

How do we improve the outcome of stage III

Optimal staging of mediastinal lymph nodes

Christophe Doms MD PhD

Department of Respiratory Diseases

University Hospitals Leuven

Belgium



15-18 April 2015, Geneva, Switzerland

Organisers



Partners



Disclosure slide

- Nothing to declare



15-18 April 2015, Geneva, Switzerland

Organisers



Partners



Heterogeneity of stage III NSCLC.

T4	N0	IIIA
T3-4	N1	IIIA
T1-3	N2	IIIA
T4	N2	IIIB
Tany	N3	IIIB



15-18 April 2015, Geneva, Switzerland

Organisers

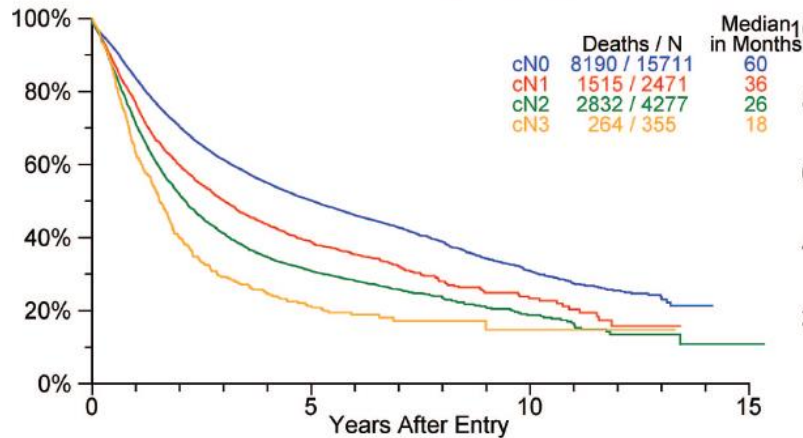


Partners

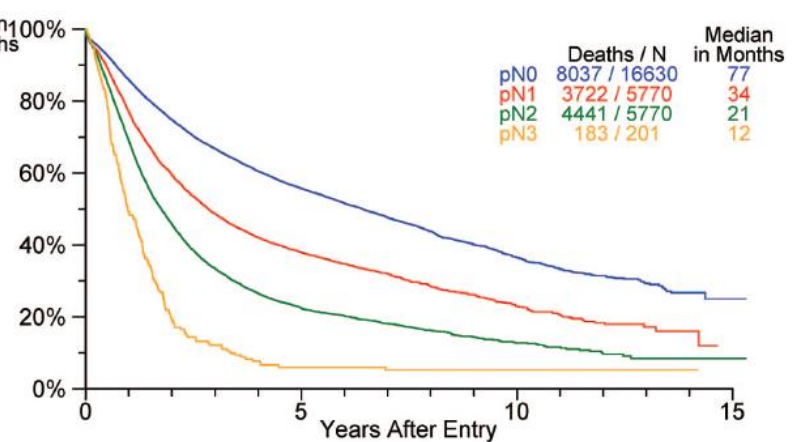


N-factor and relation to outcome

Clinical Staged, By cN



Pathologically Staged, By pN



	1 Yr	5 Yrs		HR	P
cN0	84%	50%			
cN1	77%	39%	vs cN0:	1.37	<.0001
cN2	71%	31%	vs cN1:	1.24	<.0001
cN3	63%	21%	vs cN2:	1.31	<.0001

	1 Yr	5 Yrs		HR	P
pN0	86%	56%			
pN1	77%	38%	vs pN0:	1.63	<.0001
pN2	69%	22%	vs pN1:	1.51	<.0001
pN3	49%	6%	vs pN2:	1.81	<.0001

15-18 April 2015, Geneva, Switzerland

Organisers



Partners



N-factor and relation to treatment

Category mediastinal nodal disease	Description	Impact on treatment
Incidental N2 = found at surgery/final pathology	Unforeseen N2	Adjuvant therapy (chemo/radiotherapy)
Potentially resectable N2 = at baseline preop invasive staging	Single-station N2 Multi-station N2	Surgical CMT Non-surgical CMT
Unresectable N2 or N3 = at baseline preop invasive staging	Bulky N2 N3	Non-surgical CMT



