Hôpitaux Universitaires de Genève

PLEVRE

« QUOI de neuf »

Dr. Igor WIDIKKER

Rencontres Genevoises de Pneumologie (mars 2011)

INTRODUCTION

- Stratégie de recherche pour les articles:

- Entre 2009 et 2010

- Thorax, Chest, AJRCCM, ERJ et Medline

- Mots-clés: pleura, pleural disease, pleural TB, mesothelioma, ultrasound, pleural effusion

INTRODUCTION-PLAN

- **Epanchement & TBC:** *2 études*
- **Mésothéliome:** *2 études*
- **Epanchement malin:** *1 étude*
- **Technique:** *2 études*

EPANCHEMENT TBC

- 1) Peut-on diagnostiquer la pleurésie TBC avec des IGRAs?

Eur Respir J 2009; 34: 1118–1126
DOI: 10.1183/09031936.00005309
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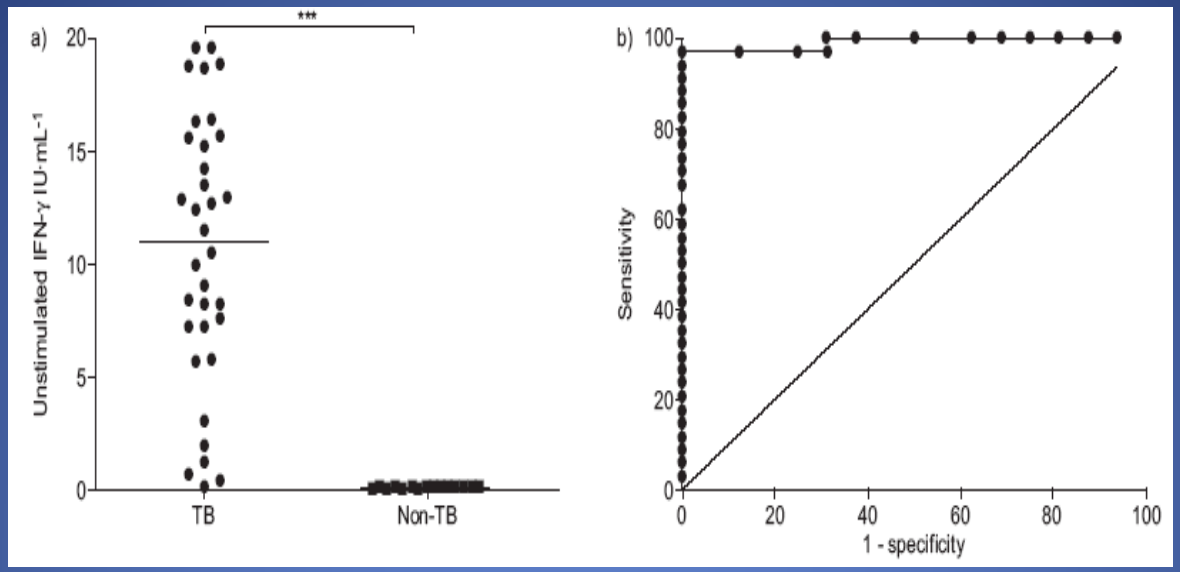
Utility of quantitative T-cell responses *versus* unstimulated interferon-γ for the diagnosis of pleural tuberculosis

K. Dheda*,#,¶, R.N. van Zyl-Smit*, L.A. Sechi+, M. Badri*, R. Meldau*, S. Meldau*, G. Symons*, P.L. Semple*, A. Maredza*, R. Dawson*, H. Wainwright§, A. Whitelaw/, Y. Vallie*, P. Raubenheimer*, E.D. Bateman* and A. Zumla¶

- Setting: Afrique du Sud
- Méthode: étude prospective sur 12 mois, 74 patients (48 TBC définitive, 7 TBC probable, 19 non-TBC), dosage IGRAs et INF-γ dans le liquide pleural
- Gold-standard: biopsie pleurale et/ou culture + pour M. tuberculosis

INF-γ pleural



IGRAs pleuraux

	Sensibilité	Spécificité
Liquide pleural		
T-SPOT.®TB	80% (65%–90%)	65% (41%–83%)
QFT-TB-GIT	51% (36%–67%)	94% (72%–94%)

Clinical Diagnostic Utility of IP-10 and LAM Antigen Levels for the Diagnosis of Tuberculous Pleural Effusions in a High Burden Setting

PLoS one March 11, 2009

Keertan Dheda[1,2,3¤*], Richard N. Van-Zyl Smit[1], Leonardo A. Sechi[4], Motasim Badri[1], Richard Meldau[1], Gregory Symons[1], Hoosein Khalfey[1], Igshaan Carr[1], Alice Maredza[1], Rodney Dawson[1], Helen Wainright[1], Andrew Whitelaw[5,6], Eric D. Bateman[1], Alimuddin Zumla[3]

1 Lung Infection and Immunity Unit & CTBRI, UCT Lung Institute & Division of Pulmonology, Department of Medicine, University of Cape Town, Cape Town, South Africa, 2 Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa, 3 Centre for Infectious Diseases and International Health, University College Medical School, London, United Kingdom, 4 Department of Biomedical Sciences, University of Sassari, Sardinia, Italy, 5 National Health Laboratory Service, Cape Town, South Africa, 6 Division of Medical Microbiology, Department of Clinical Laboratory Sciences, University of Cape Town, Cape Town, South Africa

- Même setting et méthode que l'étude précédente

- Dosage dans le liquide pleural: IP-10 (protéine INF-γ inductible), ADA (adénosine déaminase) et Ag LAM (lipoarabinomannan)

ADA *versus* IP-10

Table 1. Performance outcomes of ADA, microbiological investigations, a nucleic-acid-amplification-test [NAAT] and unstimulated IFN-γ levels for the diagnosis of TB pleural effusion in 74 TB suspects using the *definite and non-TB* groups.

	Cut-point	Sens %	Spec %	PPV %	NPV %	Accuracy	AUC
Maximum clinical score	n/a	54 (40; 67)	89 (68;97)	92 (77; 98)	43 (29;59)	64 (52;74)	n/a
Protein	>30 g/l**	94 (83;98)	12 (3; 34)	75 (62; 84)	40 (12; 77)	72 (60; 81)	0.72
	>60 g/l***	46 (33; 60)	94 (78; 99)	94 (79; 99)	39 (26; 54)	59 (47; 70)	
ADA	>30 iu/l**	96 (86; 99)	69 (44; 86)	90 (78; 96)	85 (58; 96)	89 (78; 94)	0.93
	>47 iu/l***	91 (80; 98)	94 (72; 99)	98 (85; 99)	79 (57; 92)	92 (82; 97)	
	>13 iu/l#	100 (92;100)	38 (19;62)	82 (70;90)	100 (61;100)	84 (73;91)	
NAAT	30 000 RLU	6 (2;18)	93 (69.99)	67 (9;91)	28 (17;42)	29 (18;42)	0.50
IP-10	28170 pg/ml***	80 (64; 91)	82 (57; 97)	91 (78;97)	64 (43;80)	81 (69;89)	0.82
IP-10	4035 pg/ml#	100 (91;100)	53 (31;74)	83 (70;91)	100 (71;100)	86 (75;93)	0.77

RÉSUMÉ

- **IGRAs:**
  - T-SPOT.TB: Se 80% et Sp 65%, VPP 83%
  - QFT-TB-GIT: Se 51% et Sp 94%, VPP 95%

- **INF-γ:**
  - Se 97% et Sp 100%, VPP 100%

- **IP-10:**
  - Se 100% et Sp 53%
  - VPN 100% (limite à 4035 pg/ml)

- **ADA:**
  - Se 96% et Sp 69%
  - VPN 85% (limite à 30 iu/l)

CONCLUSION EPANCHEMENT PLEURAL TBC

- INF- γ:
  - Se/Sp est excellente
  - pas disponible aux HUG ou en ville

- IGRAs pleuraux (Quantiféron):
  - Sp 94% → test d'avenir ?
  - pas disponible aux HUG ou en ville

- ADA:
  - test de routine, peu coûteux

L'amiante tue chaque année au moins 100 personnes en Suisse

SANTÉ | En Suisse, de nombreux travailleurs ont été exposés à l'amiante sur leur lieu de travail.

