

Surgery for single zone N2 NSCLC

David Waller FRCS(CTh)
Consultant Thoracic Surgeon
Glenfield Hospital, Leicester, UK
No disclosures to declare

- Establish your line in the sand
- Why surgery is not considered for N2 disease ?
- Why there may be a role for primary surgery in N2 disease?
- What is necessary before primary surgery for N2 ?
- The N2 paradox

- Establish your line in the sand
- Why surgery is not considered for N2 disease ?
- Why there may be a role for primary surgery in N2 disease?
- What is necessary before primary surgery for N2 ?
- The N2 paradox
- **Can you cross the line in the sand ?**

Why surgery is not considered for N2 disease ?

Against surgery

- *“the outcome of INT 0139 and EORTC 08941 mean that evaluating the role of surgery is not a clinical priority”*
- *“using neoadjuvant therapy followed by surgery for known IIIA is not supported by current evidence”*
- *“combination chemoradiotherapy (concurrent) is the preferred treatment for known IIIA”*
- *Robinson, ACCP evidence based clinical practice guidelines. Chest 2007;132:243S*
- *“medical oncologists can be persuaded that non-surgical treatments result in fitter patients who can tolerate more consolidation regimes and biological agents”*

Where is your line in the sand ?

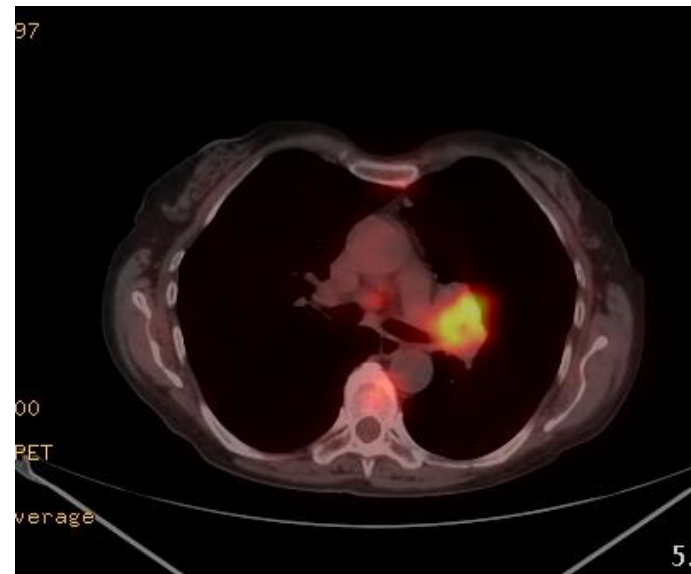
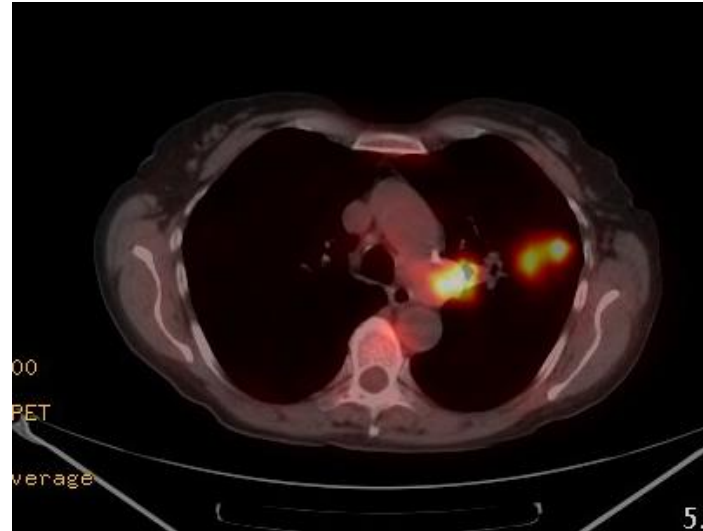


Why there may be a role for primary surgery in N2 disease?

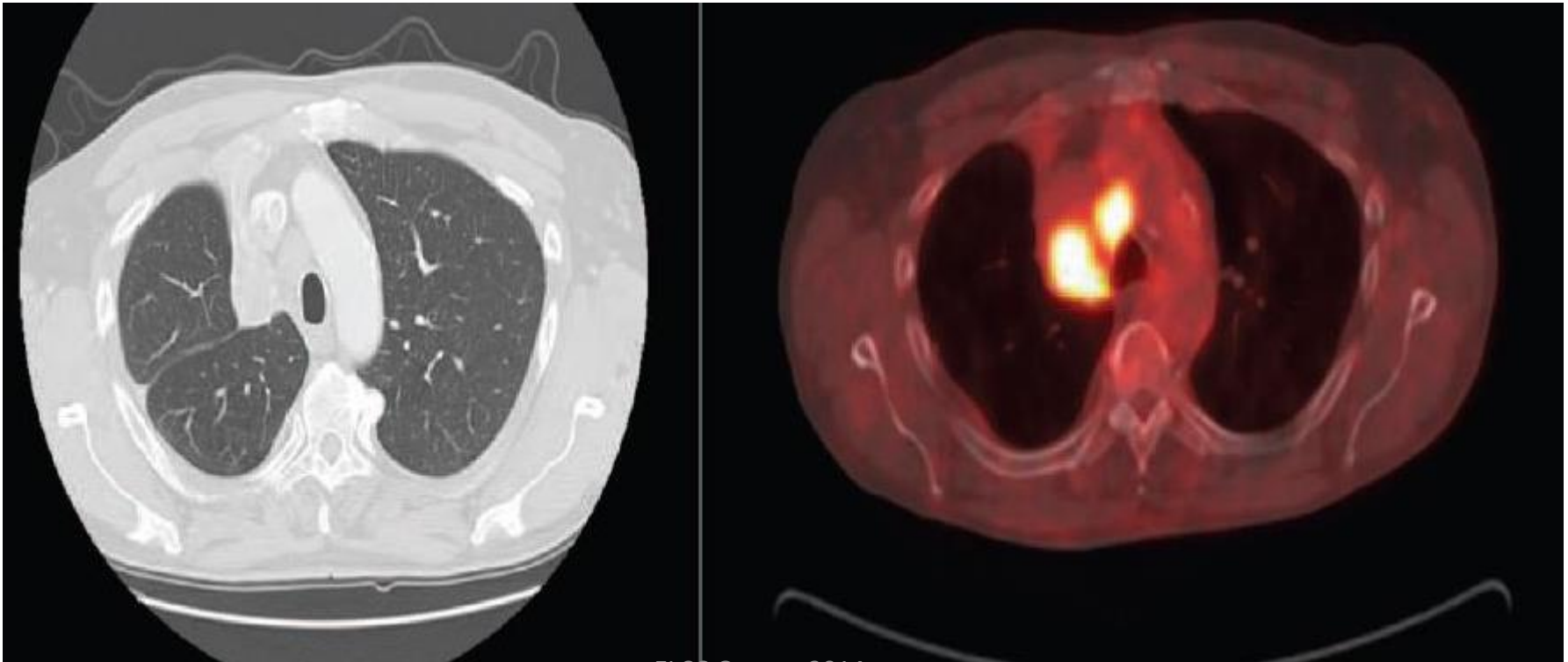
**L upper lobe tumour
+ single station 5
metastasis**