15-18 April 2015, Geneva, Switzerland

Organisers



Partners



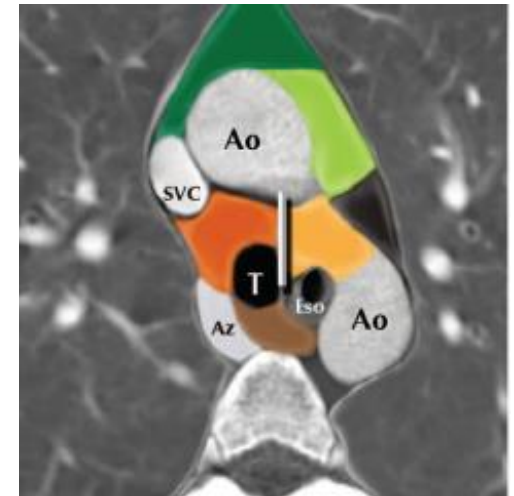
Computed Tomography : CE-MDCT

Demonstrates lymph node enlargement.

- short axis $\geq 10\text{mm}$ = suspect
- size = relative criterion !
 - sensitivity 60% - specificity 80%
- = imperfect means of nodal staging

Defines ACCP groups = need for tissue.

Anatomical borders = station allocation.



Rusch V, et al. J Thorac Oncol 2009.



15-18 April 2015, Geneva, Switzerland

Organisers



Partners



Integrated FDG-PET/CT.

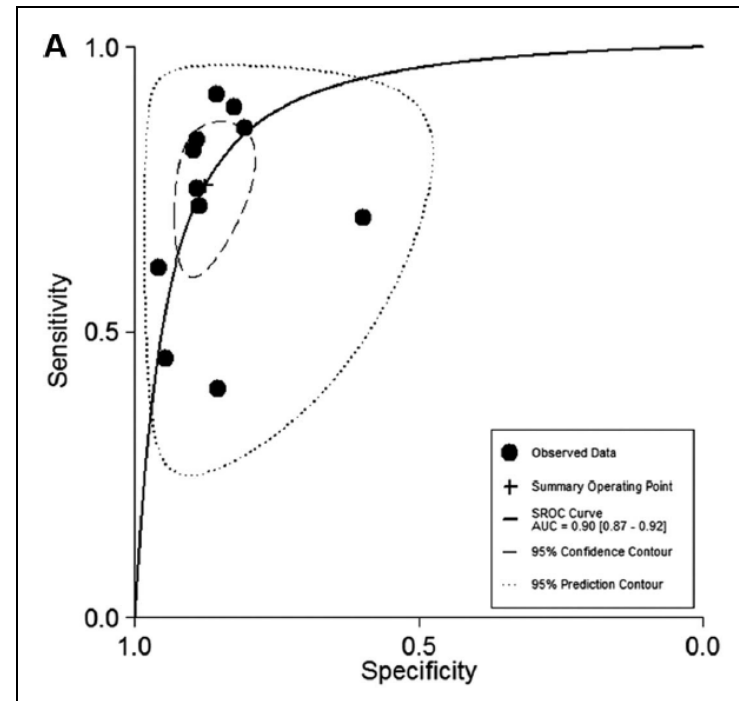
Meta-analysis integrated PET/CT

Patient-based data analysis
sensitivity 0.76 (0.65-0.84)
specificity 0.88 (0.82-0.92)

Overall NLR = 0.28 (0.19-0.40)

Overall PLR = 6.1 (4.3-8.7)

AUC = 0.90 (0.87-0.92)



Lv, et al. J Thorac Oncol 2011;6:1350.



