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UZA Kennis / Ervaring / Zorg

Loco-regional treatment for single station N2 NSCLC: **Radiotherapy**

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Disclosures

- I am not a radiation oncologist

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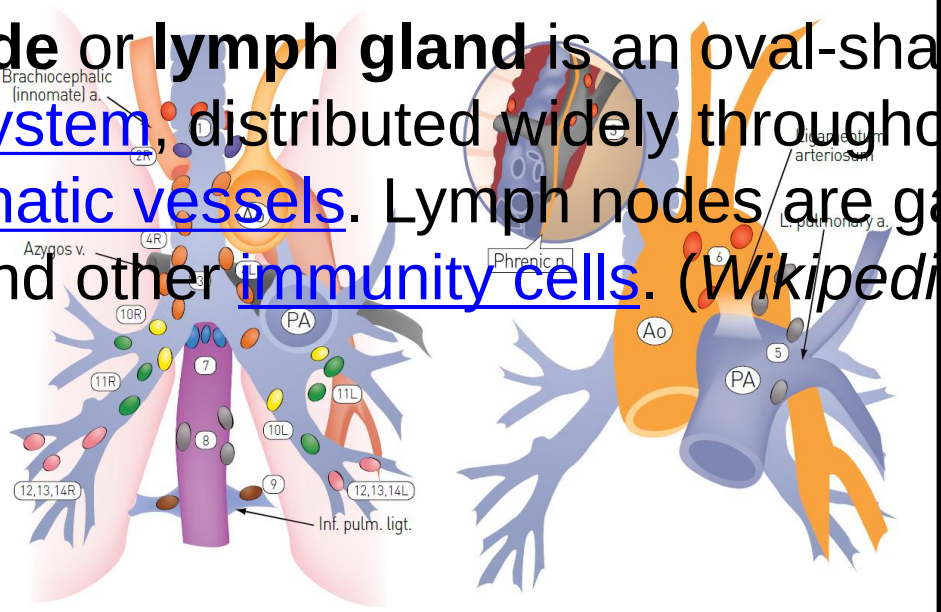
Outline

1. N2: classification and prognosis
2. Adjuvant radiotherapy in single station pN2
3. Induction (chemo-)radiotherapy in single station cN2
4. Conclusions

Mediastinal lymph node stations

A **lymph node** or **lymph gland** is an oval-shaped organ of the lymphatic system, distributed widely throughout the body and linked by lymphatic vessels. Lymph nodes are garrisons of B, T, and other immunity cells. (*Wikipedia*)



Superior Mediastinal Nodes

- 1 Highest Mediastinal
- 2 Upper Paratracheal
- 3 Pre-vascular and Retrotracheal
- 4 Lower Paratracheal (including Azygos Nodes)

N_2 = single digit, ipsilateral
N_3 = single digit, contralateral or supraclavicular

UPPER ZONE (R)

Aortic Nodes

- 5 Subaortic (A-P window)
- 6 Para-aortic (ascending aorta or phrenic)

AP ZONE (L)

Inferior Mediastinal Nodes

- 7 Subcarinal — SUBCARINAL ZONE
- 8 Paraesophageal (below carina)
- 9 Pulmonary Ligament — LOWER ZONE

N_1 Nodes

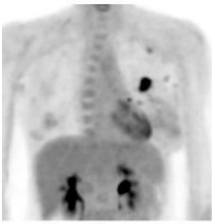
- 10 Hilar
- 11 Interlobar — HILAR ZONE
- 12 Lobar
- 10 Segmental
- 10 Subsegmental — PERIPHERAL ZONE

1. N2: classification and prognosis

1. **Infiltrative** N2/N3 involvement
2. **Discrete** clinically evident N2 involvement [by (PET-) CT-scan]
3. **Occult** N2 node involvement despite thorough preoperative staging

