Facteurs pronostiques du cancer bronchique et leur impact pratique

Prof Thierry Berghmans
Service des Soins Intensifs et Urgences Oncologiques
& Clinique d'Oncologie Thoracique
Institut Jules Bordet
Université Libre de Bruxelles
Belgique

Conflits d'intérêt

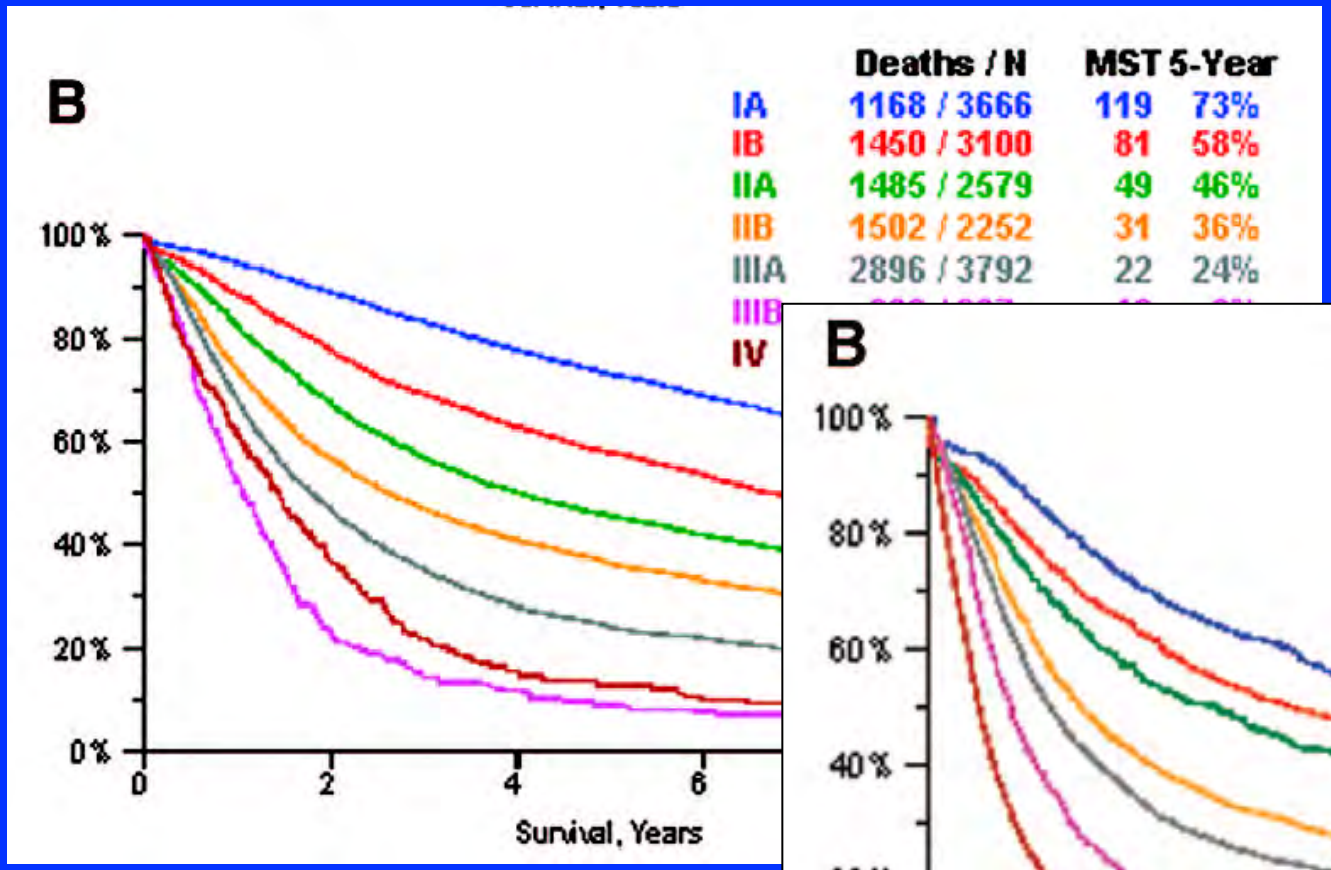
- Aucun conflit d'intérêt en relation avec le sujet traité

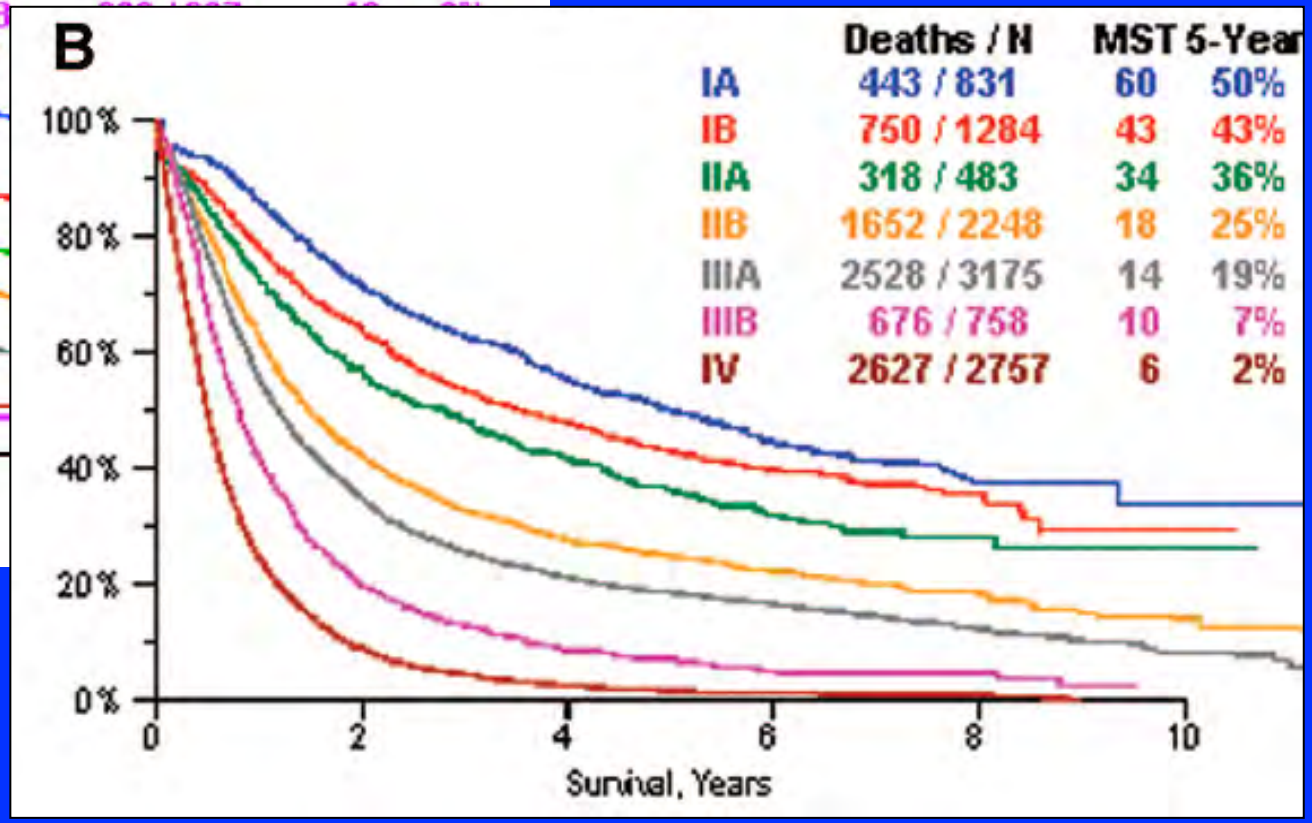
Pourquoi parler de facteurs pronostiques?

Situation clinique

- Un patient de 65 ans, sans antécédent notable, est adressé à votre consultation.
- Vous lui annoncez qu'il est atteint d'un cancer bronchique
- Il signale uniquement une modification de sa toux
- Son état général est impeccable (Karnofsky IP 90)
- *Il vous demande quel est son pronostic*

Survie des CBNPC

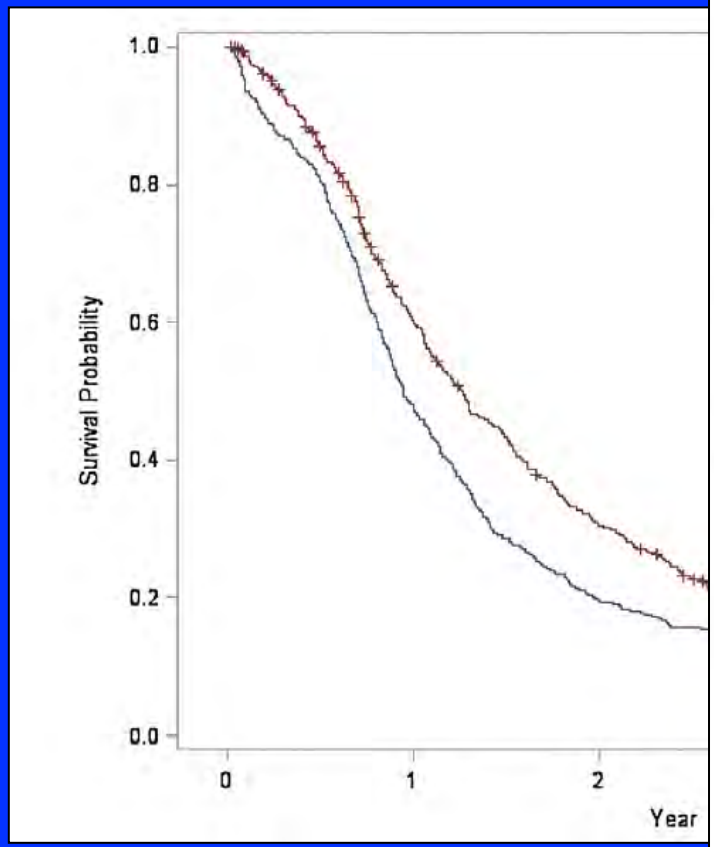


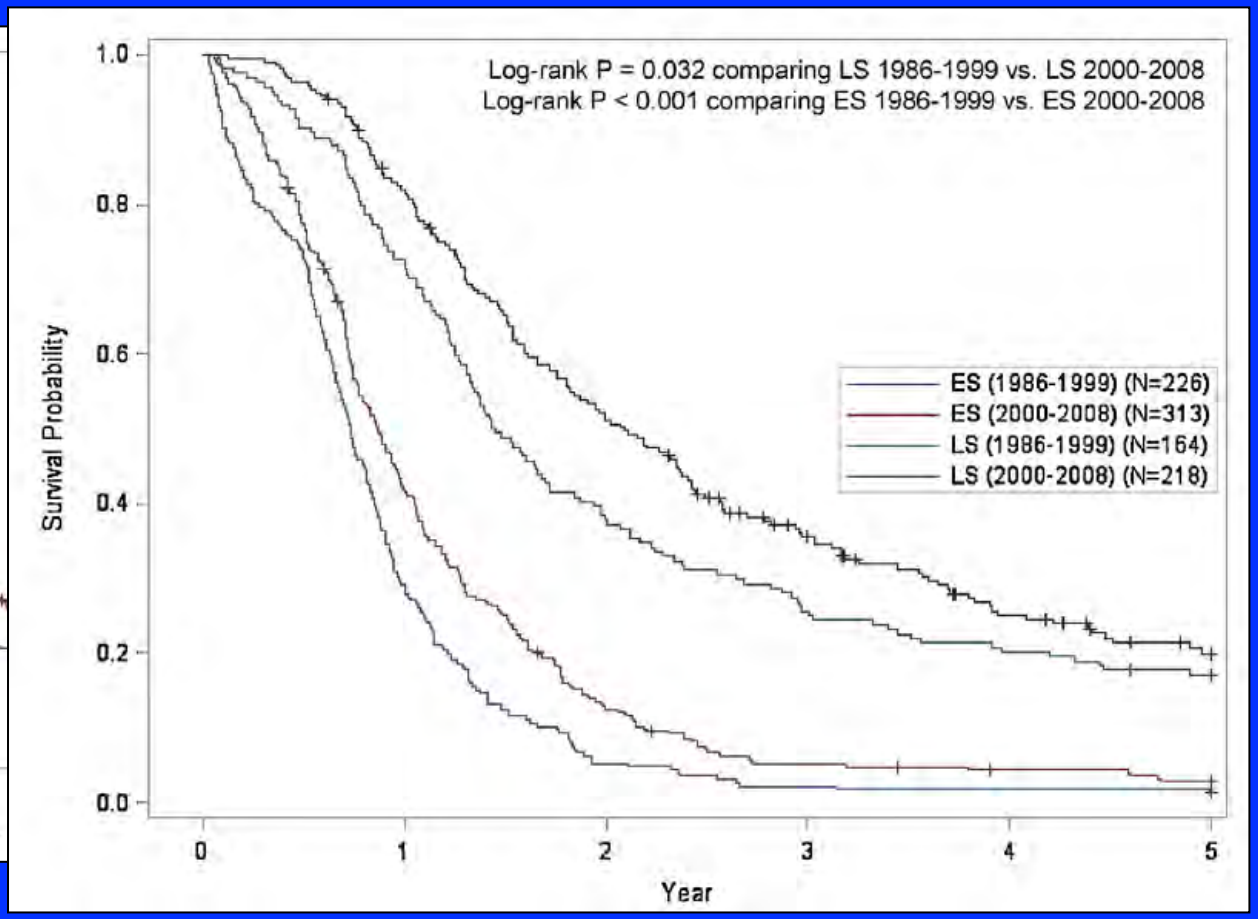


J Thorac Oncol; 2007

Temporal trends from 1986 to 2008 in overall survival of small cell lung cancer patients

Matthew B. Schabath[a,*], Anthony Nguyen[a,d], Patrick Wilson[d], Katelyn R. Sommerer[a], Zachary J. Thompson[b], Alberto A. Chiappori[c]





Qu’est-ce que le pronostic?