***Keller SM,
ECOG 3950 trial.
JTCVS 2004;128:130***

LUL single level N2 : 49 mo
v LUL N1 51 mo .
LUL N2 but no N1 : 59 mo

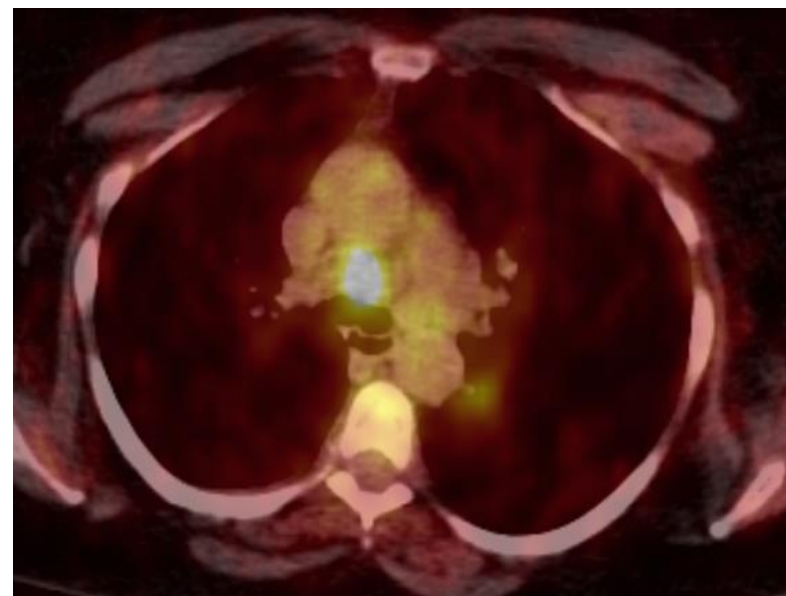
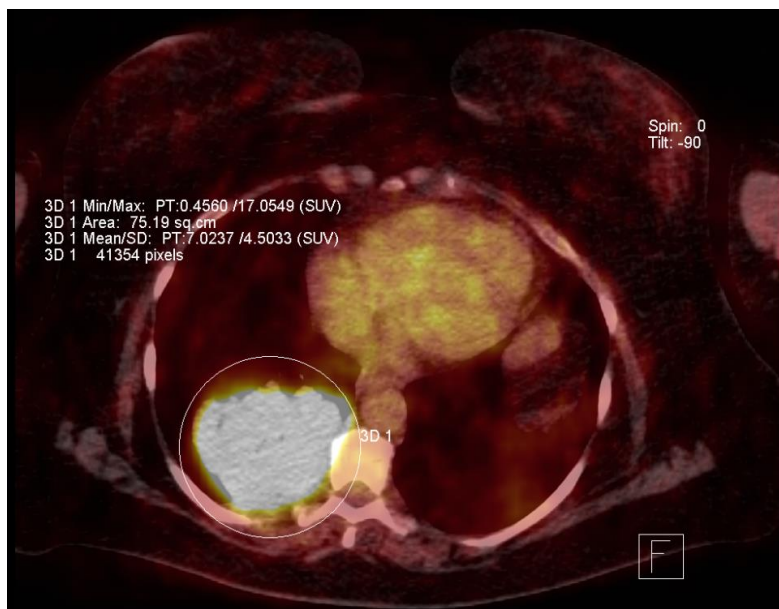


- ***Inoue, JTCVS 2004;127:1100.***
Any upper lobe single N2 : 53.5% 5 yr survival



Surgery / adjuvant chemotherapy

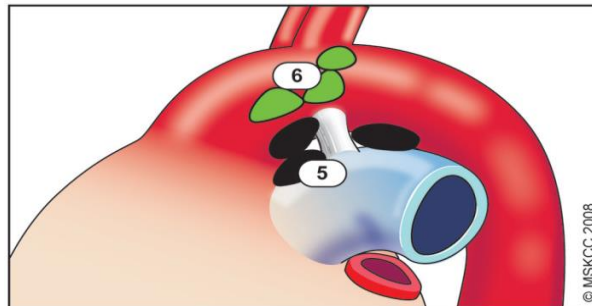
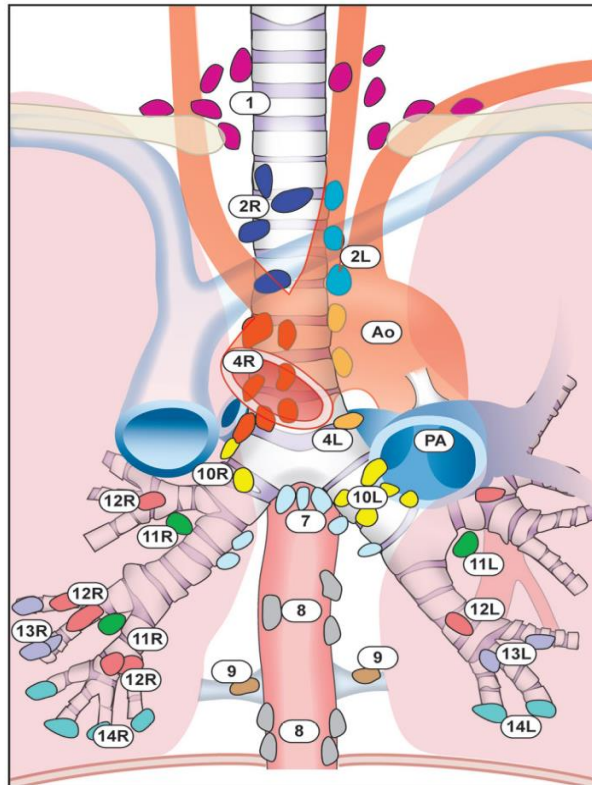
may still be preferable to radiotherapy when large tumour volume and radical chemoradiation not possible