15-18 April 2015, Geneva, Switzerland

Organisers

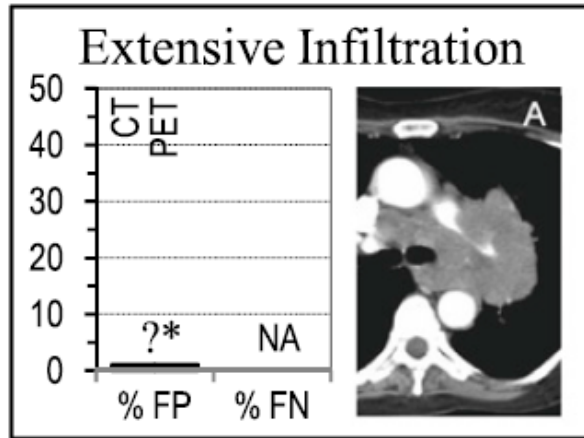


Partners



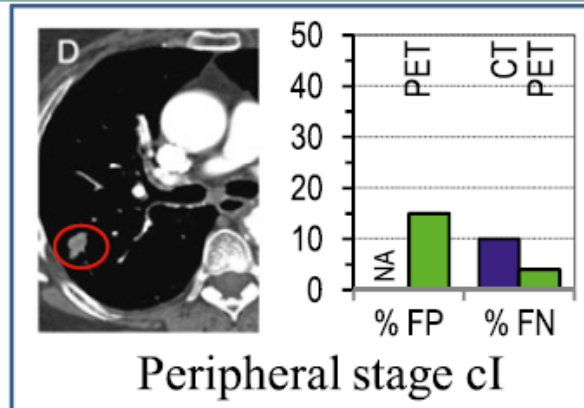
Mediastinal nodal staging NSCLC.

A
C
C
P
A

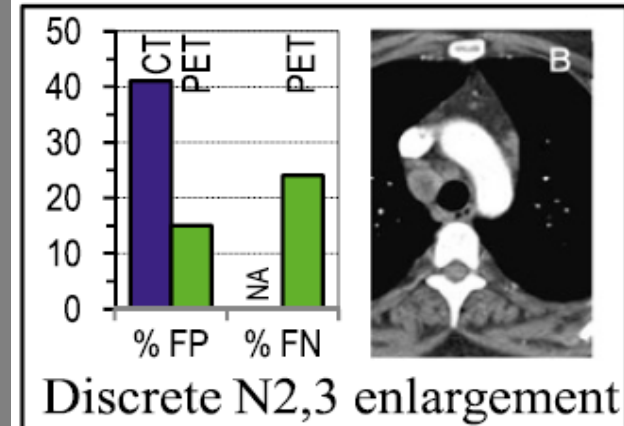


No tissue confirmation needed based on PET-CT

A
C
C
P
D

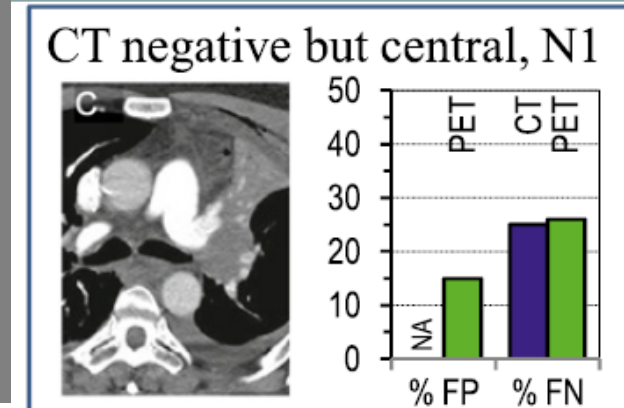


A
C
C
P
B



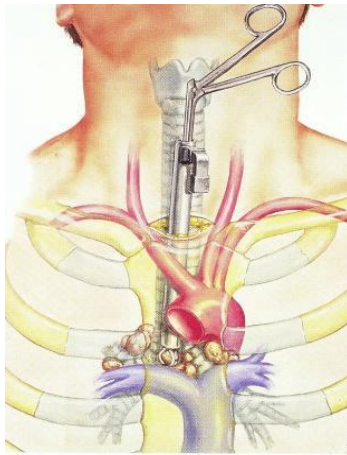
Tissue confirmation needed E(B)US +/- surgical ?

A
C
C
P
C



Invasive mediastinal nodal staging.

- Surgical : Mediastinoscopy, VATS, Chamberlain



Mediastinoscopic biopsy of subcarinal node.

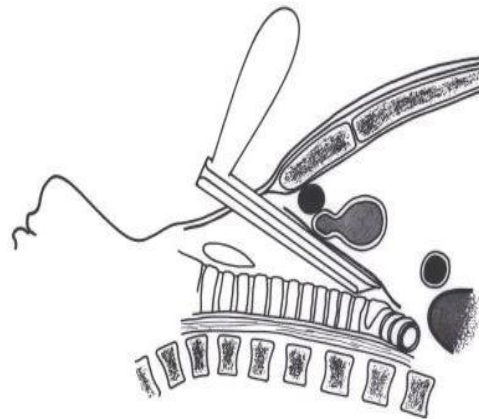
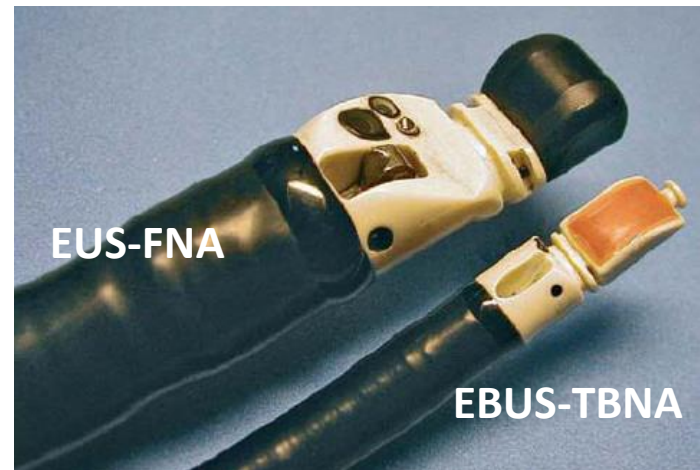