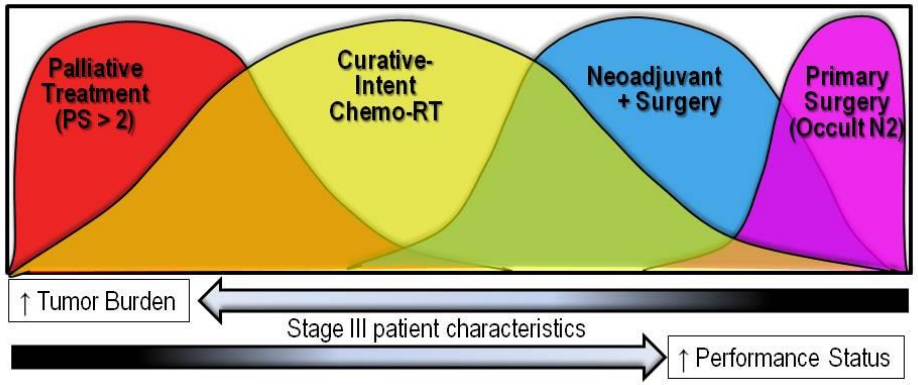
Mediastinal Infiltration

Discrete node enlargement



Clinically occult N2

Schematic of types of patients included in studies using different treatment approaches



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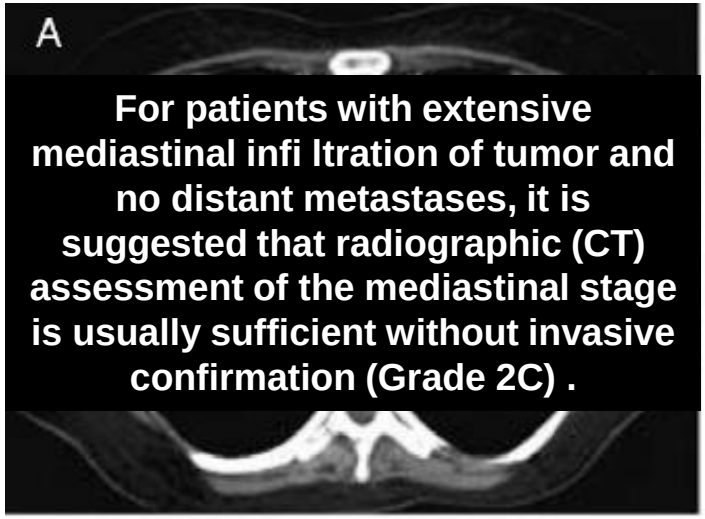
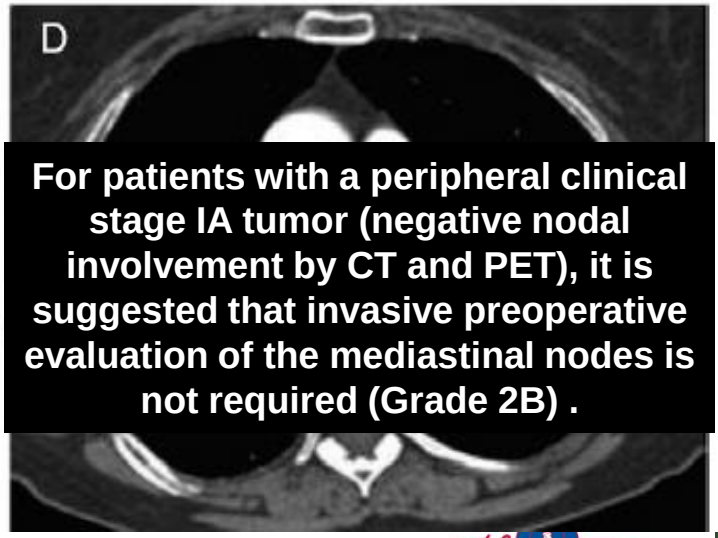
Thorough mediastinal staging



For patients with extensive mediastinal infi ltration of tumor and no distant metastases, it is suggested that radiographic (CT) assessment of the mediastinal stage is usually sufficient without invasive confirmation (Grade 2C) .

In patients with high suspicion of N2,3 involvement, either by discrete mediastinal lymph node enlargement or PET uptake (and no distant metastases), a needle technique (endobronchial ultrasound [EBUS]-needle aspiration [NA], EUS-NA or combined EBUS/EUS-NA) is recommended over surgical staging as a best first test (Grade 1B) .

In patients with an intermediate suspicion of N2,3 involvement, ie, a radiographically normal mediastinum (by CT and PET) and a central tumor or N1 lymph node enlargement (and no distant metastases), a needle technique (EBUS-NA, EUS-NA or combined EBUS/EUS-NA) is suggested over surgical staging as a best first test (Grade 2B).



For patients with a peripheral clinical stage IA tumor (negative nodal involvement by CT and PET), it is suggested that invasive preoperative evaluation of the mediastinal nodes is not required (Grade 2B) .

