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Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small cell lung cancer

Paul De Leyn (chairman), Christophe Dooms, Jaroslaw Kuzdzal, Didier Lardinois, Bernward Passlick, Ramon Rami-Porta, Akif Turna, Paul Van Schil, Frederico Venuta, David Waller, Walter Weder, Marcin Zielinski

- No financial or other relevant disclosures

Revised ESTS guidelines for preoperative mediastinal lymph node staging for NSCLC

1. ESTS guidelines 2007
2. Rationale-methodology
3. Impact of new IASLC Lymph node map
4. Primary mediastinal staging
5. Restaging
6. Conclusions

ELSEVIER

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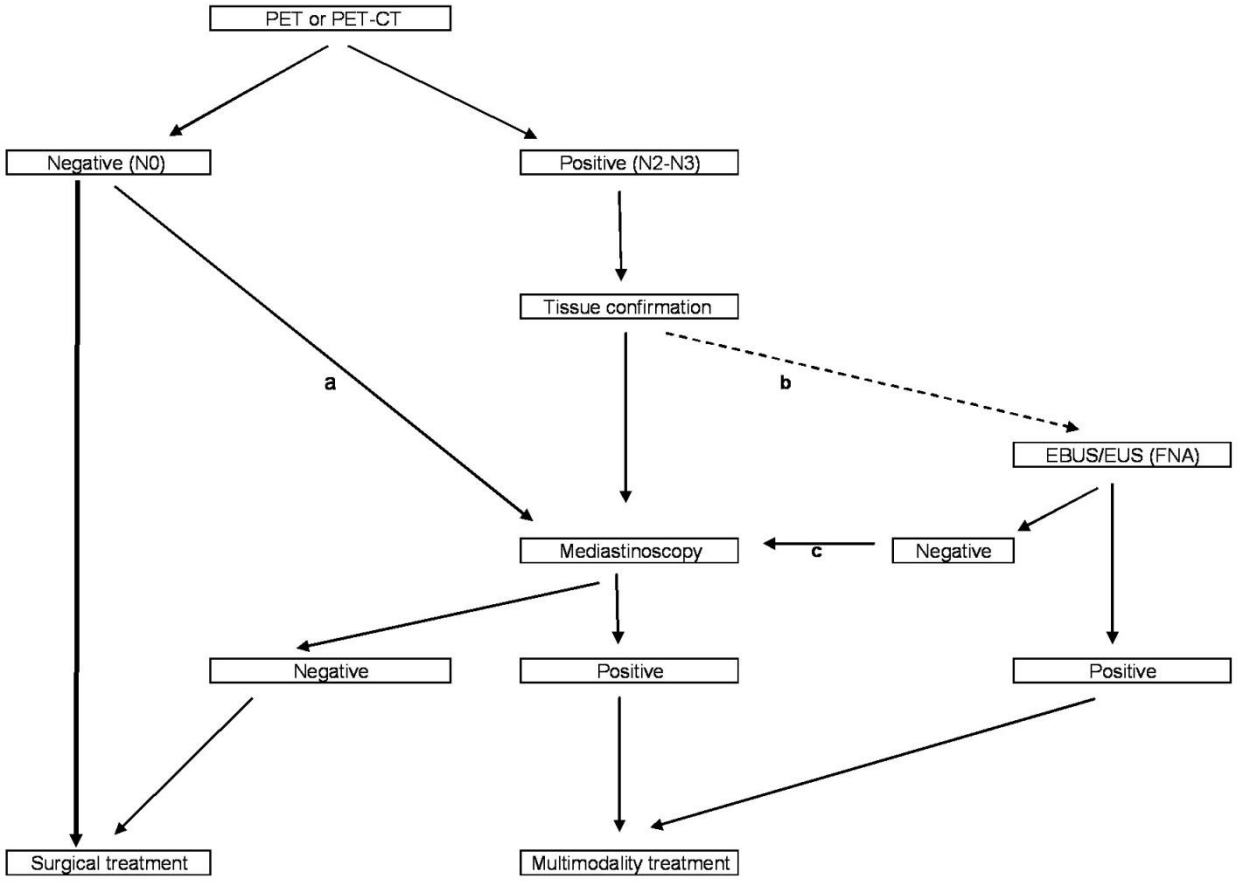
ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer

Paul De Leyn [a,*], Didier Lardinois [b], Paul E. Van Schil [c], Ramon Rami-Porta [d], Bernward Passlick [e], Marcin Zielinski [f], David A. Waller [g], Tony Lerut [a], Walter Weder [b]

ESTS guideline 2007



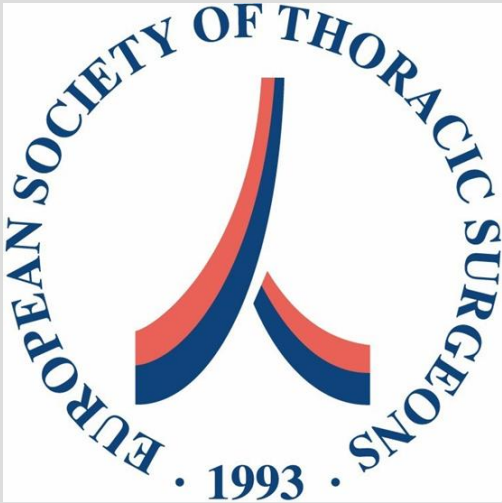
a : in central tumours, tumours with large LNs and/or PET N1 disease invasive staging remains indicated
b : endoscopic techniques are minimally invasive and can be the first choice
c : due to its higher NPV mediastinoscopy remains indicated

EUS : esophageal ultrasound
EBUS : endobronchial ultrasound
NPV : negative predictive value

De Leyn et al.
Eur J Cadiothorac Surg
2007;32:1-8

Rationale for revision

- **The new IASLC lymph node map**
- **More literature available on endoscopic staging (EBUS/EUS FNA)**
- **Restaging**



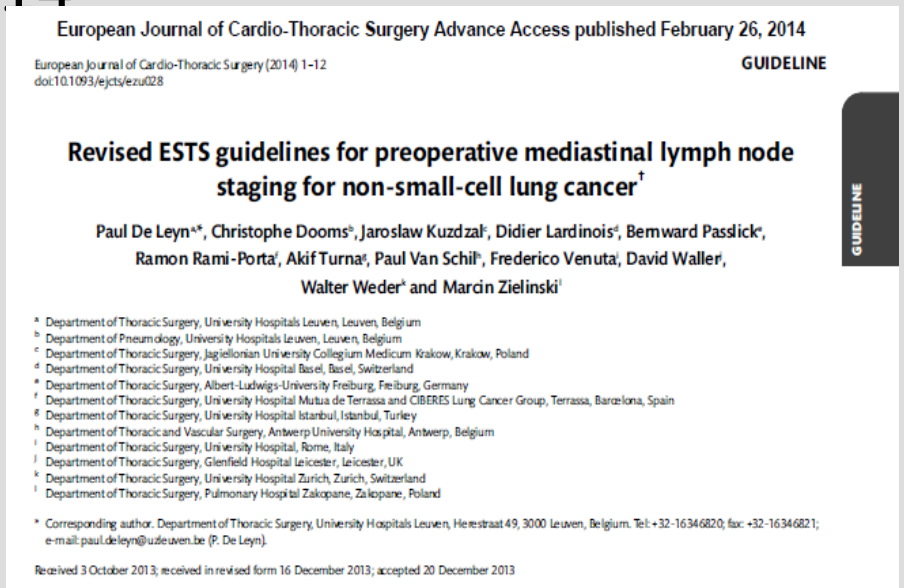
Methodology

- Approved by council ESTS Essen meeting (june 2012)
- Members of working group were selected on their experience (publications) on mediastinal staging
- Several meetings (Essen, Zürich, Brussels and Birmingham)
- Members reviewed relevant publications

Consensus

Methodology

- Presentation at yearly meeting (may 2013)
- Paper on website (june-juli 2013) for input by all ESTS members
- Paper submitted for publication (october 2013)
- Published European Journal of Cardiothoracic Surgery februari 2014



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doi:10.1093/ejcts/ezu028

GUIDELINE

Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer†

Paul De Leyn[a,*], Christophe Dooms[b], Jaroslaw Kuzdzal[c], Didier Lardinois[d], Bernward Passlick[e], Ramon Rami-Porta[f], Akif Turna[g], Paul Van Schil[h], Frederico Venuta[i], David Waller[j], Walter Weder[k] and Marcin Zielinski[l]

[a] Department of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium
[b] Department of Pneumology, University Hospitals Leuven, Leuven, Belgium
[c] Department of Thoracic Surgery, Jagiellonian University Collegium Medicum Krakow, Krakow, Poland
[d] Department of Thoracic Surgery, University Hospital Basel, Basel, Switzerland
[e] Department of Thoracic Surgery, Albert-Ludwigs-University Freiburg, Freiburg, Germany
[f] Department of Thoracic Surgery, University Hospital Mutua de Terrassa and CIBERES Lung Cancer Group, Terrassa, Barcelona, Spain
[g] Department of Thoracic Surgery, University Hospital Istanbul, Istanbul, Turkey
[h] Department of Thoracic and Vascular Surgery, Antwerp University Hospital, Antwerp, Belgium
[i] Department of Thoracic Surgery, University Hospital, Rome, Italy
[j] Department of Thoracic Surgery, Glenfield Hospital Leicester, Leicester, UK
[k] Department of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland
[l] Department of Thoracic Surgery, Pulmonary Hospital Zakopane, Zakopane, Poland

* Corresponding author. Department of Thoracic Surgery, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium. Tel: +32-16346820; fax: +32-16346821; e-mail: paul.deleyn@uzleuven.be (P. De Leyn).