Fig. 38. Schematic lateral view of mediastinoscope introduced in the correct plane beneath the pretracheal fascia.



- Endosonography :
 - EndoBronchial UltraSound - TBNA
 - Esophageal UltraSound - FNA



15-18 April 2015, Geneva, Switzerland

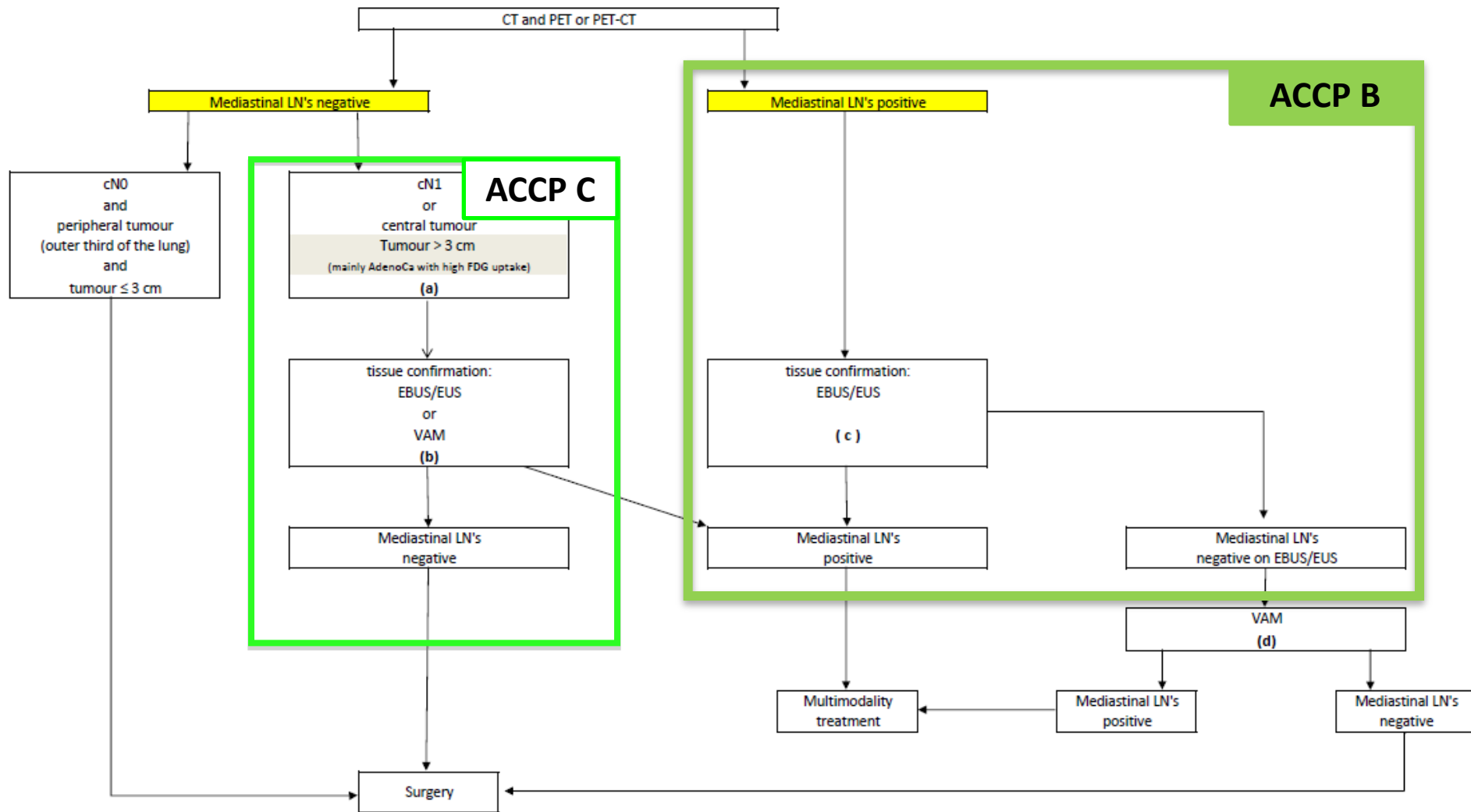
Organisers



Partners



ESTS mediastinal nodal staging algorithm



De Leyn et al. Eur J Cardiothorac Surg 2014;45:787.

Studies comparing EBUS to mediastinoscopy

A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer

(*J Thorac Cardiovasc Surg* 2011;142:1393-400)

Kazuhiro Yasufuku, MD, PhD,^a Andrew Pierre, MD, MSc,^a Gail Darling, MD,^a Marc de Perrot, MD, MSc,^a

pN2/3 35%

ACCP B : 36%

cN1 : 5%

Endobronchial Ultrasound versus Mediastinoscopy for Mediastinal Nodal Staging of Non-Small-Cell Lung Cancer

(*J Thorac Oncol*. 2015;10: 331–337)

Sang-Won Um, MD, PhD,* Hong Kwan Kim, MD, PhD,† Sin-Ho Jung, PhD,‡ Joungho Han, MD, PhD,§
Kyung Jong Lee, MD,* Hye Yun Park, MD, PhD,* Yong Soo Choi, MD, PhD,† Young Mog Shim, MD, PhD,†

pN2/3 59%

ACCP B : 85%

cN1 : 15%



15-18 April 2015, Geneva, Switzerland

Organisers



Partners



A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer

N=153

EBUS

mediastino

p-value

ES+SS

N2/N3 prevalence = 35%

Sensitivity, % (95% CI)	81 (68-90)	79 (62-87)	NS	92 (81-98)