Silvestri, CHEST 2013

Is clinical single station N2 a fallacy?

Relationship between clinical and pathological L/N status (N2 single or multiple)

	pN2 single	pN2 multiple	Total
cN2 single	15 (35%)	28 (65%)	43 (100%)
cN2 multiple	6 (18%)	27 (82%)	33 (100%)
Total	21 (28%)	55 (72%)	76 (100%)

Sensitivity: 71%
Specificity: 49%
Positive predictive value: 35%

No conflict

Matsunaga, EJCTS 2013

Is single N2 involvement prognostic?

Series	Clin/ pathol	Station/zone	Single/ multiple	N	Median OS (m)	P value	Median PFS (m)	P value
Betticher 2003 (SAKK)	Clin	Station	Single	62	NR	**0,013**	16	0,29
			Multiple	20	22		10	

Conclusions (1)

- **Clinical** ‘single station N2’
  - Is a prognostic factor which is only moderately identifiable preoperatively

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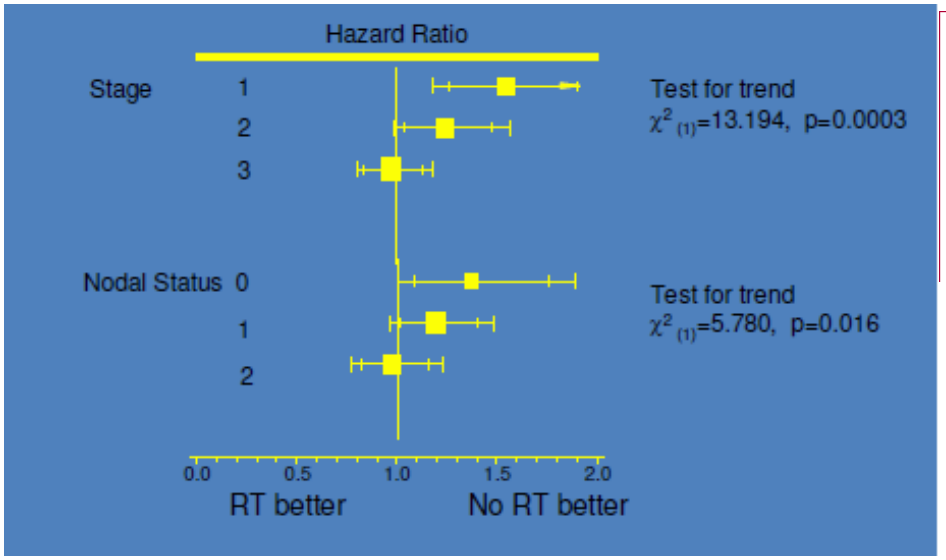
Caveats!

- A prognostic factor is not necessarily predictive
  - (*although it is attractive to imply it*)
- Association is not causation
  - Patients with good prognostic factors are selected for a certain treatment
  - This good prognosis is not attributable to the fact they underwent this treatment
- Introduction of routine PET-CT and/or EBUS changes the *a priori* prevalence of cN2

2. Adjuvant radiotherapy in single station pN2

PORT Meta-analysis Trialists Group, Cochrane Database System Rev 2005
NSCLC Meta-analyses Collaborative Group, Lancet 2008

2232 pts meta-analysis; 50% PORT



8847 pts meta-analysis

	Number events/ number entered		O–E	Variance	HR (fixed)
	S+CT	S alone			
Stage (exploratory analysis)					
Platinum, without tegafur and uracil/tegafur					
Stage IA	75/221	57/193	5·57	32·17	
Stage IB	396/1021	465/1054	−35·38	213·12	
Stage II	316/641	359/650	−32·09	164·56	
Stage III	250/417	250/394	−8·03	121·31	

2013 ACCP guidelines

- **In patients with resected NSCLC (R0) who were found to have incidental (occult) N2 disease (IIIA) despite thorough preoperative staging**
  - **adjuvant platinum-based chemotherapy is recommended when they have a good performance status (Grade 1A)**
  - **sequential adjuvant radiotherapy is suggested when concern for a local recurrence is high (Grade 2C)**