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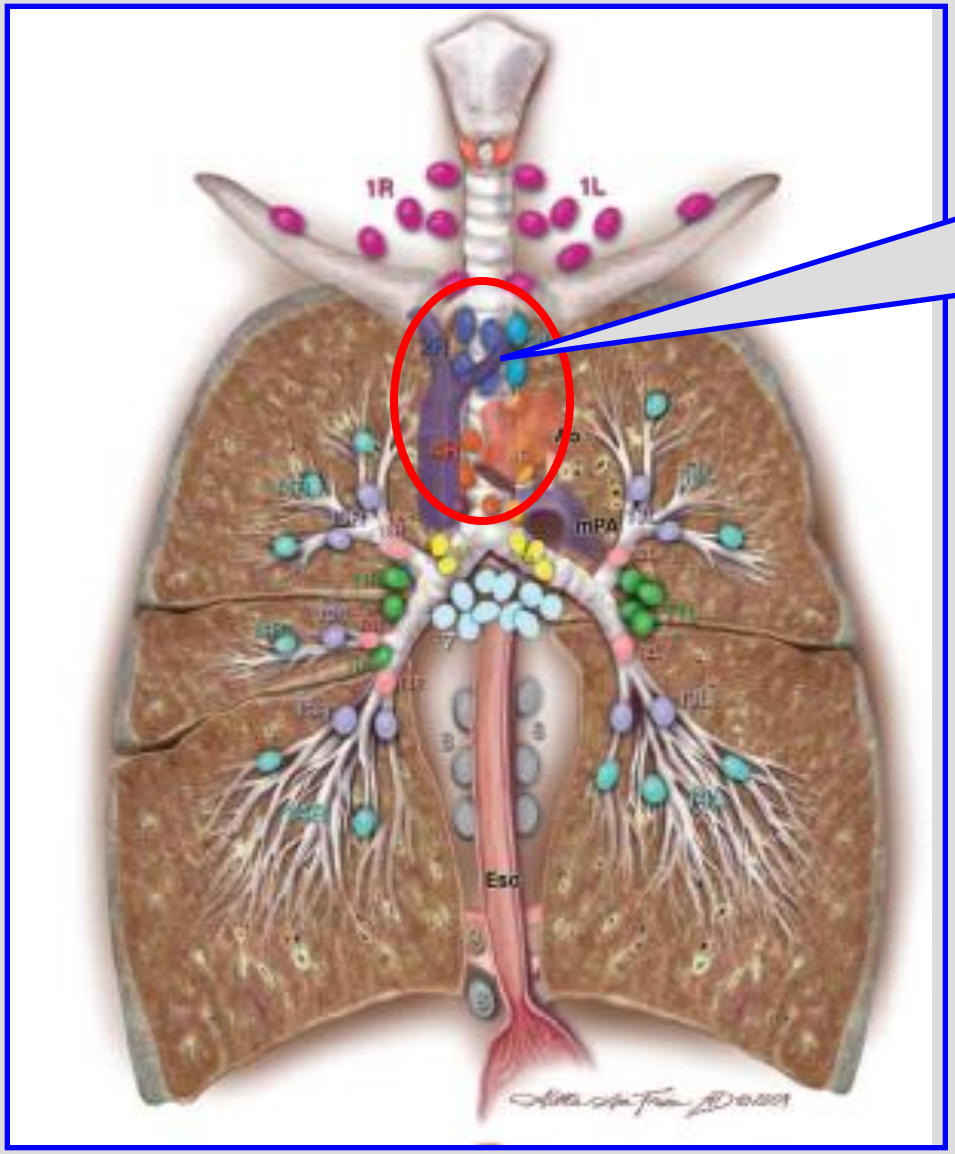
Barcelona, november 2012

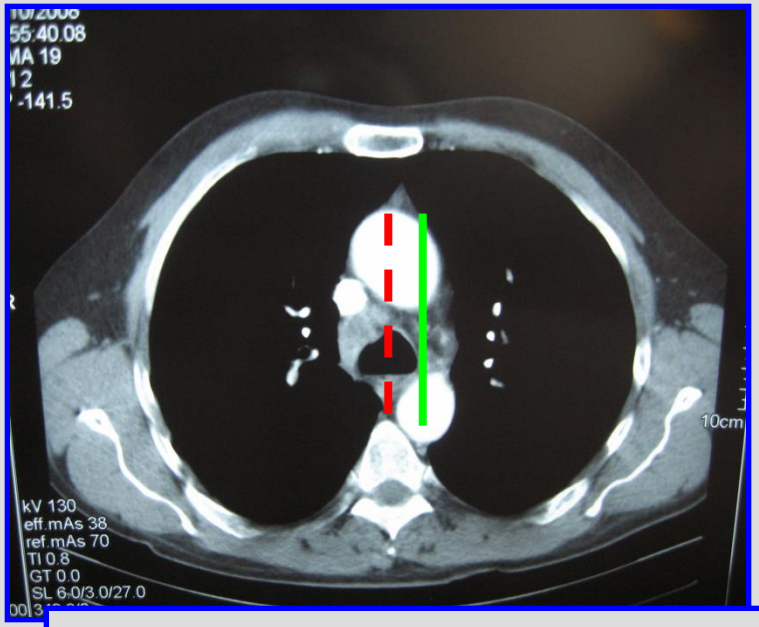
Zürich, 23/11/2012

Brussels, 22/03/2013

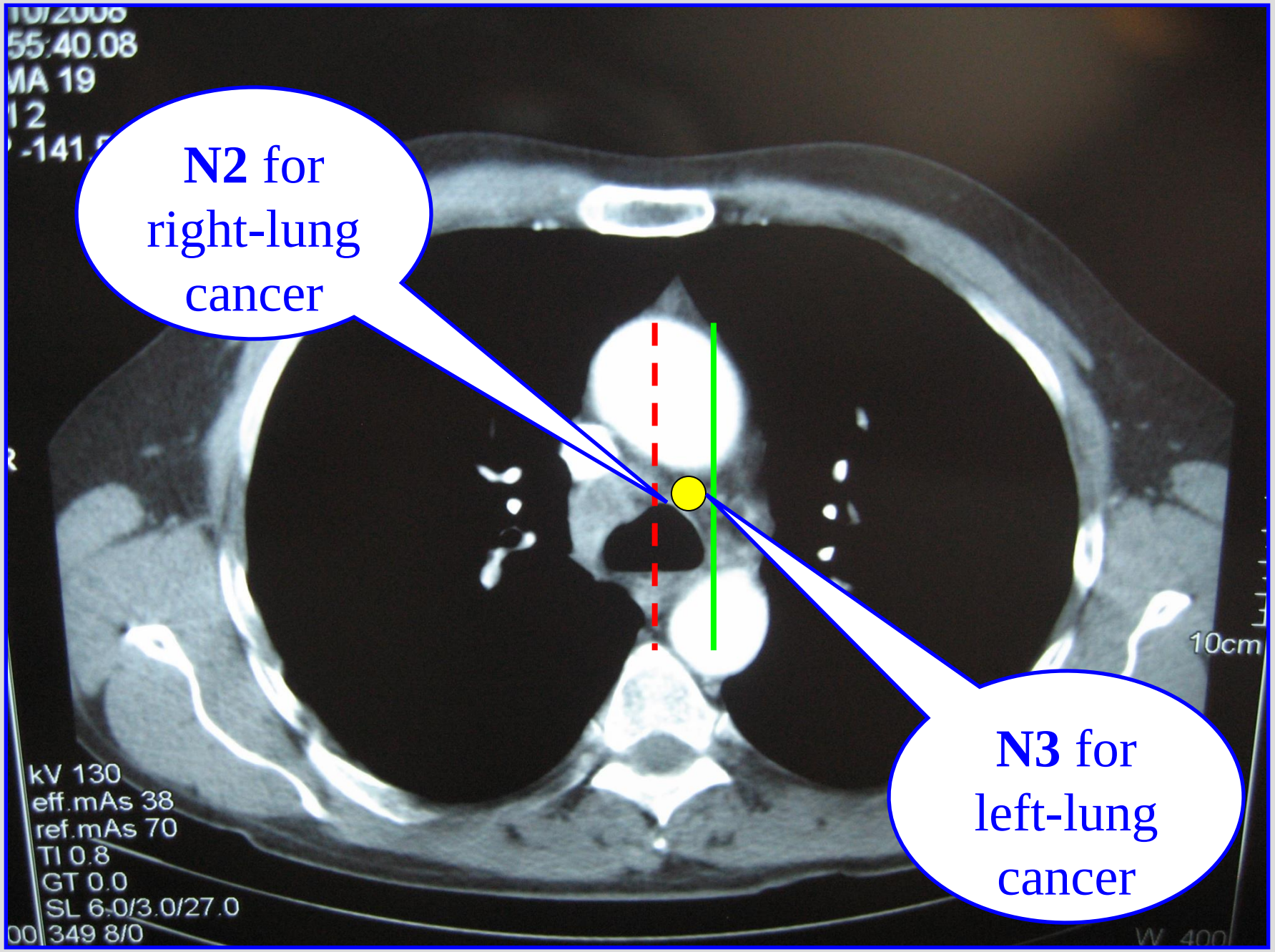
The IASLC lymph node map



Shift of the oncological midline to the left paratracheal border



Rusch V et al.
J Thorac Oncol 2009; 4: 568-577


55:40.08
MA 19
I 2
-141.5
N2 for right-lung cancer
N3 for left-lung cancer
10cm
kV 130
eff.mAs 38
ref.mAs 70
TI 0.8
GT 0.0
SL 6.0/3.0/27.0
00 349 8/0
W 400