NPV, % (95% CI)	91 (84-95)	90 (83-95)	NS	96 (90-99)
PTProb, % (95% CI)	10 (6-18)	11 (6-19)	NS	4 (1-10)

LN station	Total	Malignant	Benign	Inadequate	LN station	Total	Malignant	Benign	Inadequate
LN stations biopsied by EBUS-TBNA					LN stations biopsied by mediastinoscopy				
2R	30	12	12	6	2R	115	16	97 (2)	2
4R	137	25	74 (5)	38	4R	151	26	124 (4)	1
2L	2	1	0	1	2L	26	1	23	2
4L	108	15	39 (1)	54	4L	132	12	118 (4)	2
7	149	25	101 (2)	23	7	149	24	122 (4)	3
Total	426	78	226 (8)	122	Total	573	79	484 (14)	10

Number of false-negative LN stations in parentheses. LN, Lymph node; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

Number of false-negative LN stations in parentheses. LN, Lymph node; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration.

Kazuhiro Yasufuku, MD, PhD,^a Andrew Pierre, MD, MSc,^a (J Thorac Cardiovasc Surg 2011;142:1393-400)

Endobronchial Ultrasound versus Mediastinoscopy for Mediastinal Nodal Staging of Non-Small-Cell Lung Cancer

Sang-Won Um, MD, PhD, Hong Kwan Kim, MD, PhD,† Sin-Ho Jung, PhD,‡ Joungho Han, MD, PhD,§ Kyung Jong Lee, MD,* Hye Yun Park, MD, PhD,* Yong Soo Choi, MD, PhD,† Young Mog Shim, MD, PhD,†*

Primary end point : EBUS-TBNA not inferior to mediastinoscopy to detect pN2/3.

Statistics for 60% pN2/3 prevalence - non-inferiority margin 10% - alternative superiority margin 5%.