Facteur pronostique vs facteur prédictif

- ***Facteur pronostique***
- Facteur corrélé à un critère d'évaluation utilisé pour prédire le futur du patient indépendamment du traitement appliqué

- ***Facteur prédictif***
- Facteur permettant de prédire l'efficacité du traitement proposé

DNA Repair by ERCC1 in Non–Small-Cell Lung Cancer and Cisplatin-Based Adjuvant Chemotherapy

Ken A. Olaussen, Ph.D., Ariane Dunant, M.S., Pierre Fouret, M.D., Ph.D., Elisabeth Brambilla, M.D., Ph.D., Fabrice André, M.D., Ph.D., Vincent Haddad, M.S., Estelle Taranchon, M.S., Martin Filipits, Ph.D., Robert Pirker, M.D., Helmut H. Popper, M.D., Rolf Stahel, M.D., Ph.D., Laure Sabatier, Ph.D., Jean-Pierre Pignon, M.D., Ph.D., Thomas Tursz, M.D., Ph.D., Thierry Le Chevalier, M.D., and Jean-Charles Soria, M.D., Ph.D., for the IALT Bio Investigators*

Table 2. Overall Survival According to Attributed Treatment and ERCC1 Status.

Group	All Patients	Chemotherapy Group	Control Group	Hazard Ratio for Death (95% CI)*	P Value
Patients with ERCC1-negative tumors				0.65 (0.50–0.86)	0.002
Deaths — no./total no. of patients	218/426	105/224	113/202		
Rate of survival at 5 yr — % (95% CI)	44 (38–49)	47 (40–55)	39 (32–47)		
Median survival — mo	48	56	42		
Patients with ERCC1-positive tumors				1.14 (0.84–1.55)	0.40
Deaths — no./total no. of patients	172/335	92/165	80/170		
Rate of survival at 5 yr — % (95% CI)	43 (37–49)	40 (32–49)	46 (37–55)		
Median survival — mo	52	50	55		
All patients				0.84 (0.68–1.03)	
Deaths — no./total no. of patients	390/761	197/389	193/372		
Rate of survival at 5 yr — % (95% CI)	43 (39–47)	44 (39–50)	42 (37–48)		
Median survival — mo	50	53	48		
Hazard ratio for death (95% CI)†	0.88 (0.71–1.10)	1.16 (0.86–1.56)	0.66 (0.49–0.90)	—	—
P value	0.26	0.34	0.009	—	0.009‡

Prédictif

Pronostique

NEJM 2006

Qu'est-ce qu'un facteur pronostique?

- Facteurs « conventionnels »
  - Paramètres cliniques (indice de performance, co-morbidités, extension de la maladie…) ou variables biologiques conventionnelles (LDH, sodium, neutrophiles …)
- Biomarqueurs
  - Marqueurs tumoraux (CEA, Cyfra, CA125…)
  - Variables associées au comportement biologique de la maladie (EGFR …)
  - Signatures biologiques
  - Cellules tumorales circulantes
  - Facteurs métaboliques

Quelle utilité pour un facteur pronostique?

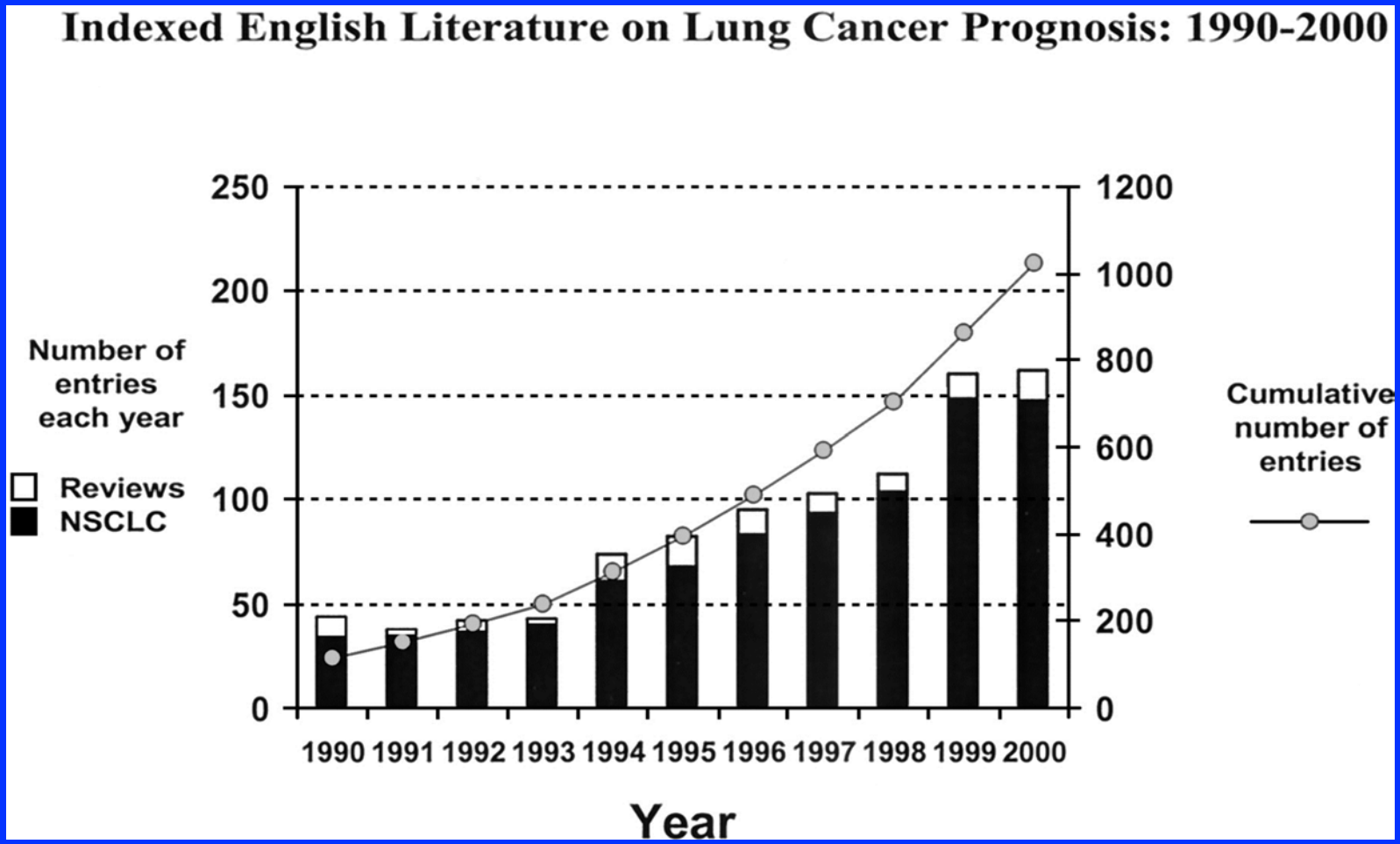
- Guide dans le choix thérapeutique
- Comparaison de groupes de patients
- Définition des critères d'inclusion et stratification des patients dans études cliniques
- Compréhension de mécanismes physiopathologiques en vue de nouvelles études
- Pronostic individuel → **NON**

Facteurs pronostiques dans les cancers bronchiques
Analyse critique de la littérature

CHEST

Prognostic Factors in Non-small Cell Lung Cancer*: A Decade of Progress

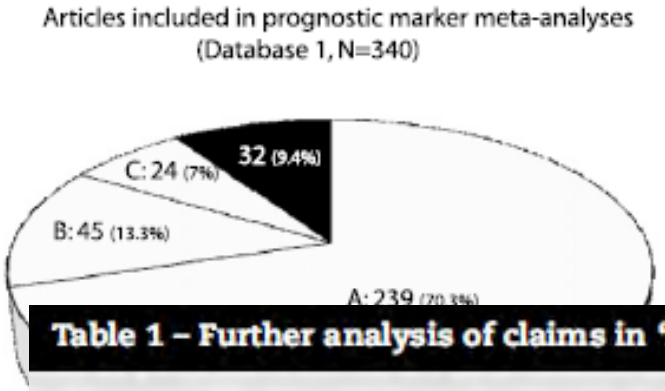
Chest. 2002;122(3):1037-1057. doi:10.1378/chest.122.3.1037



Brundage et al, Chest 2002

Biais de publication

Almost all articles on cancer prognostic markers report statistically significant results



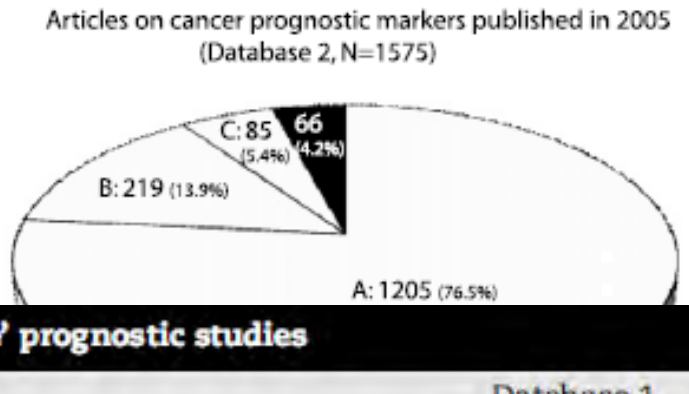


Table 1 – Further analysis of claims in 'negative' prognostic studies

	Database 1, N (%)	Database 2, N (%)
Not admitted to be fully 'negative'	27 (7.9)	45 (2.8)
Significance for other (non-prognostic) analyses	6 (1.7)	11 (0.6)
Discussion of non-significant trends	2 (0.6)	5 (0.3)
Offered apologies	9 (2.8)	13 (0.8)
Significance for other analyses + discussion of non-significant trends	1 (0.3)	3 (0.2)
Significance for other analyses + offered apologies	6 (1.7)	7 (0.5)
Discussion of non-significant trends + offered apologies	3 (0.8)	4 (0.3)
All three mechanisms	–	2 (0.1)
Admitted to be fully 'negative'	5 (1.5)	21 (1.3)

Kyzas et al Eur J Cancer 2007

Hétérogénéité

- Comparaison des études est difficile!
- ☞ Populations étudiées
- ☞ Critères diagnostiques et traitements appliqués
- ☞ Type d'analyse statistique
- ☞ Variables prises en considération
- ☞ Inclusion de facteurs postérieurs au traitement comme la réponse à la thérapeutique administrée
- ☞ Objectifs étudiés

Facteurs additionnels: la classification anatomopathologique

International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma

Journal of Thoracic Oncology • Volume 6, Number 2, February 2011

Facteurs additionnels: la classification internationale

A New International Staging System for Lung Cancer*

Clifton F. Mountain, M.D., F.C.C.P.