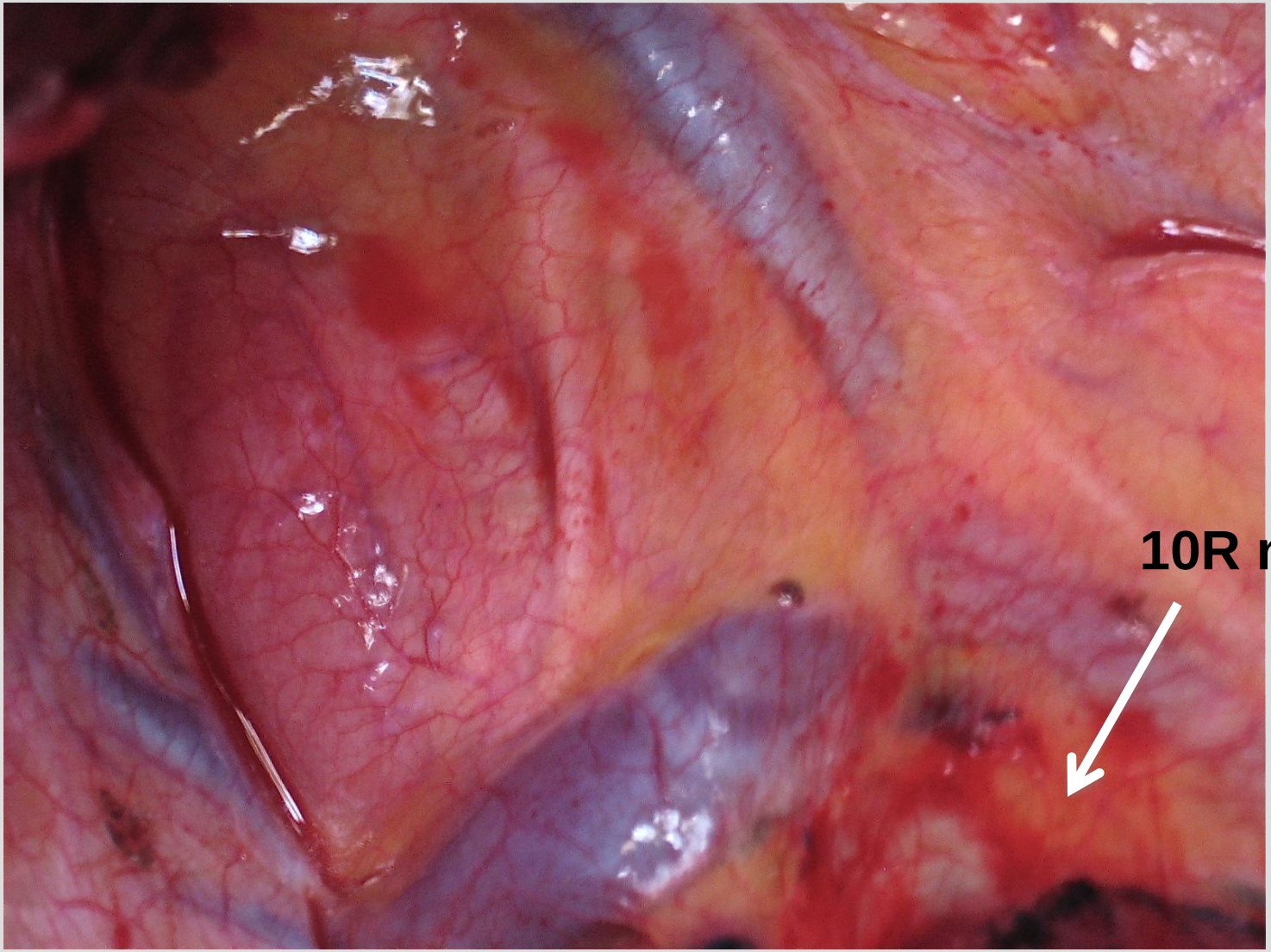
The IASLC lymph node map

Anatomical borders are clearly defined

Lower border of 4R : lower border of azygos vein

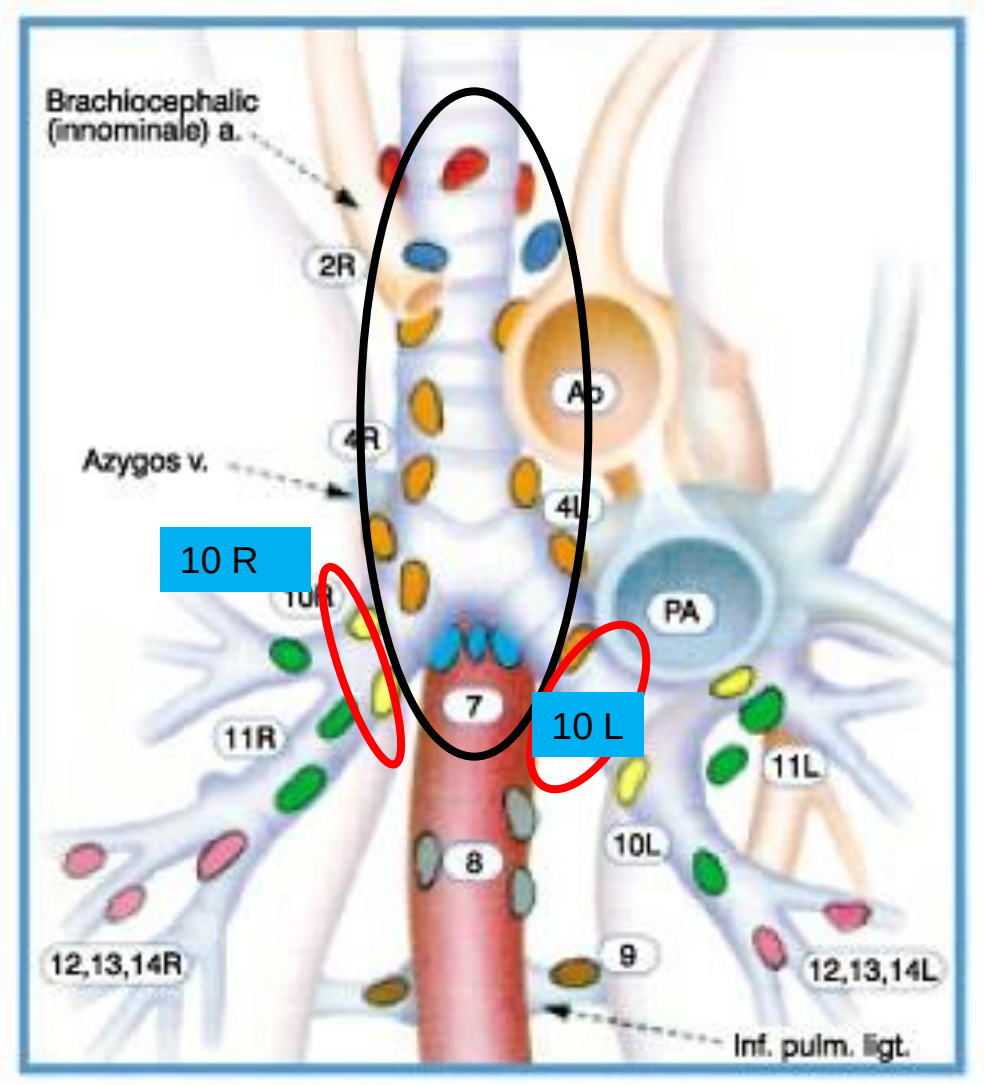
Lower border of 4L : upper rim of the left pulmonary artery

Rusch V et al.
J Thorac Oncol 2009; 4: 568-577



Courtesy Dr Rami Ramon-Porta

ESTS recommendation on invasive staging (2014)



Always explore and biopsy
4R, 4L, 10 L
If present : 2R, 2L
On indication : 10R and 10L

Preoperative LN staging in NSCLC

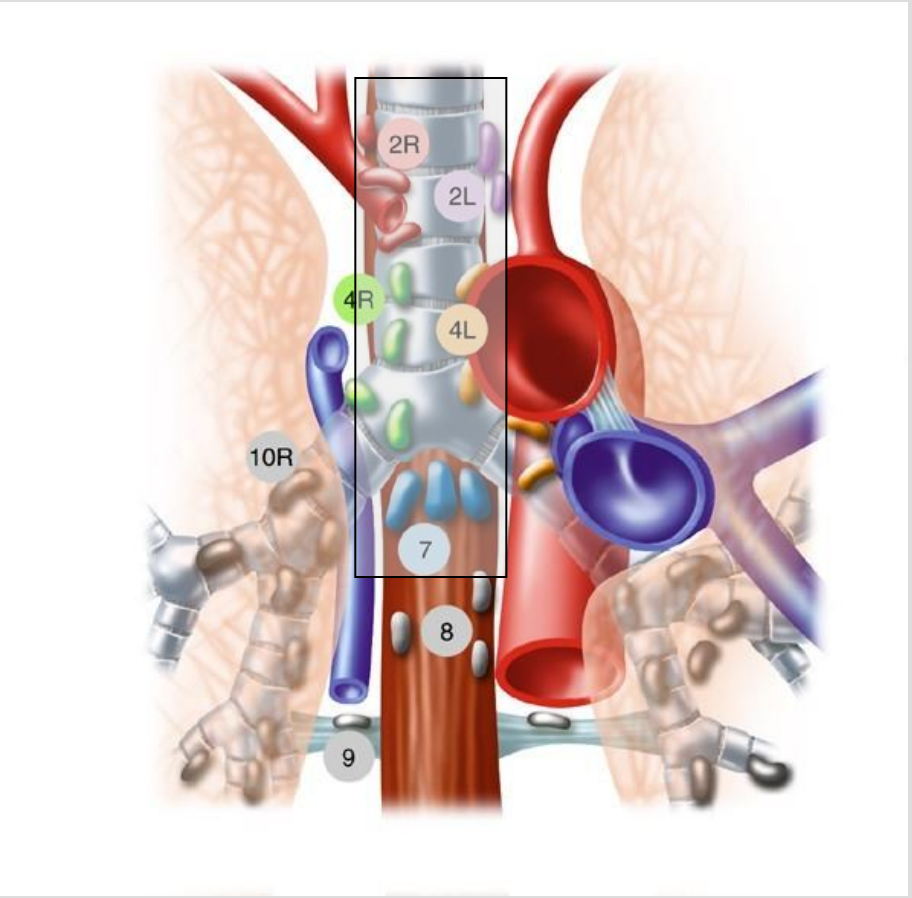
- **Imaging techniques**
  - CT scan
  - PET-CT scan
  - DW MRI