Tribune de Genève, 2009

MESOTHELIOME

- 2) Quelle est la place pour la mésothéline pleurale dans le diagnostic de l'épanchement pleural suspect de malignité?

Clinical Impact and Reliability of Pleural Fluid Mesothelin in Undiagnosed Pleural Effusions

Am J Respir Crit Care Med Vol 180. pp 437–444, 2009

Helen E. Davies[1], Ross S. Sadler[2], Silvia Bielsa[3], Nicholas A. Maskell[4], Najib M. Rahman[1], Robert J. O. Davies[1], Berne L. Ferry[2], and Y. C. Gary Lee[1,3]

[1]Oxford Centre for Respiratory Medicine and University of Oxford, Oxford; [2]Department of Clinical Immunology, Churchill Hospital, Oxford; [3]Centre for Respiratory Research, University College London, London; and [4]University of Bristol and Southmead Hospital, Bristol, United Kingdom

- Setting: Grande-Bretagne (Oxford)
- Méthode: étude prospective sur 13 mois, 166 patients investigués pour un épanchement pleural suspect de malignité
- Gold-standard: histo-cytologie avec confirmation immuno-histochimique pour le mésothéliome

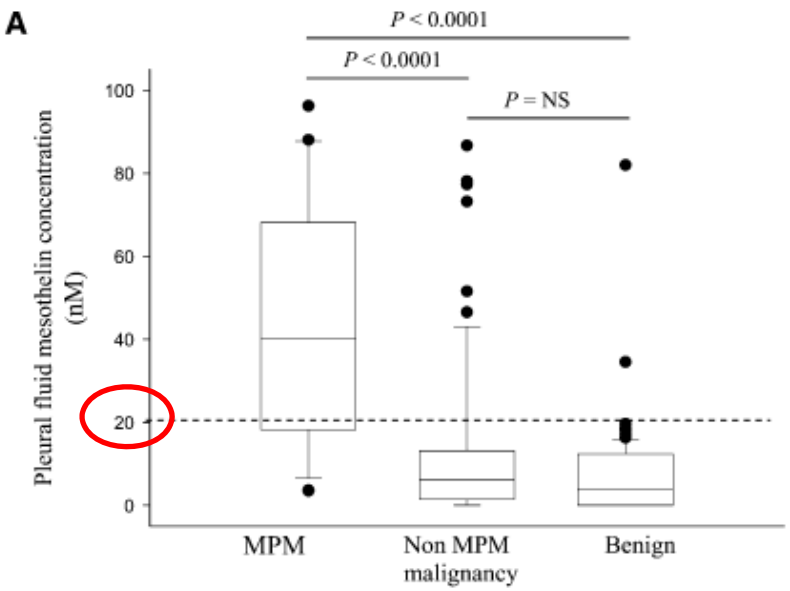
CARACTERISTIQUES

TABLE 1. BASELINE PATIENT CHARACTERISTICS

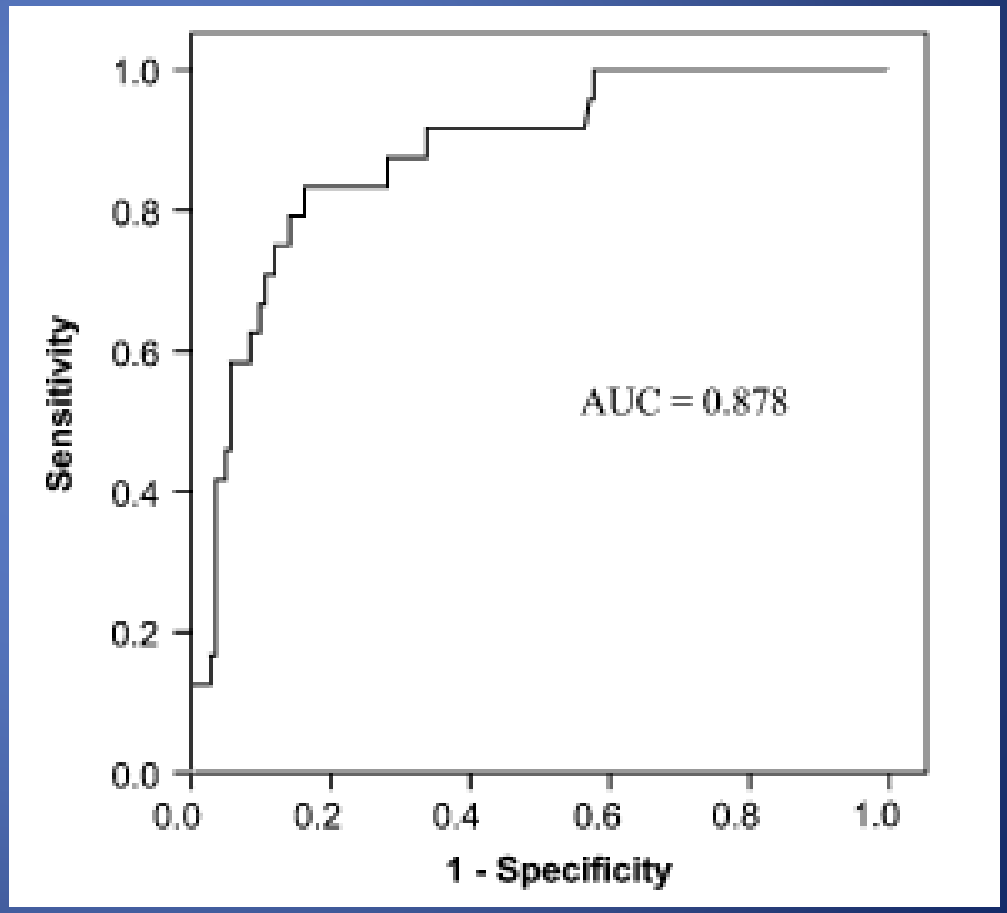
	Mesothelioma (*n* = *24*)	Nonmesothelioma Malignancy (*n* = *67*)	Benign Pleural Effusion (*n* = *75*)
Age, yr (mean ± SD)	72 ± 7.5	68 ± 15.6	71 ± 16.0
Male sex, n (%)	24 (100)	29 (43.3)	59 (78.7)
Pleural fluid, median (IQR25–IQR75)			
Protein, g/L	51 (41–54)	44 (36–48)	40 (30–46)
LDH,* IU/L	263 (160–507)	215 (123–462)	226 (86–1,067)
Glucose, mmol/L	3.4 (2.1–5.2)	5.6 (4.5–7.1)	4.7 (2.1–6.3)
pH	7.31 (7.26–7.37)	7.40 (7.28–7.43)	7.28 (7.07–7.47)

Definition of abbreviations: IQR = interquartile range; IU = international units; LDH = lactate dehydrogenase.
* Normal upper limit of serum LDH in our laboratory: 200 IU/L.

