UniversitätsKlinikum Heidelberg

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Proliferation in lung cancer: Worth measuring?

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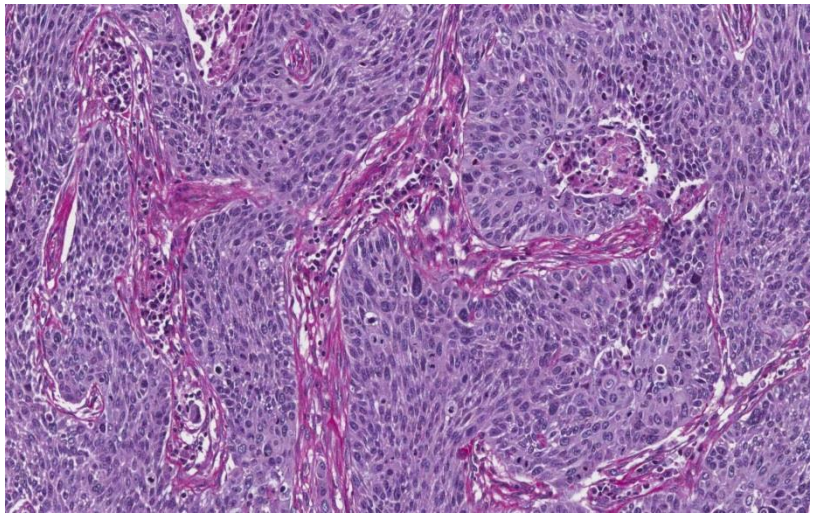
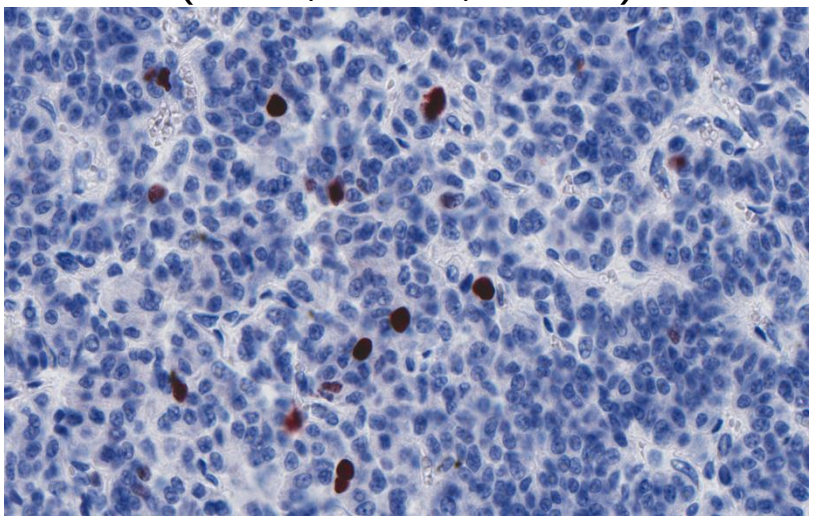
- No disclosures
- No conflicts of interest

Measurement of Proliferation

Mitosis



Proliferation-associated antigens
(Ki-67, PHH3, others)



Ki-67

- generated by immunizing mice with nuclei of the Hodgkin lymphoma cell line L428 (Gerdes et al., 1983).
- Ki = Kiel (city in northern Germany), 67 = number of the original clone in the 96-well plate.
- Ki-67 protein is present during all active phases of the cell cycle (G1, S, G2, and mitosis), but is absent from resting cells (G0).
- associated with ribosomal RNA transcription.
- Ki-67 and MIB-1 monoclonal antibodies are directed against different epitopes of the same proliferation-related antigen, MIB-1 is generally considered the most specific antibody.

Gerdes J, Schwab U, Lemke H, Stein H (1983). "Production of a mouse monoclonal antibody reactive with a human nuclear antigen associated with cell proliferation". Int. J. Cancer 31 (1): 13–20.

Proliferation Assessment in Routine Diagnostics

- Mitotic count established for breast cancer grading, FNCLCC grading etc.
- Ki-67 currently only established for neuroendocrine tumors (NETs) of the GI tract.
- Ki-67 is frequently used for breast cancer in many institutions.

Proliferation in Cancer

PubMed Search Results (April 2015)

- „Cancer“ AND „Proliferation“ = 164513 hits
- „Lung Cancer“ AND „Proliferation“ = 13300 hits
- „Lung Cancer“ AND „Ki-67“ = 983 hits
- „Lung Cancer“ AND „MIB-1“ = 196 hits

British Journal of Cancer (2004) 91, 2018–2025

www.bjcancer.com

- 37 studies of NSCLC, SCLC (n=1) and carcinoids (n=2) published between 1991 and 2002
- 3983 patients total

Ki-67 expression and patients survival in lung cancer: systematic review of the literature with meta-analysis

B Martin*[,1], M Paesmans[2], C Mascaux[1,4], T Berghmans[1], P Lothaire[3], A-P Meert[1,4], J-J Lafitte[5] and J-P Sculier[1]

[1]Critical Care Department and Thoracic Oncology, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, Brussels, Belgium; [2]Data Centre, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, Brussels, Belgium; [3]Department of Surgery, Institut Jules Bordet, Centre des Tumeurs de l'Université Libre de Bruxelles, Brussels, Belgium; [4]FNRS (Fonds National de la Recherche Scientifique), Belgium; [5]Department of Chest Medicine and Thoracic Oncology, CHRU Lille, Hôpital Calmette, Lille, France

there was no statistical difference in quality scores between the significant and nonsignificant studies evaluable for the meta-analysis, we were allowed to aggregate the survival results. The combined hazard ratio for NSCLC, calculated using a random-effects model was 1.56 (95% CI: 1.30–1.87), showing a worse survival when Ki-67 expression is increased. In conclusion, our meta-analysis shows that the expression of Ki-67 is a factor of poor prognosis for survival in NSCLC.