- **Endoscopic techniques(Tissue diagnosis)**
  - Conventional TBNA
  - Endoscopic (ultrasonograpy) : EUS-FNA and EBUS-FNA

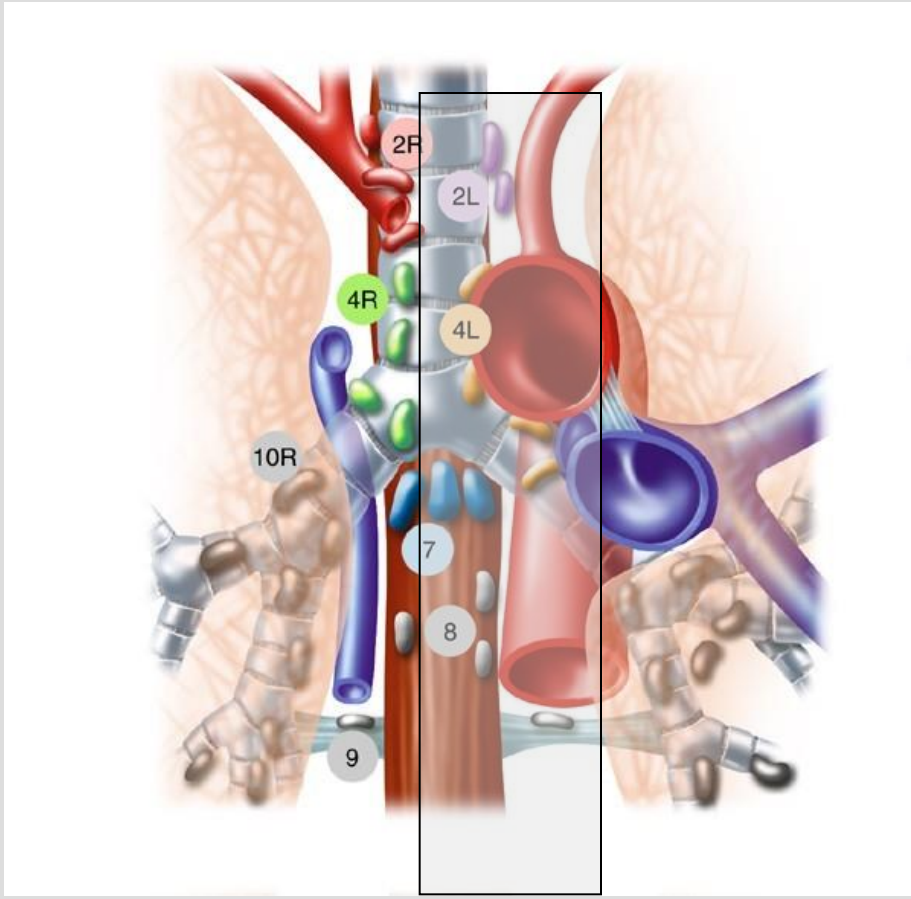
- **Surgical staging techniques(Tissue diagnosis)**
  - Cervical mediastinoscopy
  - Anterior mediastinotomy
  - Extended mediastinoscopy
  - VATS
  - VAMLA
  - TEMLA

→ **Vary in accuracy and morbidity**
NPV (Working group aims at NPV 90%)

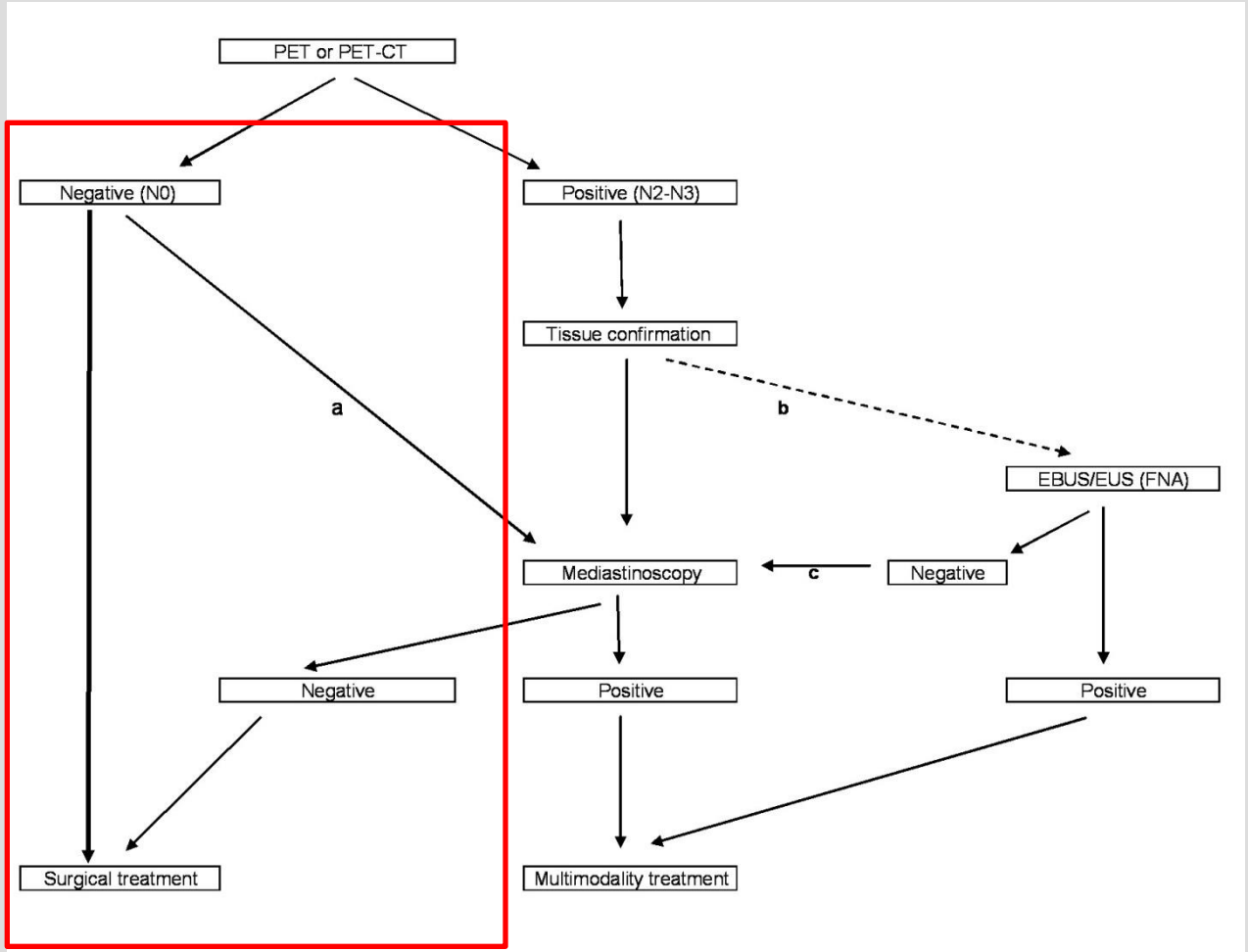
Cervical mediastinoscopy
Endo**B**ronchial **U**ltra**S**onography-FNA
(EBUS-FNA)



Esophageal **U**ltra**S**onography-FNA
EUS-FNA



ESTS guideline 2007



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De Leyn et al.
Eur J Cadiothorac Surg
2007;32:1-8

NPV of PET and CT for stage T1-2N0 NSCLC : A Meta-Analysis

- Meta-analysis (ten studies with a total of 1122 patients)

	NPV (mediastinal metastasis)
T1* (Tumour ≤ 3 cm)	94%
T2* (Tumour > 3 cm)	89%

*Sixt edition of TNM version

Adenocarcinoma histology (Risk ratio : 2.72) and **high FDG uptake** in primary lesion were associated with geater risk of occult nodal metastasis

Wang et al., Clinical lung cancer 2011;13:81-9

False-negative rate after **PET-CT scan** for mediastinal staging in clinical stage I NSCLC

- Prospective study evaluating ESTS guidelines in operable NSCLC n=153)
- All patients had dedicated thoracic CT and PET-CT (N0)
- Central tumours were excluded
- When clinical stage I, resection with systematic mediastinal dissection

	NPV
T1* (Tumour ≤ 3 cm)	92%
T2* (Tumour > 3 cm)	85%

*Sixt edition of TNM version

Gómez-Caro et al. Europ J cardiothorac Surg 2012;42:93-100

Centrally located Tumour?