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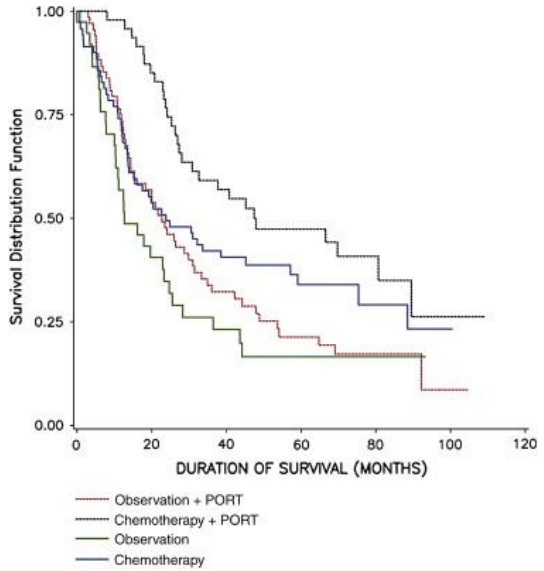
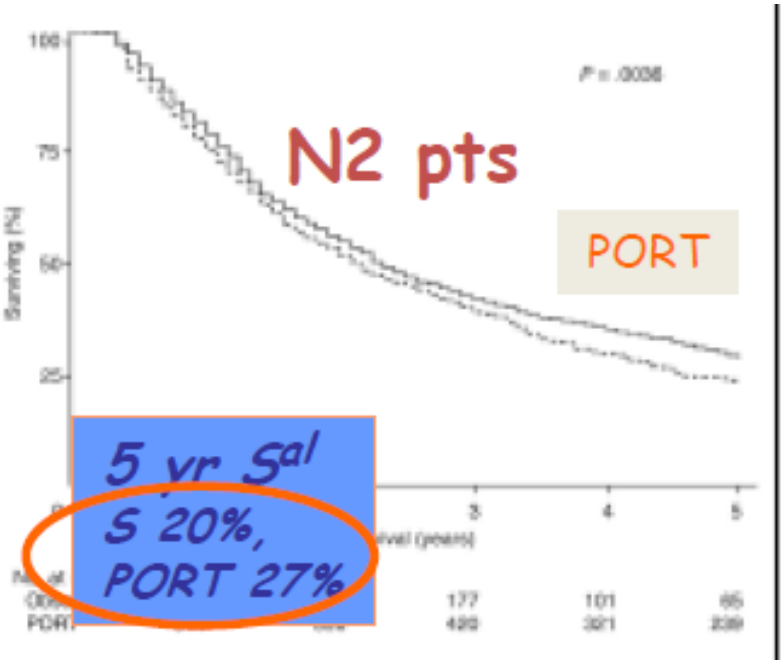
PORT in pN2