British Journal of Cancer (2004) **91,** 2018–2025. doi:10.1038/sj.bjc.6602233 www.bjcancer.com
Published online 16 November 2004

- Ki-67 range: 10-78%
- Ki-67 cut-off: 1-60%

Table I Main characteristics and results of the eligible studies

	All studies		NSCLC						SCLC		Carcinoid tumours		Any histology any stage	
			Any stage (I–IV)		Locoregional (I–II)		Surgical treatment (I–III)							
	Total	S	Total	S	Total	S	Total	S	Total	S	Total	S	Total	S
Number of studies	37 (20)	15 (10)	10 (5)	4 (4)	8 (5)	3 (2)	11 (6)	3 (2)	1 (1)	1 (1)	2 (1)	2 (1)	5 (2)	2 (0)

NSCLC = non-small-cell lung cancer; SCLC = small-cell lung cancer; S = number of studies identifying Ki-67 positivity as a statistically significant prognostic factor; () = number of studies evaluable for meta-analysis.

→ Overall 15/37 studies (40.5%) demonstrated a negative prognostic effect for Ki-67.

→ Only 5 NSCLC studies identifying Ki-67 as a statistically significant prognostic factor were available for meta-analysis

Table 3 HR value for NSCLC subgroups according to histology subtypes and stages

Subgroup	Studies	Patients	Fixed effect HR (95% CI)	Heterogeneity test	Ramdom effect HR (95% CI)
Adenocarcinoma	$n=4$	258	2.45 (1.66–3.64)	$P=0.26$	
Nonsquamous carcinoma	$n=3$	158	2.47 (1.32–4.57)	$P=0.90$	
Stage I	$n=4$	783	1.56 (1.26–1.93)	$P=0.17$	
Stage I–II	$n=4$	437	1.16 (0.82–1.66)	$P=0.21$	
Stage I–III	$n=6$	533	1.79 (1.40–2.28)	$P=0.04$	1.82 (1.26–2.64)

→ Hazard ratios for histological NSCLC subtypes could only be analyzed for 258 adenocarcinomas and 158 non-squamous carcinomas

Lung Cancer 79 (2013) 1–7

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Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Review

Clinical impact of ki-67 labeling index in non-small cell lung cancer

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- Literature review from 2000 – 2012 (April).
- Exclusion of articles in which data on NSCLC histology could not be extracted.
- A total of 28 articles investigating Ki-67 in NSCLC were included.
- 25 articles reported solely on surgically treated stage I-III patients.

Table 1
Studies reporting on prognostic information of ki-67 labeling index in NSCLC (cut-off 5–25%).

Author/year	Histology (%)	No. pts.	Stage	Cutoff level % (no. pts.)	End-point	Median survival months	3y	5y	Univariate analysis	Multivariate analysis
Yamashita et al. (2011) [46]	ADC: 23 SQC: 16 BAC: 52 Oth: 9	44	T1	<5% (31) ≥5 (13)	PFS	– –	96 77	96 30	=0.04	=0.04
Inoue et al. (2007) [53]	ADC 100	97	IA–IIIA	<5 (67) >5 (30)	DFS	– –	– –	99 76	<0.001	0.12
Haga et al. (2003) [31]	ADC: 63 SQC: 36	187	I	<10 (31) ≥10 (27)	OS	– –	95 80	90 70	=0.0014[a]	–
Woo et al. (2008) [47]	ADC: 100	184	I	<10 (105) ≥10 (79)	PFS	– –	95 72	93.2 68.6	<0.001	–
Carbognani et al. (2002) [54]	ADC: 22 SQC: 63 LCC: 15	78	I–IIIA	<10 (50) >10 (28)	OS	– –	– –	– –	0.76	0.94
Tsubochi et al. (2006) [32]	ADC: 54 SQC: 44 AdSq: 2 LCC: <1	219	I–III	<20 (na) ≥20 (na)	OS	– –	– –	– –	=0.0008[b]	=0.026[b]
Minami et al. (2002) [34]	ADC:100	47	I	<20 (25) ≥20 (25)	OS		92.0 77.3	88.0 53.1	=0.004	Not sign
Shiba et al. (2000) [35]	ADC: 59 SQC: 38 AdSq: 1 LCC: 1	156	I–III	<20 (75) ≥20 (78)	OS			67.7 39.6	=0.0043	=0.0087[c]
Rigau et al. (2002) [49]	ADC: 37 SQC: 49 LCC: 14	86	I–IV	≤20 (75) ≥20 (11)	OS	– –	– –	– –	–	=0.73
David et al. (2004) [57]	ADC: 46 SQC: 30 NOS: 25	61	I–IV	≤20 (na) >20 (na)	OS	– –	– –	– –	=0.92	–
Cagini et al. (2000) [33]	ADC: 28 SQC: 44 LCC: 22 BAC: 5	99	I–II	<20 (48) ≥20 (37)	OS	– –	– –	45 67	=0.4	–
Demarchi et al. (2000) [36]	ADC:100	64	I–IIIB	<22.22 (32) ≥22.22 (32)	OS	– –	70 35	26 25	<0.01	=0.44

[a] Multivariate analysis included only adenocarcinoma histology and smokers.
[b] Worse prognosis with high ki-67.
[c] Multivariate analysis included only Non-squamous carcinoma histology.

Overall cut-off levels ranged from 5% - 30%

- 13 papers did not explain how the cut-off was decided.
- 3 papers used the median Ki-67 labeling index, 1 study the H-score median.
- 7 studies refered to cut-off values from previous studies.
- only 1 study used the best discriminatory value.
- 8 studies did not mention the number of analyzed tumor cells.

Table 2
Studies reporting on prognostic information of ki-67 labeling index in NSCLC (cut-off 25–30%).

