



# Les techniques invasives et minimalement invasives dans le staging du cancer bronchopulmonaire

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# Invasive Mediastinal Staging

- Purpose : to exclude
  - Involvement of mediastinal **contralateral side**
  - **Extensive** involvement of the **ipsilateral side**  
➔ medical management
- **Before PET introduction**
  - Nearly all cases (low performance of CT scan)
  - Or enlarged lymph nodes on CT scan
- **After PET introduction**
  - Positive hot spots (inflammatory processes)
  - Additional situations (PET + N1 tumors, mediastinal lymph nodes > 16 mm on CT scan, low SUV tumors, central tumors)



# Survival prognostic factors for N2 disease

## ● Favourable


- Complete resection
- One-level metastasis
- cN0-N1
- T1-T2N2
- Intranodal microscopic metastasis
- Without subcarinal nodal involvement
- T < 20 mm

## ● Unfavourable

- Incomplete resection
- Multi-level metastasis
- Radiological N2 disease
- T3-T4N2
- Extranodal expansion
- Number
- Subcarinal node involvement
- T > 50 mm

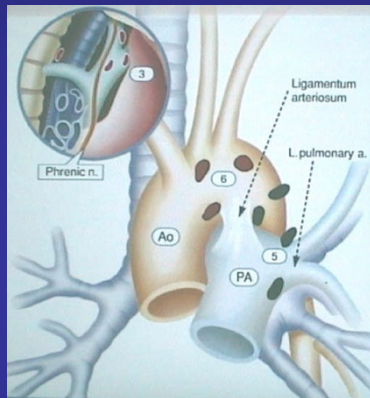


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  - Positive hot spots in N2/N3 zones (inflammatory processes)
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# Surgical mediastinal staging procedures

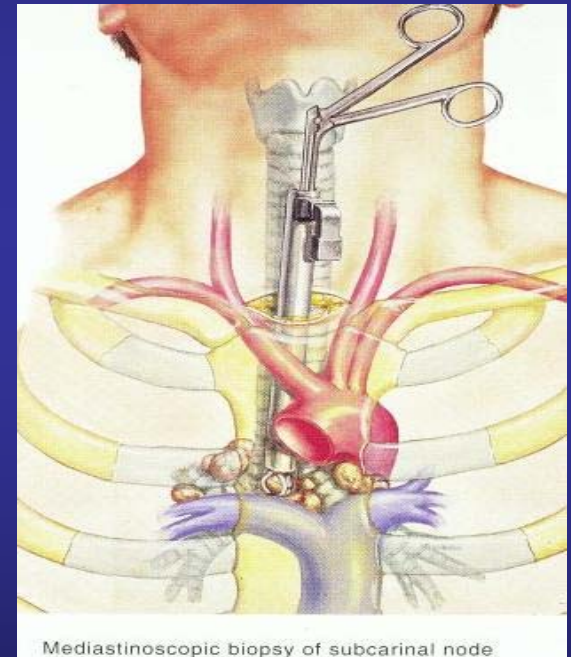


**Cervical mediastinoscopy**  
(+/- extended mediastinoscopy)

**Anterior mediastinotomy**  
(Chamberlain)

**Video-mediastinoscopy**

**Thoracoscopic staging**



Mediastinoscopic biopsy of subcarinal node



# Cervical mediastinoscopy

- Usually under general anesthesia
- Morbidity (2%) and mortality (0.08%)
- Stations 2R,2L,4R,4L, anterior 7, pretracheal 1 and 3
- Videomediastinoscopy
  - Better visualization
  - More extensive sampling (including posterior 7), even complete dissection
  - Improvement in sensitivity and false negative rates



# Accuracy of standard cervical mediastinoscopic biopsies in LC

Source	Years	No of patients	Sensitivity %	Specificity %	FP %	FN %	Prevalence %
19 papers	83-03	6505	78	100	0	11	39



# Cervical Mediastinoscopy in LC patients

Studies	Patients Nb	Patient type	Sensitivity, %	Specificity, %	FP %	FN %	Prevalence
12	5118	c I-III	82	100	0	10	38
5	1029	c II-III	82	100	0	13	49
2	358	c I	42	100	0	8	15
Total	6505		78	100	0	11	39





# Comparison of characteristics of invasive tests

<i>Tests</i>	<i>Sensitivity</i> %	<i>Specificity</i> %	<i>FP rate</i> %	<i>FN rate</i> %	<i>Patient population</i>
<i>Medscopy</i>	81	100	0	9	cN0-N2
<i>TTNA</i>	91	100	0	22	c N2
<i>EUS-NA</i>	88	91	2	23	c N2
<i>TBNA</i>	76	96	0	29	c N2

**Mediastinoscopy is the gold standard !**



# Guidelines : invasive intrathoracic staging

Royal College of Radiologists 1999

ACCP 2003

ASCO 2003

NICE 2005

ACCP 2007

Mediastinal sampling if enlarged LN (> 1 cm)

- Extensive infiltration: TTNA or EUS-NA or TBNA
- CT enlarged discrete LN : mediastinoscopy
- PET + LN : mediastinoscopy
- CT normal LN : mediastinoscopy
- PET – LN : mediastinoscopy