N=127	EBUS	mediastino	p-value
N2/N3 prevalence = 59%			
Sensitivity, % (95% CI)	88 (78-94)	81 (70-89)	0.04
NPV, % (95% CI)	85 (73-93)	79 (67-88)	0.02
PTProb, %	17	27	

Sang-Won Um, MD, PhD, Hong Kwan Kim, MD, PhD,† Sin-Ho Jung, PhD,‡. (J Thorac Oncol. 2015;10: 331–337)*

Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer

A Randomized Trial

	SS	ES	p-Value
Sensitivity, % (95% CI)	79 (66-88)	85 (74-92)	0.47
NPV, % (95% CI)	86 (76-92)	85 (75-92)	0.99
complications	6%	1%	0.03

	SS	ES+SS	p-Value
	N=118	N=123	
N2/N3 detected ; n (%)	41 (35)	62 (50)	0.02
Sensitivity, % (95% CI)	79 (66-88)	94 (85-98)	0.02

Annema et al. JAMA 2010;304:2245.



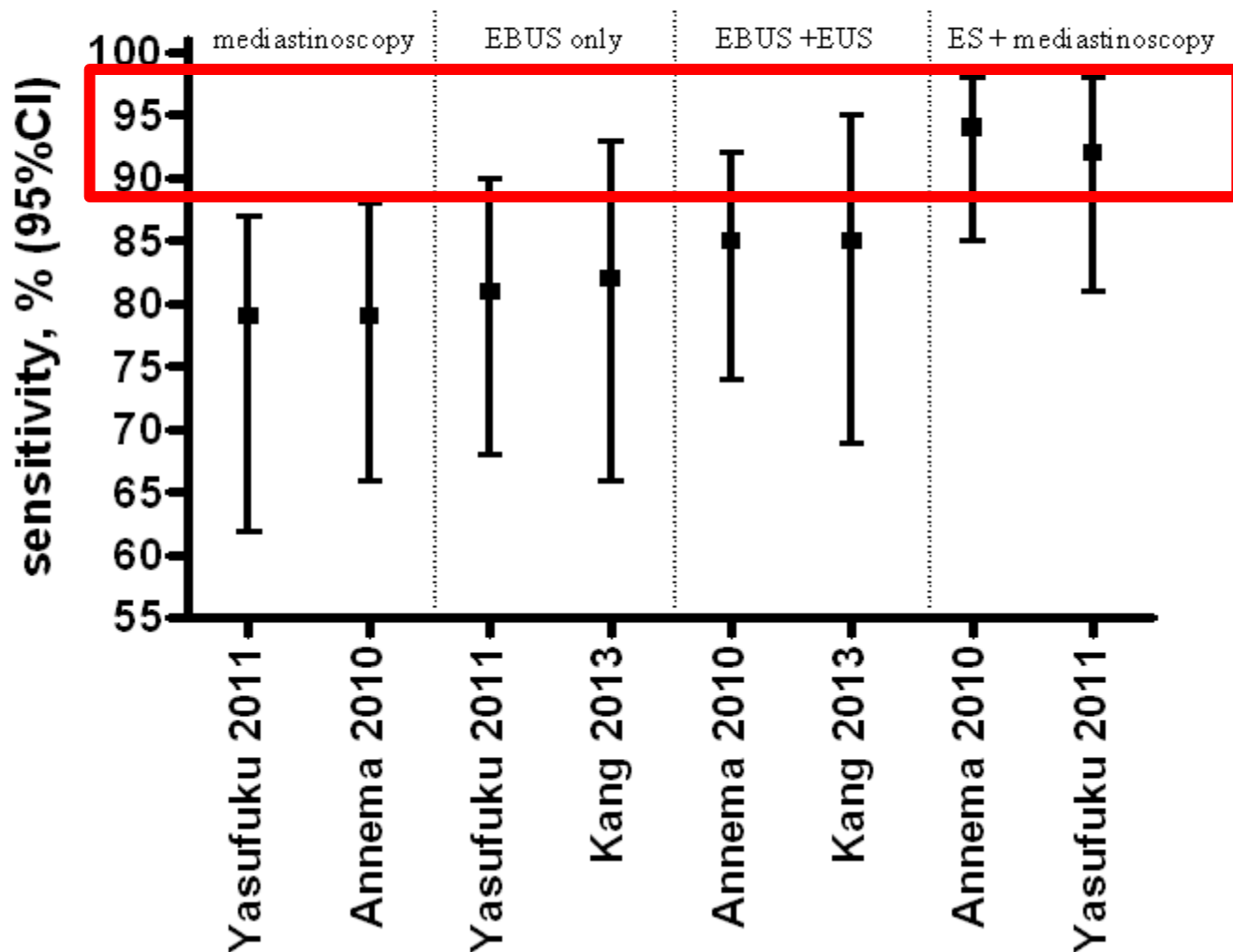
Organisers



Partners



Sensitivity to detect N2/N3 disease.