- ***Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data.***
Lancet 2010; 375: 1267–1277.
- “application of the overall hazard ratio to survival in the control group by stage suggests absolute improvements in 5-year survival of 5% (3–8) for **stage III disease (from 30% to 35%)**”

Rusch VW, J Thorac Oncol. 2009;4:568-77.

The IASLC lung cancer staging project



Supraclavicular zone

- 1 Low cervical, supraclavicular, and sternal notch nodes

Superior Mediastinal Nodes

Upper zone

- 2R Upper Paratracheal (right)
- 2L Upper Paratracheal (left)
- 3a Pre-vascular
- 3p Retrotracheal
- 4R Lower Paratracheal (right)
- 4L Lower Paratracheal (left)

Aortic Nodes

AP zone

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

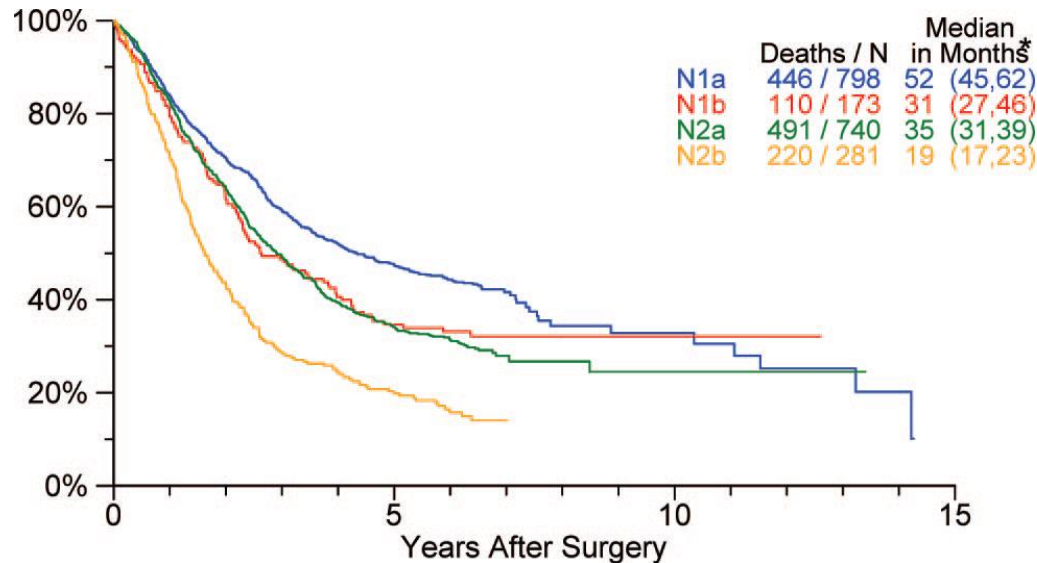
Inferior Mediastinal Nodes

Subcarinal zone

- 7 Subcarinal

Lower zone

- 8 Paraesophageal (below carina)
- 9 Pulmonary ligament



	1 Yr	5 Yrs		HR	P
N1a	86%	48%			
N1b	79%	35%	vs N1a:	1.32	<.0090
N2a	83%	34%	vs N1b:	1.04	0.7137
N2b	71%	20%	vs N2a:	1.65	<.0001

*estimates of median survival, followed by 95% confidence intervals in parentheses

- Single zone N2a disease has similar prognosis to multistation N1b disease

- These results are based on ***postoperative*** pathological staging
- Which are based on ***intraoperative*** lymph node dissection
- Thus this needs to be simulated ***preoperatively***
- ***Mediastinoscopy + lymph node dissection***

What is necessary before primary surgery for N2 ?

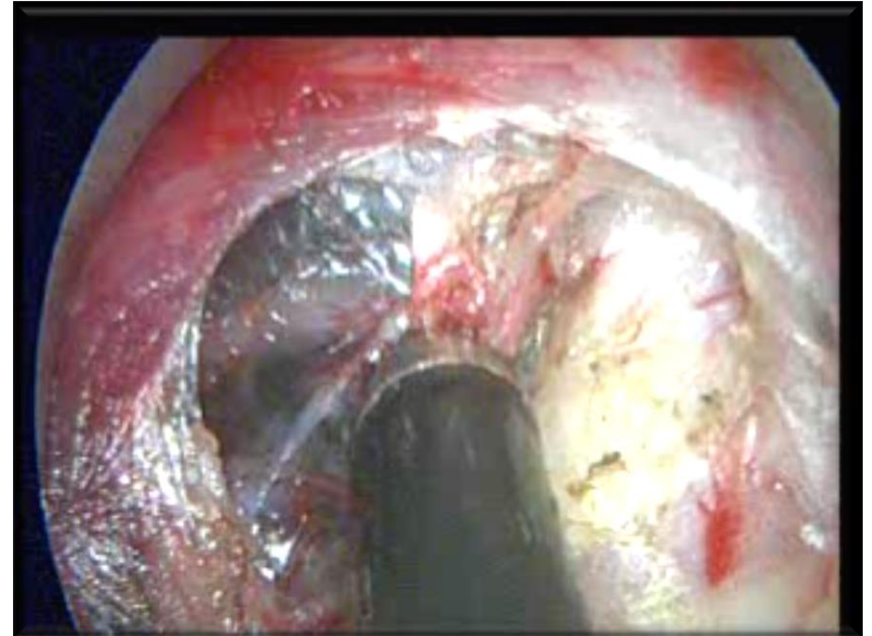
Primary resection is indicated in single-zone N2 disease

- Single zone N2 may be suspected by low to moderate PET uptake in remaining N2 zones
- The need is to ***exclude*** nodal involvement rather than prove it
- EBUS/EUS is validated in confirming the positive usually in high prevalence states
- **VAMLA** is best at confirming the negative
- **sensitivity of 93.8%, a specificity of 100%, and a false-negative rate of 0.9%.**

What should we achieve by mediastinoscopy ?

