and phase III trials** using induction chemotherapy have been reported in the literature
- **Chemotherapy followed by surgery** in highly selected patients with or without postoperative radiotherapy suggested an **improvement in resectability** and in long term survival up to 54% at 5-year over single-modality therapy



BACKGROUND

- These trials were biased by the **small number** of the patients, and by need to change standards during trial accrual to increase the number of patients → **lacking in the homogeneity of the group**
- Besides, only few patients underwent mediastinoscopy or EBUS-TBNA to pathologically confirm the N+



We retrospectively analyzed patients with “potentially resectable”, pathologically proven N2 NSCLC after induction chemotherapy, with the aim to identify prognostic factors to improve survival but also to identify the best group of survivor to investigate future therapies.



IEO experience 1998-2013

141 patients with “potentially resectable” pN2 NSCLC (122 mediastinoscopy or 19 EBUS-TBNA) underwent surgery after induction CT

All patients underwent cisplatin-based induction CT

Type of induction CT		Number of cycles	
Platinum/gemcitabine	(107/141) 76%	2-3	103/141(73%)
Platinum/other	(34/141) 24%	More than 3	38/141(27%)

We excluded patients with distant metastases, pN2 bulky or with infiltration of surrounding mediastinal structures, and/or progression disease.



Results

141 patients with “potentially resectable” pN2 NSCLC underwent surgery after induction CT

Explorative	15 (10.6%)
Pneumonectomy	27 (19.1%)
Lobectomy	96 (68.1%)
Segmentectomy	3 (2.1%)

R0	113 (80.1%)
R1	11 (7.8%)
R2	17 (12.1%)

Histology	All patients
Unknown	6 (4.3%)
Squamous carcinoma	48 (34.0%)
Adenocarcinoma	79 (56.0%)
Other	8 (5.7%)



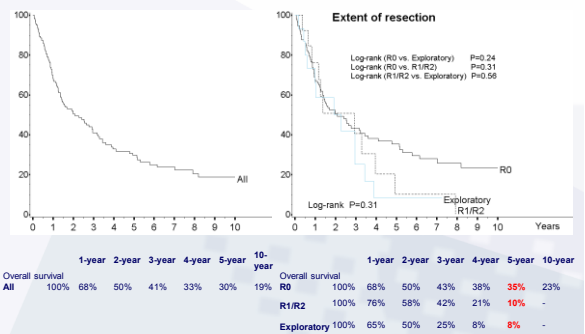
Results

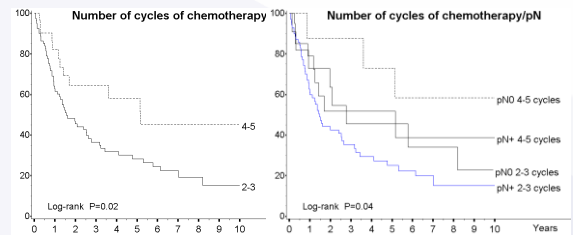
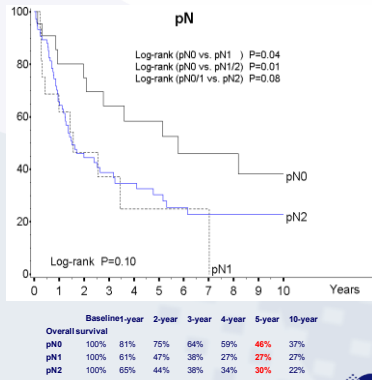
141 patients with “potentially resectable” pN2 NSCLC underwent surgery after induction CT

C stage	All	Resected	Explorative
	141	126	15
IIIa	127 (90.1%)	115 (91.3%)	12 (80.0%)
IIIb	14 (9.9%)	11 (8.7%)	3 (20.0%)
P stage			
Complete response	8 (5.7%)	8 (6.3%)	-
Ia/Ib	9 (6.4%)	9 (7.1%)	-
IIa/IIb	16 (11.3%)	16 (12.7%)	-
IIIa	84 (59.6%)	84 (66.7%)	-
IIIb	24 (17.0%)	9 (7.1%)	15 (100.0%)

- pN0 down staging in 17%,
- pN1 down staging in 13%
- persistent pN2 in 70%

All patients underwent explorative thoracotomy, incomplete resection (R1 or R2) or persistent N2 underwent adjuvant radiotherapy with mean dose of 52 Gy (range 29-65) or adjuvant chemotherapy





Overall survival	Baseline	1-year	2-year	3-year	4-year	5-year	10-year
2-3	100%	63%	45%	37%	32%	28%	15%
4-5	100%	82%	64%	64%	58%	48%	45%

Overall survival	Baseline	1-year	2-year	3-year	4-year	5-year	10-year
pN0 2-3	100%	73%	64%	46%	46%	46%	24%
pN0 4-5	100%	90%	90%	80%	76%	76%	61%
pN+ 2-3	100%	61%	42%	35%	29%	25%	15%
pN+ 4-5	100%	78%	51%	51%	51%	51%	38%

Multivariate analysis

Variable	HR (95% CI)	P-value
pN+ (multiple N2)	1.00	
pN+	0.57 (0.35-0.92)	0.02
pN0	0.54 (0.25-1.19)	0.13
Complete pathological response	0.23 (0.07-0.77)	0.02
2-3 cycles chemotherapy	1.00	
4-5 cycles chemotherapy	0.46 (0.25-0.85)	0.01

Major complications	14 (9.9%)
Hemothorax	3 (2.1%)
Empyema	1 (0.7%)
Cardiac dislocation	1 (0.7%)
Bronchial fistula	2 (1.4%)
Chylothorax	1 (0.7%)
Renal failure	2 (1.4%)
Gastric bleeding	1 (0.7%)
Pneumonia/ARDS	5 (3.5%)
Post operative tracheotomy	1 (0.7%)

} Re-thoracotomy

Minor complications	52 (36.9%)
Anemia	18 (12.8%)
Atrial fibrillation	22 (15.6%)
Prolonged air leak	12 (8.5%)
Atelectasia	7 (5.0%)
Pleural effusion	2 (1.4%)

No intraoperative mortality was observed.
Two patients (1.4%) died within 30 days following surgery

CONCLUSIONS

- Chemotherapy played an essential role in the **sterilization of lymph node metastasis** resulting in a significant increase in survival when compared with patients in whom the nodal down staging was not the case N+ (46% vs. 28% at 5 years)
- **Number of cycles of chemotherapy** were strictly related to a better survival. In patients with "potentially resectable" pN2 disease we reach up to 76% survival at 5 yrs by using 4-5 cycles of third-generation induction chemotherapy, with an acceptable morbidity and mortality
- a restaging after 2-3 cycles becomes important to understand if they are good responders or not, and whether to continue chemotherapy or candidate them to surgery



CONCLUSIONS

- pN1 patients (partial response to chemotherapy) have a bad survival rate, similar to persistent N2 → a restaging after chemotherapy should be better performed with **EBUS-TBNA** which is able to investigate also the N1 lymph node stations
- Finally, it will be essential to investigate the group of best survivors in term of genetic and molecular target such as MiRNA identifying possible "pretreatment prognostic factor" as predictive signature of chemotherapy efficacy (ongoing study).



Thank you!!!