Revisions in the International System for Staging Lung Cancer

Clifton F. Mountain

Chest 1997;111;1710-1717

The IASLC Lung Cancer Staging Project: Proposals for the Revision of the TNM Stage Groupings in the Forthcoming (Seventh) Edition of the TNM Classification of Malignant Tumours

Peter Goldstraw, FRCS, John Crowley, PhD,† Kari Chansky, MS,† Dorothy J. Giroux, MSc,† Patti A. Groome, PhD,‡ Ramon Rami-Porta, MD,§ Pieter E. Postmus, PhD,|| Valerie Rusch, MD,¶ and Leslie Sobin, MD,# on behalf of the International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions*

2ème édition (1974)		3ème édition (1978)		4ème édition (1987)		5ème édition (1997)	
Stade		Stade		Stade		Stade	
I	T1N0M0 T2N0M0 T1N1M0	IA IB	T1N0M0 T2N0M0 T1N1M0	I	T1N0M0 T2N0M0	IA IB	T1N0M0 T2N0M0
II	T2N1M0	II	T2N1M0	II	T1N1M0 T2N1M0	IIA IIB	T1N1M0 T2N1M0 T3N0M0
III	T3 N2 M1	III	T3N0/1M0 T1-4N2M0	IIIA IIIB	T1-2N2M0 T3N0-2M0 T1-4N3M0 T4N0-3M0	IIIA IIIB	T1-2N2M0 T3N1-2M0 T1-4N3M0 T4N0-3M0
		IV	M1	IV	M1	IV	M1

IA ⇔ IB M1→ Stade IV	T1N1M0 → II T3 → T3/T4 N2 → N2/N3 III → IIIA/IIIB	IA ⇔ IB IIA ⇔ IIB T3N0 → stade IIB

Facteurs pronostiques conventionnels

1. CBNPC

Facteurs pronostiques dans les CBNPC

Principaux FP

- **Stade**
- **Indice de performance**
- Sexe
- Age
- Histologie
- Caractéristiques de la tumeur primitive (c/p T) ou de l'extension ganglionnaire (c/p N)

Autres FP potentiels

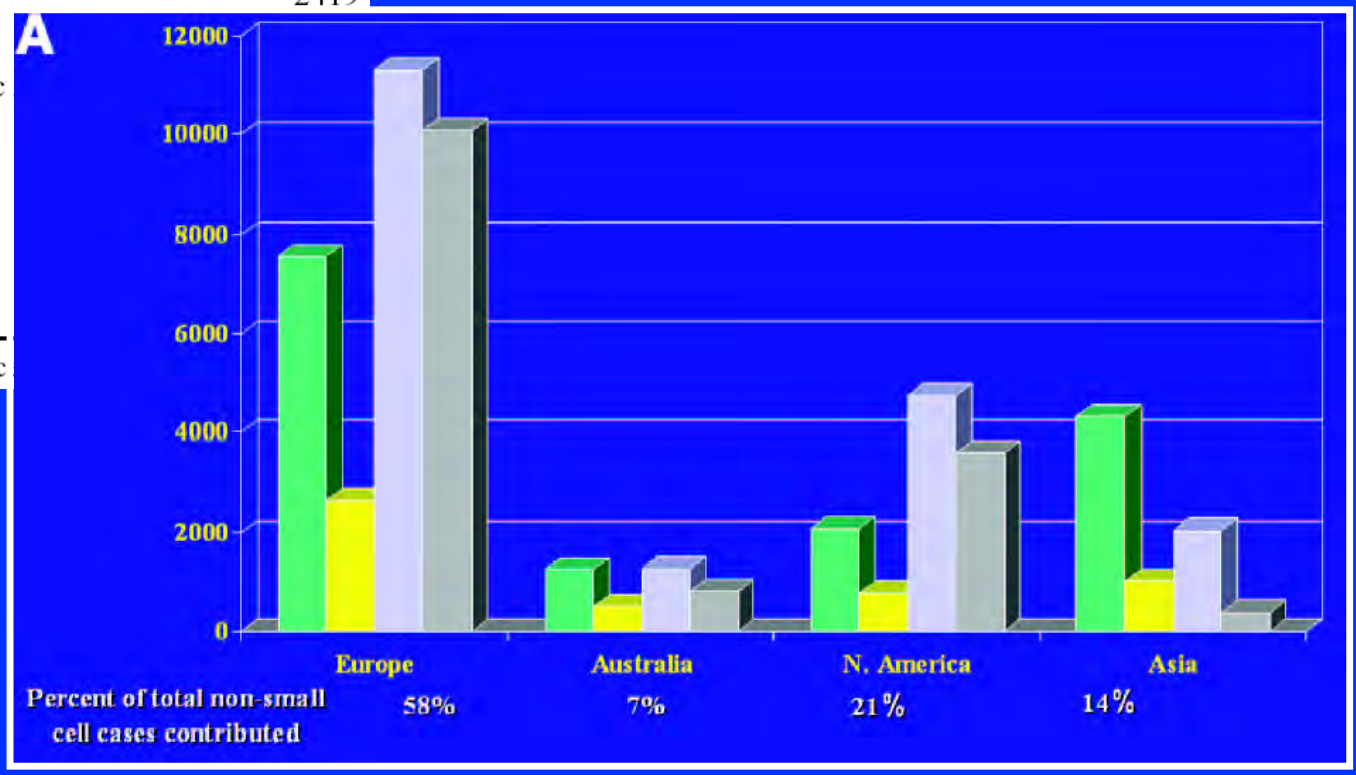
- Variables Biologiques (LDH, calcemia, phosphatases alcalines, leucocytose, taux de neutrophiles)
- Caractéristiques du patients (perte de poids, BMI, co-morbidités, statut tabagique, ethnicité)
- Caractéristiques tumorales (grade histologique, nombre de sites métastatiques, symptômes, invasion vasculaire ou locale, épanchement malin, localisation du site primitif)
- Paramètres thérapeutiques (CT adjuvante, type de CT, réponse objective response au traitement).

L'étude rétrospective de l'IASLC

TABLE 3. Numbers of cases submitted to the database showing exclusions and the numbers remaining for analysis

Total cases submitted	100,869
Excluded from current analyses	19,374
Outside of 1990–2000 time frame	5467
Incomplete survival data	1192
Unknown histology	2419
Incomplete stage information	
Recurrent cases and other (e.g., not known if rec diagnosed, occult tumors)	
Carcinoids, sarcomas, other histologies	
Included in analyses	
SCLC	
NSCLC	

SCLC, small cell lung cancer; NSCLC, non-small c



J Thorac Oncol 1; 2006

The Impact of Additional Prognostic Factors on Survival and their Relationship with the Anatomical Extent of Disease Expressed by the 6th Edition of the TNM Classification of Malignant Tumors and the Proposals for the 7th Edition

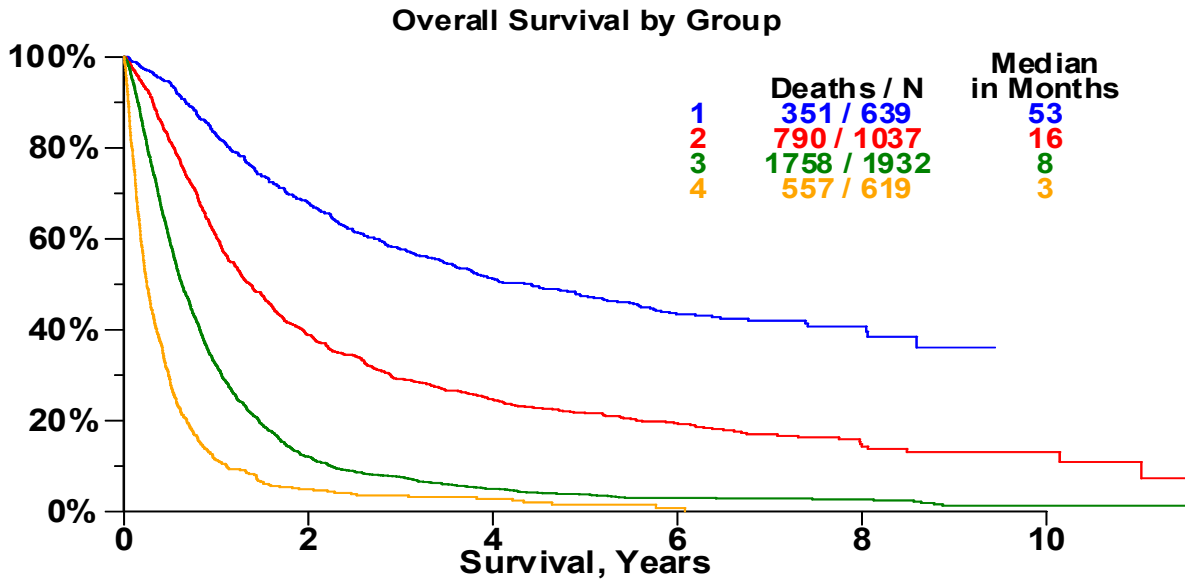
TABLE 2. Multivariate Analysis of Prognostic Factors for Survival in NSCLC, Using General Characteristic Variables (Clinical TNM Stage as Proposed by IASLC Staging Project, Age, Gender, PS, Histological Cell Type)

Variable	*n*/*N* (%)	HR (95% CI)	*P*
Stage II	1531/12426 (12%)	1.80 (1.65, 1.97)	<0.001
Stage IIIA	2048/12426 (16%)	2.71 (2.49, 2.95)	<0.001
Stage IIIB/IV	7280/12426 (59%)	5.34 (4.95, 5.76)	<0.001
Age (continuous)	*N* = 12426	1.01 (1.00, 1.01)	<0.001
Squamous cell type	5304/12426 (43%)	0.93 (0.89, 0.97)	<0.001
Male gender	9764/12426 (79%)	1.17 (1.11, 1.23)	<0.001
PS 1 (vs.0)	6294/12426 (51%)	1.38 (1.32, 1.44)	<0.001
PS 2 (vs. 0)	1423/12426 (11%)	2.09 (1.95, 2.23)	<0.001
PS 3–4 (vs. 0)	579/12426 (5%)	3.48 (3.17, 3.83)	<0.001

Sculier et al, J Thorac Oncol 2008

Séparation en 4 groupes

Survival by amalgamated groups, 4,227 NSCLC Cases (Validation Set)



1 = IA/IB/IIA, any Age, any P.S.
2 = IIB/IIIA, any Age, P.S. 0-1
3 = IIB/IIIA, any Age, P.S. 2; IIIB/IV, any Age, P.S. 0; IIIB/IV, Age <81, P.S. 1
4 = IIB/IIIA, any Age, P.S. 3-4; IIIB/IV, any Age, P.S. 2-4;
IIIB/IV, Age >=81, P.S. 1

Sculier et al, J Thorac Oncol 2008

Stades avancés (IIIB/IV) : variables biologiques de routine

Variable	*P*	HR
Age ≥75 yr	0.0415	1.39
Male	0.4761	0.93
PS (ordered: 0, 1, 2, 3–4)	<0.0001	1.44
Calcium >10.4 mg/dl	0.0077	1.77
Albumin <32 g /dl	0.013	1.33
Sodium <135 mmol/l	0.4823	1.09
Hemoglobin <12 g/dl for females, 13 g/dl for males	0.1235	1.16
WBC >10,000 cells/μl	<0.0001	1.60

Sculier et al, J Thorac Oncol 2008

Facteurs pronostiques pour le cancer bronchique identifiés par niveau de preuve par l'IASLC staging project

Variable	NSCLC
Clinical extent of disease[a]	++++
Performance status[b]	+++ (≥IIB only)
Age	++ (≥IIIB only)
Male gender	+
Squamous cell type	+ (IIIA only)
PET SUV_{max}	+
Calcium	+[c]
Albumin	+[c]
Sodium	+§[c]
White blood cells	+[c]
Hemoglobin	+§[c]