MESOTHELINE DANS DIFFERENTS EPANCHEMENTS



Median pleural fluid mesothelin (nM)	40.3	6.1	3.7
QR25-QR75	18.3 – 68.1	1.5 – 13.2	0.0 – 12.4



MESOTHELINE PLEURALE vs CYTOLOGIE

TABLE 2. COMPARISON OF ADDITIONAL DIAGNOSTIC VALUES OF PLEURAL FLUID CYTOLOGY AND MESOTHELIN CONCENTRATION FOR MESOTHELIOMA AND ALL MALIGNANCIES

	Sensitivity	Specificity	PPV	NPV
Mesothelioma				
Cytology positive	34	100	100	82
Mesothelin positive*	71	90	53	95
Either cytology or mesothelin positive	74	71	31	94
Both cytology and mesothelin positive	35	92	42	89
All malignancies				
Cytology positive	57	100	100	66
Mesothelin positive	33	97	95	55
Either cytology or mesothelin positive	67	100	100	72
Both cytology and mesothelin positive	23	100	100	53

MESOTHELINE PLEURALE *versus* CYTOLOGIE

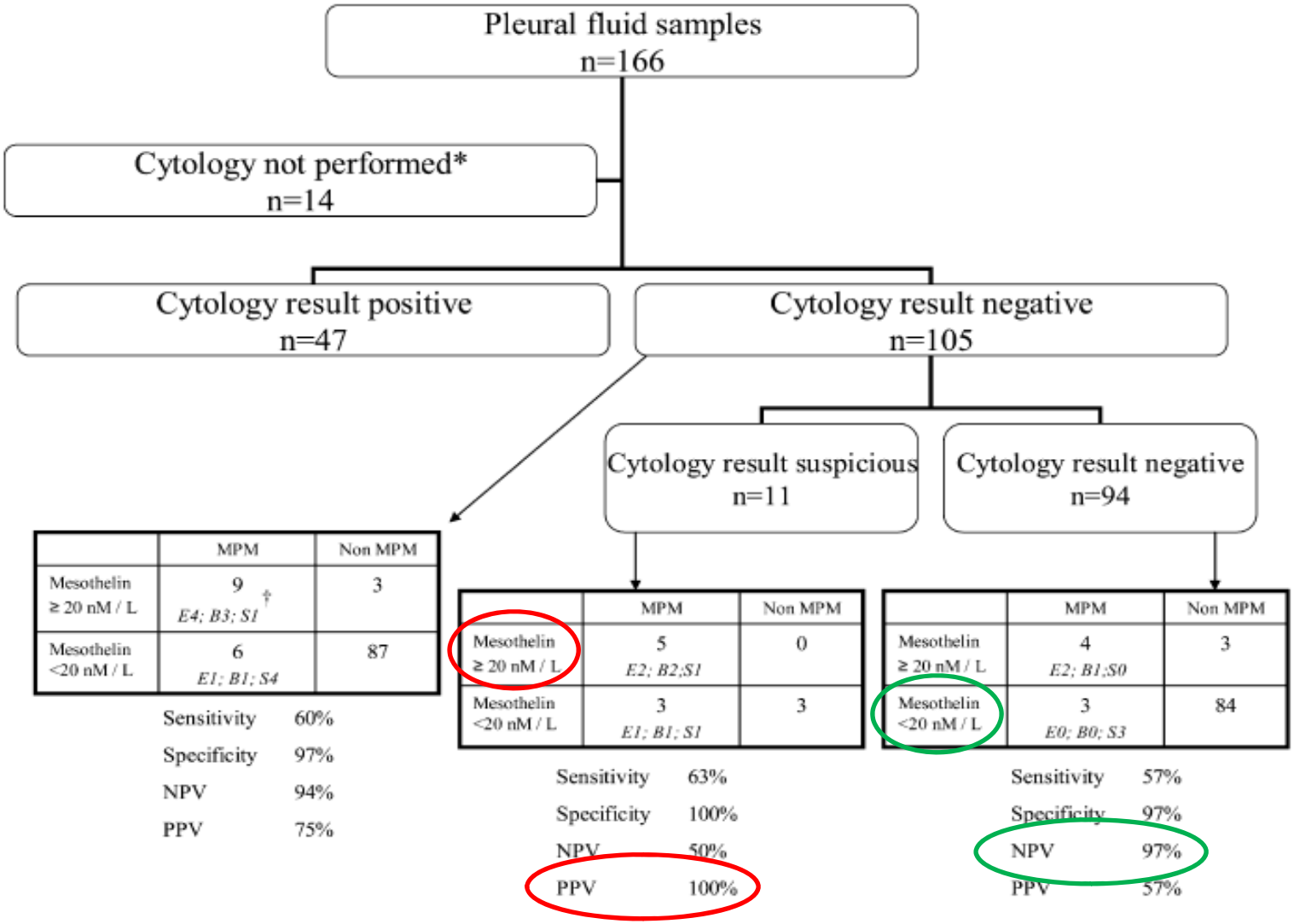
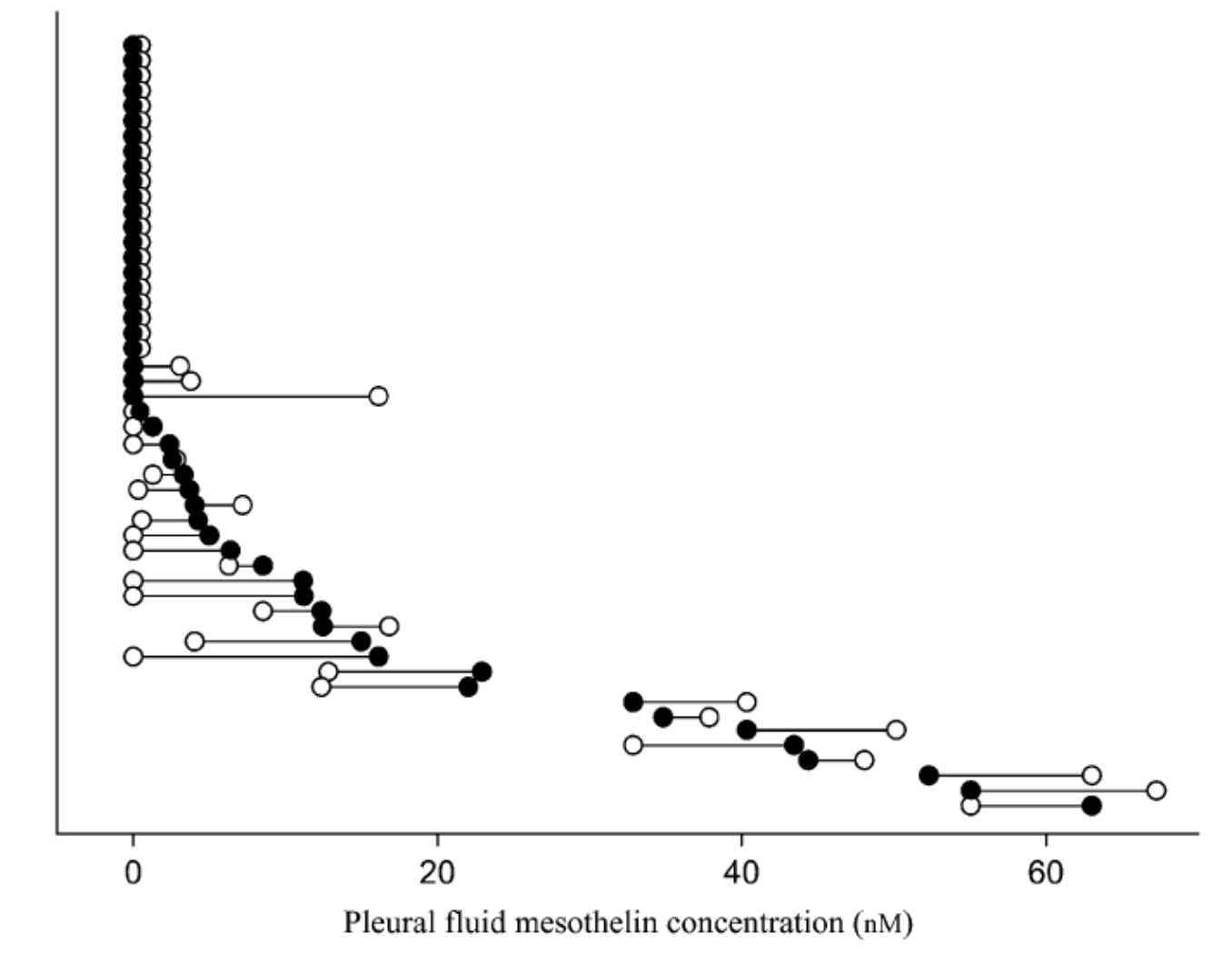