VAMLA

- Video assisted mediastinoscopic lymphadenectomy
- Witte B, Hürtgen M, *J Thorac Oncol.* 2007;2:367.
- guided by anatomical landmarks, similar to open lymphadenectomy.
en bloc resection of the right and central compartments and lymphadenectomy of the left-side
- average number of 20.7 (5-60) nodes were obtained

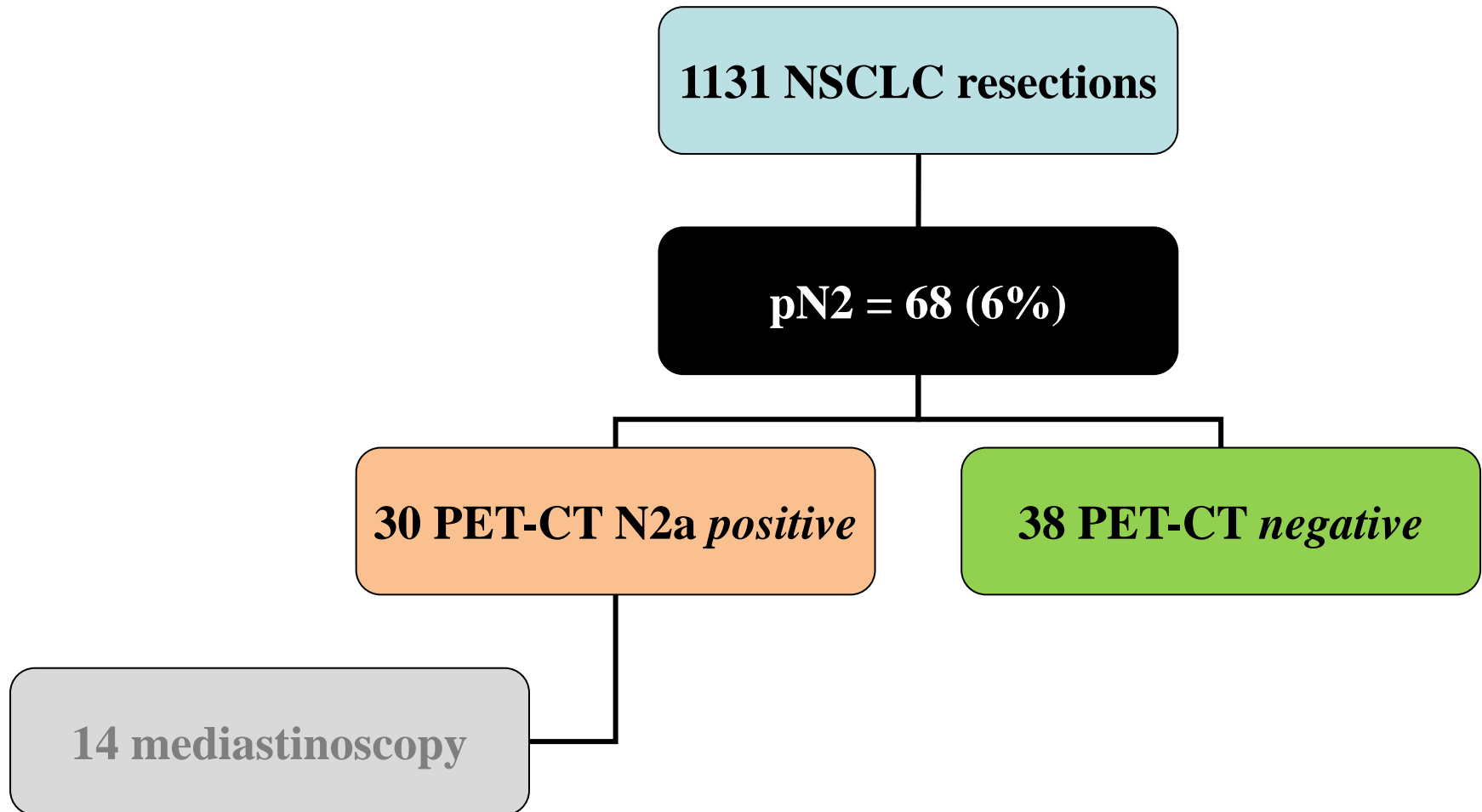


The N2 paradox

- In patients who have incidental(occult) N2 disease found at surgical resection despite thorough preoperative staging *and in whom complete resection of the lymph nodes and primary tumour is technically possible*, **completion of the planned lung resection** and mediastinal lymphadenectomy is suggested

- In patients who have incidental(occult) N2 disease found at surgical resection despite thorough preoperative staging and in whom complete resection of the lymph nodes and primary tumour is technically possible, **completion of the planned lung resection** and mediastinal lymphadenectomy is suggested **BUT**
- In patients with discrete N2 involvement identified preoperatively , **primary surgical resection** followed by adjuvant therapy is **not recommended**

The N2 paradox: similar outcomes of pre and postoperatively identified single-zone N2a NSCLC
Tsitsias T et al, Eur J Cardiothorac Surg 2013