Sculier et al, J Thorac Oncol 2008

Relationship Between Tumor Size and Survival in

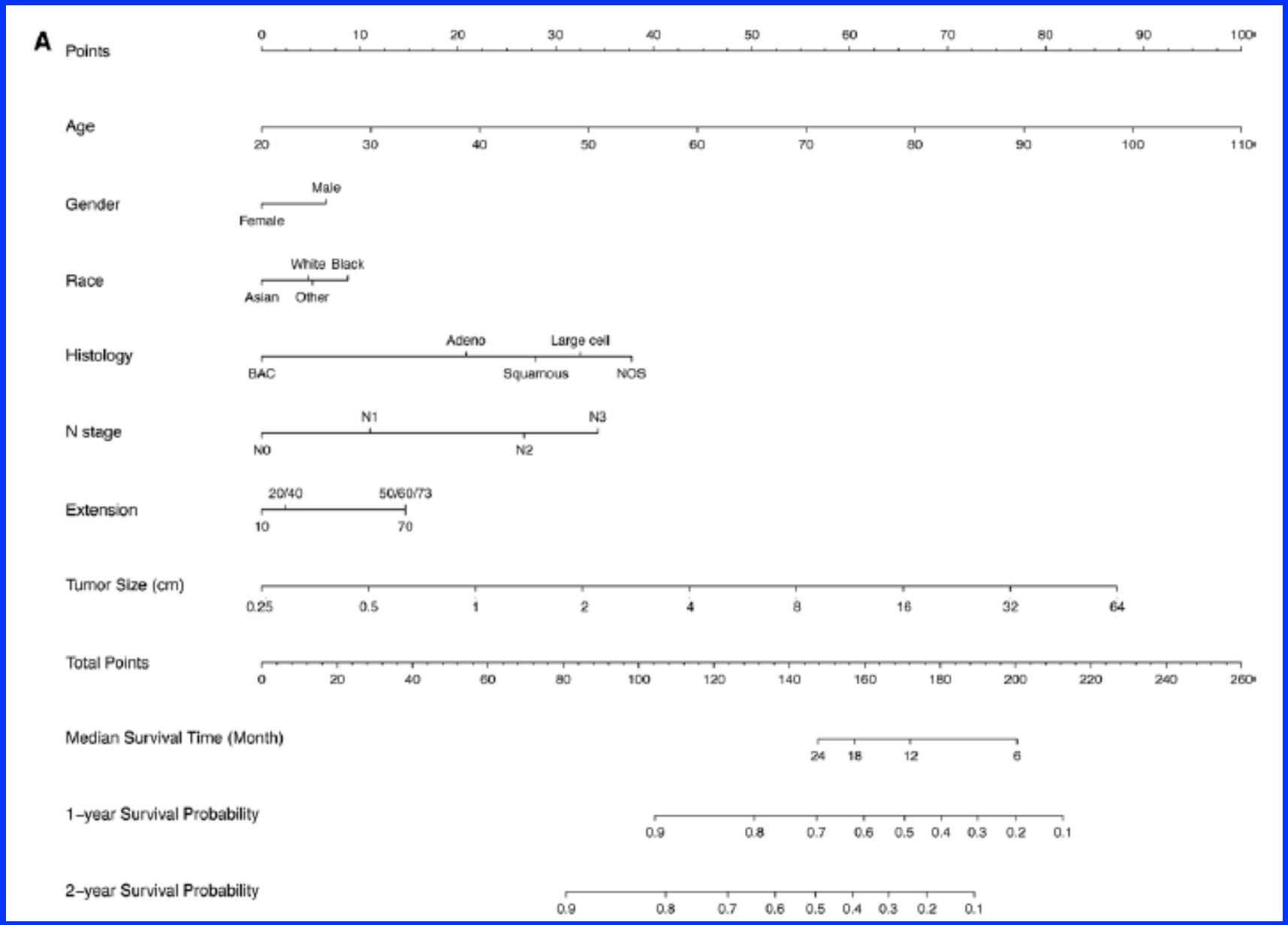
cer (NSCLC)

, Epidemiology, Registry

TABLE 2. Patient Demographics/Characteristics and Multivariate Analysis for OS

Category	Percentage* (N = 52,287)	Multivariate Analysis: Hazard Ratio (95% confidence interval)	Multivariate Analysis: *P* value
Age (year): median (range)	70 (20–103)	1.032 (1.031–1.034) per year increase	
Sex			
Female	46	Reference	Reference
Male	54	1.199 (1.165–1.234)	<0.001
Race			
White	85	Reference	Reference
Black	9	1.131 (1.081–1.184)	<0.0001
Asian	5	0.872 (0.817–0.930)	<0.0001
Other/unknown	1	1.004 (0.840–1.201)	0.963
Histology			
Adenocarcinoma	38	Reference	Reference
Bronchoalveolar carcinoma	8	0.569 (0.523–0.618)	<0.0001
Large cell carcinoma	6	1.382 (1.306–1.463)	<0.0001
Squamous cell carcinoma	31	1.224 (1.182–1.268)	<0.0001
NOS	18	1.650 (1.587–1.715)	<0.0001
Extension of primary tumor			
E1	59	Reference	Reference
E2	22	1.075 (1.037–1.115)	<0.0001
E3	9	1.506 (1.439–1.575)	<0.0001
E4	10	1.504 (1.440–1.572)	<0.0001
N stage			
N0	61	Reference	Reference
N1	10	1.353 (1.290–1.419)	<0.0001
N2	25	2.089 (2.022–2.159)	<0.0001
N3	3	2.548 (2.387–2.720)	<0.0001
Primary tumor size (cm)			
Median (range)	3.2 (0.3–38)	1.352 (1.326–1.378) per onefold increase	<0.0001

Zhang et al, J Thorac Oncol 2015



Zhang et al, J Thorac Oncol 2015

Ann Thorac Cardiovasc Surg 2011; 17: 469–480 doi: 10.5761/atcs.oa.10.01637

Original Article

Female Gender Is an Independent Prognostic Factor in Non-small-cell Lung Cancer: A Meta-analysis

- Revue systématique avec méta-analyse
- 39 publications (86800 patients)
- Meilleur pronostic pour sexe féminin
  - HR 0,78 ; p < 0,0001
- Trois analyses en sous-groupe
  - effet observé probablement pas lié au stade d'extension, au sous-type histologique ou au statut tabagique.

2. CBPC

Determinants of Improved Outcome in Small-Cell Lung Cancer: An Analysis of the 2,580-Patient Southwest Oncology Group Data Base

Table 6. Cox Multivariate Analyses of SWOG Limited-Stage Disease Trials

Favorable Variables Entire Data Base (n = 1,316)	Significance, Overall Survival* P	Hazards Ratio	Favorable Variables Recent Studies Only (n = 508)	Significance, Overall Survival† P	Hazards Ratio
Performance status 0-1	< .00005	1.4	Normal LDH	< .00005	1.6
Recent studies since 1978	< .00005	1.4	Performance status 0-1	.002	1.4
Age < 70 years	< .00005	1.5	Female sex	.004	1.4
Female sex	.0001	1.3	Study 8269	.005	1.5
Study 8269	.0009	1.5	Absence of effusion	.051	1.3
White race	.0095	1.3	—	—	—

Table 7. Cox Multivariate Analyses of SWOG Extensive-Stage Disease Trials

Favorable Variables Entire Data Base* n = 1,192 (P, hazards ratio)	Favorable Variables Stage Added† n = 414 (P, hazards ratio)	Favorable Variables Laboratory Values Added‡ n = 128 (P, hazards ratio)
Performance status 0-1 (P < .00005, 1.5)	Study 8606 (P = .006, 1.8)	Normal LDH (P = .0006, 1.9)
Study 8606 (P = .0002, 1.9)	Single lesion (P = .01, 1.9)	Study 8606 (P = .0008, 2.2)
Age < 70 years (P = .006, 1.3)	—	—

Albain et al J Clin Oncol 1990

Trends in the outcomes for patients with limited stage small cell lung cancer: An analysis of the Surveillance, Epidemiology, and End Results database☆

Multivariate analysis of overall survival for patients with LS-SCLC

	HR	CI (95%)	p
Age			
>70	1.66	1.55–1.78	<0.0001
60–69	1.25	1.17–1.34	<0.0001
<60	1.00 (Ref.)		
Gender			
Female	0.91	0.87–0.96	0.0007
Male	1.00 (Ref.)		
Race			
African American	1.19	1.08–1.30	0.0004
Other	1.07	0.95–1.20	0.2821
White	1.00 (Ref.)		
Laterality			
Right	0.99	0.94–1.05	0.8301
Left	1.00 (Ref.)		
Size			
<3 cm	0.60	0.55–0.64	<0.0001
3–5 cm	0.76	0.70–0.83	<0.0001
>5 cm	1.00 (Ref.)		
Subsite			
Main bronchus	1.12	1.02–1.24	0.0153
Upper lobe	0.99	0.93–1.06	0.7942
Middle lobe	0.97	0.86–1.09	0.5534
Lower lobe	1.00 (Ref.)		
Radiotherapy use by year of diagnosis			
No radiotherapy			
1983–1987	1.00 (Ref.)		
1988–1992	0.67	0.60–0.75	<0.0001
1993–1998	0.77	0.69–0.85	<0.0001
Radiotherapy			
1983–1987	1.03	0.93–1.12	0.5719
1988–1992	0.59	0.52–0.65	<0.0001
1993–1998	0.53	0.47–0.58	<0.0001

Lally et al, Lung Cancer 2009

Prognostic Factors for Survival in Extensive Stage Small Cell Lung Cancer (ED-SCLC)

The Importance of Smoking History, Socioeconomic and Marital Statuses, and Ethnicity

TABLE 4. Cox Multivariate Analysis of ED-SCLC Patients

Variable	HR	95% CI	p
Smoking			
No	1.00		
Yes	1.310		
Unknown	1.234		
Ethnicity			
Caucasian	1.00		
African American	0.973		
Asian	0.785		
Hispanic	0.917		
Other	2.934		
Gender			
Male	1.00		
Female	0.823		
Age	1.012		
Socioeconomic status (SES)[a]	0.965	(0.939–0.993)	0.0128
Marital status[b]			
Married	1.00		<0.0001
Unmarried[c]	1.179	(1.095–1.269)	
Chemotherapy[b]			
No	1.00		<0.0001
Yes	0.335	(0.309–0.364)	
Radiation			
No	1.00		<0.0001
Yes	0.721	(0.670–0.776)	
Surgery[b]			
No	1.00		0.1700
Yes	0.791	(0.565–1.106)	

Ou et al, J Thorac Oncol 2009

Small-Cell Lung Cancer: Prognostic Factors and Changing Treatment Over 15 Years

Table 3 Adjust for Pat and 20

Sex		
Male		
Female		
Age (years)		
< 70		
≥ 70		
Treatment		
Surgery only		
Radiation only		
Chemotherapy or		
Surgery + other		
Chemoradiation		
Other treatment		
No treatment		
Hospital Category		
CCC		
COMP		
TRH		
Race		
White	1	Ref
Black	1.08	1.01–1.14
Other	0. 95	0. 87–1.03

	Hazard Ratio	95% Co Inte
Sex		
Male	1.19	1.15
Female	1	R
Age (years)		
< 70	1	R
≥ 70	1.48	1.44

	Hazard Ratio	95% Co Inte
Treatment		
Surgery only	0. 73	0. 65
Radiation only	1.71	1.59
Chemotherapy only	1.56	1.51
Surgery + other[a]	0. 59	0. 54
Chemoradiation	1	R
Other treatment	1.23	1.10
No treatment	2.62	2.50

Variable	Hazard Ratio	95% Confidence Interval
Sex		
Male	1.13	1.10–1.16
Female	1	Ref[a]
Age (years)		
< 70	1	Ref
≥ 70	1.33	1.30–1.36
Non-Hispanic black	0.98	093–1.02

Variable	Hazard Ratio	95% Confidence Interval
Treatment		
Surgery alone or in combination	0.82	0.74–0.92
Radiation only	1.84	1.75–1.93
Chemotherapy only	1	Ref
Radiation and chemotherapy	0.92	0.89–0.94
Other treatment	1.11	1.02–1.20
No treatment	2.59	2.50–2.68
Diagnostic Year		
1992	1.01	0.99–1.05
1997	1.05	1.02–1.08
2002	1	Ref

Gaspar et al, Clin Lung Cancer 2012

The Impact of Additional Prognostic Factors on Survival and their Relationship with the Anatomical Extent of Disease Expressed by the 6th Edition of the TNM Classification of Malignant Tumors and the Proposals for the 7th Edition

TABLE 7. Multivariate Analysis of Prognostic Factors for Survival in SCLC, Using General Characteristic Variables (Limited vs. Extensive Stage, Age, Gender, PS)

Variable	*n*/*N* (%)	HR (95% CI)	*P*
Age	*N* = 6609	1.01 (1.01, 1.02)	<0.001
Extensive stage (vs Lim.)	3739/6609 (57%)	2.13 (2.02, 2.25)	<0.001
Male (vs. female)	4368/6609 (66%)	1.25 (1.19, 1.32)	<0.001
PS 1	3161/6609 (48%)	1.36 (1.28, 1.44)	<0.001
PS 2	1060/6609 (16%)	1.93 (1.78, 2.09)	<0.001
PS 3–4	349/6609 (5%)	3.45 (3.05, 3.89)	<0.001

TABLE 8. Multivariate Analyses of Prognostic Factors for Survival in Limited and Extensive SCLC, Using General Characteristic Variables (Age, Gender, PS)