Figure 2. Flow diagram of pleural fluid and mesothelin results. *Cytology not performed, underlying malignancy clinically unlikely; †E = epithelioid mesothelioma; B = biphasic; S = sarcomatoid; the remaining cases were cytologically proven (subtype not defined). MPM = malignant pleural mesothelioma; NPV = negative predictive value; PPV = positive predictive value.

VARIABILITE DES DOSAGES DE LA MESOTHELINE PLEURALE



CONCLUSION

- **Mésothéliome:**

  - Mésothéline pleurale: Se 71% Sp 90%
  - Cytologie: Se 34% Sp 100%

- Si la cytologie est:

  a) **suspecte** → mésothéline (>20nM): VPP 100%

  b) **négative** → mésothéline (<20nM): VPN 97%

- Dosage de la mésothéline pleurale est:

  a) **reproductible**

  b) **pas affectée** par un processus inflammatoire (pleurodèse ou bactérie)

MESOTHELIOME

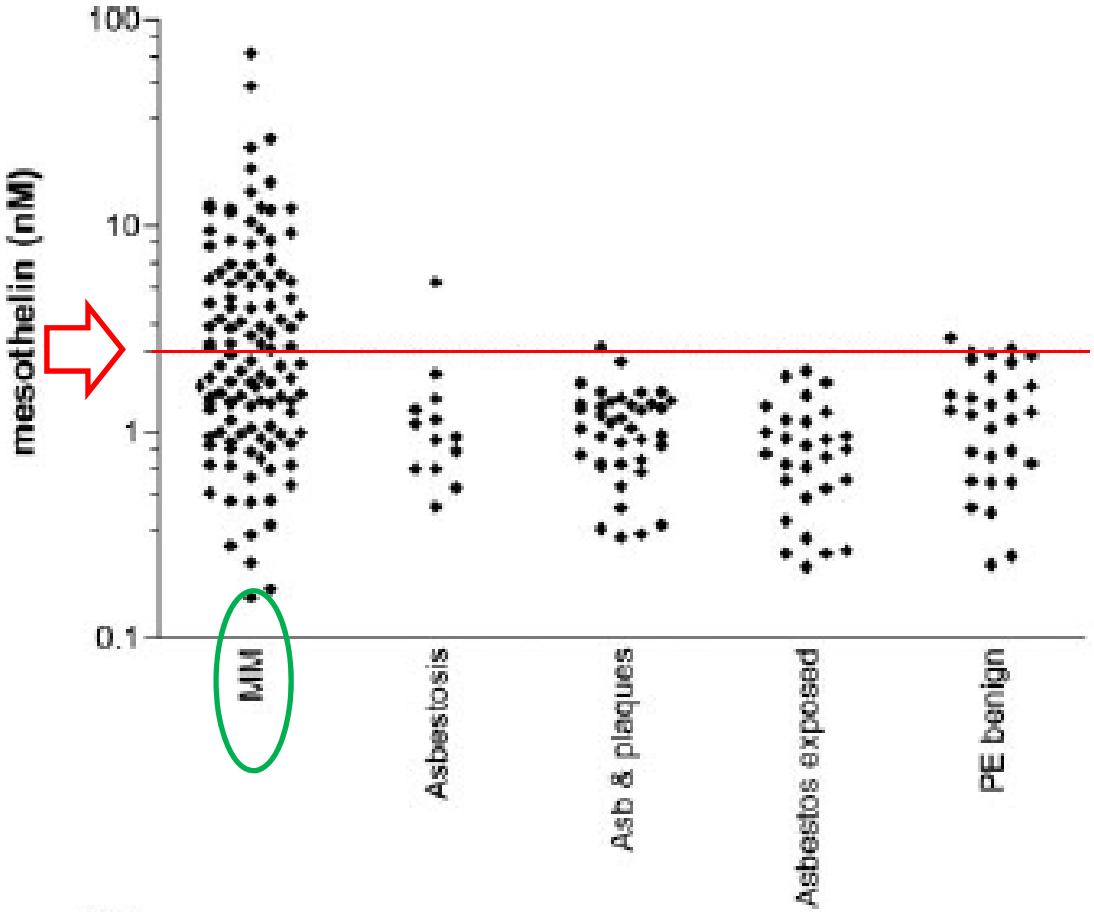
- 3) Faut-il screener les personnes exposées à l’amiante? (rôle de la mésothéline sérique)

CHEST Original Research
NEOPLASTIC DISEASES

Combined CA125 and Mesothelin Levels for the Diagnosis of Malignant Mesothelioma*

(CHEST 2007; 132:1239–1246)

Jenette Creaney, PhD; Ivonne van Bruggen, BSc; Michelle Hof, BSc; Amanda Segal, MBBS; Arthur W. Musk, MBBS, MD, FCCP; Nick de Klerk, PhD; Nora Horick, MSc; Steven J. Skates, PhD; and Bruce W. S. Robinson, MBBS, MD



Soluble Mesothelin-related Protein in an Asbestos-exposed Population

The Dust Diseases Board Cohort Study

Am J Respir Crit Care Med Vol 178. pp 832–837, 2008

Eun-Kee Park[1], Alessandra Sandrini[1,2], Deborah H. Yates[1,2], Jenette Creaney[3], Bruce W. Robinson[3], Paul S. Thomas[4], and Anthony R. Johnson[1]

[1]Research and Education Unit, Dust Diseases Board, Sydney, Australia; [2]Department of Thoracic Medicine, St. Vincent's Hospital, Sydney, Australia; [3]National Research Center for Asbestos Related Disease, Western Australian Institute of Medical Research, University of Western Australia, and Sir Charles Gairdner Hospital, Nedlands, Perth, Australia; and [4]Faculty of Medicine, School of Medical Sciences, University of New South Wales, Sydney, Australia

- Setting: Australie (Sydney), caisse de compensation
- Méthode: étude de cohorte, prospective sur 12 mois, personnes saines exposées à l'amiante, dosage de la mésothéline sérique (si >2.5nM: ad CT thorax puis PET-FDG)
- Gold-standard: absent (pas de patients avec un mésothéliome)