Biopsy if enlarged LN (>1cm) on CT (even PET -)  
Or PET + LN

Histo/cytological sampling if enlarged LN (>1cm) on CT  
Or PET + LN (PET - enlarged LN should not be controlled)

- Extensive infiltration : radiographic assessment
- CT enlarged discrete LN (PET + or -) : invasive or minimally invasive
- Central tumor or N1 : mediastinoscopy (needles 2nd choice)
- Peripheral stage I tumor and PET + mediastinum : mediastinoscopy (needles 2nd choice)



# Ultrasound puncture bronchoscope

- **Convex probe with a frequency of 7.5 MHz**
  - Linear transducer that scans parallel to the insertion direction of bronchoscope
  - Contact with/without balloon inflated with saline
- **Ultrasound scanner**
- **Doppler mode**
- **Bronchoscope** : outer diameter of 6.7 mm, direction of view is 30° toward oblique, channel diameter of 2.0 mm
- **Dedicated 22-gauge needle**



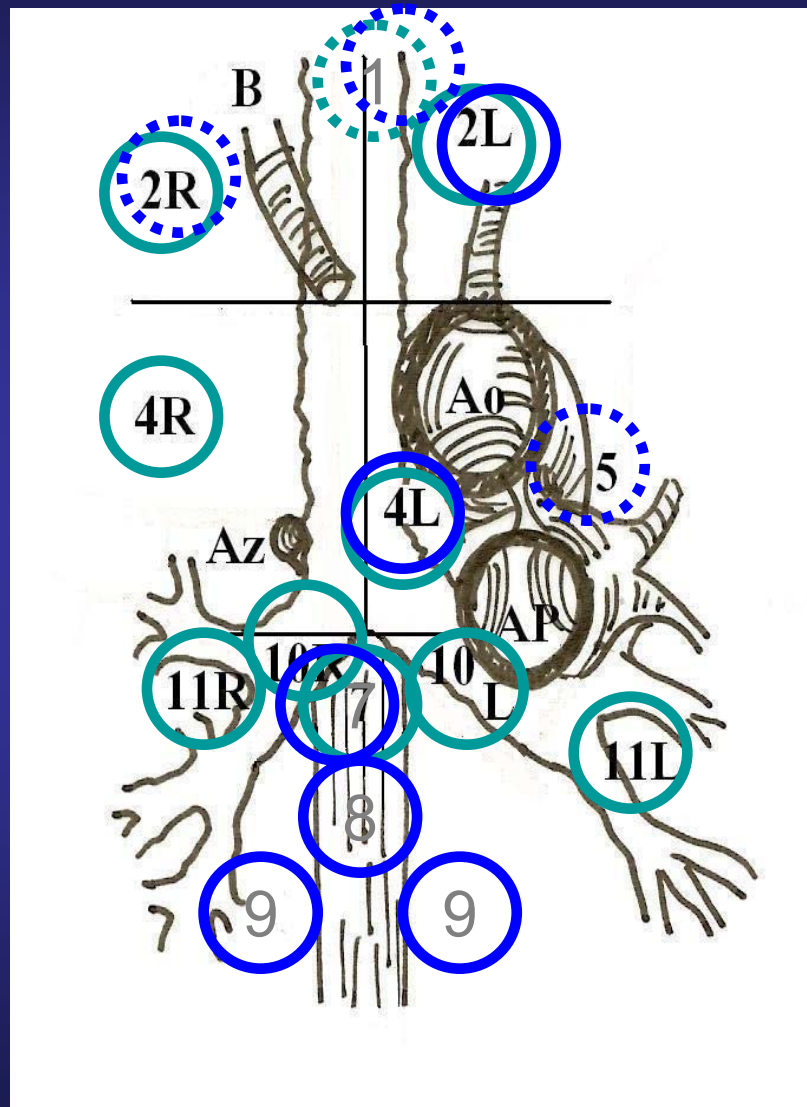


# EBUS-EUS

- Outpatient basis; 20-30 min
  - Conscious sedation (iv midazolam)
  - EBUS : anaesthesia of the airways
  - O<sub>2</sub> (2 L/min; nasal prongs)
  - Transcutaneous hemoglobin saturation and cardiac rhythm monitoring
- NB : EBUS under general anaesthesia in some centers



# EBUS-EUS complementarity



○ EBUS

○ EUS



# Technical aspects EUS/EBUS

- **Standardized order of examination and sampling**
  - **Examination** : from distally to proximally
    - EUS : left adrenal gland and liver lobe
    - All accessible mediastinal lymph nodes
      - EBUS : also N1 stations in a diagnostic+staging strategy
      - Detection of lymph nodes down to a size of 2-3 mm
    - Shape, size, demarcation and echo pattern not accurate enough for distinction benign-malignant
  - **Sampling** : because of the risk of contamination
    - from N3 to N2 stations
    - Also
      - EUS : left adrenal gland
      - EBUS : N1 or the tumor at the end of the procedure, for diagnostic purpose only