Variable	*n*/*N* (%)	HR (95% CI)	*P*
Limited stage			
Age	*N* = 2870	1.01 (1.01, 1.02)	<0.001
Male	1838/2870 (64%)	1.21 (1.11, 1.32)	<0.001
PS 1	1338/2870 (47%)	1.42 (1.30, 1.55)	<0.001
PS 2	277/2870 (10%)	1.72 (1.49, 1.98)	<0.001
PS 3–4	129/2870 (4%)	3.68 (3.03, 4.47)	<0.001
Extensive stage			
Age	*N* = 3739	1.01 (1.01, 1.02)	<0.001
Male	2530/3739 (68%)	1.28 (1.20, 1.38)	<0.001
PS 1	1823/3739 (49%)	1.32 (1.21, 1.43)	<0.001
PS 2	783/3739 (21%)	1.98 (1.79, 2.18)	<0.001
PS 3–4	220/3739 (6%)	3.32 (2.84, 3.88)	<0.001

TABLE 10. Multivariate Model for Survival Performed in SCLC in a set of 650 Patients for which the 5 Laboratory Variables were Available

Variable	*P*	HR
Stage: ED	<0.0001	1.931
Age ≥75 yr	0.4064	1.146
Male	0.0007	1.336
PS (ordered: 0, 1, 2, 3–4)	<0.0001	1.283
Calcium >10.4 mg/dl	0.9451	1.019
Albumin <32 g/dl	0.0168	1.385
Sodium <135 mmol/l	0.0483	1.221
Hemoglobin <12 g/dl for females, 13 g/dl for males	0.0579	0.833
WBC >10,000 cells/μl	0.7929	1.024

Sculier et al, J Thorac Oncol 2008

Facteurs pronostiques pour le cancer bronchique identifiés par niveau de preuve par l'IASLC staging project

Variable	SCLC
Clinical extent of disease[a]	++++
Performance status[b]	+++
Age	++
Male gender	++
Squamous cell type	N/A
PET SUV_{max}	N/A
Calcium	—
Albumin	+
Sodium	+§
White blood cells	—
Hemoglobin	—

Sculier et al, J Thorac Oncol 2008

Autres FP potentiels

Facteur pronostique	Références
Sites spécifiques de métastases	Wu, Asian Pac J Cancer Prev. 2012
Nombre de sites métastatiques	Foster, Cancer 2009
LDH	Hansen, Lung Cancer 2010
CRP	Hong, Yonsei Med J 2012
Interstitial Lung Disease	Togashi, Clin Lung Cancer 2012
Comorbidités	Kuo, JTO 2011
Syndrome VCS	Arinc, Med Oncol 2010

Facteurs pronostiques biologiques « Biomarqueurs »

FP biologiques

- Principalement étudiés sur des biopsies ou des prélèvements chirurgicaux, plus rarement sur des prélèvements sanguins.
- Essentiellement analyse des protéines, de l'ARN (ARNmessager, microARN) ou de l'ADN.
- Limite = nombre d'analyses sur même échantillon
- Techniques à haut rendement (microarrays…) → investigation de milliers de marqueurs moléculaires sur un même échantillon et durant la même expérience

➢ Développement de signatures génomiques

Principales critiques

- Taille de l'échantillon faible
- Etudes unicentriques
- Différents case-mix et absence de prise en compte des FP conventionnels
- Manque de standardisation
- Hétérogénéité des analyses statistiques
- Manque d'étude de validation
- Risque de biais +++

Méthodologie pour évaluer FP par IHC (1)

mPhase	Objectives	Suggested sample size	Data to include in publication
1	To verify: 1. Specificity of antibody and assay technique 2. Cellular localisation of expression 3. Expression changes in tumour cells compared with normal cells	10–20	Source of antibody and dilution Technical details Nature of samples Pattern of expression changes
2	To investigate the prognostic significance of markers in samples from a single institution	50–300	Details of scoring system Cut-offs for log-rank test of survival and their justification Type of survival (disease-free or overall) correlation Univariate and multivariate HR, 95% CI, p value Kaplan–Meier plot

Zhu et al J Clin Pathol, 2006

Méthodologie pour évaluer FP par IHC (2)

Meta-analyses of mPhase 2 studies to determine markers that show evidence and potential strengths as prognostic markers	⩾10 studies	Inclusion and exclusion criteria Details of meta-analysis results Effects of assay technique, cut-off Potential for publication bias Overall strength of HR and significance

Zhu et al J Clin Pathol, 2006

Références	Biomarqueur	n études	Résultats	Valeur pronostique
Huncharek, 1999 (72)	K-RAS	8	RR 2,35 à 2 ans	péjorative
Mascaux, 2005 (73)	K-RAS	28	HR 1,35	péjorative
Meng, 2013 (74)	K-RAS (mutation)	41	HR 1,45	péjorative
Huncharek, 2000 (75)	Gène p53	8	RR 1,52	péjorative
Mitsudomi, 2000 (76)	p53	43	$p < 0,05$	péjorative
Steels, 2001 (77)	p53	50	HR 1,44	péjorative
Choma, 2001 (78)	Aneuploïdie	35	OR 0,67 à 4 ans	péjorative
Meert, 2002 (79)	EGF-R	11	HR 1,14	péjorative (sous-groupe IHC)
Nakamura, 2006 (80)	EGF-R	18	HR 1,14	non
Meert, 2003 (81)	c-erbB2	20	HR 1,55	péjorative
Nakamura, 2005 (82)	c-erbB2	20	HR 1,32	péjorative
Delmotte, 2002 (83)	VEGF	18	HR 1,48	péjorative

Références	Biomarqueur	n études	Résultats	Valeur pronostique
Meert, 2002 (84)	MVC	7-9	HR 1,80-1,99	péjorative
Trivella, 2007 (85)	MVC	17	HR 1,03	péjorative (sous-groupe)
Martin, 2003 (86)	Bcl-2	18	HR 0,72	favorable
Martin, 2004 (87)	Ki-67	16	HR 1,56	péjorative
Mascaux, 2006 (88)	COX2	10	HR 1,39	péjorative
Fan, 2008 (89)	Survivine	8	HR 1,88	péjorative
Huang, 2013 (90)	Survivine	29	HR 1,95	péjorative
Roth, 2011 (91)	ERCC1	8	HR 2,04	péjorative
Chen, 2013 (92)	SOX2	8	HR 0,65	favorable
Wang, 2013 (93)	miR-21 miR-155	9 5	HR 2,00 HR 1,65	péjorative
Li, 2013 (94)	HIF1a HIF2a	7 3	HR 1,50 HR 2,02	péjorative
Xu, 2014 (95)	STAT3 pSTAT3	17	HR 0.71 HR 0.67	péjorative

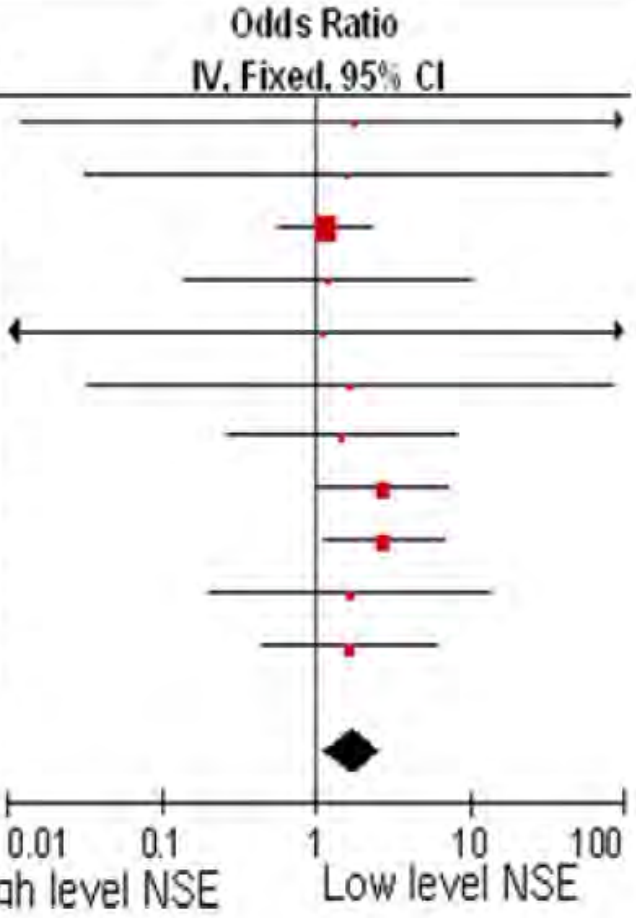
Serum neuron-specific enolase levels were associated with the prognosis of small cell lung cancer: a meta-analysis

Wei-Xin Zhao · Jian-feng Luo

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Ando 2004	0.593	2.563	0.7%	1.81 [0.01, 274.89]
Bremnes 2003	0.463	1.997	1.2%	1.59 [0.03, 79.60]
Jin 2001	0.14	0.37	34.0%	1.15 [0.56, 2.38]
Johnson 1993	0.171	1.107	3.8%	1.19 [0.14, 10.39]
Jorgensen 1996	0.094	6.49	0.1%	1.10 [0.00, 367385.23]
Liu 2004	0.511	2.01	1.2%	1.67 [0.03, 85.67]
Ono 2012	0.375	0.876	6.1%	1.45 [0.26, 8.10]
Quoix E 2000	0.997	0.505	18.2%	2.71 [1.01, 7.29]
Shibayama 2001	1.007	0.476	20.5%	2.74 [1.08, 6.96]
Song 2004	0.505	1.091	3.9%	1.66 [0.20, 14.06]
XUE 2011	0.492	0.671	10.3%	1.64 [0.44, 6.09]
Total (95% CI)			**100.0%**	**1.74 [1.14, 2.65]**

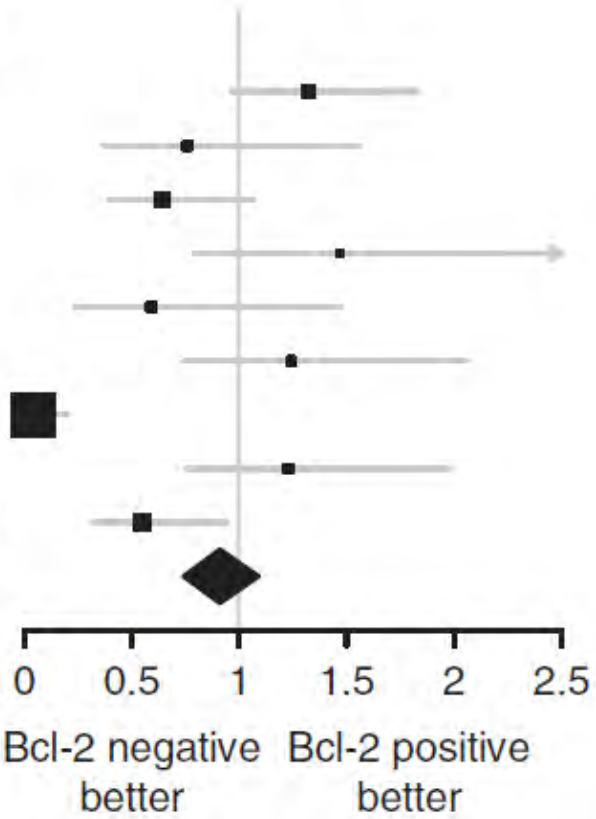
Heterogeneity: $Chi^2 = 3.11$, df = 10 (P = 0.98); $I^2 = 0\%$

Test for overall effect: Z = 2.56 (P = 0.01)



Bcl-2 and β_1-integrin predict survival in a tissue microarray of small cell lung cancer

Study	Cases	Events	HR	Lower CI	Upper CI
Kaiser (1996)	146	109	1.32	0.96	1.82
Takayama (1996)	38	21	0.76	0.37	1.56
Dingemans (1999)	91	71	0.64	0.39	1.07
Maitra (1999)	42	24	1.47	0.79	2.78
Zereu (2003)	58	33	0.59	0.24	1.47
Paik (2006)	64	45	1.24	0.74	2.06
Ilievska (2008)	40	32	0.04	0	0.2
Lee (2008)	77	72	1.23	0.76	1.97
Lawson	117	109	0.55	0.32	0.94
Total	**673**	**516**	**0.91**	**0.74**	**1.09**