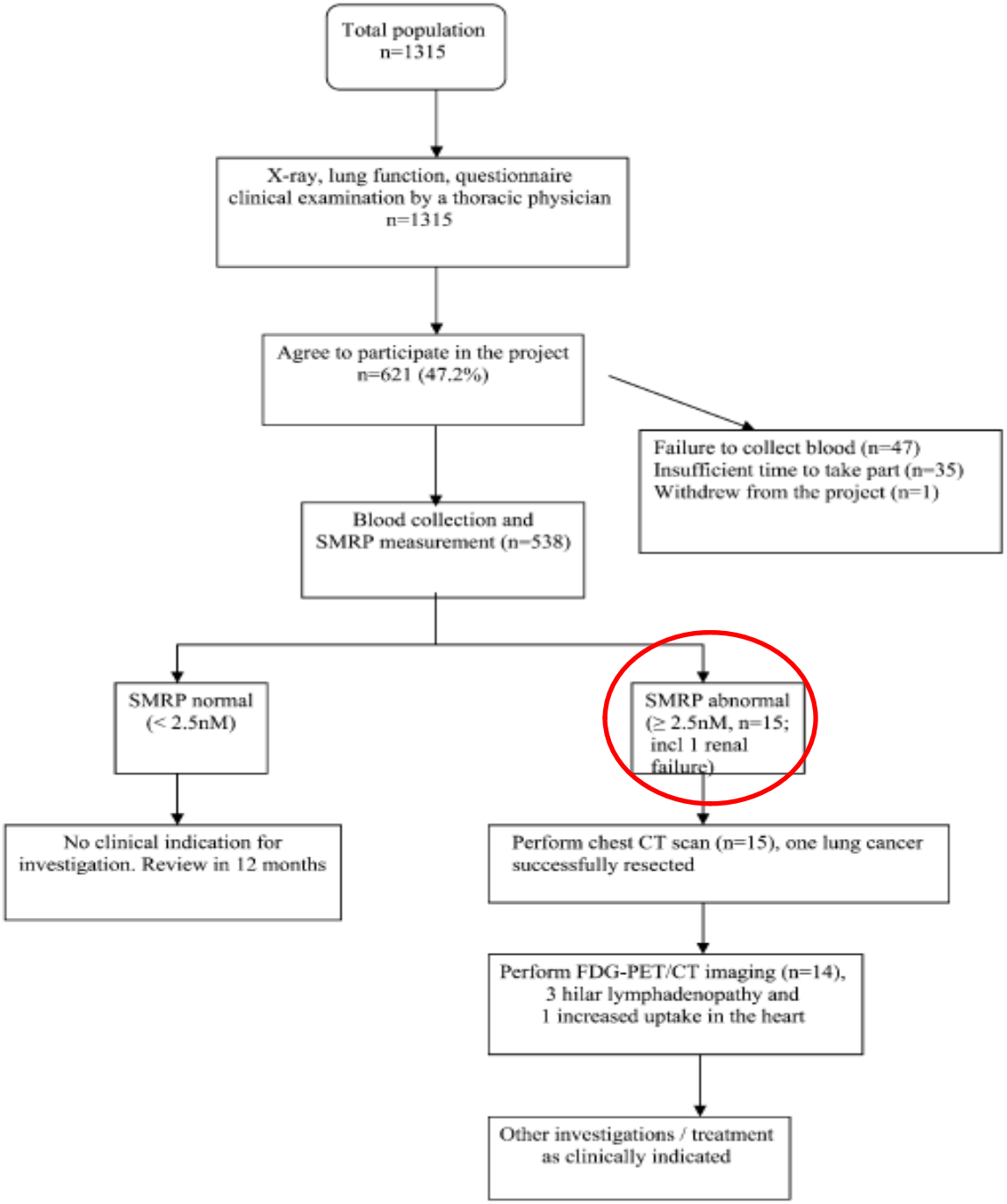


Figure 1. Study flow chart. CT = computed tomography; FDG-PET/CT = ^{18}F-fluorodeoxy-glucose positron emission tomography/computed tomography. SMRP = soluble mesothelin-related protein.

TAUX DE MESOTHELINE SERIQUE CHEZ DES PERSONNES EXPOSEES

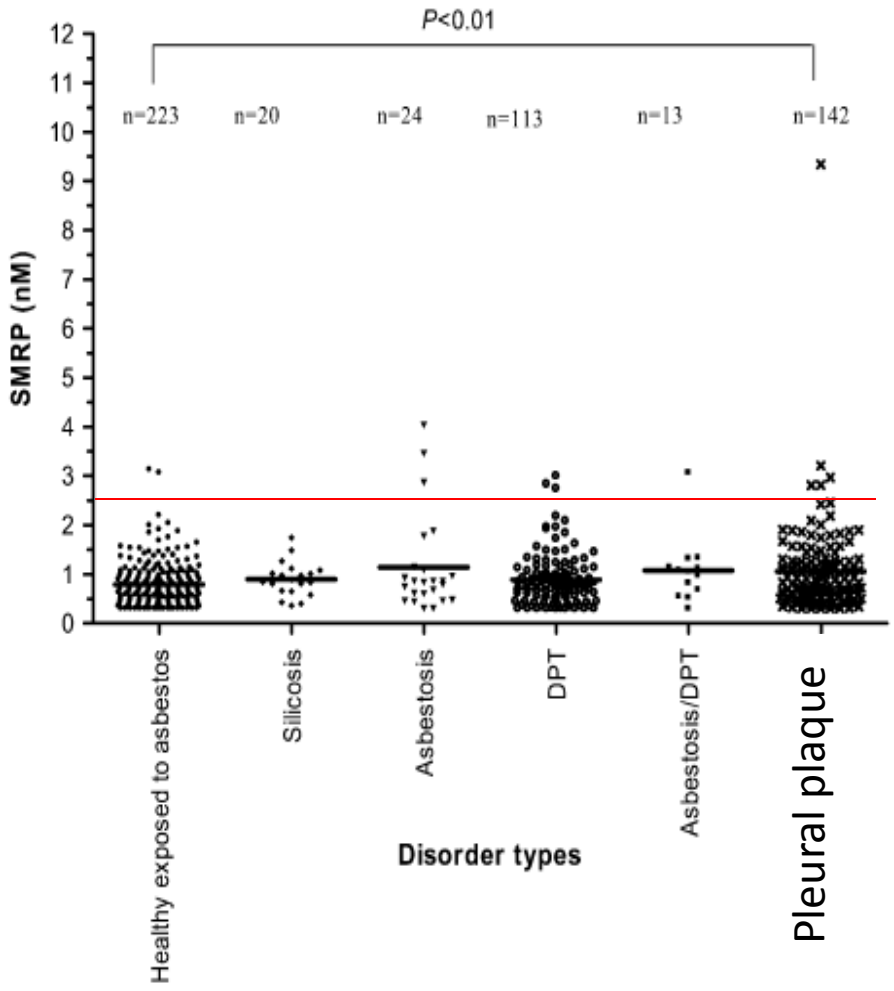


Figure 2. Soluble mesothelin-related protein (SMRP) levels (nM) in (*1*) healthy individual exposed to asbestos, or with (*2*) silicosis, (*3*) asbestosis, (*4*) diffuse pleural thickening (DPT), (*5*) combined asbestosis and DPT, or (*6*) pleural plaques alone (PPs). *Horizontal scale bars* denote mean levels. There were significant differences between the groups (analysis of variance, $P = 0.002$).

CONCLUSION

- **Mésothéline sérique:**

  - pas d’utilité pour screener une population asymptomatique exposée à l’amiante (nombreux faux-positifs)

  - difficulté de juger sa valeur prédictive

EPANCHEMENT PLEURAL MALIN

- 4) Quel est le volume minimum nécessaire au diagnostic de l’épanchement malin?