# Technical aspects : sampling

- Accessible lymph node for puncture : **short diameter**  
 **$\geq 5$  mm**
- Optimal number of aspirations per lymph node station, if ROSE not used
  - EBUS-TBNA : **3**
  - EUS-FNA : **4**



# Technical aspects

- **Cytopathological specimens**
  - in some cases, tissue cores
- **Results** : positive (tumor cells), negative (lymphocytes or lymphoid tissue), inadequate (blood only, bronchial epithelial cells, cartilage)
- **ROSE** (rapid on-site sample evaluation)
  - Shortening the procedure



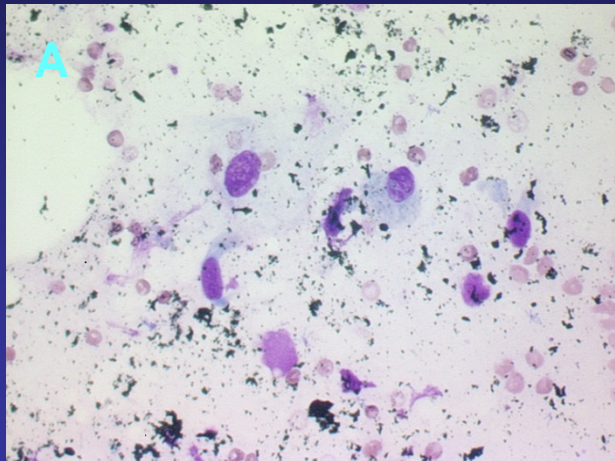


# EBUS-TBNA : Tolerance and Complications

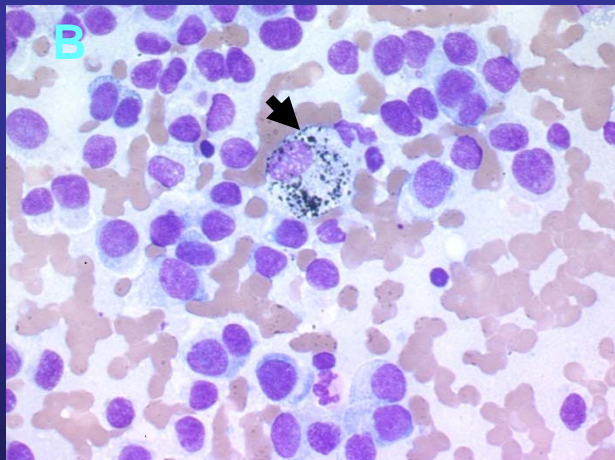
- Tolerance under local anaesthesia
  - Cough is frequent (active smokers, open tracheostomy)
- Complications
  - Only mild bleeding
  - Pneumothorax (1/~500 examinations)
  - Low incidence of bacteremia (Steinfort DP et al. Eur Respir J 2009, doi:10.1183/09031936.00151809) and other infectious complications