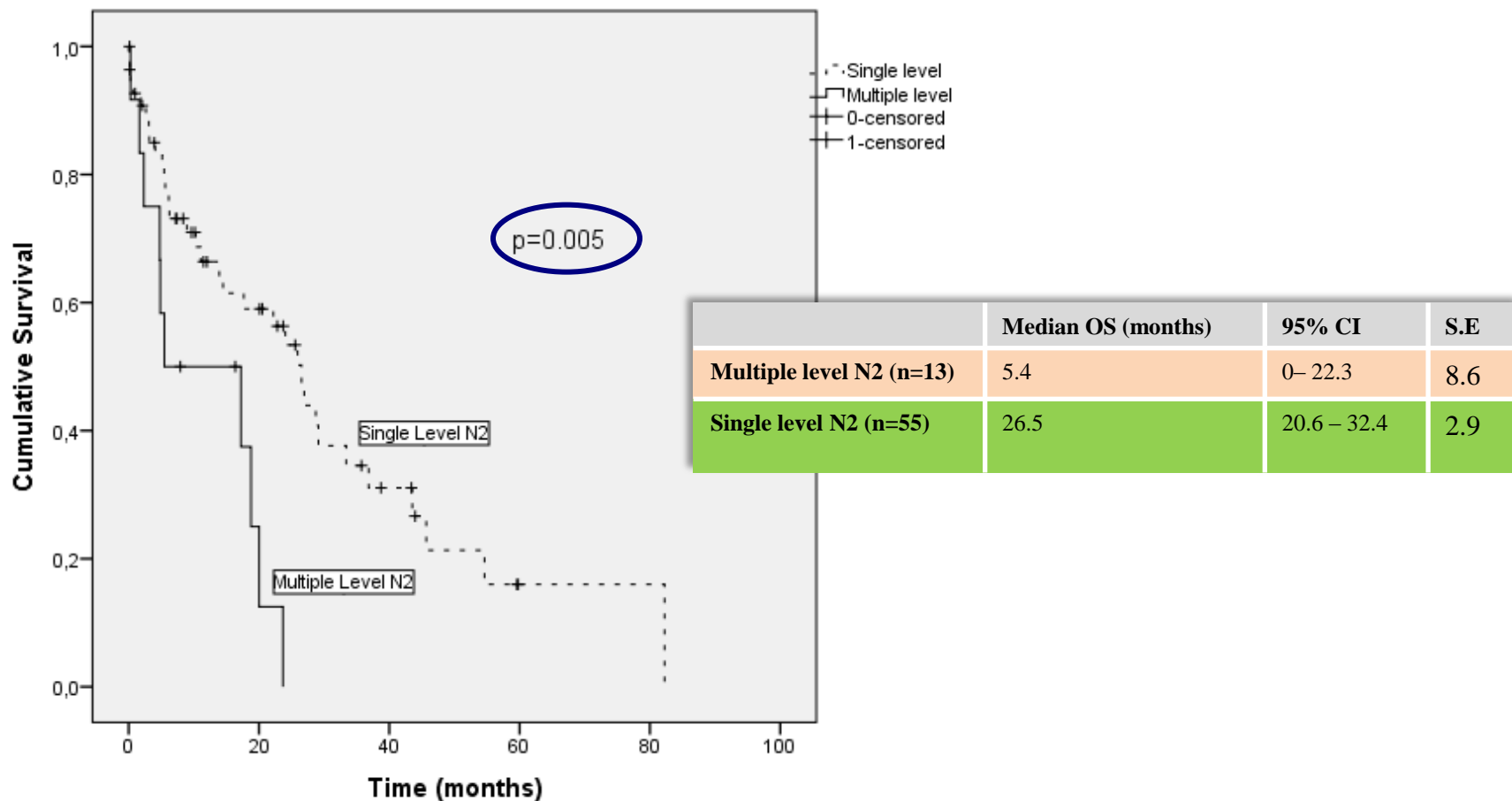
Similar clinical data

	Overall	PET N2 +	PET N2 -	<i>P</i> value
No of patients	68	30	38	
Age (mean)	65 (± 9.4)	64 (± 9.6)	66 (± 9.2)	0.32
Gender (M/F)	33/35	11/19	22/16	0.09
PreFEV1 (median)	71%	69%	71%	0.73
Cardiac co-morbidities	14 (21%)	5	9	0.55
Procedures				0.85
Pneumonectomy	13	6	7	
Intrapericardial pneumonectomy	2	1	1	
Lobectomy	29	11	17	
Bilobectomy	5	2	3	
Sleeve Lobectomy	10	4	6	
Segmentectomy	9	6	3	
Neo-adjuvant Chemotherapy	10	5	5	0.73