Risk factors for occult mediastinal metastasis in clinical stage I NSCLC

- Retrospective analysis (n=221)
- Prevalence of N2 disease in patients with clinical stage I NSCLC
- PET and CT negative mediastinum

% Occult N2 metastases

	Centrally Located tumors	Peripherally located tumors
All tumor sizes	**21.6%**	**2.9%**
0 - 2.0 cm	14.3%	2.9%
2.1 - 3.0 cm	30%	5.3%

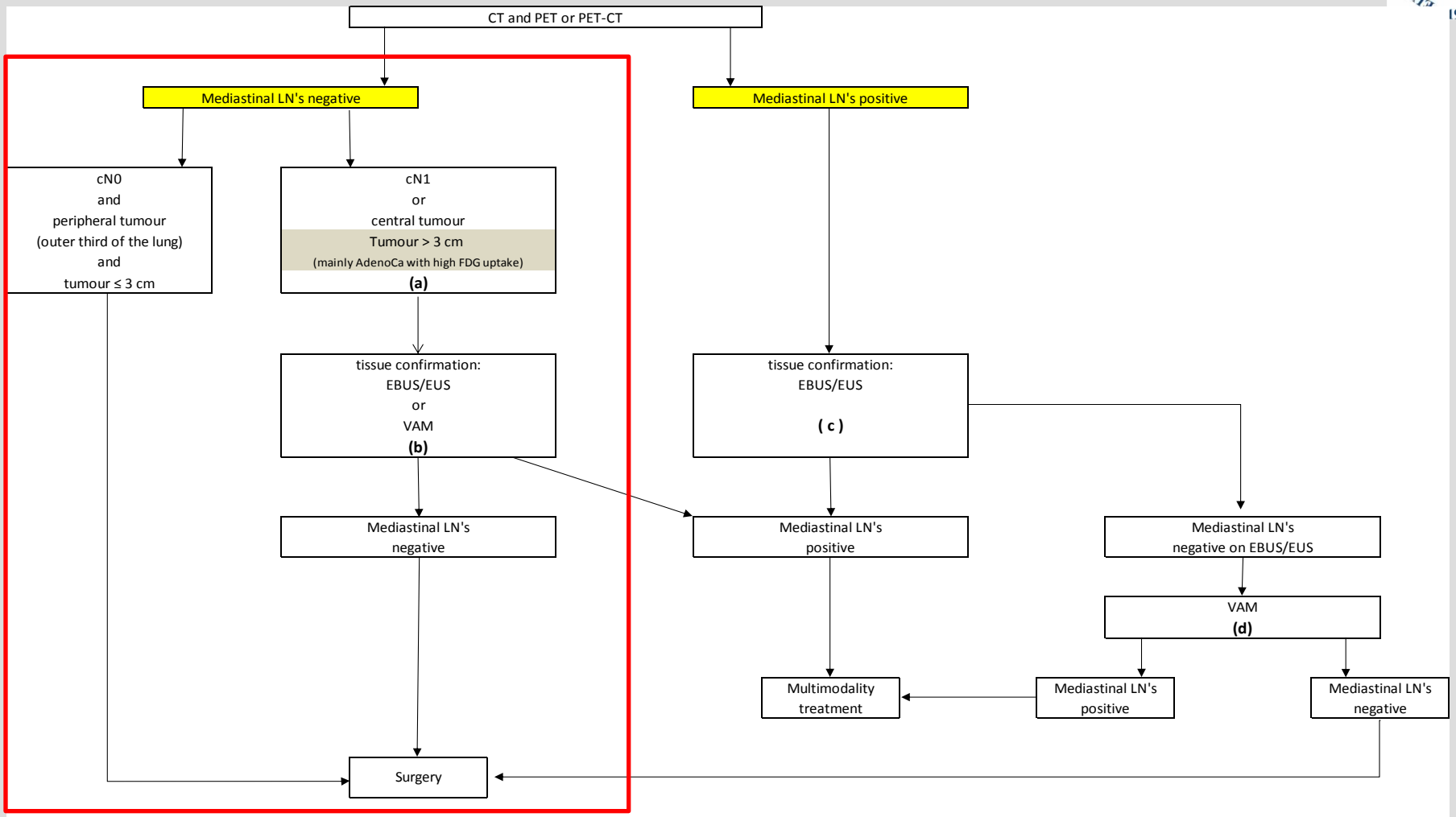
Lee et al., Ann Thorac Surg 2007;84:177-81

Problems in the current diagnostic standards of clinical **N1** NSCLC

- Retrospective analysis (n=143)
- Prevalence of N2 disease in patients with clinical N1 (CT enlarged LNs > 1 cm) NSCLC
- PET not used
- Prevalence N2-3 : 30%

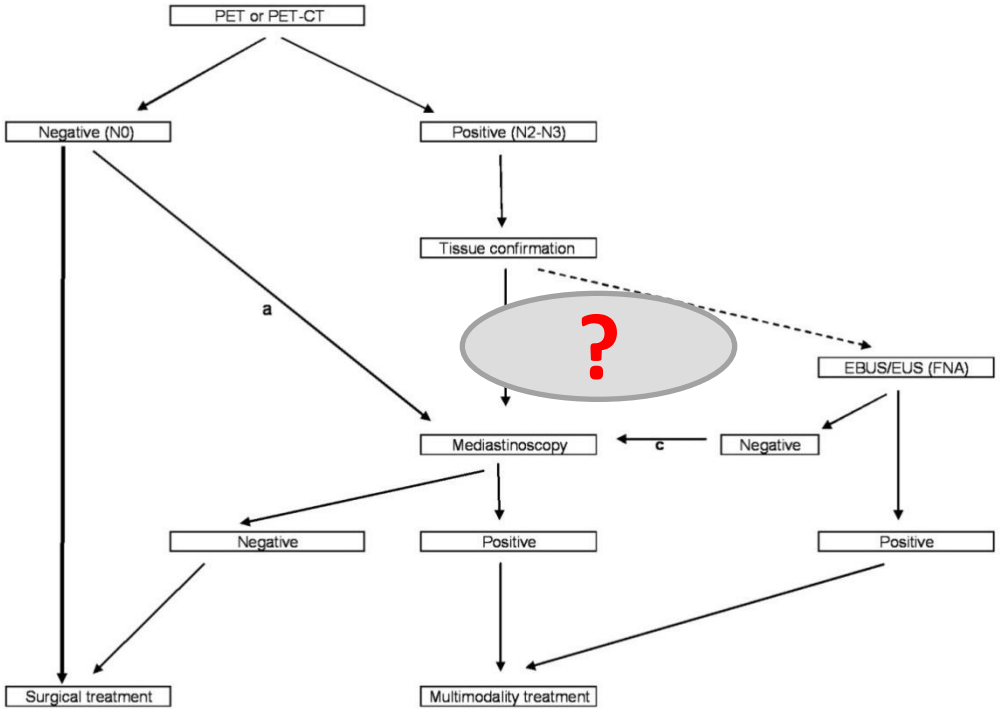
Hishida et al., Thorax 2008;63:526-531

ESTS guidelines 2014



(a) : In tumours > 3 cm (mainly in adenocarcinoma with high FDG uptake) invasive staging should be considered
(b) : Depending on local expertise to adhere to minimal requirements for staging
(c) : endoscopic techniques are minimally invasive and are the first choice if local expertise with EBUS/EUS needle aspiration is available
(d) : due to its higher NPV, in case of PET positive or CT enlarged mediastinal LN's, videoassisted mediastinoscopy (VAM) with nodal dissection or biopsy remain indicated when endoscopic staging is negative. Nodal dissection has an increased accuracy over biopsy

ESTS guidelines 2007



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Invasive mediastinal staging?
ASTER

- Prospective, multicenter randomised study
- Ghent, Leiden, Leuven, Papworth
- Inclusion : NSCLC with indication for invasive staging, based on ESTS guidelines 2007
  - PET positive N1-N2 nodes
  - CT N2 nodes ≥ 1 cm
  - Central tumors
- Endpoints : sensitivity to detect N2/N3; rate of futile thoracotomies

Annema et al; JAMA 2010;304:2245-32

Invasive mediastinal staging?
ASTER

Inclusion : NSCLC with indication for invasive staging, based on ESTS guidelines 2007

PET positive N1-N2 nodes
CT N2 nodes ≥ 1 cm
Central tumors

Surgical staging
N=118

Endoscopic ultrasonography staging (EBUS/EUS-FNA),
if negative followed by surgical staging
N=123