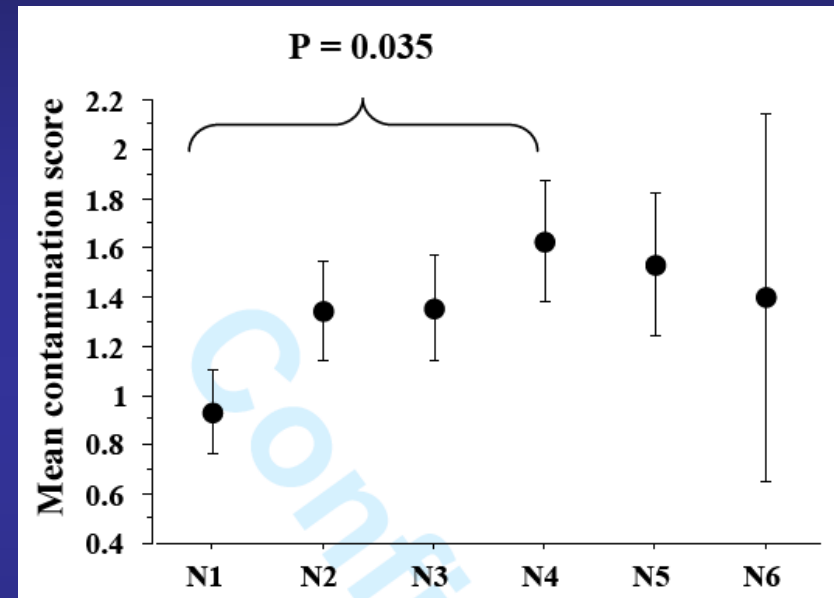
# EBUS-TBNA needles



EBUS-TBNA



Wang needle

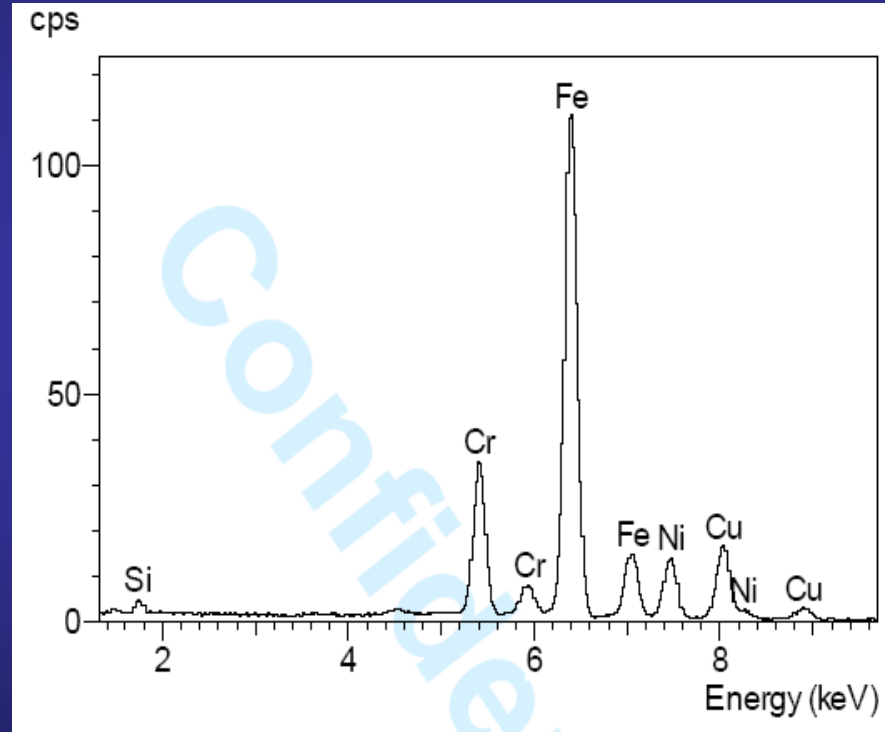
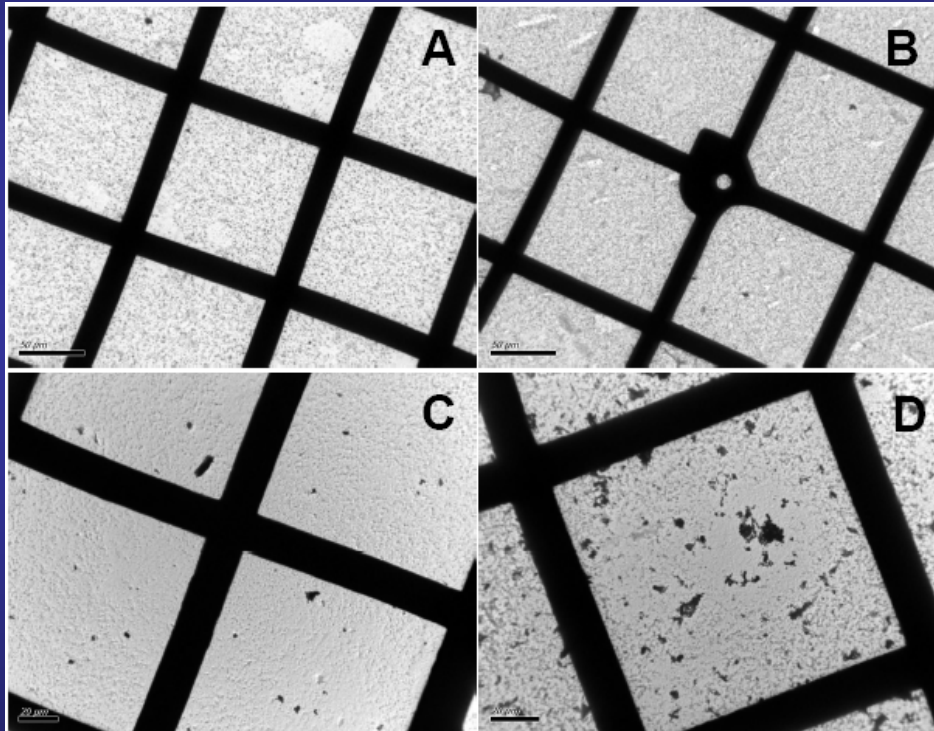