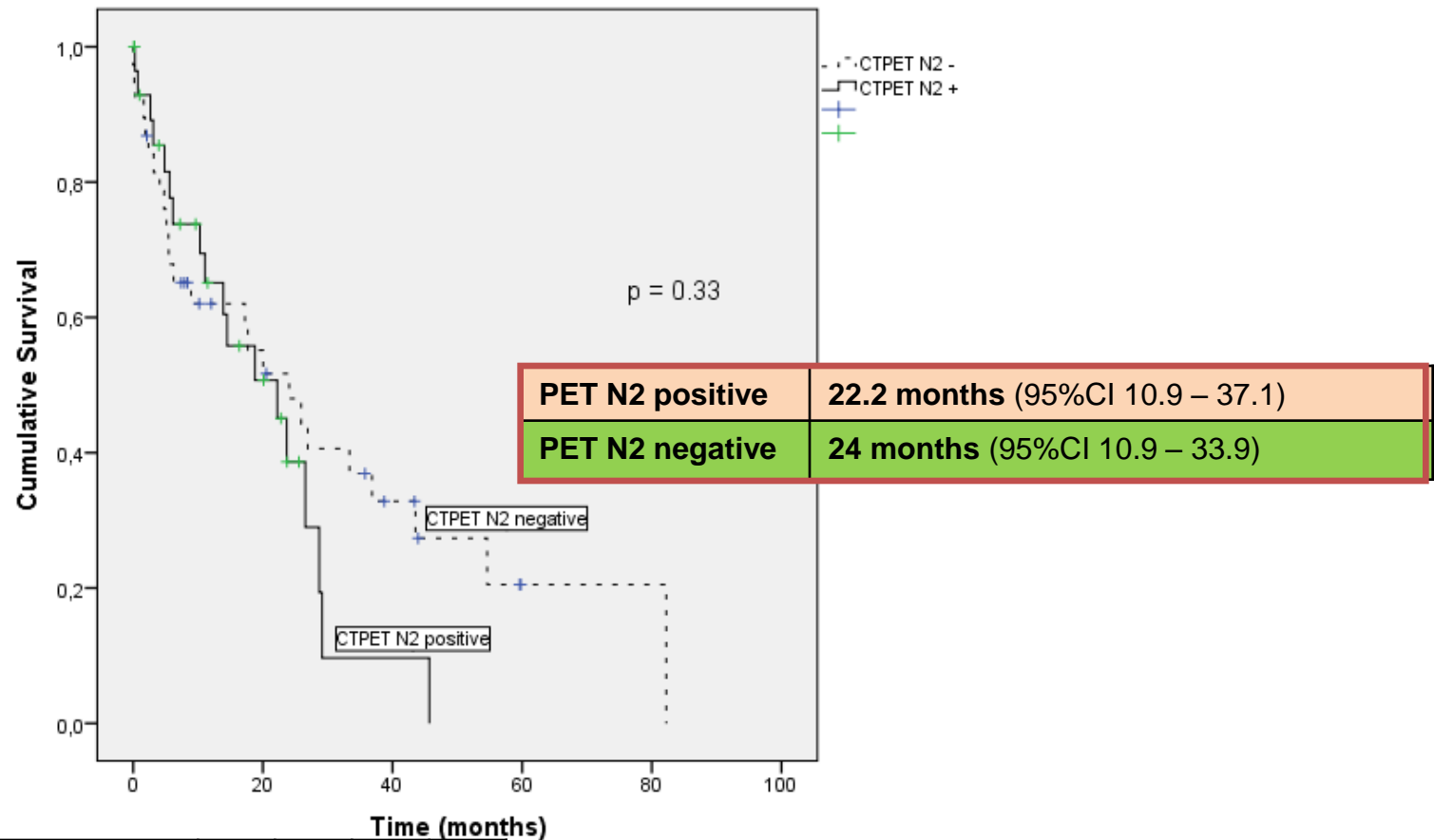
Similar pathological data

	Overall	PET N2 +	PET N2 -	p-value
Tumour size- mm (median)	45 (130)	41 (110)	50 (120)	0.41
Cell type AdenoCa Squamous CC Miscellaneous	41 23 4	18 9 3	23 14 1	0.45
<u>Resection margin</u> R0 R1 R2 Rx	45 15 2 6	20 6 1 3	25 9 1 3	0.95
<u>Recurrence rate</u> Loco-regional Distant	32% 11.7 % 19.1%	40% 16.6% 20%	26% 7.8% 18.4%	0.29 0.27 0.86
Adjuvant chemotherapy	43%	51%	37%	0.30

Survival was significantly better in single level pN2a than multiple level pN2b



There was no difference in overall survival if resected N2 was PET positive or negative



Time (months)	12	18	24	36
PET N2 Negative (38)	18	15	13	8
PET N2 Positive (30)	14	13	5	1

- Survival after resection of pN2 disease is adversely affected by the need for **pneumonectomy, multizone pN2b** involvement and by **non-compliance with adjuvant chemotherapy**

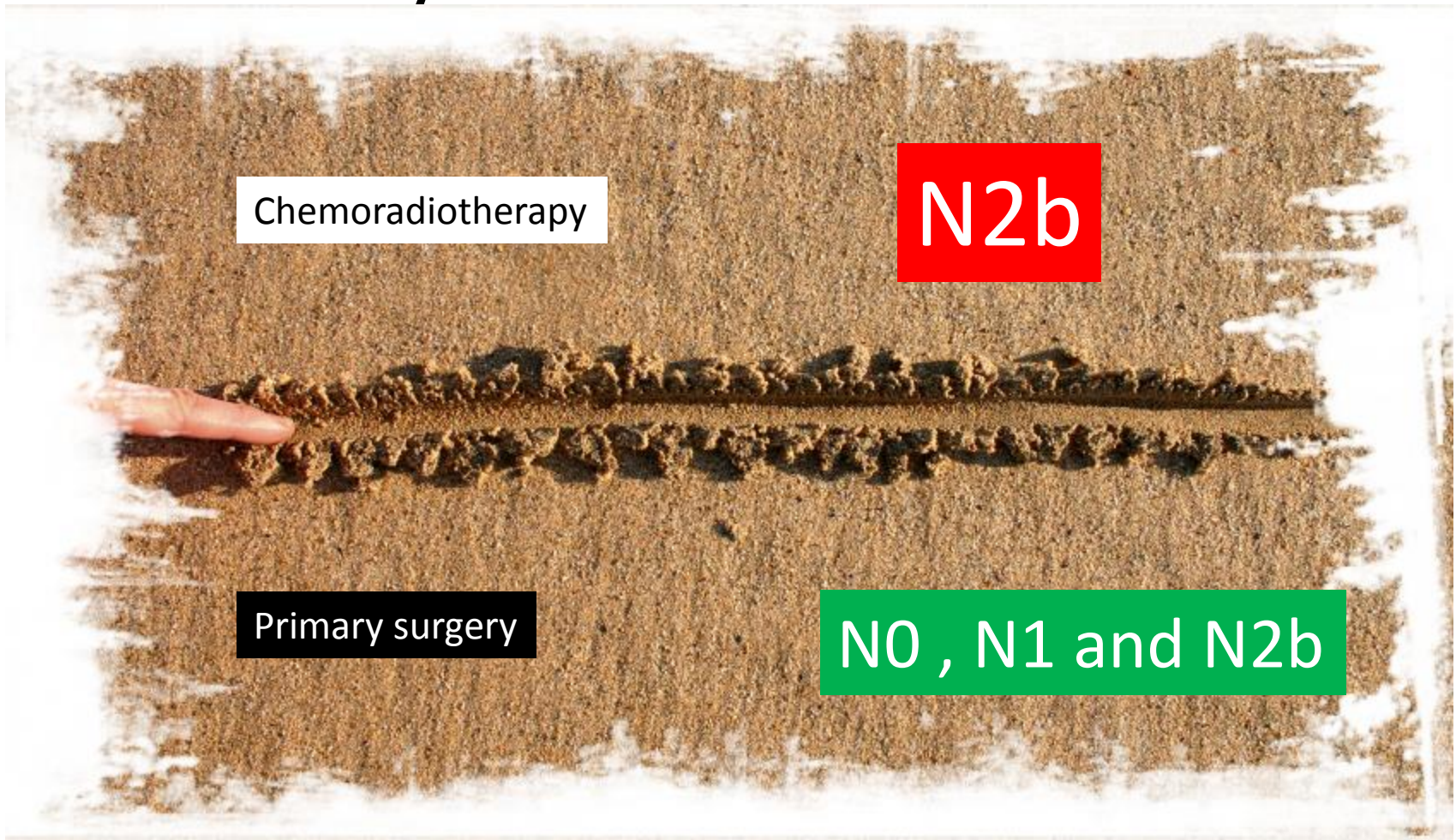
- Survival after resection of pN2 disease is adversely affected by the need for **pneumonectomy, multizone pN2b** involvement and by **non-compliance with adjuvant chemotherapy**
- long-term survival is no different between those patients who have a negative preop PET-CT and are found to have pN2 after resection, and those who are single-zone cN2a positive before resection on PET-CT (HR 1.37, P = 0.335).