Organisers



Partners



ASTER

Endosonography
(n=120)

Endosonography
and surgical
staging (n=120)

Patients that need
surgical staging to
detect one
false-negative
endosonography (n)

All patients	..	..	11
Prevalence	0.55	0.55	..
Sensitivity	0.85 (0.74-0.92)	0.94 (0.85-0.98)	..
Negative likelihood ratio	0.15 (0.09-0.28)	0.06 (0.03-0.17)	..
Post-test probability	0.15 (0.10-0.25)	0.07 (0.04-0.17)	..

Abnormal mediastinum by imaging	..	..	7
Prevalence	0.63	0.63	..
Sensitivity	0.86 (0.76-0.93)	0.97 (0.89-0.99)	..
Negative likelihood ratio	0.14 (0.08-0.27)	0.03 (0.01-0.14)	..
Post-test probability	0.20 (0.12-0.32)	0.05 (0.02-0.20)	..



15-18 April 2015, Geneva, Switzerland

Organisers



Partners



Sensitivity to detect N2/N3 disease.

	Endosonography modality	c-stage on imaging	Prevalence pN2/3	N patients incl/analysed	Sensitivity (95%CI)	NPV (95%CI)	Post-test Prob (95%CI)
Wallace 2008	EBUS+EUS	I-III	30%	138/134	0.93 (0.79-0.98)	0.97 (0.90-0.99)	0.03 (0.01-0.10)
Herth 2010	EBUS+EUS-B	II-III	51%	150/139	0.96 (0.87-0.99)	0.96 (0.87-0.99)	0.04 (0.01-0.13)
Annema 2010	EUS+EBUS	I-III	54%	123/123	0.85 (0.74-0.92)	0.85 (0.75-0.92)	0.15 (0.10-0.25)
Hwangbo 2010	EBUS+EUS-B	I-III	31%	150/143	0.91 (0.78-0.97)	0.96 (0.90-0.99)	0.04 (0.02-0.11)
Ohnishi 2011	EBUS+EUS	I-III	28%	115/110	0.84 (0.66-0.94)	0.94 (0.86-0.98)	0.06 (0.03-0.15)
Kang 2013	EBUS+EUS-B	I-III	40%	160/148	0.88 (0.76-0.95)	0.93 (0.85-0.97)	0.08 (0.04-0.16)
Oki 2014	EBUS+EUS-B	I-III	23%	150/150	0.69 (0.51-0.83)	0.91 (0.85-0.95)	0.10 (0.05-0.17)
Liberman 2014	EBUS+EUS	I-IV*	32%	166/166	0.89 (0.76-0.95)	0.95 (0.89-0.98)	0.05 (0.02-0.12)

Dooms C, et al. Eur Resp Mon 2015.



15-18 April 2015, Geneva, Switzerland

Organisers



Partners



Implication of these trials

1. Initial mediastinal evaluation by endosonography

E(B)US should be the standard in stage III NSCLC

→ reduction in invasive surgical staging

2. A negative endosonography should be followed by a surgical staging modality (mediastinoscopy).



15-18 April 2015, Geneva, Switzerland

Organisers



Partners



Rationale for combined EBUS-EUS.

Station	EUS-FNA	EBUS-TBNA
2R	+/-	+
2L	+	+
3P	+	+
4R	-	+
4L	+	+
5	(+/-)	-
6	-	-
7	+	+
8-9	+	-
10	+/-	+
11	-	+



How to perform combined EBUS-EUS.

Table 1—Classification of Type and Thoroughness of Clinical Mediastinal Staging of Lung Cancer

Type/Name	Description	Thoroughness	Detailed Definition
1/Surgical	Mediastinoscopy, Chamberlain, VATS	A, Complete removal ^a	Complete lymphadenectomy by TEMPLA or VAMLA (1, 2R, 2L, 3, 4R, 4L, 7, 8; and 5, 6 if LUL tumor)
		B, Systematic sampling ^a	Mediastinoscopy with sampling/exploration of 2R, 2L, 4R, 4L, 7, and 5, 6 if LUL tumor
		C, Selective sampling	Mediastinoscopy with biopsy of ≥ 1 station, and must include any node suspicious by imaging
		D, Poor	Mediastinoscopy with visual assessment only; no node biopsy or no nodal tissue in samples
2/Needle- based	EUS-NA, EBUS-NA, TBNA, TTNA	A, Complete sampling ^a	Sampling of each visible node in each station (1, 2R, 2L, 3, 4R, 4L, 7, 8; and 5, 6 if LUL tumor), ≥ 3 passes per node or ROSE ^b
		B, Systematic sampling ^a	Nodes in each station sampled (2R, 4R, 7, 4L, 2L, and 5, 6 if LUL tumor), ≥ 3 passes per node or ROSE ^b
		C, Selective sampling	Biopsy of ≥ 1 station, which must include a node suspicious by imaging or ≥ 1 cm by US if present, or < 3 passes and no ROSE
		D, Poor	Visual assessment only; no node biopsied or no lymphatic tissue in aspirates