Prospective Study To Determine the Volume of Pleural Fluid Required To Diagnose Malignancy

CHEST 2010; 137(1):68–73

Jennifer Swiderek, MD; Samer Morcos, MD; Vijayalakshmi Donthireddy, MD; Rajesh Surapaneni, MD; Vicki Jackson-Thompson, BS; Lonni Schultz, PhD; Sudha Kini, MD; Paul Kvale, MD, FCCP

- Setting: Etats-Unis (Michigan)
- Méthode: étude mono-centrique sur 6 ans, 102 patients avec épanchement pleural suspect de malignité, 3 aliquots (10mL, 60mL, 150mL)
- Gold-standard: confirmation histologique ou cytologique de malignité

FROTTIS DIRECT/CYTOCENTRIFUGEUSE

Table 3—*Direct Smear/Cytospin Only Results (n = 107)*

Volume, mL	Sensitivity	Specificity	PPV	NPV
10	48.7% (38/78)	96.6% (28/29)	97.4% (38/39)	41.2% (28/68)
60	62.8% (49/78)	89.7% (26/29)	94.2% (49/52)	47.3% (26/55)
150	69.2% (54/78)	86.2% (25/29)	93.1% (54/58)	51.0% (25/49)
P Values for Pairwise Comparisons				
10 vs 60	.0058	.166	.096	.045
10 vs 150	< .001	.095	.126	.009
60 vs 150	.090	.563	.645	.304

FROTTIS DIRECT/CYTOCENTRIFUGEUSE et CELLBLOCK

Table 4—*Direct Smear/Cytospin and Cell Block Results Combined (n = 71)*

Volume	Sensitivity	Specificity	PPV	NPV
10	75.9% (41/54)	94.1% (16/17)	97.6% (41/42)	55.2% (16/29)
60	79.6% (43/54)	94.1% (16/17)	97.7% (43/44)	59.3% (16/27)
150	87.0% (47/54)	82.3% (14/17)	94.0% (47/50)	66.7% (17/21)
P values for Pairwise Comparisons				
10 vs 60	.090	NA	.483	.478
10 vs 150	.0099	.314	.074	.033
60 vs 150	.181	.314	.060	.117

CONCLUSION

- **Volume minimum = 60 mL**

TECHNIQUE

- 5) Quels sont les facteurs de risque d'un fibrothorax à long terme (12 mois) chez des patients traités pour une pleurésie TBC?

Sonographic septation: a predictor of sequelae of tuberculous pleurisy after treatment

Y-F Lai,[1] M-C Su,[2] H-H Weng,[3] J-T Wu,[1] C-T Chiu[1]

Thorax 2009 64: 806-809

- Setting: Taiwan
- Méthode: étude prospective sur 12 mois, 87 patients avec pleurésie TBC prouvée, échographie pleurale à l'admission et Rx thorax tous les 2 mois
- Outcome: le fibrothorax est défini comme un épaississement pleural >10mm sur Rx thorax

CARACTERISTIQUES

Table 1 Patient characteristics with RPT >10 mm and ⩽10 mm

Characteristics	RPT > 10 mm (n = 20)	RPT ⩽10 mm (n = 67)	p Value
Male gender (%)	90.0	64.2	0.029
Age (years (SD))	61.2 (20.3)	65.1 (17.6)	0.345
Symptoms to treatment, days	11 (7–30)	10 (7–14)	0.620
Smokers (%)	55.0	34.3	0.096
Alcohol abuse (%)	15.0	9.0	0.424
Diabetes mellitus (%)	20.0	20.9	0.931
Pulmonary TB (%)	30.0	23.9	0.581
Initially large amount of pleural effusion (%)	65.0	40.3	0.148
Loculated pleural effusion (%)	20.0	16.4	0.740
Positive pleural biopsy culture (%)	25.0	31.3	0.782
Positive pleural fluid culture (%)	20.0	4.5	0.046
Sputum positive for AFB (%)	25.0	16.4	0.511

AFB, acid-fast bacillus; RPT, residual pleural thickening; TB, tuberculosis.

FACTEURS PREDICTIFS

Table 4 Initial sonographic findings of patients with pure tuberculous pleurisy with RPT >10 mm and ⩽10 mm

Sonographic features	RPT > 10 mm (n = 14)	RPT ⩽10 mm (n = 51)	p Value
Anechoic (%)	7.1	72.5	<0.001
Complex non-septated echoic (%)	21.4	21.6	1.0
Complex septated echoic (%)	71.5	5.9	<0.001

RPT, residual pleural thickening.

FACTEURS PREDICTIFS

Table 5 Odds ratio of developing RPT >10 mm assessed by multivariate logistic regression analysis

Characteristics	Odds ratio (95% CI)	p Value
Pleural fluid positive for AFB	20.9 (2.2 to 198.0)	0.008
Complex septated echoic	145.0 (22.3 to 942.3)	<0.001

CONCLUSION

- **Fibrothorax à 12 mois post-pleurésie TBC:**

  - Incidence: 23% à 1 an

  - Facteurs prédictifs: septas complexes et culture +

  - Septas complexes: VPP 84% et VPN 95%

  - Perte plus importante de la CVF chez des patients avec fibrothorax à 6 et 12 mois

  - Rôle de la fibrinolyse précoce (?)

TECHNIQUE

- 6) L’échographie pleurale est-elle meilleure que la Rx pour la détection des pneumothorax (=PNT)?

Pleural Ultrasound Compared With Chest Radiographic Detection of Pneumothorax Resolution After Drainage