- Survival after resection of pN2 disease is adversely affected by the need for **pneumonectomy, multizone pN2b** involvement and by **non-compliance with adjuvant chemotherapy**
- long-term survival is no different between those patients who have a negative preop PET-CT and are found to have pN2 after resection, and those who are single-zone cN2a positive before resection on PET-CT (HR 1.37, P = 0.335).
- Our results support a policy of intentionally resecting single-zone N2a NSCLC identified preoperatively as part of a multimodality therapy.

Where is your line in the sand ?



Where is your line in the sand now ?



Can you cross the line ?

- *Albain, Lancet 2009. Intergroup 0139/RTOG 9309*
- **Progression free survival @ 2 years doubled by surgery**
11% v 22%, $p=0.017$
- *Subset analysis :*
- **12 month median survival benefit from lobectomy :**
34 v 22 mo , $p=0.002$
- **Surgery added to chemoradiotherapy doubles 5 year survival**
18% to 36% if pneumonectomy is avoided

- *Decaluwe H, EJCTS 2009;36:433*
ypN category (ypN0-1 and ypN2-single level vs multilevel-ypN2 and ypN3) independent prognostic factors after induction chemo.

Multizone N2 disease should be restaged after induction therapy

- There is no role for primary surgery in multizone N2 disease
 - Initial histological confirmation by multizone EBUS/EUS
 - For extensive mediastinal disease, mediastinoscopy can be avoided or spared for restaging after neoadjuvant therapy
- Restaging after PET to exclude N2 by VAMLA
- But ***exclusion of mediastinal involvement*** requires mediastinoscopy or open lymphadenectomy

Witte B, Neumeister W, Huertgen M. Eur J Cardiothorac Surg. 2008;33:1124-8

How realistic is downstaging ?

- **Only 37% of patients with favorable, nonbulky, biopsy-proven N2 disease actually complete their neoadjuvant therapy, undergo restaging, and then return for attempted resection.**
Only 28% undergo complete resection.
- *Cerfolio RJ, Maniscalco L, Bryant AS. The treatment of patients with stage IIIA non-small cell lung cancer from N2 disease: who returns to the surgical arena and who survives. Ann Thorac Surg. 2008;86:912-20*

This idea has support

1.2.3 N2 disease

25. Consider radical radiotherapy or chemoradiotherapy in patients with T1–4N2 (bulky or fixed) M0 disease. [B]

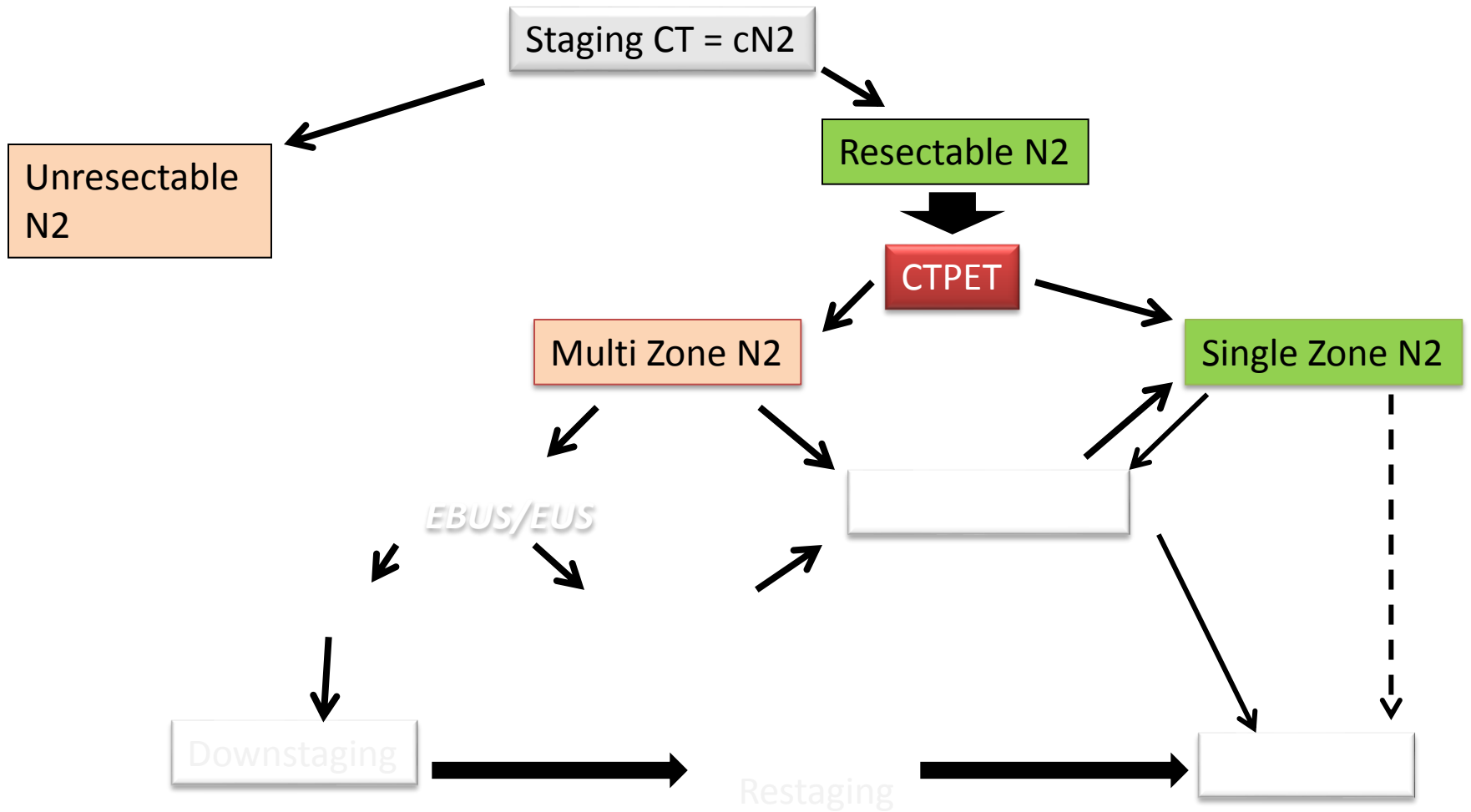
26. Consider surgery as part of multimodality management in patients with T1–3N2 (non-fixed, non-bulky, single zone) M0 disease. [B]