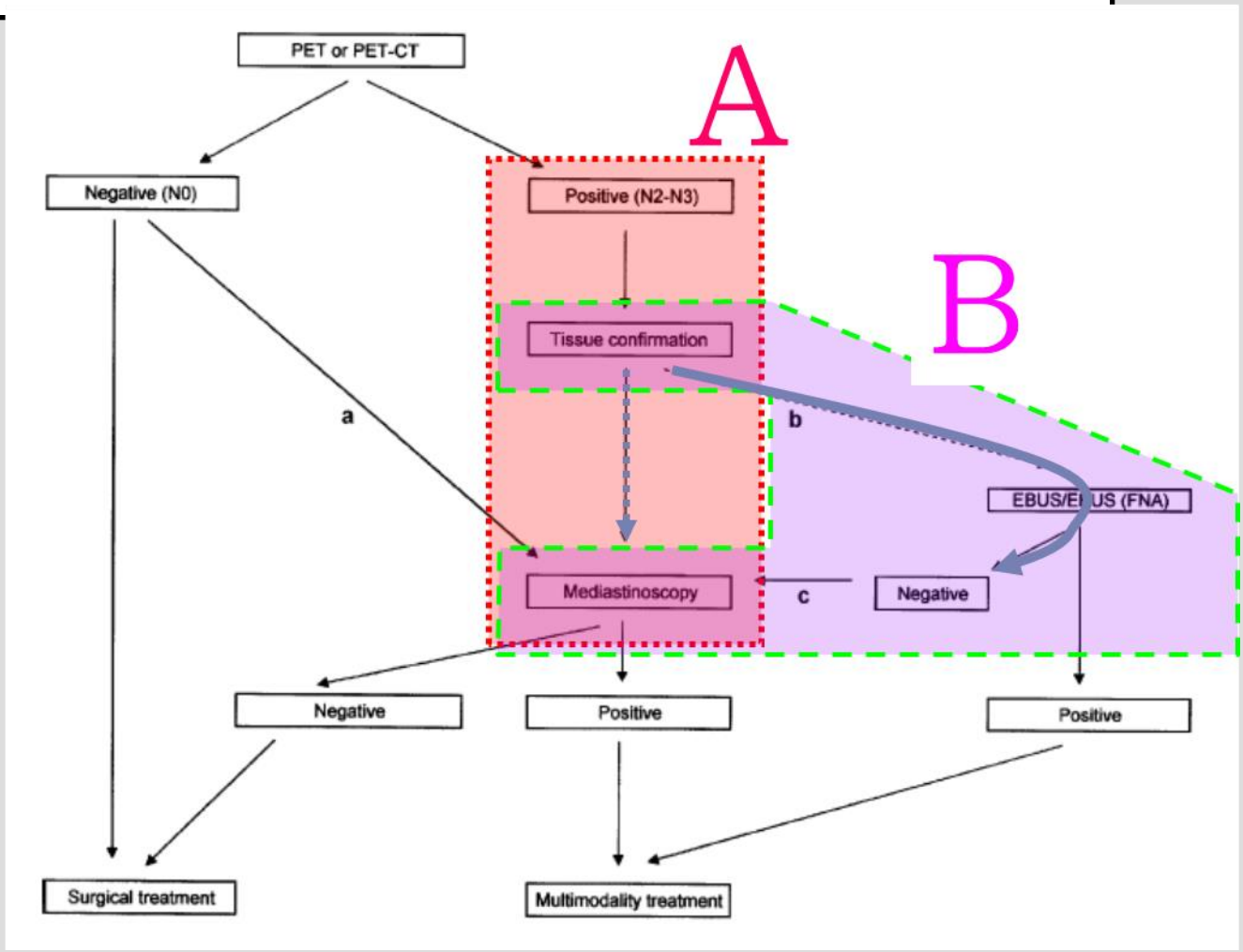
Annema et al; JAMA 2010;304:2245-32

Invasive mediastinal staging?
ASTER

	Surgical staging (n=118)	Endoscopic staging and if negative surgical staging (n=123)	
Preop detection N2/N3	35% (n=41)	50% (n=62)	P=0.02
Sensitivity for N2-N3 (preoperative)	80%	94%	P=0.04
NPV	85%	92%	P=0.23

Annema et al; JAMA 2010;304:2245-32

Invasive mediastinal staging?



Conclusion

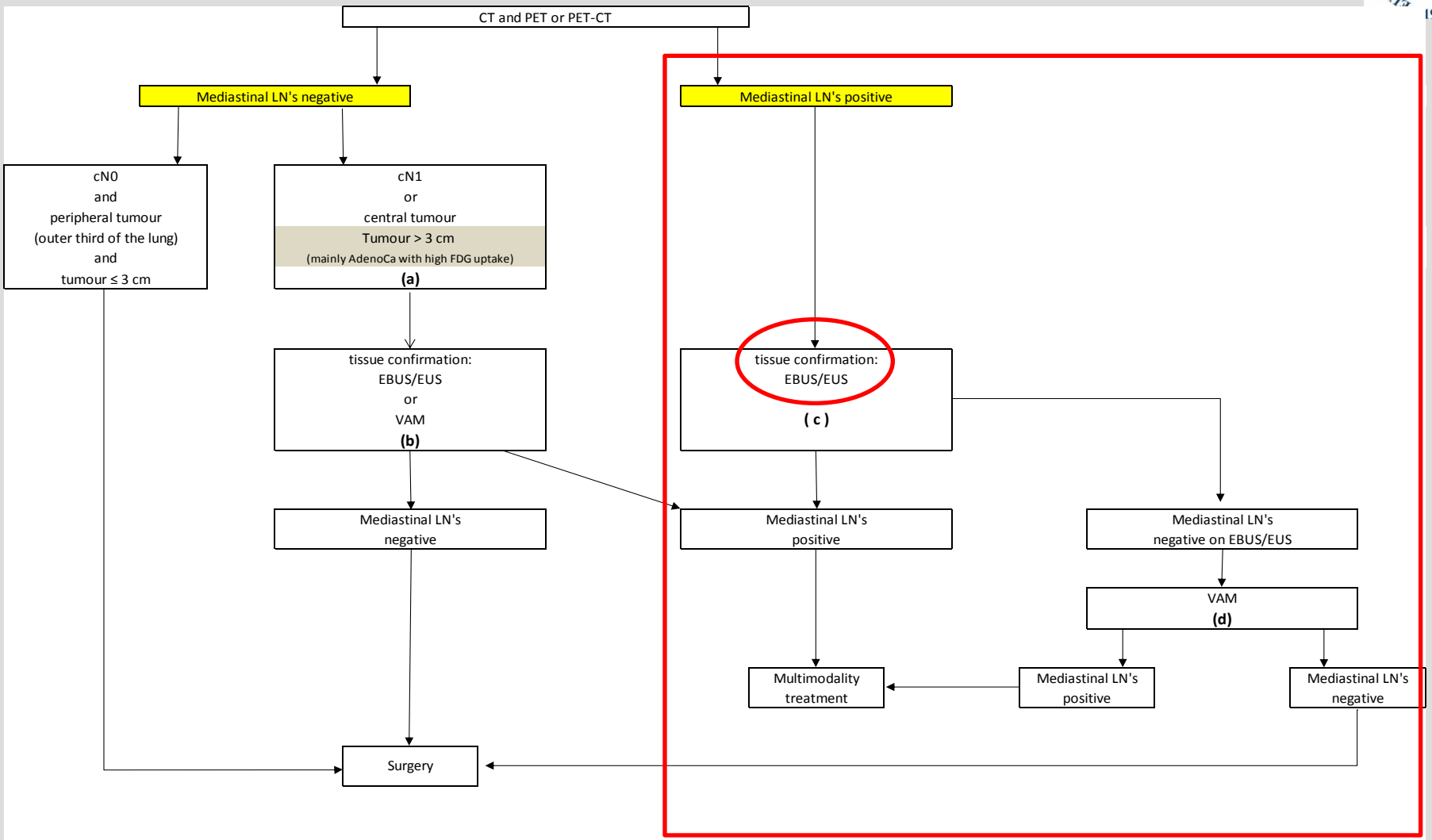
Sens 80% → 94%
NPV 85% → 92%
Fut. Th. 17% → 7%

Annema et al; JAMA, 2010;304:2245-32

Published meta-analyses on bronchial and esophageal endosonography with fine needle aspiration for mediastinal nodal staging of lung cancer

Author	Year	Modality	Pts (N)	Pooled sens % (95% CI)	Pooled Spec % (95%CI)	NLR
Micames et al	2007	EUS	1201	83 (78-87)	97 (96-98)	-
Gu et al	2009	EBUS	1298	93 (91-94)	100 (99-100)	-
Adams et al	2009	EBUS	817	88 (79-94)	100 (92-100)	0.12
Chandra et al	2012	EBUS	1658*	92 (90-93)	100 (97-100)	0.13
Zhang et al	2013	EUS + EBUS	823	86 (82-90)	100 (99-100)	0.15

ESTS guidelines 2014



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Conventional mediastinoscopy vs video-assisted mediastinoscopy (VAM)?

VAM

- Enhanced visualisation
- Bimanual dissection
- Better teaching
- Improved accuracy?
- Less complications?

De Leyn et al,
Multimedia Manual of Cardiothoracic Surgery
10.1510/mmcts.2004.000166;2004
Martin-Ucar et al., Europ J cardiothorac Surg 2004;26:393-395