Contamination score and  
Number of passes



# EBUS-TBNA rinses

CHU St-Pierre | UMC St-Pieter



Rinsing solutions after successive introduction and withdrawal of the stylet

Mineral analysis by energy dispersive X ray



# EBUS-TBNA for mediastinal staging

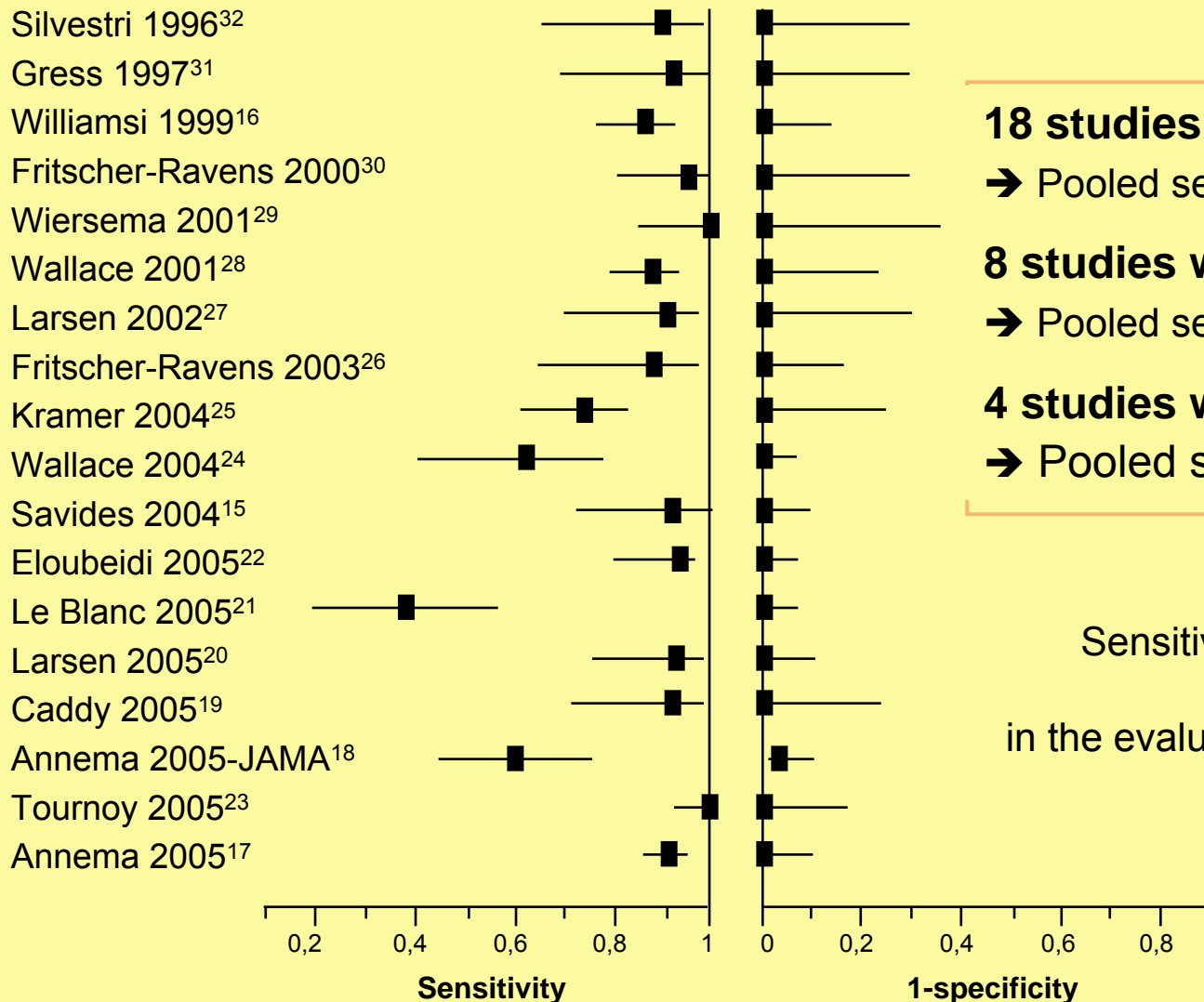


Authors	Nb patients	Enrolment	Selection	Sensitivity (%)	Specificity (%)	Prevalence (%)
Krasnik 2003	11	ND	CT or PET +	100.0	100	90.9
Rintoul 2005	20	ND	CT +	84.6	100	72.2
Vilman 2005	33	ND	Unselected	85.0	100	71.4
Yasufuku 2005	108	Consecutive	CT +	94.1	100	63.0
Herth 2006	502	Consecutive	CT +	94.0	100	99.2
Vincent 2008	152	Consecutive	CT or PET +	99.1	100	78.1
Wallace 2008	138	Consecutive	Unselected	69.0	100	30.4
Herth 2008	97	Consecutive	normal CT-PET	88.9	100	9.3
Lee 2008	102	ND	CT 5-20mm	93.8	100	33.7
Bauwens 2008	106	Consecutive	PET +	95.1	100	67.8
Ernst 2008	66	Consecutive	CT +	88.1	100	89.4



# EUS meta-analysis

CHU St-Pierre | UMC St-Pieter



**18 studies**

→ Pooled sensitivity : **83%**

**8 studies with abnormal CT**

→ Pooled sensitivity : **90%**

**4 studies with normal CT**

→ Pooled sensitivity : **58%**

Sensitivity and 1-specificity  
of EUS-FNA  
in the evaluation of lymph node  
metastasis (N2/N3).  
Error bars = 95% CI.



# Comparison of Medscopy-EUS-EBUS

	Patient Nb	Sensitivity %	Specificity %	FP %	FN %	Prevalence %
<b>Meds</b>	<b>6505</b>	<b>78</b>	<b>100</b>	<b>0</b>	<b>11</b>	<b>39</b>
<b>EUS</b>	<b>1003</b>	<b>84</b>	<b>99.5</b>	<b>0.7</b>	<b>19</b>	<b>61</b>
<b>EBUS</b>	<b>918</b>	<b>90</b>	<b>100</b>	<b>0</b>	<b>20</b>	<b>68</b>