Lawson et al, Br J Cancer 2010

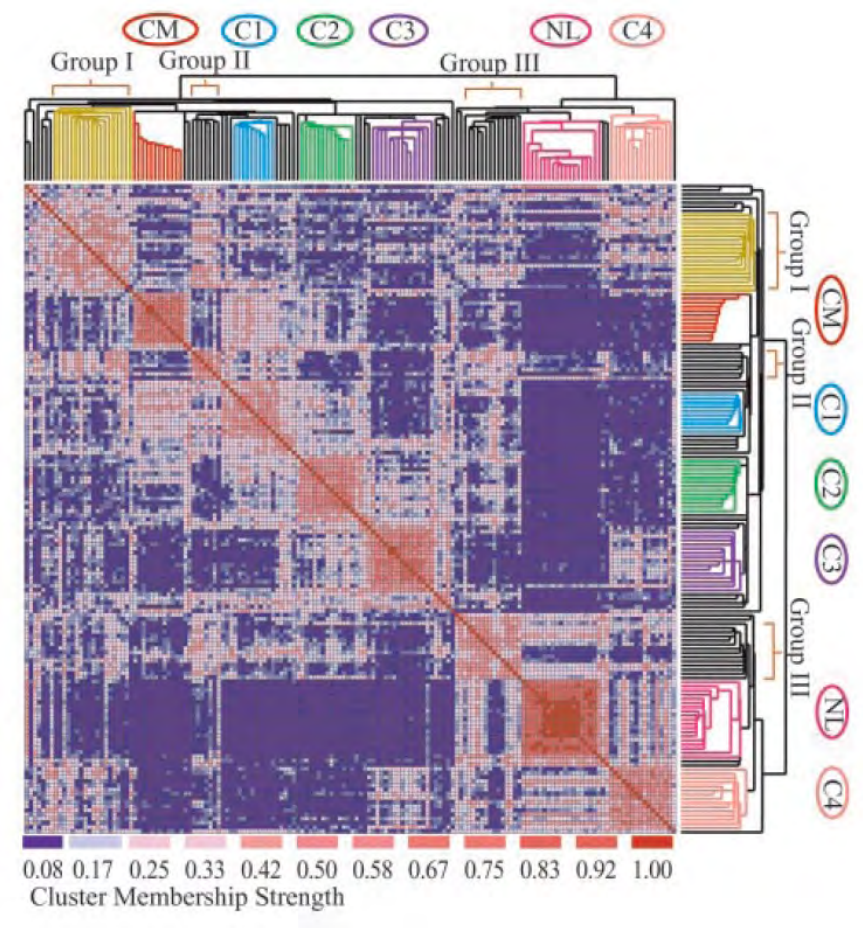
Méthodologie pour évaluer FP par IHC (3)

3	To validate the significance of best candidate markers in phase III clinical trials with tumour samples of limited availability	00s–000s	Demographics of studied patients compared towith patients in the overall trial patients Results of univariate and multivariate survival analysis results
4	To test prospectively the performance of markers in phase III randomised clinical trials by incorporating markers as stratification factors	00s–000s	

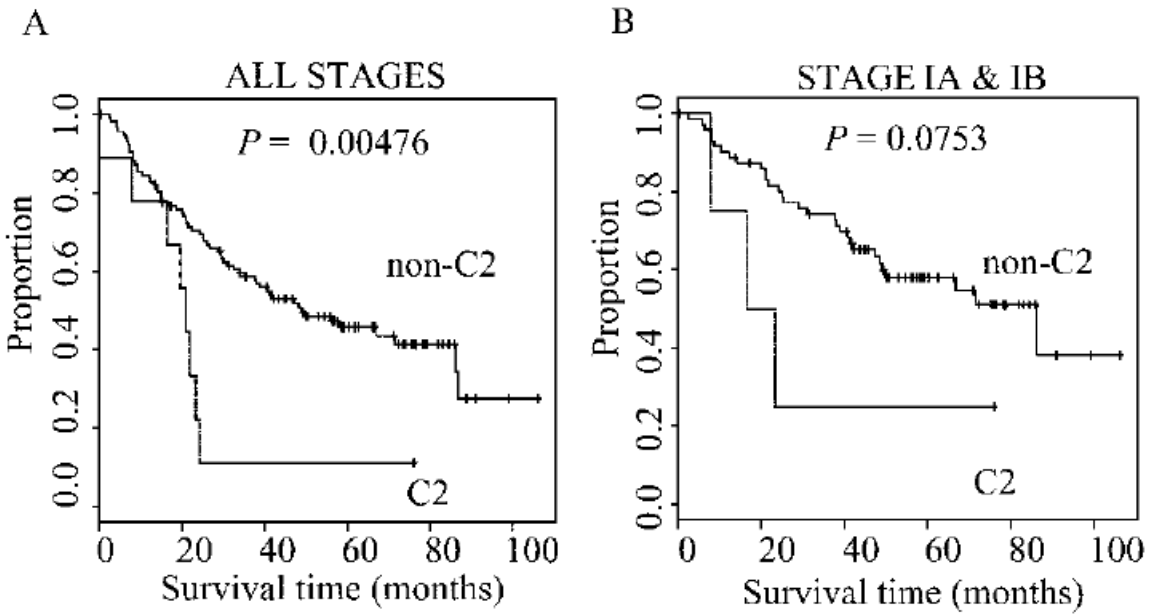
Zhu et al J Clin Pathol, 2006

Classification of human lung carcinomas by mRNA expression profiling reveals distinct adenocarcinoma subclasses

Arindam Bhattacharjee*†, William G. Richards‡§, Jane Staunton†¶, Cheng Li‖, Stefano Monti¶, Priya Vasa*, Christine Ladd¶, Javad Beheshti*, Raphael Bueno‡, Michael Gillette¶, Massimo Loda*,**, Griffin Weber*, Eugene J. Mark††, Eric S. Lander¶, Wing Wong‖, Bruce E. Johnson*, Todd R. Golub¶‡‡§§¶¶, David J. Sugarbaker‡§¶¶, and Matthew Meyerson*§§¶¶



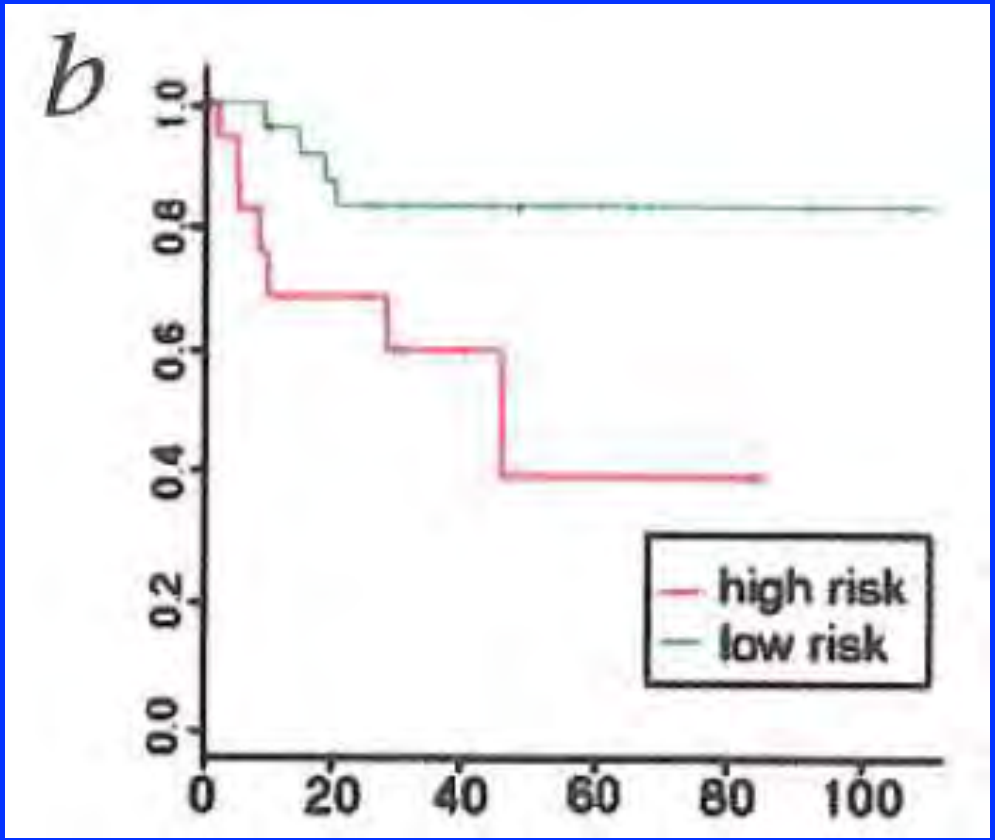
- 127 ADC réséqués
- Classification par clusters



PNAS 2001

Gene-expression profiles predict survival of patients with lung adenocarcinoma

David G. Beer[1], Sharon L.R. Kardia[2], Chiang-Ching Huang[3], Thomas J. Giordano[4], Albert M. Levin[2], David E. Misek[5], Lin Lin[1], Guoan Chen[1], Tarek G. Gharib[1], Dafydd G. Thomas[4], Michelle L. Lizyness[4], Rork Kuick[5], Satoru Hayasaka[3], Jeremy M.G. Taylor[3], Mark D. Iannettoni[1], Mark B. Orringer[1] & Samir Hanash[5]



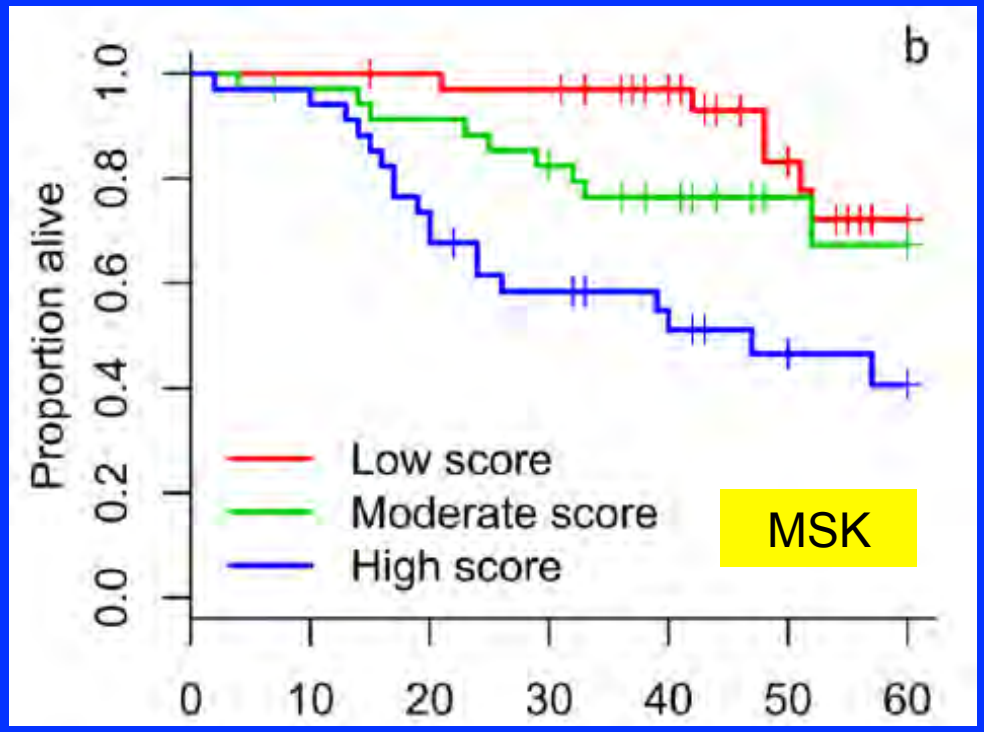
- 86 ADC réséqués de stade I-III
- 50-gene risk index

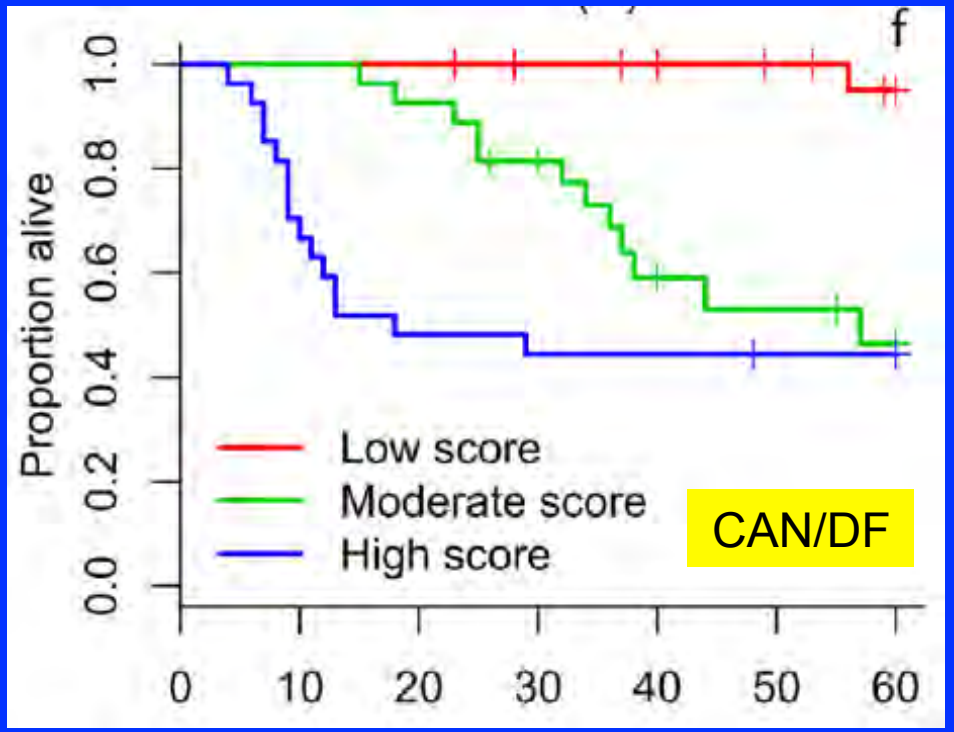
Nature Medicine 2002

Gene Expression-Based Survival Prediction in Lung Adenocarcinoma: A Multi-Site, Blinded Validation Study:

Director's Challenge Consortium for the Molecular Classification of Lung Adenocarcinoma

- Consortium → 442 spécimens chirurgicaux

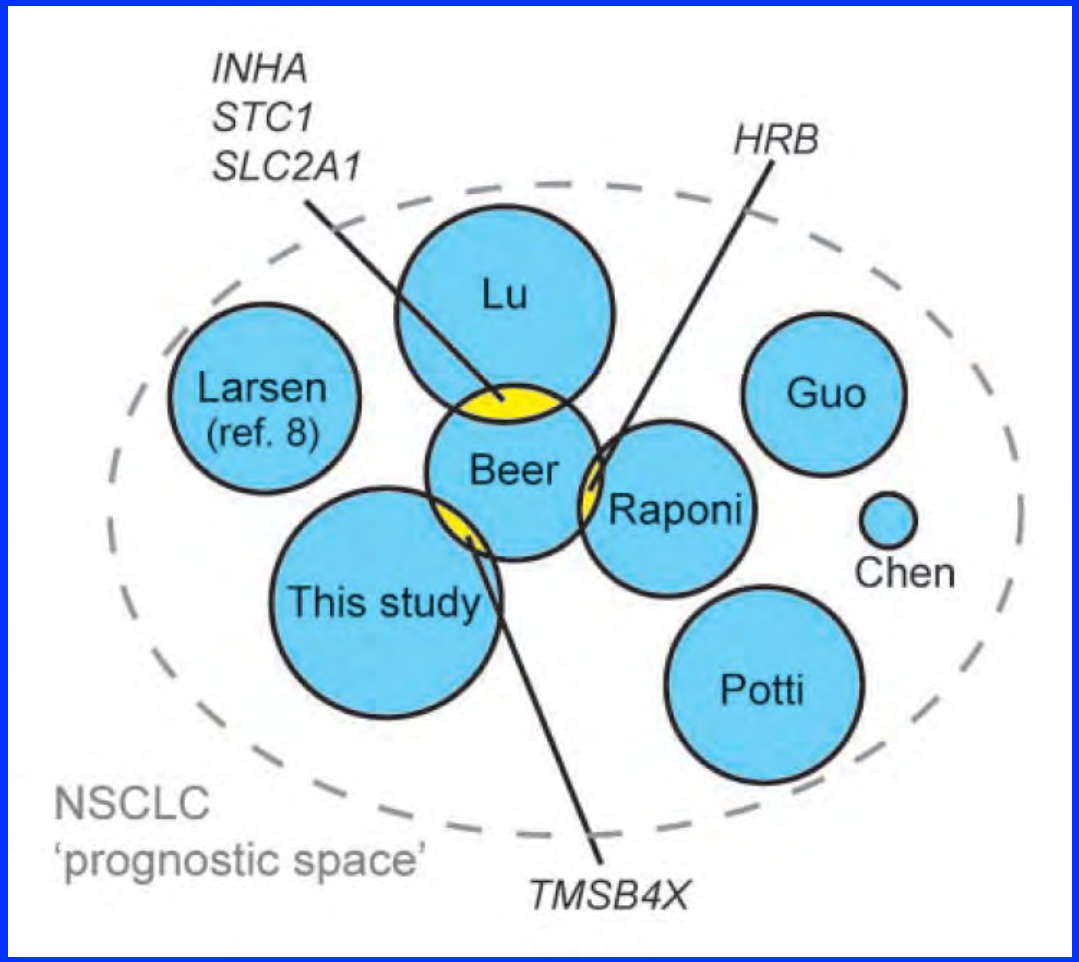




Shedden et al, Nature Medicine 2008: 822

Signatures génomiques dans CBNPC

- > 40 signatures

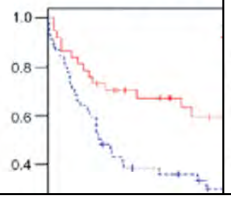


"Overlap is limited to 5 of a total of 327 genes used"

Roepman Clin cancer Res 2009: 284

Absence de validation

Erasmu

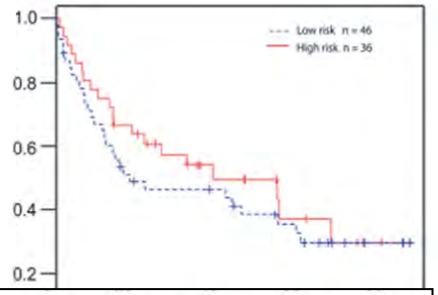


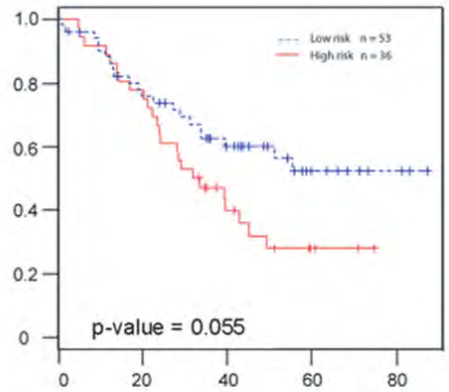
Beer et al. (2002) Nat Med 8, 816-824
Guo et al. (2008) CCR 14, 8213-8220

35 gene sig

Chen et al. (2007) NEJM 356, 11-20

16 gene signature



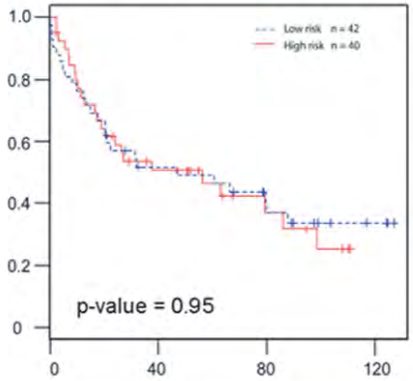


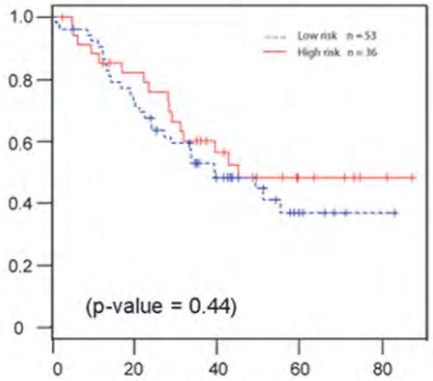
Shedden et
822-827

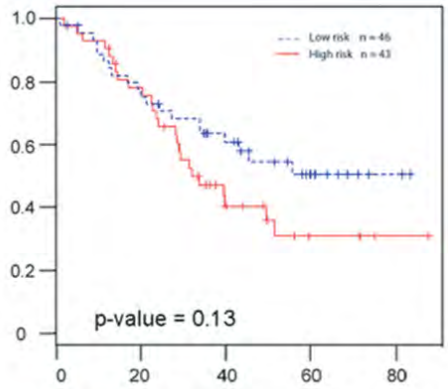
41 gene sig

Roepman et al. (2009) CCR 15, 284-290

72 gene signature

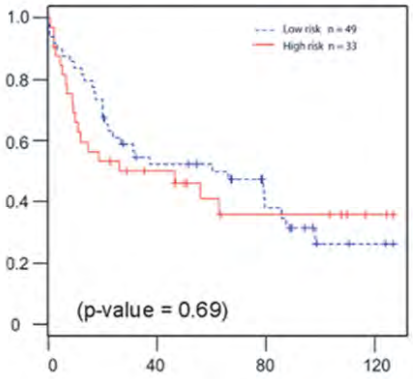


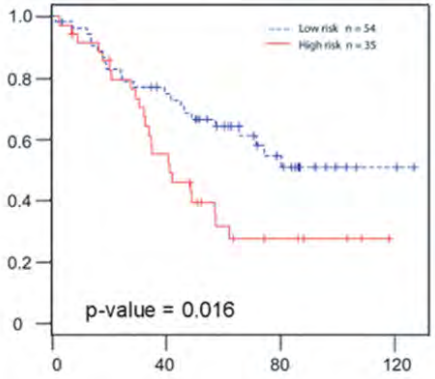




Boutros et al. (2009) PNAS 106, 2824-2828

6 gene signature





Hou et al, 2010

Signatures dépendantes de l'histologie

Predictor	AD (n = 45)			SQC (n = 46)		
	Adjusted HR		*P*	Adjusted HR		*P*
Age	1.0	0.9 to 1.0	.63	1.0	1.0 to 1.1	.26
Sex (male *v* female)	1.0	0.4 to 2.4	.95	1.0	0.4 to 2.7	.96
Stage II (*v* I)	1.7	0.6 to 4.9	.30	1.8	0.6 to 5.3	.29
Stage III+ (*v* I)	3.9	1.0 to 15.4	.06	27.3	3.3 to 226.3	< .01
SQC *v* AD	NA		NA	NA		NA
Present gene signature	2.4	1.0 to 5.8	.04	1.1	0.4 to 3.2	.87

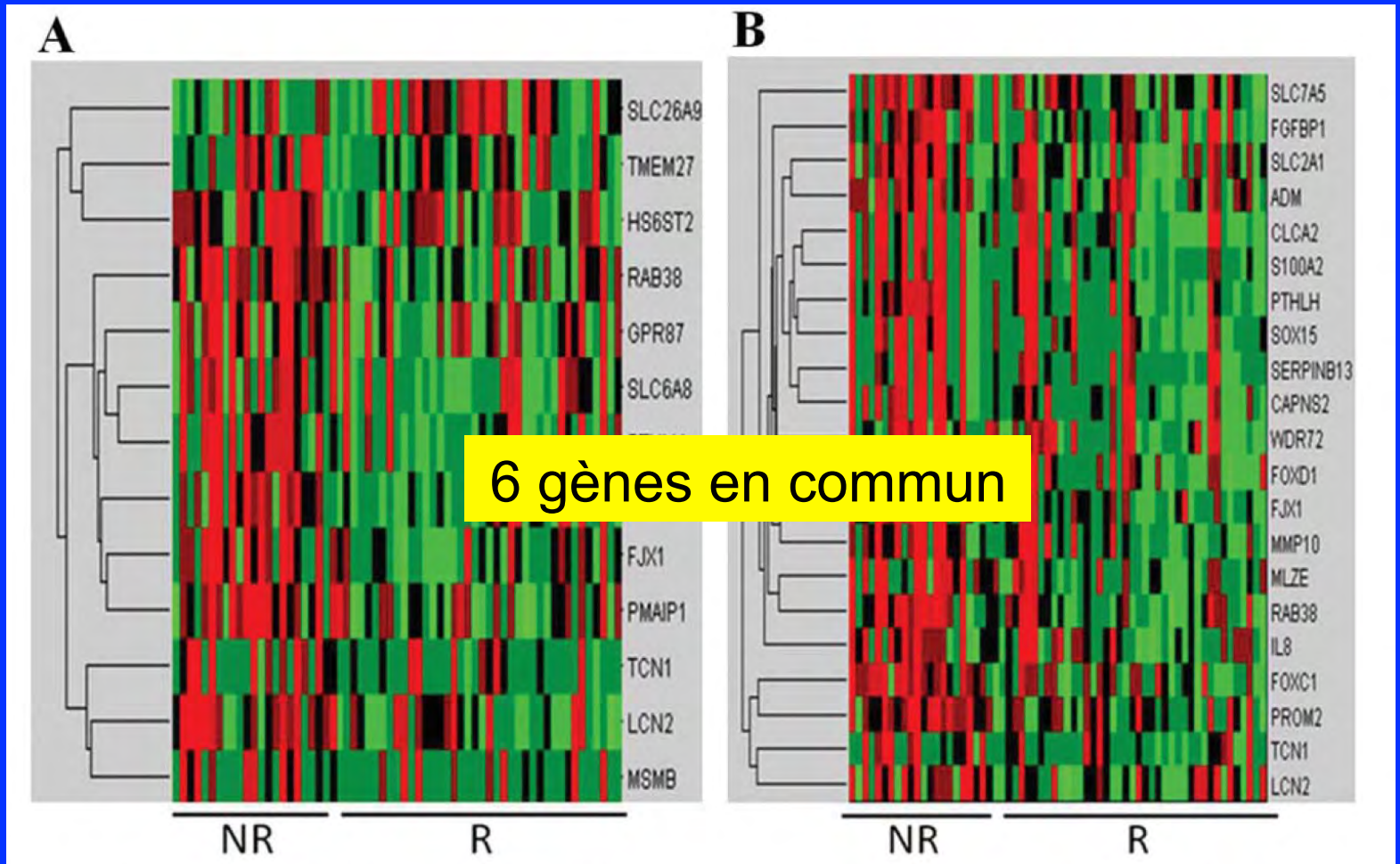
Table 2. Validation of the 12-gene signature