330 pN2 pts from ANITA
52% PORT



5 y OS (%)	N	PORT -	PORT +
S	174	17%	21%
S-CT	156	34%	47%

1987 pN2 pts from SEER
62% PORT



Douillard IJROBP 2008
Lally, J Clin Oncol 2006
Okawara, Lung Cancer 2004

Lymph node ratio = n p+ pN2/N pLN

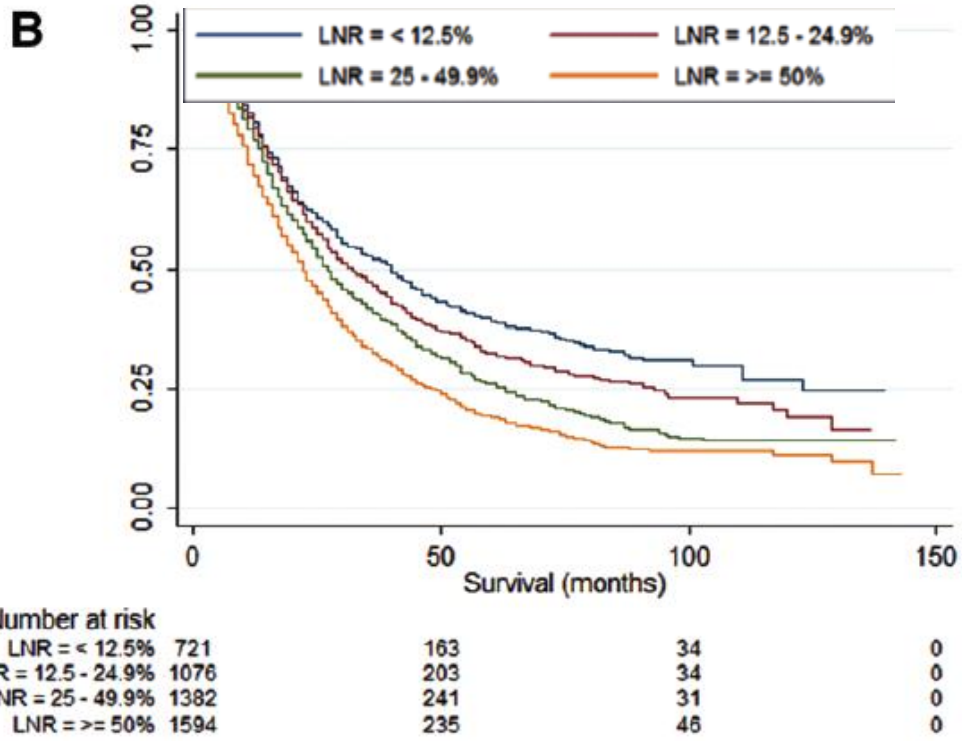


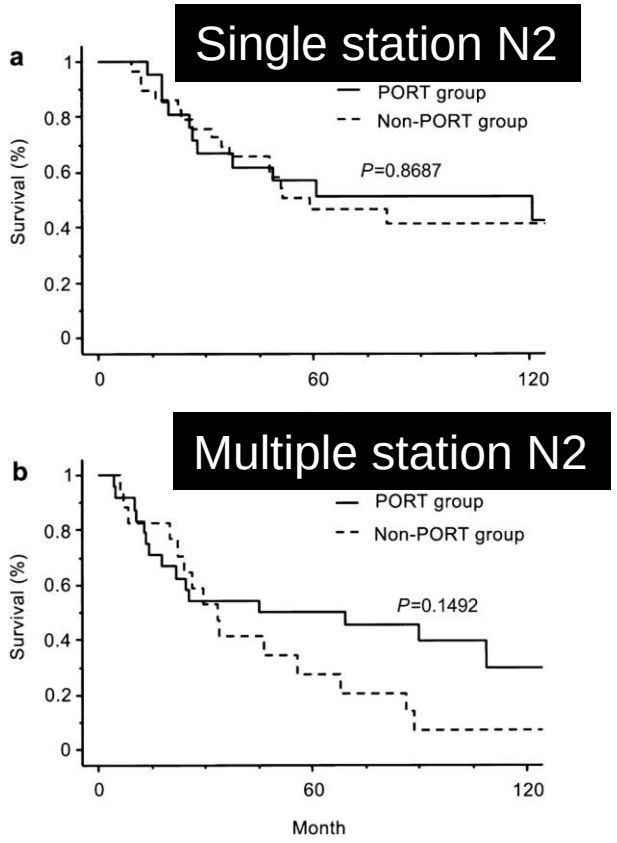
TABLE 3. Multivariate Analysis of Postoperative Radiotherapy Benefit for Overall Survival, Stratified by N-stage and LNR

	Hazard Ratio	*p*
N2	0.86 (0.79–0.94)	0.001
LNR < 12.5% (n = 528)	0.94 (0.71–1.23)	0.632
LNR12.5–24.9% (n = 829)	0.94 (0.77–1.15)	0.55
LNR 25–49.9% (n = 1042)	0.90 (0.76–1.06)	0.212
LNR ≥ 50% (n = 1197)	0.78 (0.67–0.90)	0.001

Urban, JTO 2013

Effect of number of pN2 involved

- *Matsuguma, Interact Cardiovasc Thorac Surg, 2008*
- 91 pN2 CR NSCLC
  - 50 single station pN2
  - PORT in 45: 21 single station pN2
  - OS in PORT and non-PORT group by single and multiple station N2 involvement