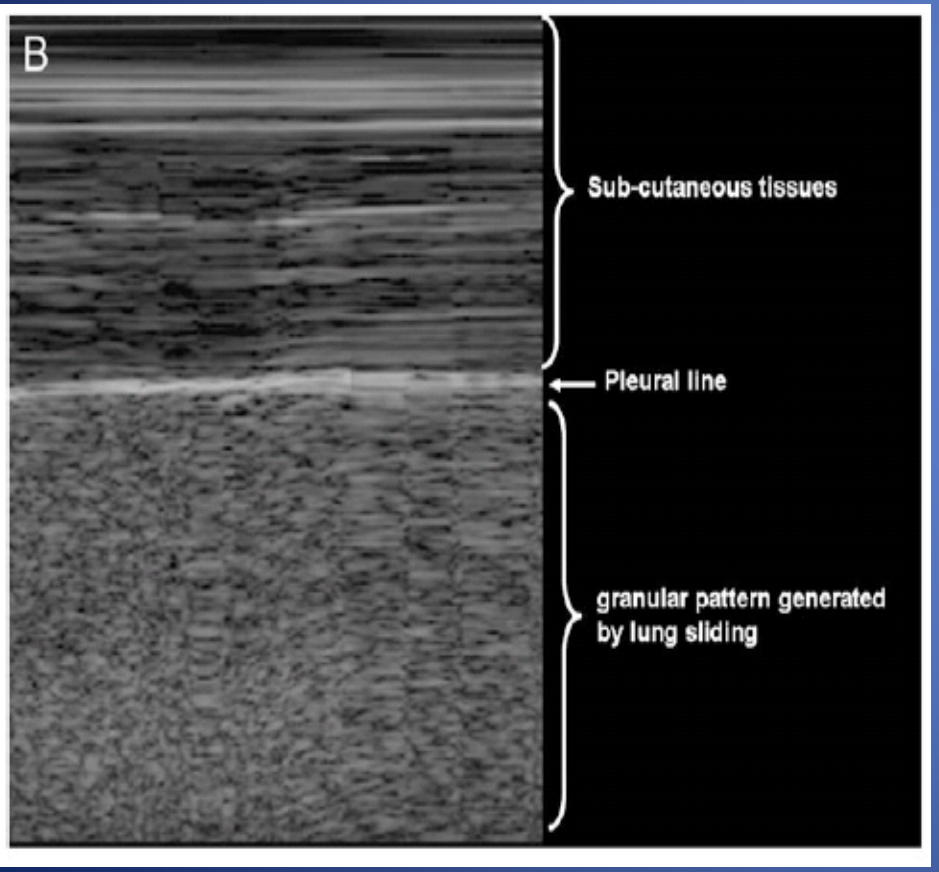
CHEST 2010; 138(3):648–655

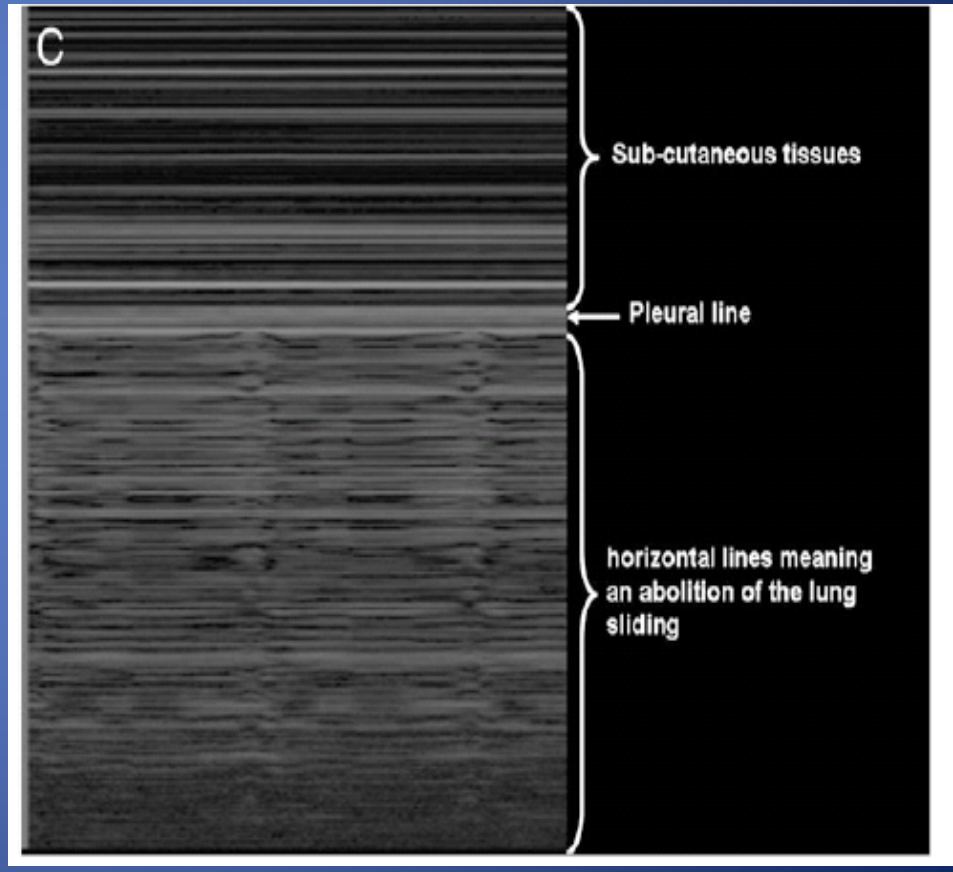
Arnaud Galbois, MD; Hafid Ait-Oufella, MD, PhD; Jean-Luc Baudel, MD; Tomek Kofman, MD; Julie Bottero, MD; Stéphanie Viennot, MD; Clémentine Rabate, MD; Salima Jabbouri, MD; Abdeslam Bouzeman, MD; Bertrand Guidet, MD; Georges Offenstadt, MD; and Eric Maury, MD, PhD

- Setting: France (unité des soins intensifs, Paris)
- Méthode: étude prospective observationnelle, 44 patients avec PNT unilatéral 1aire ou 2aire drainé,

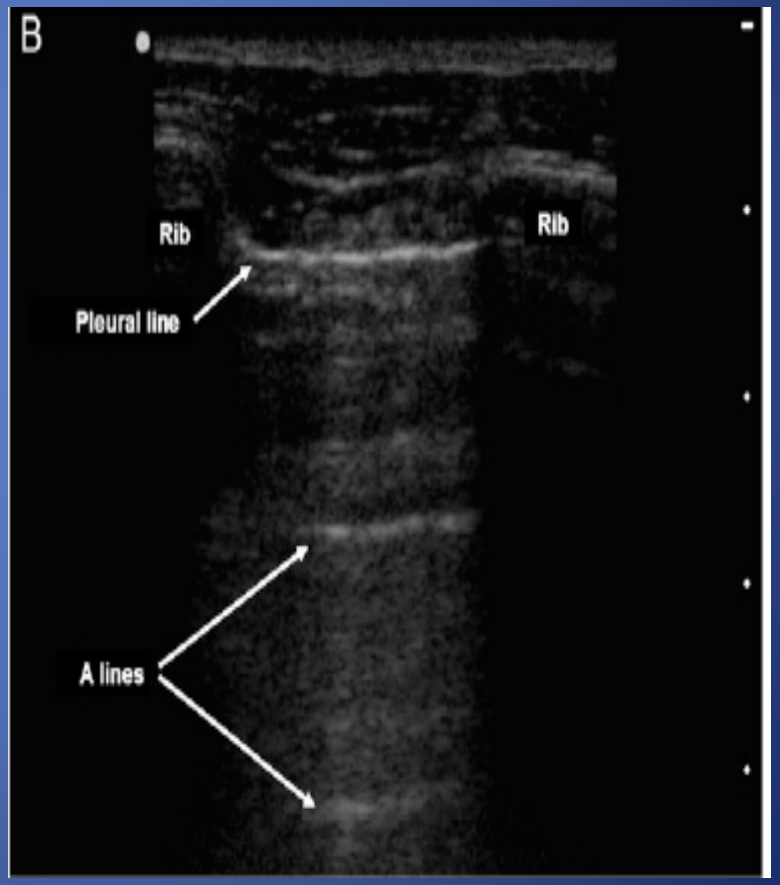
  end-point: détection PNT résiduel, impact thérapeutique, courbe d'apprentissage, temps de réalisation
- Gold-standard: CT thorax ou aspiration d'air