	Squamous cell carcinoma			Adenocarcinoma		
	n	**HR (95% CI)**	***P***	***n***	**HR (95% CI)**	***P***
In silico validation						
Duke	44	3.05 (1.14-8.21)	0.027	41	1.73 (0.59-5.12)	**0.322**
SKKU	76	2.77 (1.34-5.73)	0.006	62	1.92 (0.91-4.05)	**0.086**
DCC				327	1.23 (0.85-1.78)	**0.267**
Quantitative reverse transcriptase PCR validation						
UHN	62	3.76 (1.10-12.87)	0.035			

Sun et al, J Clin Oncol 2008: 877; Zhu et al Clin Cancer Res 2010: 5038

Comparison of Genomic Signatures of Non-small Cell Lung Cancer Recurrence between Two Microarray Platforms

JOHN WEN-CHENG CHANG[1], NIEN-CHIH WEI[2], HUNG-JU SU[3], JIE-LEN HUANG[3], TSE-CHING CHEN[4], YI-CHENG WU[5], CHIH-TENG YU[6], MING-MO HOU[1], CHIA-HSUN HSIEH[1], JIA-JUAN HSIEH[1,7], CHIAO-EN WU[1], HSIN-YI CHENG[1], TODD HSU[7] and TZU-HAO WANG[8]



6 gènes en commun

Figure 2. *Different gene expression between recurrence (R) and non-recurrence (NR) groups in Affymetrix (A) and Illumina (B) platforms. There were 13 genes selected and identified in the Affymetrix platform, while 21 genes were found in the Illumina platform. Student t test ($p<0.05$, $|NR-R|>1$) was used.*

Anticancer Res 2012: 1259

Méthodologie statistique
Analyse des “big data”

Three-Gene Prognostic Classifier for Early-Stage Non–Small-Cell Lung Cancer

Suzanne K. Lau, Paul C. Boutros, Melania Pintilie, Fiona H. Blackhall, Chang-Qi Zhu, Dan Strumpf, Michael R. Johnston, Gail Darling, Shaf Keshavjee, Thomas K. Waddell, Ni Liu, Davina Lau, Linda Z. Penn, Frances A. Shepherd, Igor Jurisica, Sandy D. Der, and Ming-Sound Tsao

Prognostic gene signatures for non-small-cell lung cancer

6-gene signature

Paul C. Boutros[a,b,1], Suzanne K. Lau[a,b], Melania Pintilie[b], Ni Liu[b], Frances A. Shepherd[c,d], Sandy D. Der[b,e], Ming-Sound Tsao[a,b,e], Linda Z. Penn[a,b], and Igor Jurisica[a,b,f,2]

J Clin Oncol 2007: 5562; PNAS 2009: 2824

CBPC: analyses transcriptomiques

Reference	Biomarquer	N	Résultats	Uni/multi
Lee, 2011	7 miR (miR-21, miR-29b, miR-34a/ b/c, miR-155, et let-7a)	31	Aucun	U
Ranade, 2010	880 miR et 473 premiR	34	Sexe et miR-92a-2* (p = 0,023) et (p = 0,015)	M
Sun, 2010	SNPs dans GST et DNA repair	248	GSS, ABCC2, et XRCC1	U
Knez, 2012	Polymorphisme	177	C3435T CT + TT genotypes meilleure survie (p = 0,028)	M
Karachaliou, 2013	ERCC1, PKM2, TOPOIIA, TOPOIIB, cMYC	184	Signature (faible expression ERCC1, PKM2, TOPOIIA et TOPOIIB) → meilleure PFS et OS (LD) et FP indépendant dans ED (HR 4.35; p=0,001et HR 3,32; p=0,019)	M

Facteurs pronostiques métaboliques

Primary Tumor Standardized Uptake Value Measured on Fluorodeoxyglucose Positron Emission Tomography Is of Prognostic Value for Survival in Non-small Cell Lung Cancer

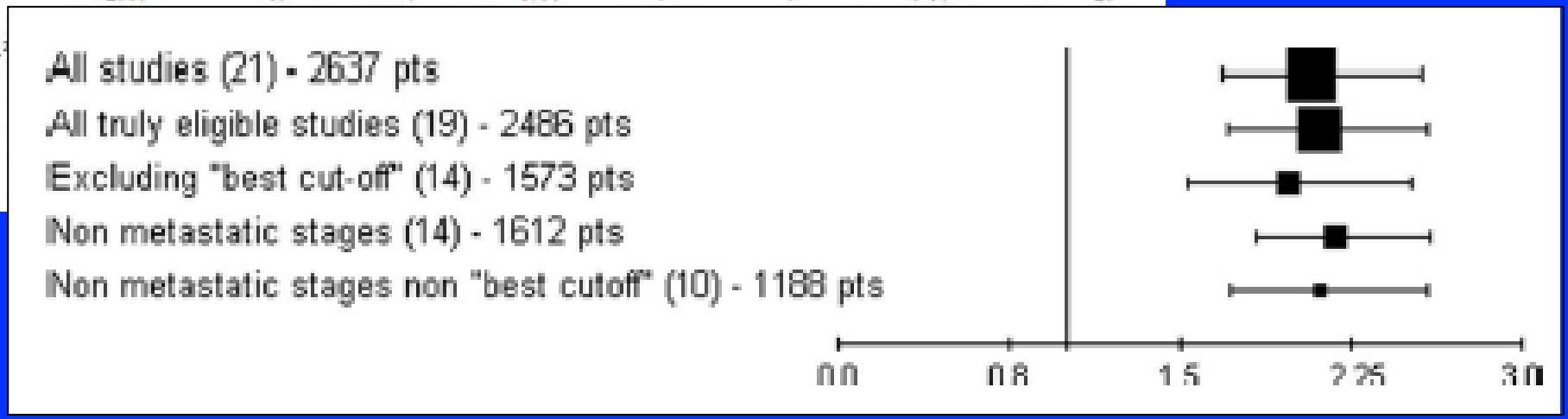
Update of a Systematic Review and Meta-Analysis by the European Lung Cancer Working Party for the International Association for the Study of Lung Cancer Staging Project

Marianne Paesmans, MSc, Thierry Berghmans, MD, PhD,† Michele Dusart, MD,‡ Camillo Garcia, MD,§ Claude Hossein-Foucher, MD, PhD,‖ Jean-Jacques Lafitte, MD, PhD,¶ Céline Mascaux, MD, PhD,# Anne-Pascale Meert, MD, PhD,† Martine Roelandts, MD,** Arnaud Scherpereel, MD, PhD,¶ Vanessa Terrones Munoz, MD,† and Jean-Paul Sculier, MD, PhD†; for the European Lung Cancer Working Party, and on behalf of the IASLC Lung Cancer Staging Project*

J Thorac Oncol. 2010;5: 612–619

TABLE 1. Characteristics of the Patient Populations Included in the 24 Eligible Studies

Study	Year of Publication	No. of Patients	Type of SUV	ISS	% ADC	% SCC	Stage	% Stage IV
Ahuja et al.[5]	1998	155	Mean	1997	?	?	I–IV	?
Sugawara et al.[6]	1999	38	Max	1986	50	32	I–IV	13
Vansteenkiste et al.[7]	1999	125	Max	1997	25	54	I–IIIB	0
Dhital et al.[8]	2000	77	Max	1986	23	58	?	?
Higashi et al.[9]	2002	57	Mean	1997	67	0	I–III	0
Jeong et al.[10]	2002	73	Max	1997	41	51	I–IV	?
Downey et al.[11]	2004	100	Max	1997	67	24	?	?
Borst et al.[a12]	2005	51	Max	?	25	33	I–III	0
Cerfolio et al.[b13]	2005	315	Max	1997	31	51	I–IV	10
Port et al.[14]	2005	64	?	?	88	8	?	?
Sasaki et al.[15]	2005	162	Max	1997	46	43	I–III	?
Eschmann et al.[16]	2006	137	Mean	1997?	29	45	IIIA/IIIB	0
Prevost et al.[17]	2006	120	Mean/max	1997	49	38	I–IV?	?
Raz et al.[23]	2006	36	?	1997	0	0	?	?
de Jong et al.[24]	2007	66	Max	1997	35	53	I–IIIA	0
Downey et al.[25]	2007	487	Max	1997	69	21	I–IV	2
Lee et al.[26]	2007	19	?	1997	?	?	I–IV	26
Na et al.[27]								
van Baardwijk et al.[								
Vesselle et al.[29]								
Zhang et al.[30]								
Goodgame et al.[31]								
Hanin et al.[32]								
Hoang et al.[33]								



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Primary tumor standardized uptake value is prognostic in non-small cell lung cancer : a multivariate pooled analysis of individual data

- Marianne Paesmans, Camilo Garcia, Ching-Yee Oliver Wong, Edward F. Patz Jr., Ritsuko Komaki, Susanne Eschmann, Ramaswamy Govindan, Johan Vansteenkiste, Anne-Pascale Meert, Wouter K. de Jong, Nasser Khaled Altorki, Kotaro Higashi, Angela Van Baardwijk, Gerben R. Borst, Lieveke Ameye, Jean-Jacques Lafitte, Thierry Berghmans, Patrick Flamen, Ramon Rami-Porta, and Jean-Paul Sculier

IPD SUV

- 11/25 auteurs ont accepté de participer
- 1563 patients (44% de l'ensemble des données publiées).
- En analyse multivariée:
  - HR pour le SUVmax = 1,43 (IC 95% 1,22–1,66)
  - autres variables associées à la survie: stade I-III, âge, taille de la tumeur primitive, le fait d'être traité par chirurgie.
- L'interaction entre le SUV et le stade était significatif, sans effet détectable du SUV dans les stades IV.

Facteurs métaboliques CBPC

Reference	Imaging	N	Mesure	Résultats	Uni/Multi
Lee, 2009	TEP-CT	67	SUVmax	meanSUV(max)	M
Inal, 2013	TEP-CT	54	SUVmax	PS, stade	M
Oh, 2012	TEP-CT	106	SUVmax, WBMTV	stade et WBMTV	M
Ziai, 2013	TEP-CT	29	SUVmax	SULtotal	M
Go, 2014	TEP-CT	145	sumSUVmax	sumSUVmax élevé (hazard ratio 2,676; p < 0,001)	M
Zhu, 2011	TEP-CT	98	Metabolic tumor volume integrated SUV, SUVmean	MTV, iSUV, stade, LDH	M
Oh, 2013	TEP-CT	91	Whole body metabolic tumor volume (WBMTV)	PS (HR = 2,31, p = 0,015), initial CT cycles (HR = 0,24, p < 0,001), nombre de foyers extra-thoraciques (HR = 2,75, p < 0,001)	M

Conclusions

- FP ont un rôle important dans la prise en charge des patients dans le cadre de protocoles thérapeutiques (équilibre entre les bras de traitement) ou dans la comparaison de groupes de patient.
- Ils ne peuvent pas être utilisés pour une prédiction individualisée du devenir d'un patient.
- Les FP reconnus sont essentiellement le stade d'extension de la néoplasie et l'indice de performance.

Conclusions

- La littérature dans le domaine des FP est particulièrement abondante et nécessite une lecture critique.
- Avant de pouvoir intégrer de nouveaux FP en routine, il est primordial, particulièrement dans l'étude des biomarqueurs, d'améliorer la méthodologie utilisée (standardisation des techniques de laboratoire et des tests statistiques) mais aussi de prévoir une validation dans des groupes indépendants de patients.