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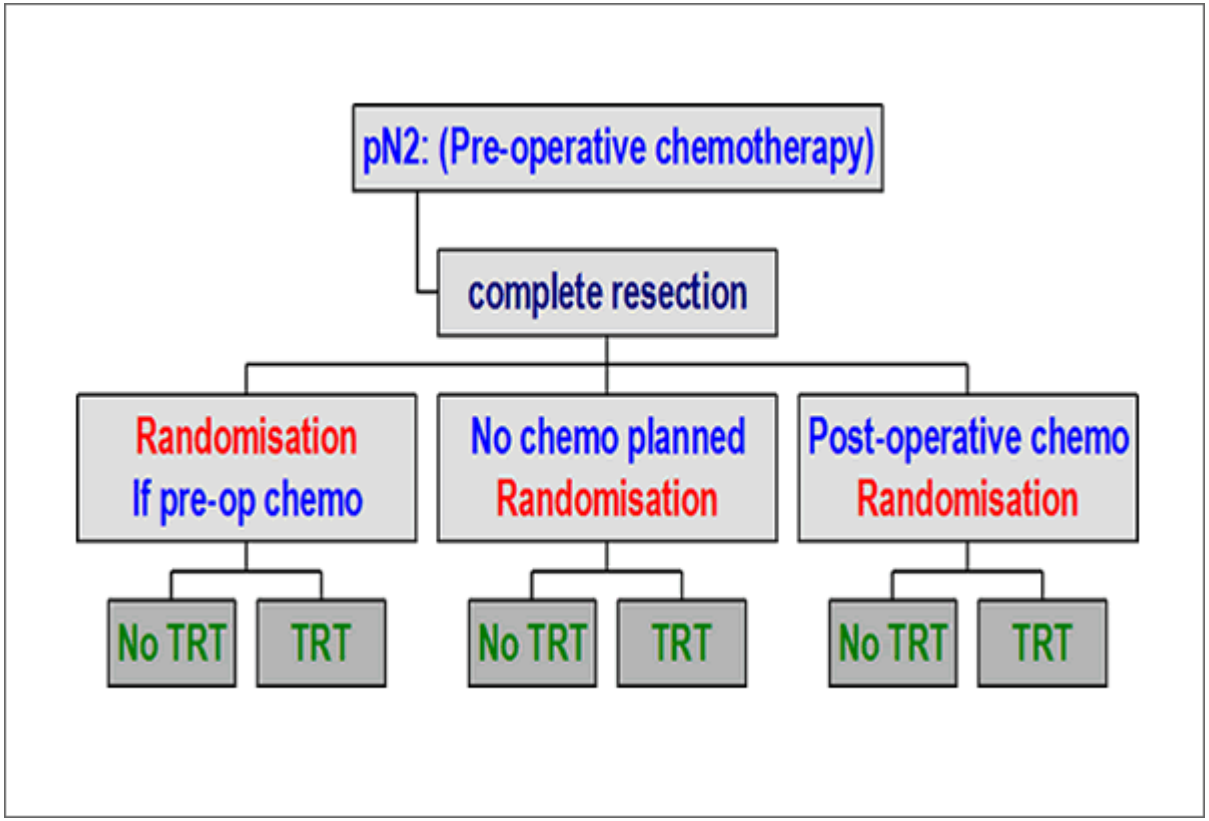

pN2: (Pre-operative chemotherapy)
complete resection
Randomisation
If pre-op chemo
No chemo planned
Randomisation
Post-operative chemo
Randomisation
No TRT
TRT
No TRT
TRT
No TRT
TRT

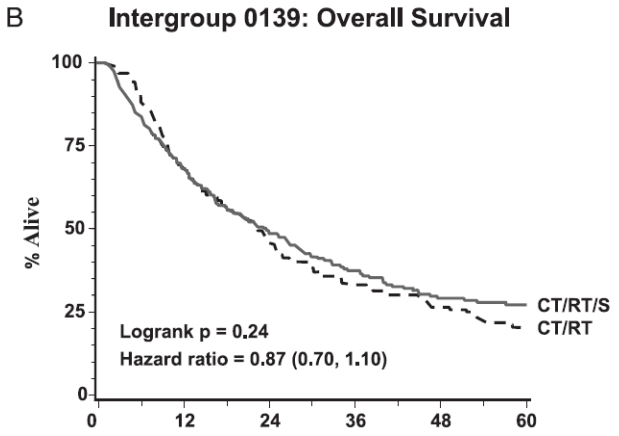
Conclusions (2)

- Clinical ‘single station N2’
  - Is a prognostic factor which is only moderately identifiable preoperatively
  - Is not predictive for a benefit of PORT

3. Induction (chemo-)radiotherapy in single station cN2

First Author	Year	No.	% with N2 confirmed	Mediastinal tumor burden	Induction Chemo-therapy	Control arm	Survival (%)				p
							2-year		5-year		
							Ind→S	ChRT	Ind→S	ChRT	
Albain[61]	2009	396	100	24% multistation	EP	ChRT	49	45	27	20	NS
Average							**37**	**34**	**22**	**19**	