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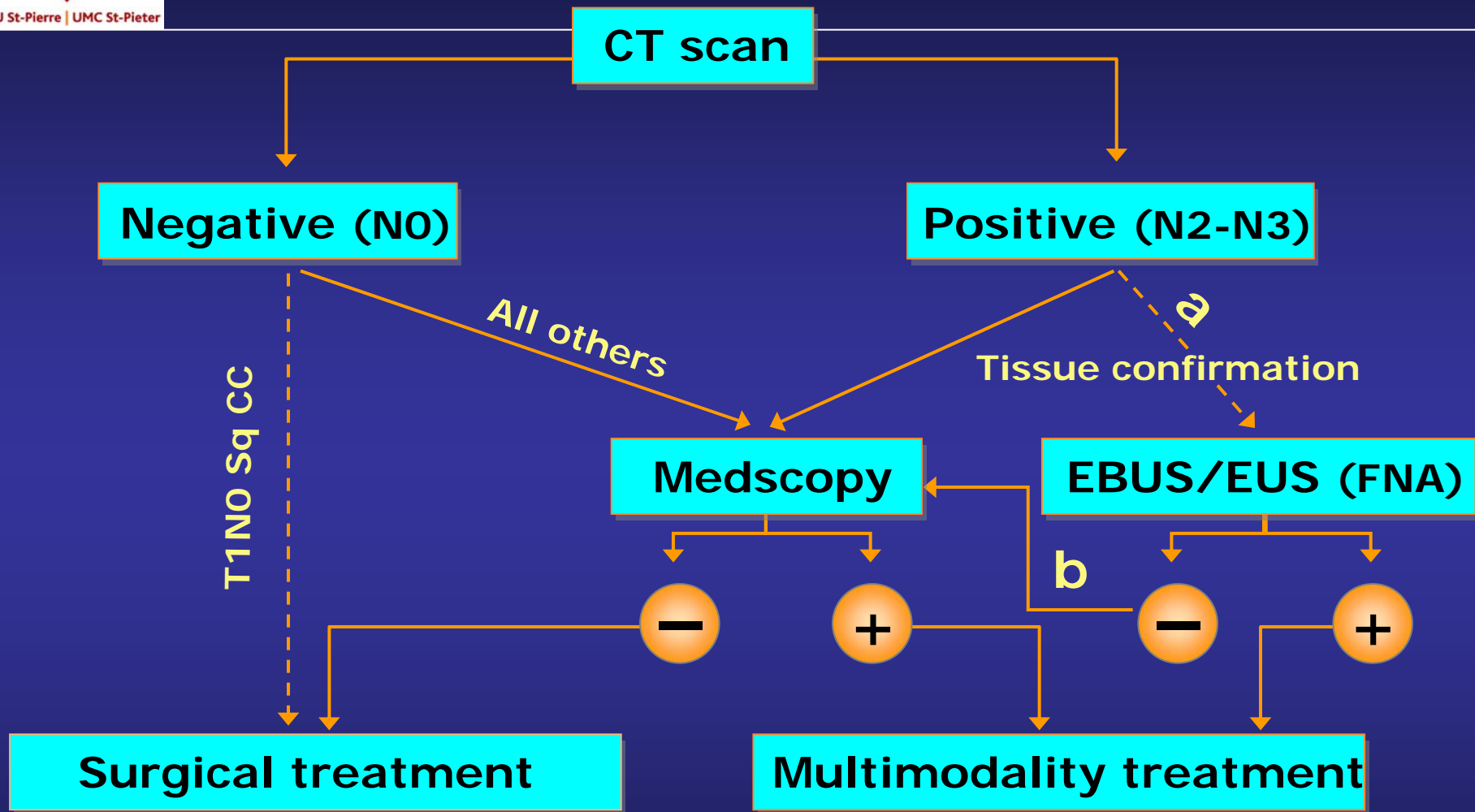
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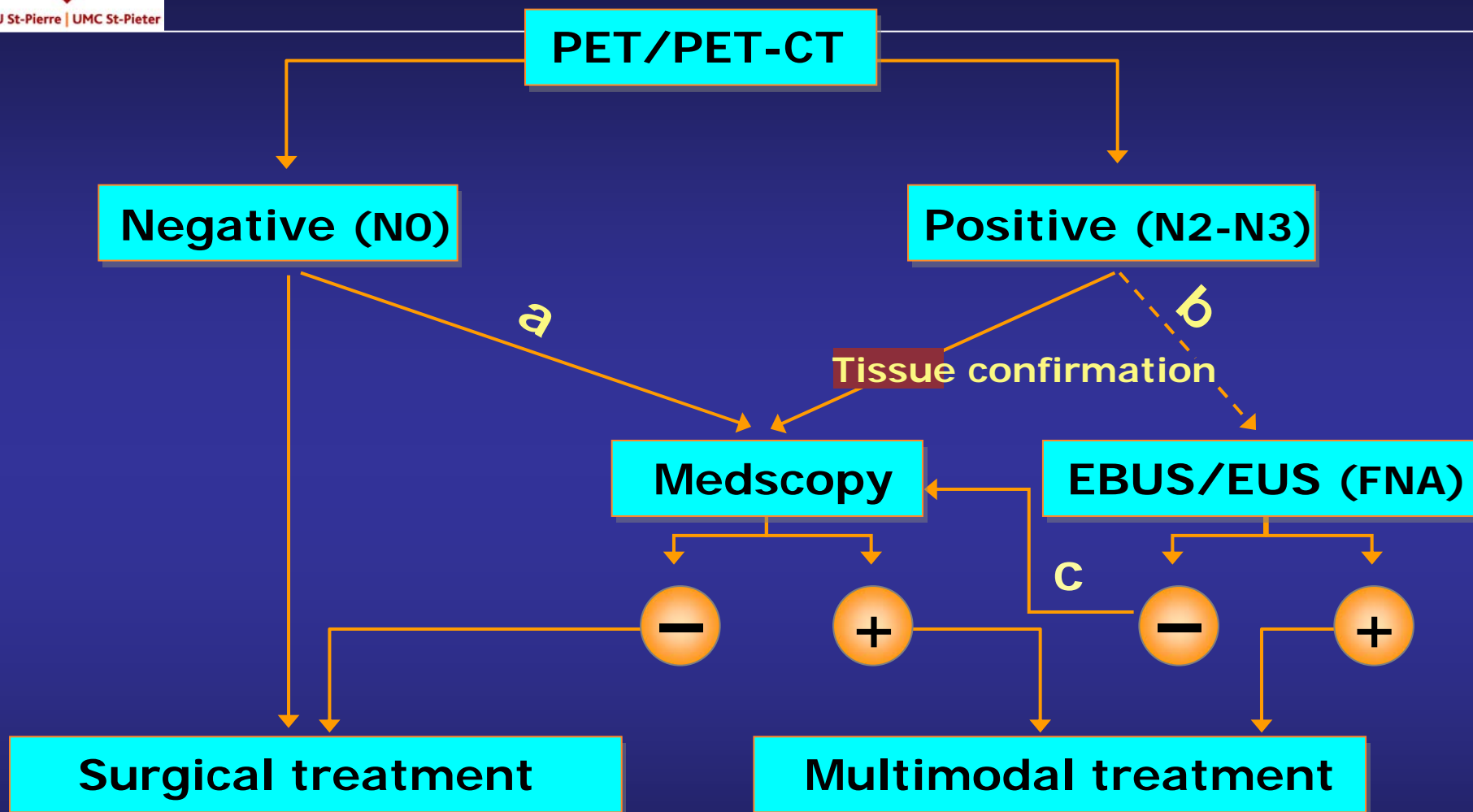
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**EBUS/EUS** : minimally invasive procedure (a) but  
lower negative predictive value than mediastinoscopy (b)