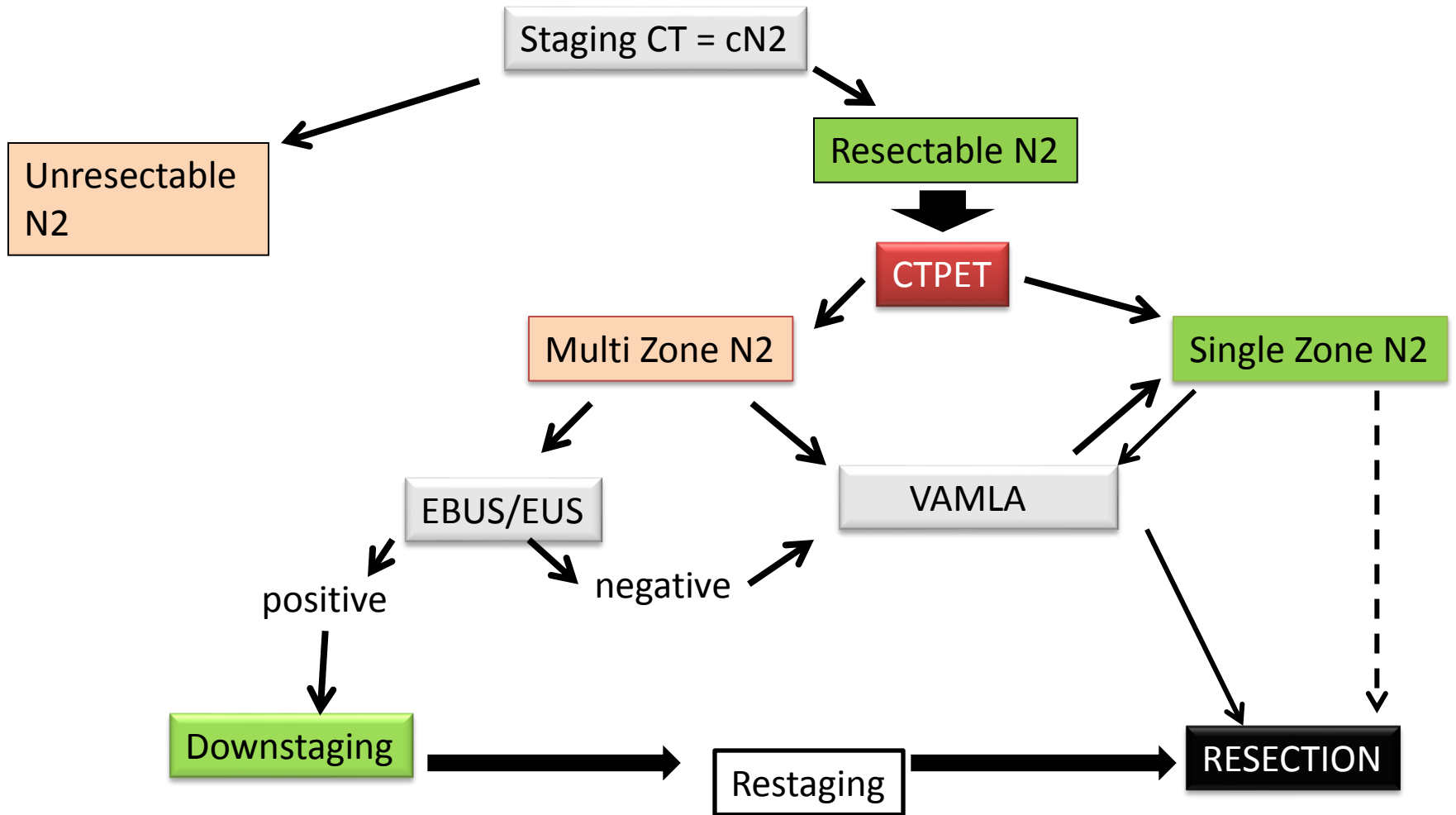
27. **RR** Consider further randomised trials of surgery added to multimodality management in patients with multi-zone N2 disease to establish if any subgroups of patients might benefit more from the addition of surgery.

Guidelines on the radical management of patients with lung cancer.

Lim E, Baldwin D, Beckles M, Duffy J, Entwisle J, Faivre-Finn C, Kerr K, Macfie A, McGuigan J, Padley S, Popat S, Screaton N, Snee M, Waller D, Warburton C, Win T; **British Thoracic Society; Society for Cardiothoracic Surgery in Great Britain and Ireland.**

Thorax. 2010 Oct;65 Suppl 3:iii1-27.





Surgical principles in N2

1. Identify unresectable N2 from initial CT
2. Confirm single-zone N2 by mediastinoscopy
3. Resection in single-zone N2 followed by adjuvant chemotherapy
4. Identify multi-zone N2 by EBUS/EUS
5. Induction chemo/radiotherapy in multi-zone N2
6. Restage by mediastinoscopy
7. Resect in downstaged NO by lobectomy