Not single station N2



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Documentation of the status of one single node station was sufficient for enrollment; the true number with multistation involvement is likely higher

2013 ACCP guidelines

- **In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), either definitive chemoradiation therapy or induction therapy followed by surgery is recommended over either surgery or radiation alone (Grade 1A)**

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Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Long-term survival of stage T4N0-1 and single station IIIA-N2 NSCLC patients treated with definitive chemo-radiotherapy using individualised isotoxic accelerated radiotherapy (INDAR)

Bart Reymen [a,*], Angela van Baardwijk [...], Gerben Bootsma [c], Cordula Pitz [d], R[...]

All PET-CT
Single station N2 involvement
pathologically proven in 78%

Patient and treatment characteristics IIIA-N2.

Characteristic	Median/n° ± SD	Range/(%)
Age	64 ± 9	44–78
Gender		
Male	24	(59)
Female	17	(41)
WHO-PS		
0	17	(41)
1	21	(51)
2	3	(7)
UICC TNM stage		
cT0N2M0	3	(7)
cT1N2M0	12	(29)
cT2N2M0	20	(49)
cT3N2M0	6	(15)
Involved nodal station		
7	20	(49)
4R	6	(15)
4L	1	(2)
2R	2	(5)
5	11	(27)
8	1	(2)
Chemotherapy		
Sequential	15	(37)
Concurrent	26	(63)
GTV (in cc)	44.21 ± 90.5	3.4–440
MLD (in Gy)	14.5 ± 3.3	7–21
Prescribed TTD (in Gy)	65 ± 6	50.4–72
Delivered TTD (in Gy)	65 ± 6.8	43.5–72
OTT (in days)	30 ± 6.7	17–48

Patterns of [...]

Recurrence	Number of patients (%)
	IIIA-N2
No	18 (44)
Yes	23 (56)
Loca	10 (24)
Loca	8 (19)
Isola	2 (5)
Regi	7 (17)
Noda	7 (17)
Isola	0 (0)
Dista	22 (54)
Dista	12 (29)
Isola	10 (24)
Isolated brain metastases	3 (7)

Median follow up: 50 m
Median OS: 26 m (15.6-36.4)
3 y OS: 37%
5 y OS 24% (estimated)
Median PFS 24 m (9.4-38.5)

IASLC International Association for the Study of Lung Cancer

European Society for Medical Oncology

Outcome in c single station N2

Series	N	PET staging	Overall survival Median (m)	5 y (%)
Betticher, 2003 , multicenter	62	None	43	
Lorent, 2004 , single center	93	Some	26	24%
Albain, 2009, intergroup- CT-RT-S	<152	None	23.6	27%
Albain, 2009, intergroup- CT-RT	<146	None	22.2	20%
Reymen, 2014, multicenter	41	All	26	24%

Conclusions (3)

- Clinical ‘single station N2’
  - Is a prognostic factor which is only moderately identifiable preoperatively
  - Is not predictive for a benefit of PORT
- In thoroughly staged patients with clinical ‘single station N2’ involvement, modern definitive chemoradiation therapy results in at least equivalent outcome as retrospective series using induction therapy followed by resection

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Subgroups of cIIIA-N2 favouring resection?

FIGURE 8. [Section 3.3.1] Selection criteria for trimodality therapy with surgery in patients with stage III (N2) lung cancer.

Selection Criteria	Assessment of commonly cited arguments				**Summary: Justification for Surgery**
	Pre-operatively identifiable?	Prognostic value?	Potential Flaw	Defines treatment value?	
"Minimal" N2	Moderate	Probably	Out-of-context	Unclear	Unclear
Single station	Moderate	Yes	Out-of-context	Unclear	Unclear
cN0,1	Yes	Yes	Out-of-context	Unclear	Unclear
Non-bulky nodes	Yes	Probably	Out-of-context	Unclear	Unclear
Good surgical risk	Yes	-	-	No	Not applicable
Downstaged	Limited	Yes	Landmark	Unclear	Unclear
	Yes		iective	Uncle	
	es				

Positive predictive value of c single node N2 on CT scan = 35%

Data taken from a group of resected patients are applied to a different group of clinically staged patients

No data define whether the inclusion of surgery in the treatment strategy further improves outcome

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SECOND OPINION

BY ROB ROGERS