a : PET N1 +; central tumors; low tumoral FDG uptake; LN size  $\geq 1.6$  cm

EBUS/EUS : minimally invasive procedure (b) but lower negative predictive value than Medscopy (c)



# Staging : Particular situations

- **Extensive infiltration of the mediastinum**
  - Radiographic assessment only (grade 2C ACCP 2007)
  - Invasive procedure sometimes required for diagnosis (blinded TBNA during the first bronchoscopy)
- **PET N1, Central tumor, Tumor with low SUV and with normal PET mediastinum**
  - Invasive staging required
  - EBUS-EUS not the first choice
    - Low prevalence of N2 and low NPV



# Radiographic groups with respect to intrathoracic radiographic characteristics

Group	Description	Definition
A	Mediastinal infiltration	Tumor mass within the mediastinum; LN cannot be distinguished or measured
B	Enlarged discrete mediastinal LN	LN $\geq$ 1 cm (short axis on transversal CT)
C	Clinical stage II or central stage I	Normal mediastinal LN (<1 cm) but enlarged N1 nodes or central tumor
D	Peripheral clinical stage I tumor	Normal mediastinal and N1 nodes and peripheral tumor



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# Impact on therapeutical strategy

- Prevent ~ 60-70 % of scheduled mediastinoscopies
- N upstaging, in comparison with mediastinoscopy alone
  - EUS + mediastinoscopy improves staging and reduces the number of futile thoracotomies