Author/year	Histology (%)	No. pts.	Stage	Cut-off level % (no. pts.)	End-point	Median survival months	3y	5y	Univariate analysis	Multivariate analysis
Huang et al. (2005) [37]	ADC: 58 SQC: 34 LCC: 8	173	I–III	<25 (na) ≥25 (na)	OS	– –	90 80	67 44.1	=0.01	–
Ngyuen et al. (2007) [48]	ADC: 57 SQC: 36 AdSq: 6 LCC: 2	53	I–III	<25 (na) ≥25 (na)	DFS	– –	– –	– –	=0.047	=0.216
Imai et al. (2009) [38]	ADC: 66 SQC: 31 LCC: 3	282	I	<25 (na) ≥25 (na)	OS	– –	96 80	96 69	=0.0001	=0.2762
Kaira et al. (2008) [39]	ADC: 62 SQC: 31 LCC: 7	321	I–III	<25 (135) ≥25 (186)	OS	– –	92 75	90 65	<0.001	=0.38
Yang et al. (2006) [40]	ADC: 60 SQC: 39 LCC: 4 Oth: 6	128	I–IIIA	<25 (28) ≥25 (100)	OS	50 42.7	62 62	55 35	=0.47	=0.30
Takahashi et al. (2002) [41]	ADC: 58 SQC: 42	62	N0	<25 (40) ≥25 (22)	DFS	– –	80 60	80 55	=0.023	=0.97
Maddau et al. (2006) [51]	ADC: 38 SQC: 42 AdSq:18 LCC: 3	180	I–III	<25 (77) ≥25 (103)	OS		58 48		=0.003	
Carvalho et al. (2000) [58]	ADC:100	45	I–IV	<27.8 (30) ≥27.8 (15)	OS	– –	– –	– –	=0.53	–
Yoo et al. (2007) [42]	ADC: 46 SQC: 54	219	I–IIIA	<30 (202) ≥30 (17)	OS	– –	– –	47 49	=0.837	=0.696
Hommura et al. (2000) [43]	ADC: 49 SQC: 42 AdSq: 4 LCC: 5	109	I–II	<30 (52) ≥30 (57)	OS	– –	85 55	78 48	=0.01	=0.004
Ngyuen et al. (2000) [55]	ADC: 57 SQC: 38 LCC: 5 BAC:1	89	I–IV	<30 (na) ≥30 (na)	OS	– –	38 35	– –	>0.05	–

Predictive Value of Ki-67 in NSCLC

Table 4
Studies on predictive information of ki-67 on chemotherapy in NSCLC.

Author/year	Histology (%)	No. pts.	Stage	Treatment	Cut-off level % (no. pts.)	RR%	*p*-Value	Survival	*p*-Value
Mohamed et al. (2008) [60]	ADC: 53 SQC: 47	28	pN2	Platinum based	<20 (13) >20 (23)	45.5 47.0[a]	=0.937	– –	–
Filipits et al. (2007) [52]	ADC: 32 SQC: 56 Oth: 12	401	I–III	Cisplatin based adjuvant	<85 (196/182) >85 (205/195) [b]/[c]	– –	–	48/45 49/50 [d]	=0.45
Yan et al. (2010) [61]	ADC: 39 Oth: 61	151	I–III	Various adjuvant	<50 (96) ≥50 (55)	– –	– –	22.24 29.37[e]	=0.517
Dingemans et al. (2001) [62]	ADC: 63 SQC: 13 LCC: 24	36	III–IV	Platinum based	<30 (20) 31–60 (11) >60 (5)	39 (7*) 80	=0.085	13 9 11[f]	=0.51
Van de Vaart et al. (2000) [63]	ADC: 22 SQC: 41 LCC: 33 Oth: 4	27	III	Concomitant RT and cisplatin	<60 (13) >60 (14)	– –	–	8.8 12.4[f]	=0.13

[a] CR + PR.
[b] H-score (0–300).
[c] Chemotherapy group/control group.
[d] % alive at 5 years.
[e] DFS months.
[f] OS months 7* including 0–60%.

→ Significant heterogeneity with respect to histology, case numbers, treatment, and cut-off levels
→ No study could provide evidence for a predictive value of Ki-67

BJC

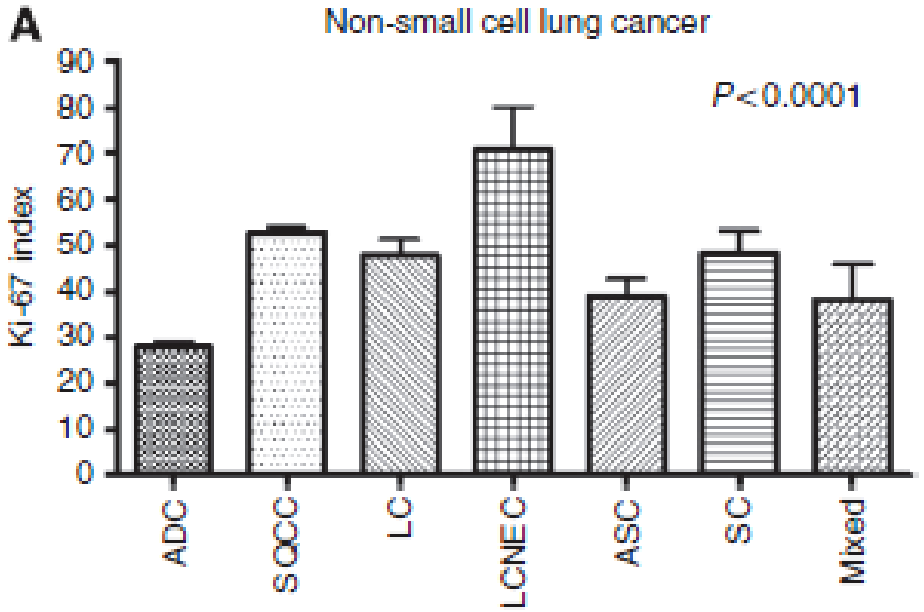
British Journal of Cancer (2014), 1–8 | doi: 10.1038/bjc.2014.402