PERTE DE GLISSEMENT PULMONAIRE

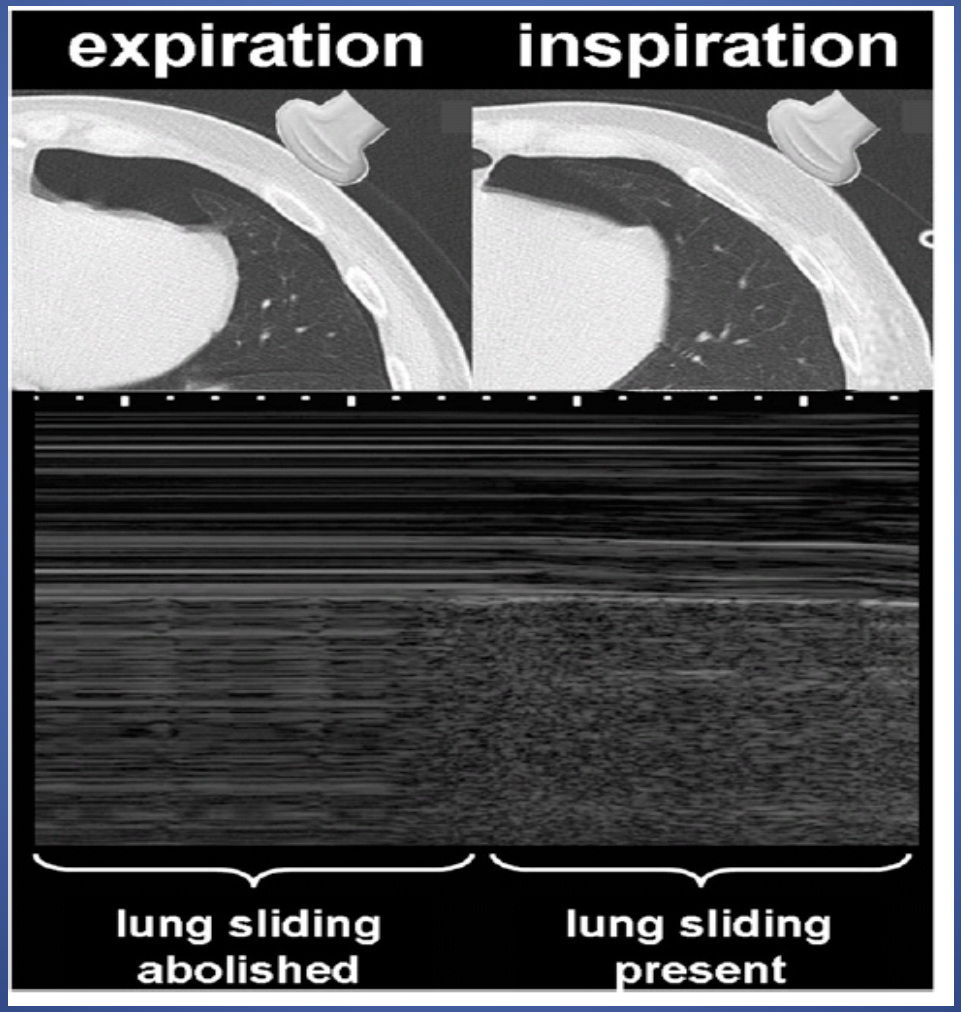


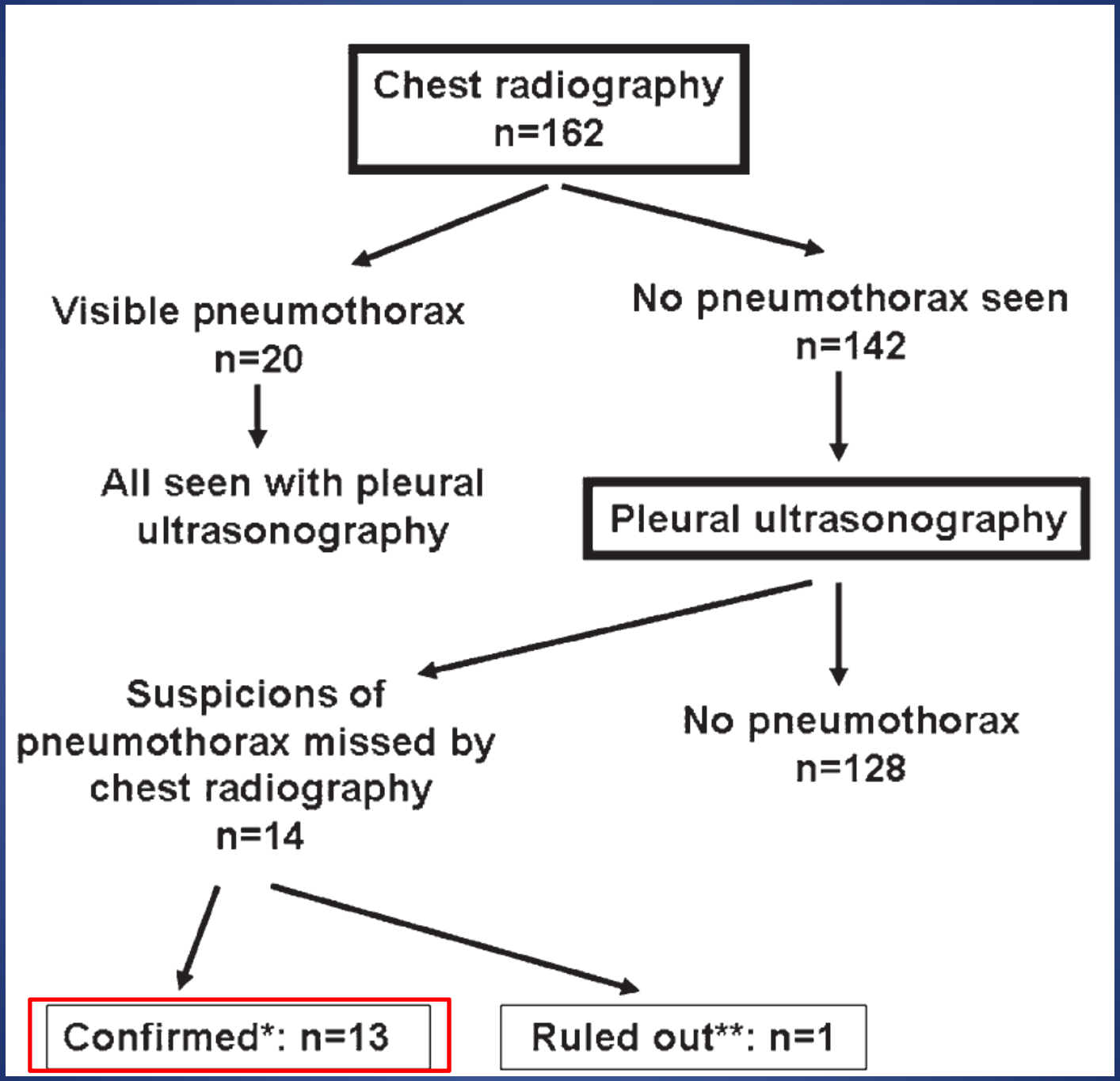


LIGNE A



« POINT PULMONAIRE »




Chest radiography
n=162
Visible pneumothorax
n=20
No pneumothorax seen
n=142
All seen with pleural
ultrasonography
Pleural ultrasonography
Suspicions of
pneumothorax missed by
chest radiography
n=14
No pneumothorax
n=128
Confirmed*: n=13
Ruled out**: n=1

CONCLUSION

- **Echographie pleurale et PNT:**

  - 39% PNT non visualisés à la Rx
  - Obtention plus rapide (35min vs 75min)
  - 2h d'entrainement suffisent

  - **PNT 1aire:** VPP 100%
  - **PNT 2aire:** VPP 90% (Ø « point pulmonaire »)

TAKE HOME MESSAGES

1) Epanchement pleural TBC:

- INF-γ → la meilleure Se/Sp
- IGRAs → Quantiféron meilleure Sp et T-SPOT-TB meilleure Se

2) Mésothéliome:

- Mésothéline pleurale → aide à la cytologie, reproductible, pas affectée par un processus inflammatoire
- Mésothéline sérique → mauvais outil de screening

TAKE HOME MESSAGES

3) Epanchement pleural malin:

- minimum 60 ml pour le diagnostic

4) Echographie pleurale:

- utile dans la détection du PNT
- prédicteur du fibrothorax à long terme post-pleurésie TBC

- **MERCI pour votre ATTENTION**

☺