VAM

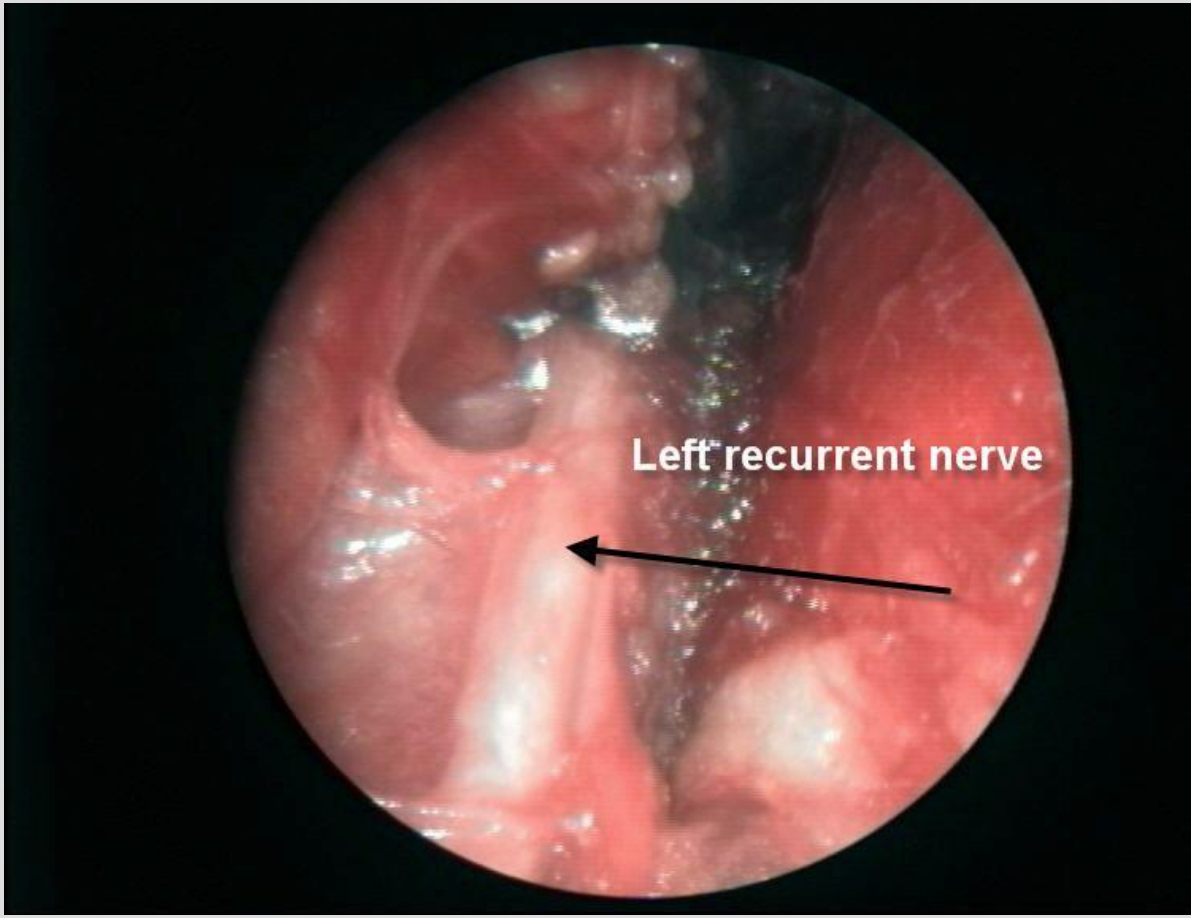


Table 4: Staging values of conventional mediastinoscopy and videomediastinoscopy

Author and reference	Type of mediastinoscopy	*n*	Sensitivity	NPV	Diagnostic accuracy
Rami-Porta and Call [37]	CM	148	0.78	0.85	0.90
	VAM	137	0.86	0.90	0.94
Venissac *et al.* [38]	VAM	240	0.91	NA	0.98
Lardinois *et al.* [39]	VAM after induction	24	0.81	NA	0.91
	VAM without induction	195	0.87	NA	0.95
Leschber *et al.* [40]	CM	52	NA	0.81	0.84
	VAM	119	NA	0.83	0.88
Karfis *et al.* [41]	VAM	87	0.8	0.59	0.85
Anraku *et al.* [42]	CM	505	0.92	0.95	0.97
	VAM	140	0.95	0.98	0.98
Cho *et al.* [43]	CM	222	0.70	0.95	0.96
	VAM	299	0.75	0.96	0.96

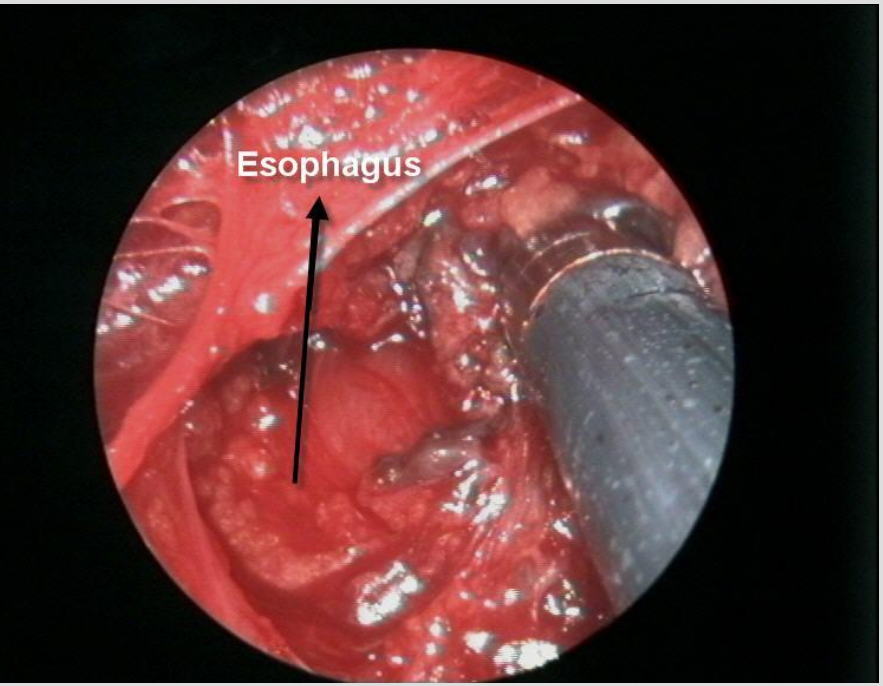
Adapted from Rami-Porta and Call [37].
CM: conventional mediastinoscopy; *n*: number of patients; NA: not available; NPV: negative predictive value; PPV: positive predictive value; VAM: video-assisted mediastinoscopy.

Best evidence topic
Overall comparison Videoassisted mediastinoscopy vs. Conventional mediastinoscopy (108 papers 1989-2011)

	VAM (n=956)	CM (n=5156)	p value
Mortality	0	0	
Morbidity	0.83 – 2.9%	0 – 5.3%	NS
No of LN biopsied	6 – 8.5%	5 – 7.13%	NS
No LN stations sampled	1.9 – 3.6%	2.6 – 2.98%	NS
Accuracy	87.9 – 98.9%	83.8 – 97.2%	NS
NPV	83.0 – 98.6%	81.0 – 98.7%	NS

Zacker et al. J Cardiothorac Surg 2012;14:81-84

ESTS recommendation on invasive staging (2014)

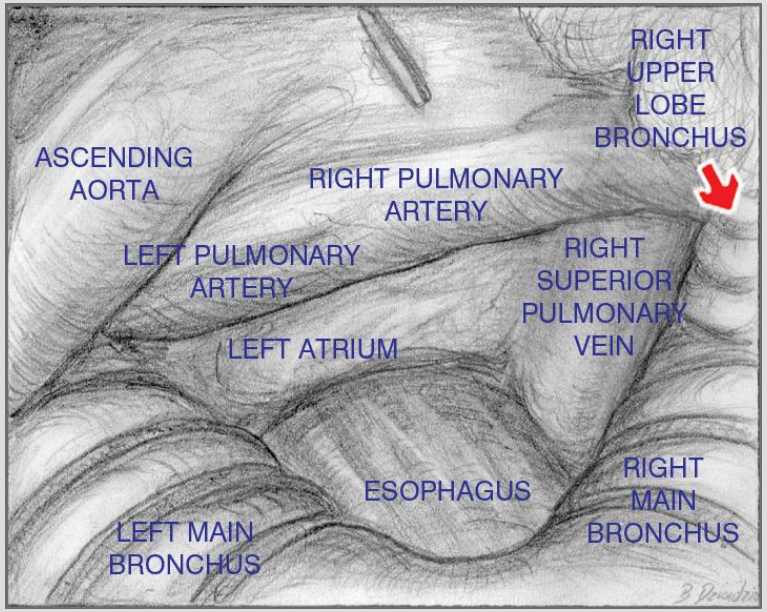


We recommend video-assisted mediastinoscopy over conventional mediastinoscopy

- Enhanced visualisation
- Better teaching
- Bimanual dissection (LN dissection)
- International standardisation of technique

Role of super mediastinoscopies?

- Video-assisted mediastinoscopic lymphadenectomy (VAMLA)
- Transcervical extended mediastinal lymphadenectomy (TEMLA)



Hürtgen et al., Eur J Cardiothorac Surg 2002;21:348-51
Kuzdzal and Zielinski, Eur J Cardiothorac Surg 2005;27:384-90

Results of VAMLA and TEMLA

Author	Procedure	N	NPV	Sensitivity	Side effect
Hürtgen et al, 2002	VAMLA	46	**100%**	100%	*Recurrent LN palsy 2.2%* *Scarring with impact on subsequent resection: 25%*
Lescher et al, 2003	VAMLA	23	**100%**	100%	*Blood loss > 100ml: 12%*
Witte et al, 2006	VAMLA	144	**NA**	100%	*Recurrent LN palsy: 3.4%* *Vascular lesions: 2.1%* *Mediastinitis: 0.7%* *Marked scarring: 19%*
Yoo et al, 2011	VAMLA	108	**NA**	NA	*Recurrent LN palsy: 3.4%*
Zielinski et al, 2013	TEMLA	256	**97.4%**	94%	*Mortality: 0,3%* *Temporary recurrent LN palsy: 2.5%* *Permanent recurrent LN palsy : 0,7%* *Pneumothorax: 0.7%* *Pleural effusion: 1,1%*

Role of super mediastinoscopies?