Keywords: lung cancer; proliferation; Ki-67; prognosis

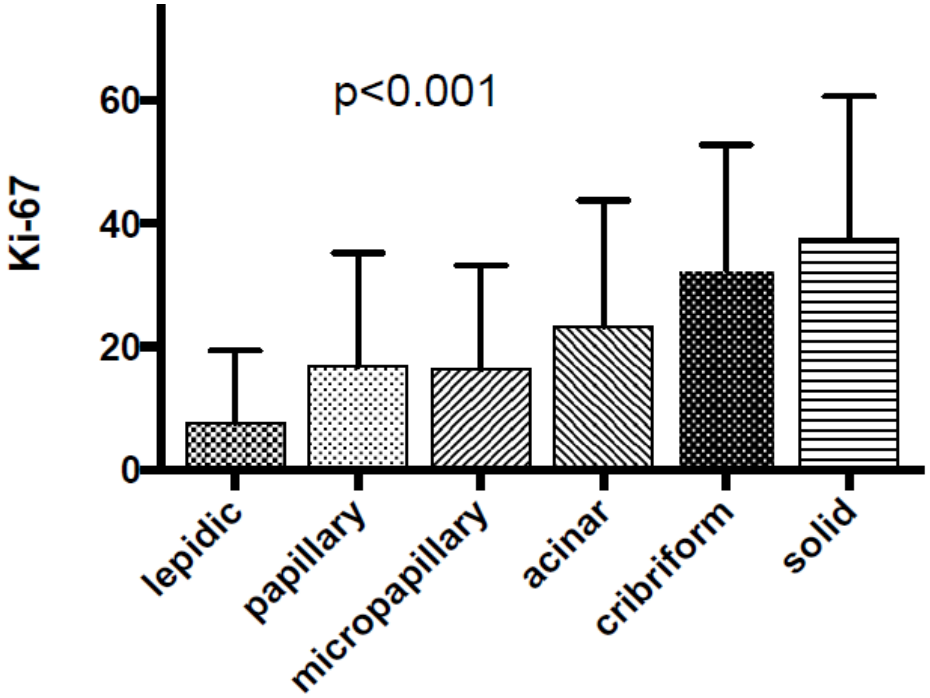
Tumour cell proliferation (Ki-67) in non-small cell lung cancer: a critical reappraisal of its prognostic role

A Warth*[,1], J Cortis[1], A Soltermann[2], M Meister[3,8], J Budczies[4], A Stenzinger[1], B Goeppert[1], M Thomas[5,8], F J F Herth[6,8], P Schirmacher[1], P A Schnabel[1,8], H Hoffmann[7], H Dienemann[7,8], T Muley[3,8,9] and W Weichert*[,1,9]

- Test cohort: 1065 NSCLCs including 482 adenocarcinomas (TMA Heidelberg)
- Validation cohort: 184 adenocarcinomas (TMA Zurich), 233 squamous cell carcinomas (TMA Heidelberg)
- Antibody: MIB-1 clone
- Evaluation: Counting of Ki-67 positive tumor cells/100 tumor cells



ADC = Adenocarcinoma
SQCC = Squamous Cell Carcinoma
LC = Large Cell Carcinoma
LCNEC = Large Cell Neuroendocrine Carcinoma
ASC = Adeno-squamous Carcinoma
SC = Sarcomatoid Carcinoma



Warth A, Cortis J, Soltermann A, Meister M, Budczies J, Stenzinger A, Goeppert B, Thomas M, Herth FJ, Schirmacher P, Schnabel PA, Hoffmann H, Dienemann H, Muley T, Weichert W.: Tumour cell proliferation (Ki-67) in non-small cell lung cancer: a critical reappraisal of its prognostic role. Br J Cancer. 2014 Sep 9;111(6):1222-9.

Warth A, Muley T, Kossakowski C, Stenzinger A, Schirmacher P, Dienemann H, Weichert W.: Prognostic impact and clinicopathological correlations of the cribriform pattern in pulmonary adenocarcinoma. J Thorac Oncol. 2015 Apr;10(4):638-44.

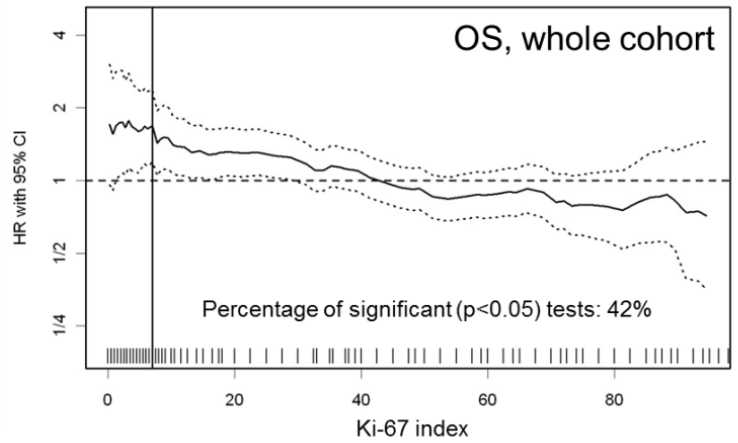
Table 1. Association of proliferative activity with staging parameters for the whole test cohort of non-small cell lung cancers (NSCLC), the test cohort adenocarcinoma subgroup (ADC), and the test cohort squamous cell carcinoma subgroup (SQCC)