Complete sampling = **NA of each node**
Systematic sampling = **NA of each station**
Selective sampling = **NA of suspicious node**

Detterbeck et al. Chest 2010;137:436-442

Rationale for combined EBUS-EUS.

EBUS-centred versus EUS-centred mediastinal staging in lung cancer: a randomised controlled trial

Kang HJ, *et al.* *Thorax* 2013;**0**:1–8. doi:10.1136/thoraxjnl-2013-203881

pN2/3 40%

ACCP B : 54%

cN1 : 11%

1. Sensitivity to detect pN2/3
2. Impact on stage III subgroups



15-18 April 2015, Geneva, Switzerland

Organisers



Partners



EBUS-centred versus EUS-centred mediastinal staging in lung cancer: a randomised controlled trial

Table 2 Diagnostic values of procedures in the detection of mediastinal metastasis

	Group A: EBUS-centred (n=74)	Group B: EUS-centred (n=74)	p Value
Diagnostic accuracy, % (n/n)	93.2 (69/74) (87.5 to 99.0)	97.3 (72/74) (93.6 to 101.0)	0.245
Accuracy of first procedure*, % (n/n)	91.9 (68/74) (85.7 to 98.1)	86.5 (64/74) (78.7 to 94.3)	0.290
p Value	0.754	0.016	
Sensitivity, % (n/n)	85.3 (29/34) (68.9 to 95.0)	92.0 (23/25) (74.0 to 99.0)	0.431
Sensitivity of first procedure, % (n/n)	82.4 (28/34) (65.5 to 93.2)	60.0 (15/25) (38.7 to 78.9)	0.056
p Value	0.742	0.008	
NPV, % (n/n)	88.9 (40/45) (75.9 to 96.3)	96.1 (49/51) (86.5 to 99.5)	0.176
NPV of first procedure, % (n/n)	87.0 (40/46) (73.7 to 95.1)	83.1 (49/59) (71.0 to 91.6)	0.581
p Value	0.777	0.029	

Stage shift by second procedure 7% 48%
 station 4L stations 7 & 2/4R

	Group A: EBUS-centred (n=80)	Group B: EUS-centred (n=80)	p Value
Total procedure time, mean (SD), min:s	38:3 (7:13)	39:4 (9:30)	0.422
EBUS procedure time, mean (SD), min:s	23:5 (5:39)	18:1 (6:6)	<0.0001
EUS procedure time, mean (SD), min:s	6:4 (5:15)	13:5 (8:3)	<0.0001
No. of nodal stations, mean (SD)	3.5 (0.9)	3.7 (1.2)	0.232
No. nodal stations by EBUS-TBNA, mean (SD)	3.0 (0.8)	2.5 (0.8)	0.000
No. nodal stations by EUS-FNA, mean (SD)	0.9 (0.9)	1.9 (1.2)	<0.0001

Kang H, et al. Thorax 2014;69:261-268.

Conclusion : optimal mediastinal nodal staging of clinical stage III NSCLC.

- CE-CT = imperfect means of mediastinal nodal staging
- PET/CT : guides in next step (tissue verification or direct surgery)
- EBUS/EUS = preferred invasive mediastinal staging procedure
- Sensitivity to detect pN2/3 : EBUS/EUS = VAM
- Combined EBUS/EUS = EBUS followed by EUS(-B) :
 - 'systematic' instead of 'selective' sampling
 - 7% shift in nodal type of stage III
- Confirmatory VAM after negative EBUS/EUS :
 - posttest probability of pN2 lowered to 5%
 - bimanual nodal dissection (also stations 2L and 4L)



Thank you for your attention !



15-18 April 2015, Geneva, Switzerland

Organisers



Partners