- Performed in very selected experienced centers
- High accuracy
- Morbidity may be increased
- Not recommended for routine use

Mediastinal restaging after neo-adjuvant therapy for N2 disease

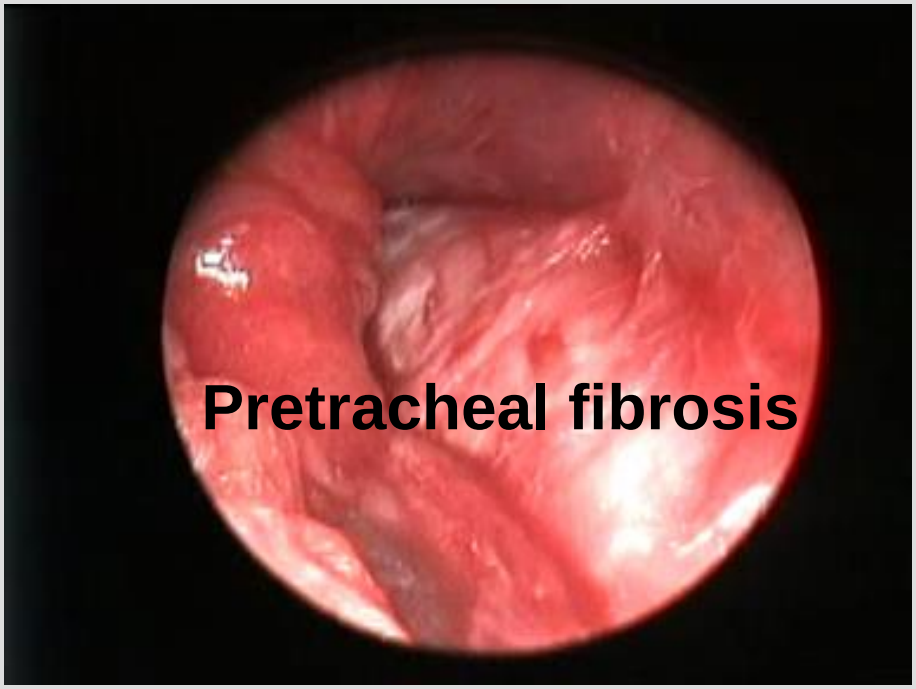
- Mainly patients with mediastinal downstaging or major response will benefit from surgical multimodality treatment
- Accuracy of PET-CT is lower compared with baseline staging
- Invasive mediastinal staging (histology) is indicated
- Remediastinoscopy or EBUS-EUS/FNA

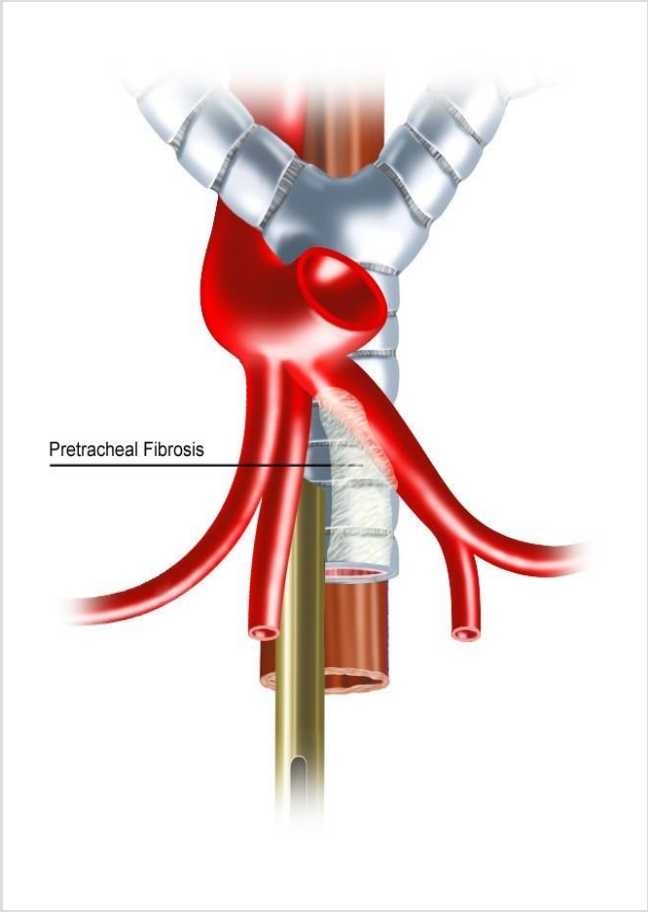
Invasive restaging techniques

Technique	Author	N	Sensitivity	NPV	Accuracy
Remediastino	Call, 2012	83	0.74	0.79	0.87
Remediastino	Marra, 2008	104	0.61	0.85	0.88
Remediastino	Stamatis, 2005	165	0.74	0.86	0.92
Remediastino	De Leyn, 2006	30	0.29	0.52	0.84
EBUS-FNA	Herth, 2008	124	0.76	0.20	0.77
EBUS-FNA	Szulowski, 2010	61	0.67	0.78	0.80
TEMLA	Zielinski, 2013	78	0.97	0.99	NA

Restaging the mediastinum
remediastinoscopy

Re-mediastinoscopy : fibrosis and adhesions



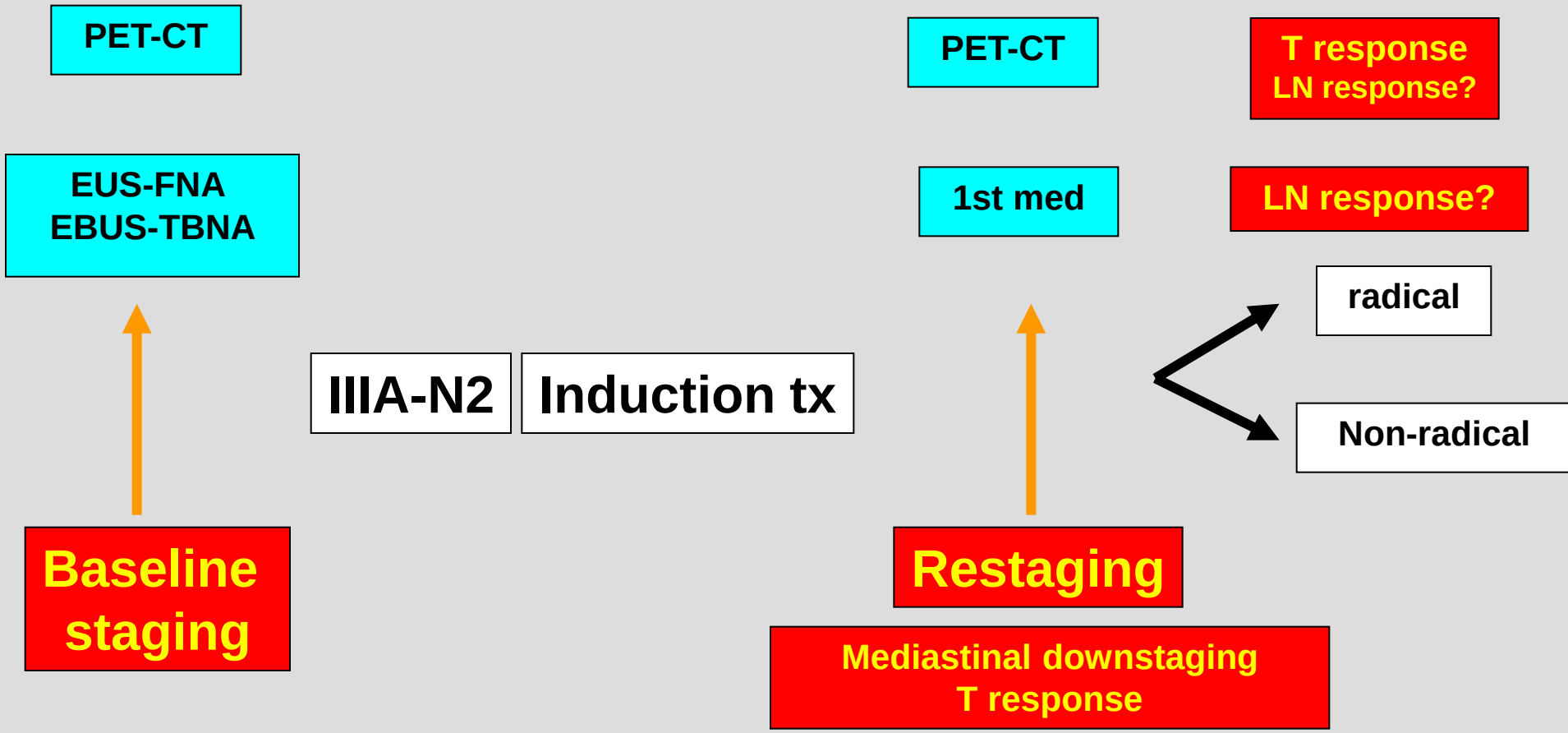


Postinduction videomediastinoscopy without previous mediastinoscopy

	No pretreatment (n=195)	Induction chemoTx (n=24)
Sensitivity	87%	81%
Specificity	100%	100%
Accuracy	95.6%	91%
Complication rate	4%	0%

Lardinois, Ann Thorac Surg 2003; 75:1102-1106

Possible new staging algorithm?



Conclusions

- New IASLC map (midline)
- Minimal recommendations : routine biopsy of 4R, 4L, and 7. If present biopsy 2R and 2L. On indication 10 R and 10L can be biopsied
- In peripheral T1a-b invasive staging can be omitted
- In central tumours or N1 disease (CT or PET) invasive staging is indicated
- In T > 3cm (especially adenocarcinoma with high SUV) invasive staging should be considered

Conclusions

- Surgical staging remains indicated after negative endoscopical staging in clinically suspicious LNs
- For surgical staging VAM with nodal dissection (especially station 7) is recommended
- Choice of invasive staging technique is dependent on local availability and expertise
- Each center should analyse its own results


Thank you!
University Hospital Leuven, Belgium
Department of Thoracic Surgery
Leuven Lung Cancer Group (www.LLCG.be)