Characteristics	All NSCLC	Ki-67 mean	Ki-67 s.d.	*P*-value	ADC	Ki-67 mean	Ki-67 s.d.	*P*-value	SQCC	Ki-67 mean	Ki-67 s.d.	*P*-value
All cases												
	1065	40.7	27.5		482	25.8	24.6		437	52.8	24.3	
UICC stage												
I	389	36.6	28.7		198	21.5	22.2		161	52.6	25.4	
II	337	44.5	25.7	0.001	103	34.1	25.3	<0.001	172	52.2	23.4	0.888
III	311	41.4	27.1		165	31.2	25.0		98	53.7	24.2	
IV	28	42.9	28.1		16	34.7	27.3		6	59.0	19.9	
Tumour stage												
pT1	198	39.5	29.4		92	23.0	23.0		84	53.9	26.2	
pT2	672	40.0	26.9	0.010	306	28.9	24.8	0.123	278	51.6	24.1	0.374
pT3	174	46.2	26.7		70	31.1	25.4		69	56.8	21.6	
pT4	21	29.5	26.1		14	23.6	22.2		6	46.7	29.9	
Nodal status[a]												
pN0	545	38.4	28.1		258	24.5	23.4		224	51.9	25.7	
pN1	261	45.5	25.4	0.008	83	34.5	25.4	0.005	136	53.4	21.8	0.807
pN2	247	40.0	27.5		138	30.5	25.4		71	54.1	24.6	
pN3	5	38.0	29.4		3	22.5	16.4		1	37.5		
Distant metastasis												
M0	1038	40.6	27.5	0.814	467	27.8	24.5	0.484	431	52.7	24.3	0.527
M1	27	41.9	28.1		15	32.3	26.5		6	59.0	19.9	

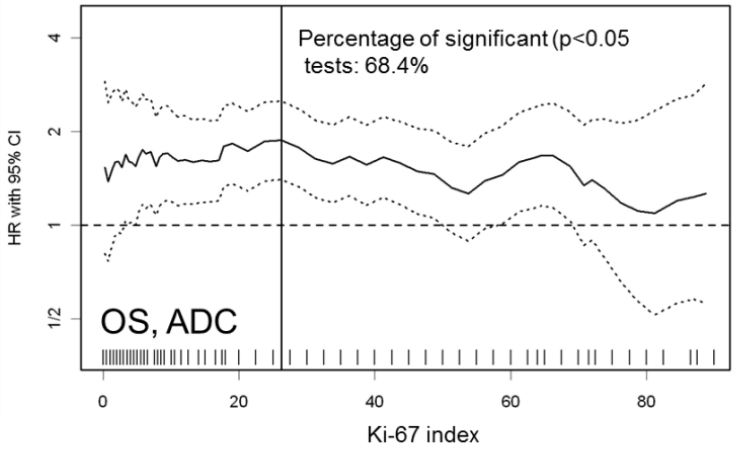
Abbreviations: s.d. = standard deviation; UICC = Union Internationale Contre le Cancer.

[a]For seven cases data of nodal status were not available (limited resection).

A



B



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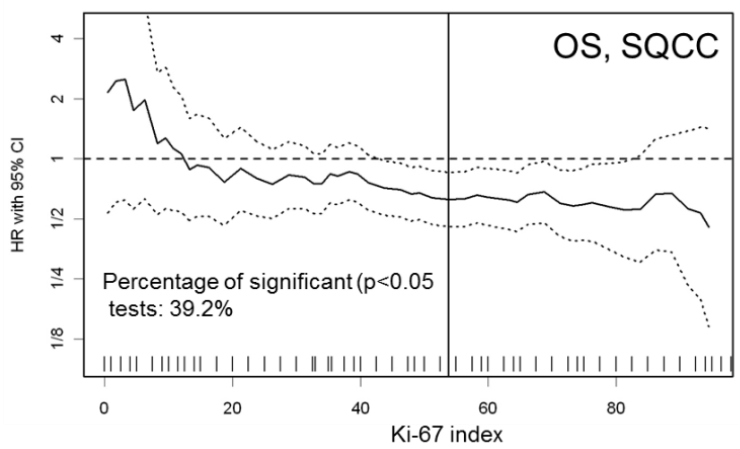
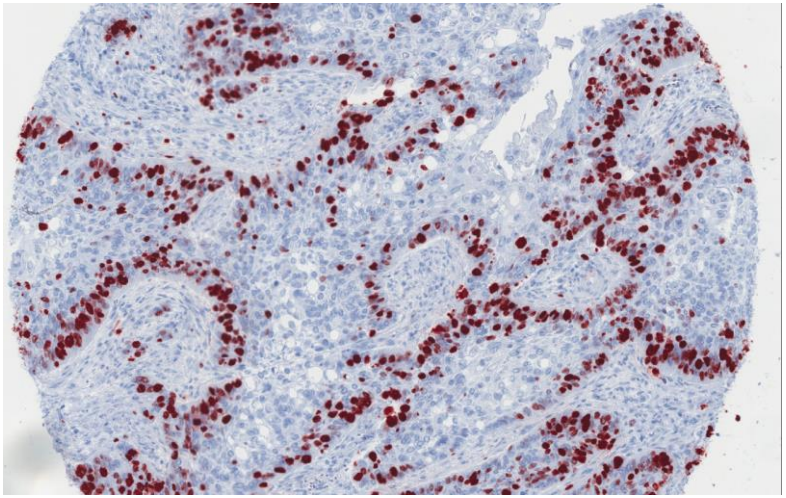
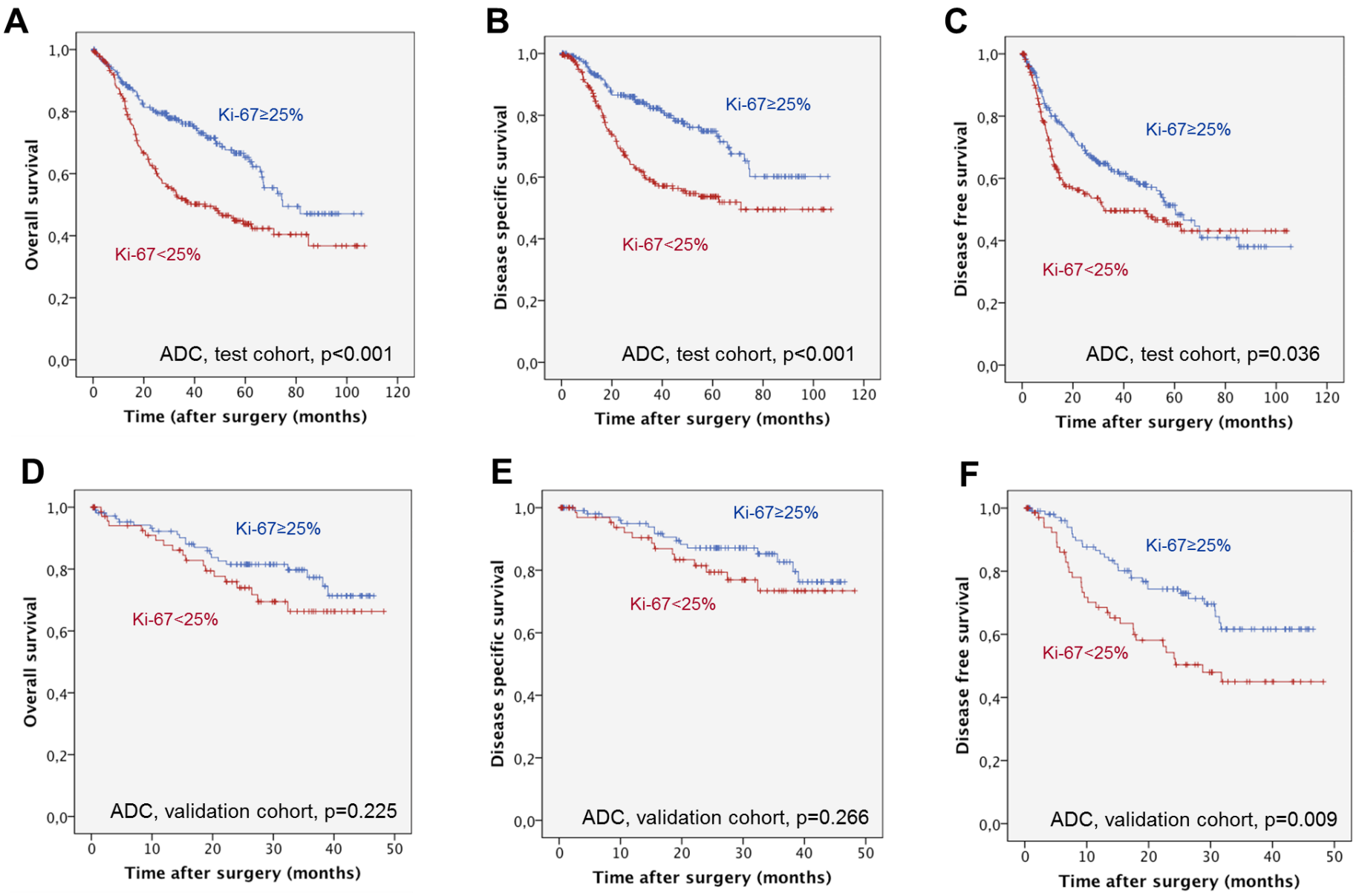