*Annema et al. JAMA 2005;294:931/Larsen SS et al. Lung Cancer 2005;49:377*

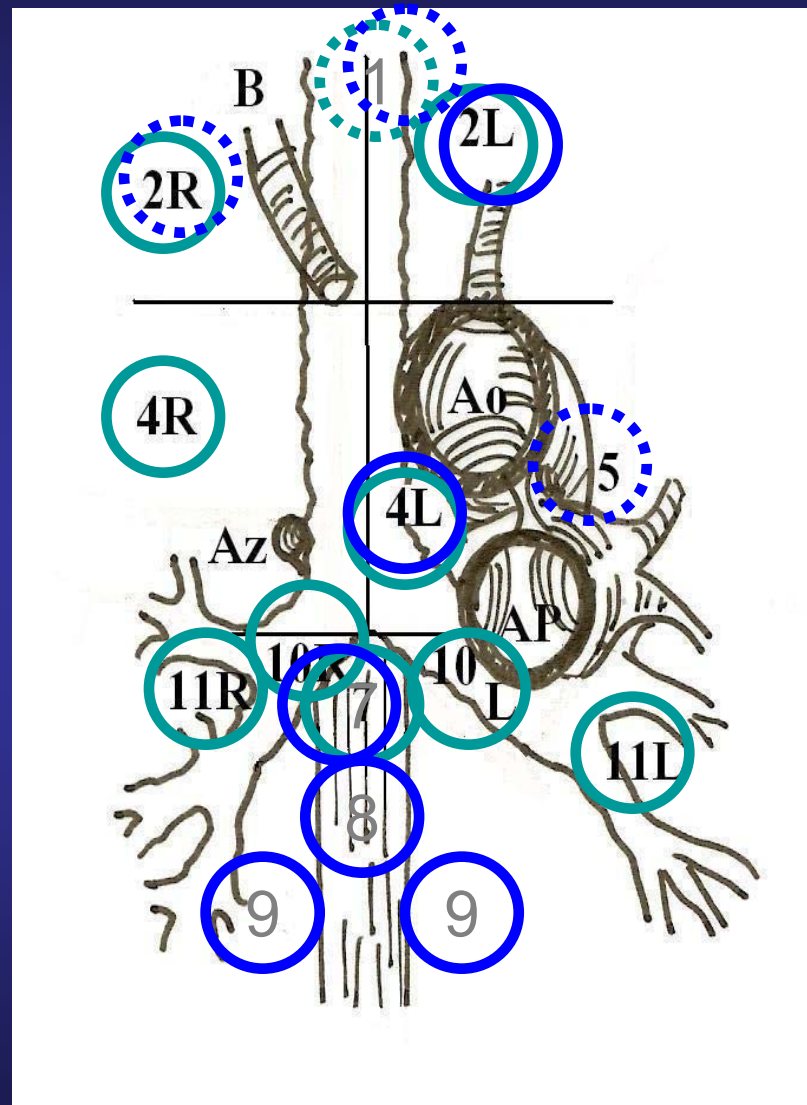
**–Combined EBUS + EUS equal to or superior to mediastinoscopy ?**

*Herth et al. Am J Respir Crit Care Med 2005;171:1164/Vilman et al. Endoscopy 2005;37:833/ Wallace et al. JAMA 2008;299:540*

***Waiting for the results of the ASTER STUDY : randomized clinical trial comparing complete endoscopic ultrasound staging with surgical staging (current standard of care)***



# EBUS-EUS complementarity





# Staging/diagnosis of SCLC

- Three belgian centers 2007-2009
- 94 SCLC diagnosed using EBUS
  - Preceding non-diagnostic standard bronchoscopy
  - 37 (39%) peripheral tumors and 20 (21%) cases without primary tumours (cTX)
  - TX-4 N0-3 M1 : 35 (37%)
  - TX-4 N0-1 M0 : 8 (9%)
  - FDG-PET before diagnosis : 58 (62%)



# Evaluation after NSCLC induction treatment

- Only downstaged patients seem to benefit from multimodality treatment including surgery
- Role of linear EBUS/EUS for restaging?





# Surgical restaging

	yc-med	Remediastinoscopy				VATS
	Lardinois 2003	Mateu-Navarro 2000	Van Schil 2003	Stamatis 2003	De Leyn 2006	Jaklitsch 2005
Sens	0.81	0.7	0.71	0.78	0.29	0.75
Acc	0.91	0.8	0.84	0.78	0.60	-
NPV	-	0.58	0.75	0.95	0.52	0.76
n	24	24	32	155	30	70



# EUS-FNA in mediastinal restaging (initial N2)

Ref.	Nb of patients	EUS-FNA diagnostic value				
		PPV	NPV	Sensitivity	Specificity	Accuracy
<b>Annema 2003</b>	<b>19 PR 14 SD 5</b>	<b>100%</b>	<b>67%</b>	<b>75%</b>	<b>100%</b>	<b>83%</b>
<b>Varadarajulu 2006</b>	<b>14</b>	<b>100%</b>	<b>86%</b>	<b>86%</b>	<b>100%</b>	<b>86%</b>



# EBUS-TBNA in mediastinal restaging (tissue-proven IIIA-N2)

Number	Sensitivity	Specificity	Negative predictive value	Accuracy
124	76% (89/117)	100%	20% (7/35)	77%

**CT restaging : 66 PR; 58 SD**

*Herth F et al. J Clin Oncol 2008 Jun 2 (Epub ahead of print)*



# Initial and post-induction invasive mediastinal staging

## Initial

## Post-induction

## Limitations

Mediastinoscopy

Remediastinoscopy

Mediastinoscopy

EBUS/EUS

EBUS/EUS

EBUS/EUS

EBUS/EUS

Mediastinoscopy

Remediastinoscopy  
technically difficult;  
Accuracy decreased

False negative  
EBUS/EUS  
incomplete  
staging by EBUS/EUS

False negative  
EBUS/EUS  
incomplete  
staging by EBUS/EUS

False negative  
EBUS/EUS



# General conclusions : invasive mediastinal staging of NSCLC

- **Mediastinoscopy** is the gold standard
- **Initial staging**
  - EBUS and EUS are safe and accurate and will reduce the need for mediastinoscopy as well as cost
    - Indications : enlarged LN and/or FDG-PET positive LN
  - Combined EBUS and EUS may be a superior approach
- **Restaging** : the best combination (staging-restaging) needs to be assessed