- Dichotomization of a continous prognostic parameter means loss of prognostic information.
- A clinically relevant cut-off value should maximize the hazard ratio between the groups.
  → mean/median values are not optimal
- 25% Ki-67 index was found as the optimal cut-off value for adenocarcinomas.

Ki-67 in SQCC





→ Ki-67 was found a stage-independend predictor of survival in adenocarcinomas (p=0.004; HR for overall survival 1.56)

MODERN PATHOLOGY (2012) 25, 1117–1127

A grading system combining architectural features and mitotic count predicts recurrence in stage I lung adenocarcinoma

Kyuichi Kadota[1,2], Kei Suzuki[1], Stefan S Kachala[1], Emily C Zabor[3], Camelia S Sima[3], Andre L Moreira[4], Akihiko Yoshizawa[4,5], Gregory J Riely[6], Valerie W Rusch[1], Prasad S Adusumilli[1,7] and William D Travis[4]

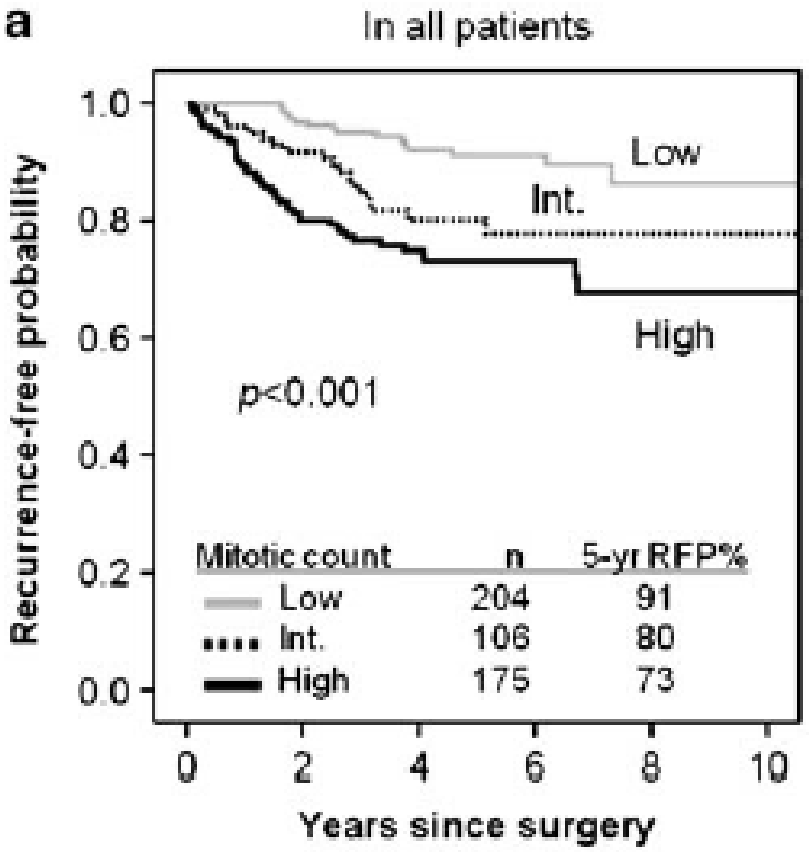


Table 2 Association between nuclear features and recurrence

Variables	N	%	*5-year RFP (%)*	P-*value*
Nuclear diameter				**0.007**
Small	232	48	86	
Intermediate	150	31	82	
Large	103	21	74	
Nuclear atypia				**0.006**
Mild	231	48	87	
Moderate	139	29	81	
Severe	115	24	75	
Nuclear/cytoplasmic ratio				0.068
Low/intermediate	391	81	80	
High	94	19	91	
Chromatin pattern				0.092
Homogeneous	85	18	87	
Fine granular	229	47	83	
Coarse granular	171	35	79	
Prominence of nucleoli				0.059
Indistinct	133	27	87	
Distinct	217	45	82	
Large	135	28	87	
Intranuclear inclusion				0.190
Absence	441	91	82	
Presence	44	9	88	
Mitotic count				**<0.001**
Low	204	42	91	
Intermediate	106	22	80	
High	175	36	73	
Atypical mitoses				**<0.001**
Absence	362	75	86	
Presence	123	25	72	

Abbreviation: RFP, recurrence-free probability.
Significant *P*-values are shown in bold: all *P*-values from log-rank test.

(*J Thorac Oncol.* 2015;10: 673–681)

ORIGINAL ARTICLE

Mitosis Trumps T Stage and Proposed International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society Classification for Prognostic Value in Resected Stage 1 Lung Adenocarcinoma

Edwina Elizabeth Duhig, FRCPA,† Andrew Dettrick, FRCPA,‡§|| David Burleigh Godbolt, FRCPA,‡ John Pauli, FRCPA,|| Anthony van Zwieten, BSc(Hons),‡ Aaron Richard Hansen, FRACP,¶# Ian Anthony Yang, PhD,†** Kwun Meng Fong, PhD,†** Belinda Edith Clarke, PhD,†‡ and Rayleen Veronica Bowman, PhD†***

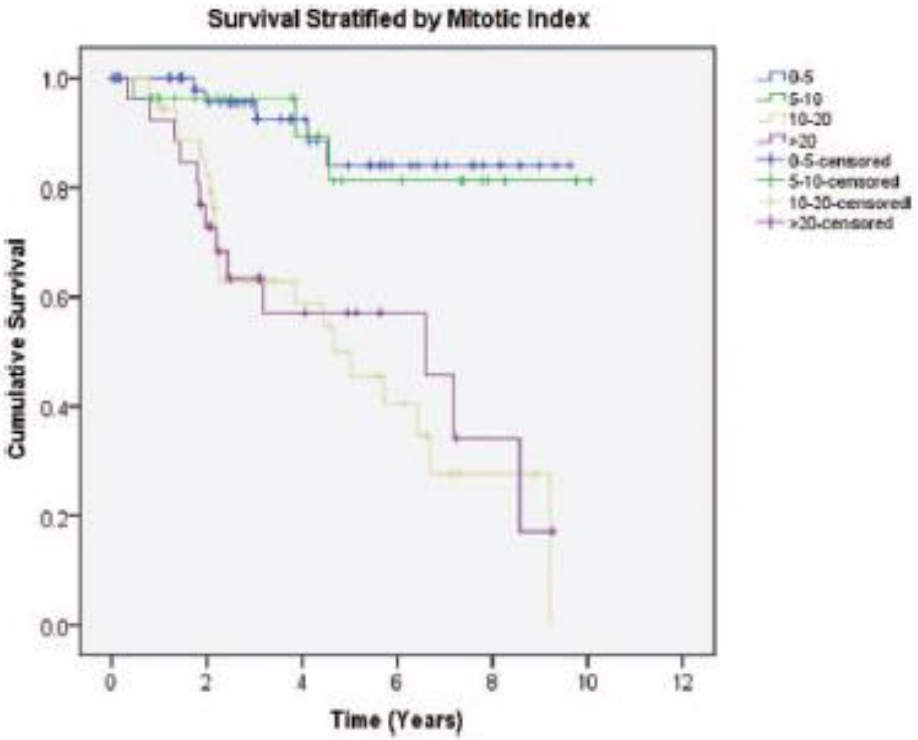


FIGURE 4. Survival stratified by Mitosis count. Survival stratified by mitosis counts showed clear divergence with statistically poorer survival for tumors with mitosis counts above 10/10 high-power fields (log-rank $p < 0.0001$).

TABLE 3. Multivariate Analysis

					95% Confidence Interval for Hazard Ratio	
	B	SE	*p*	Hazard Ratio	Lower	Upper
Sex (0 = male, 1 = female)	−0.606	0.359	0.091	0.545	0.270	1.101
Age (0 = below median, 1 = above median)	−0.071	0.322	0.826	0.932	0.495	1.753
Stage (7th edition) (0 = 1A, 1 = 1B)	0.181	0.355	0.610	1.199	0.598	2.403
Nuclear grade (0 = grade 2 or 3, 1 = grade 4)	0.354	0.355	0.318	1.425	0.711	2.858
Necrosis (0 = 0%, 1 = 1% or greater)	0.333	0.406	0.412	1.395	0.629	3.090
Mitosis count (0 = 0–10 per 10 HPF, 1 ≥ 10 per 10 HPF)	1.523	0.452	0.001	4.585	1.893	11.110
Differentiation (0 = moderate/well, 1 = poor)	−0.027	0.357	0.940	0.973	0.484	1.959

Multivariate Cox regression analysis entering age, sex, and the significant covariates from univariate analyses (all as dichotomous variables).
B, regression coefficient; SE, standard error; hazard ratio, risk of death for prognostic variables (category 1 vs. category 0); HPF, high-power field.

Prognostic and Predictive Value of Gene Expression Profiles in Adenocarcinomas

Clin Cancer Res; 19(22); 6261–71.

Clinical Cancer Research

Imaging, Diagnosis, Prognosis

Validation of a Proliferation-Based Expression Signature as Prognostic Marker in Early Stage Lung Adenocarcinoma

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OPEN

Validation of a Molecular and Pathological Model for Five-Year Mortality Risk in Patients with Early Stage Lung Adenocarcinoma

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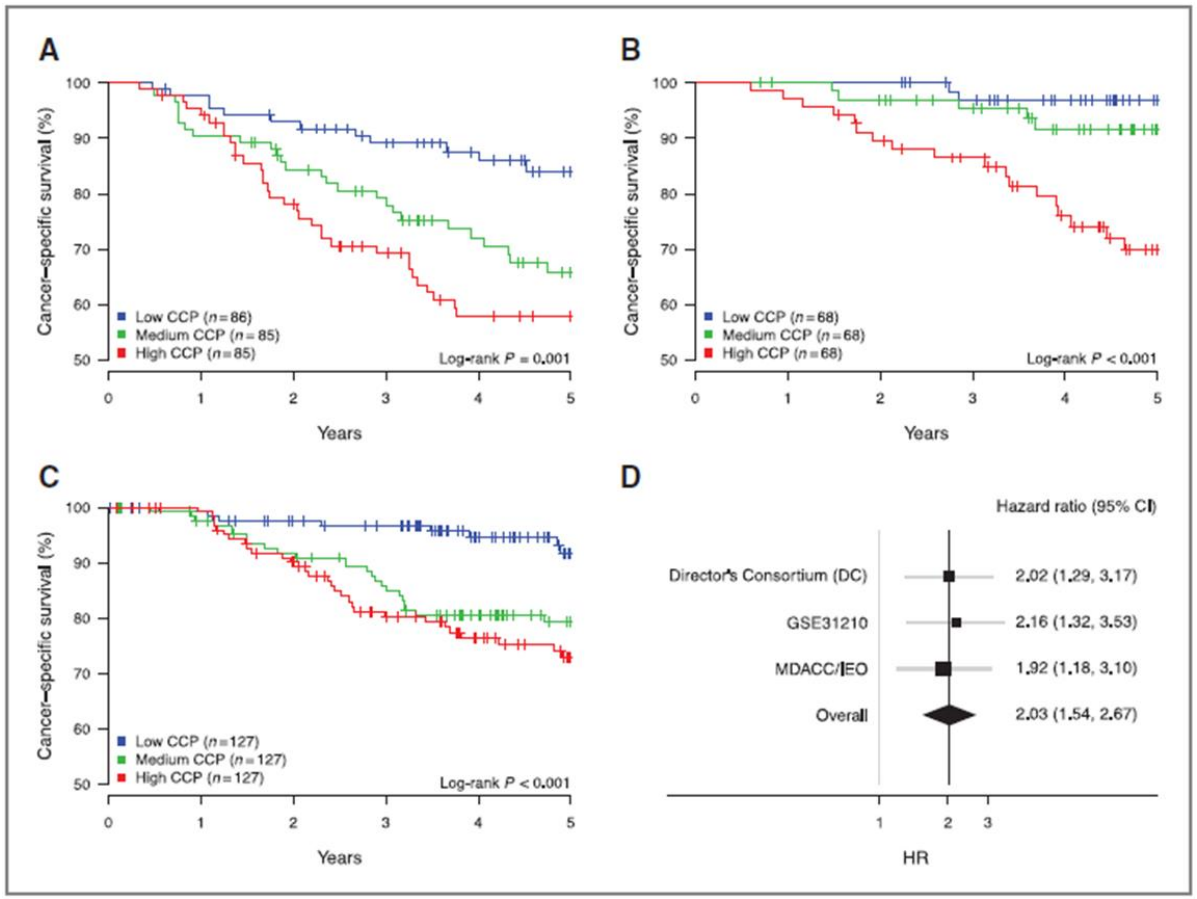
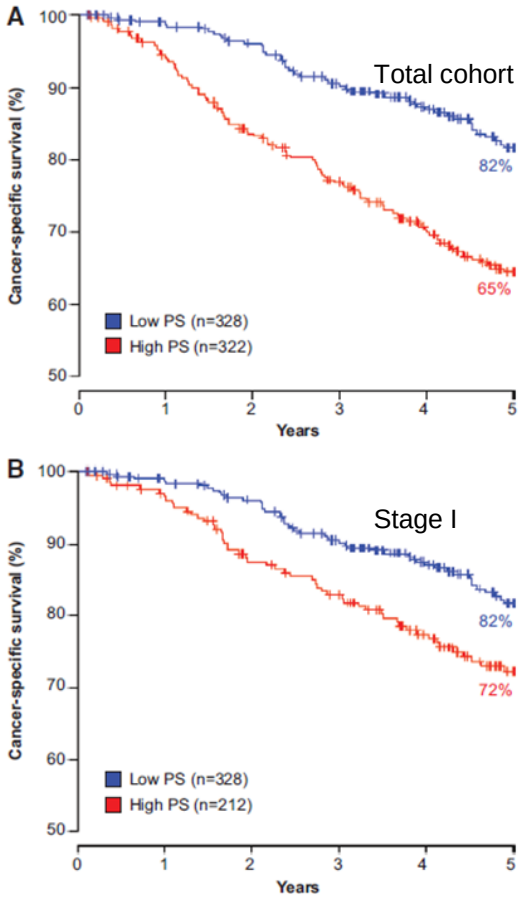
- Establishment of a cell cycle progression (CCP) score based on the quantitative mRNA expression of 31 cell cycle-associated genes.

- One CCP unit represents a 2-fold change in expression levels (unweighted).



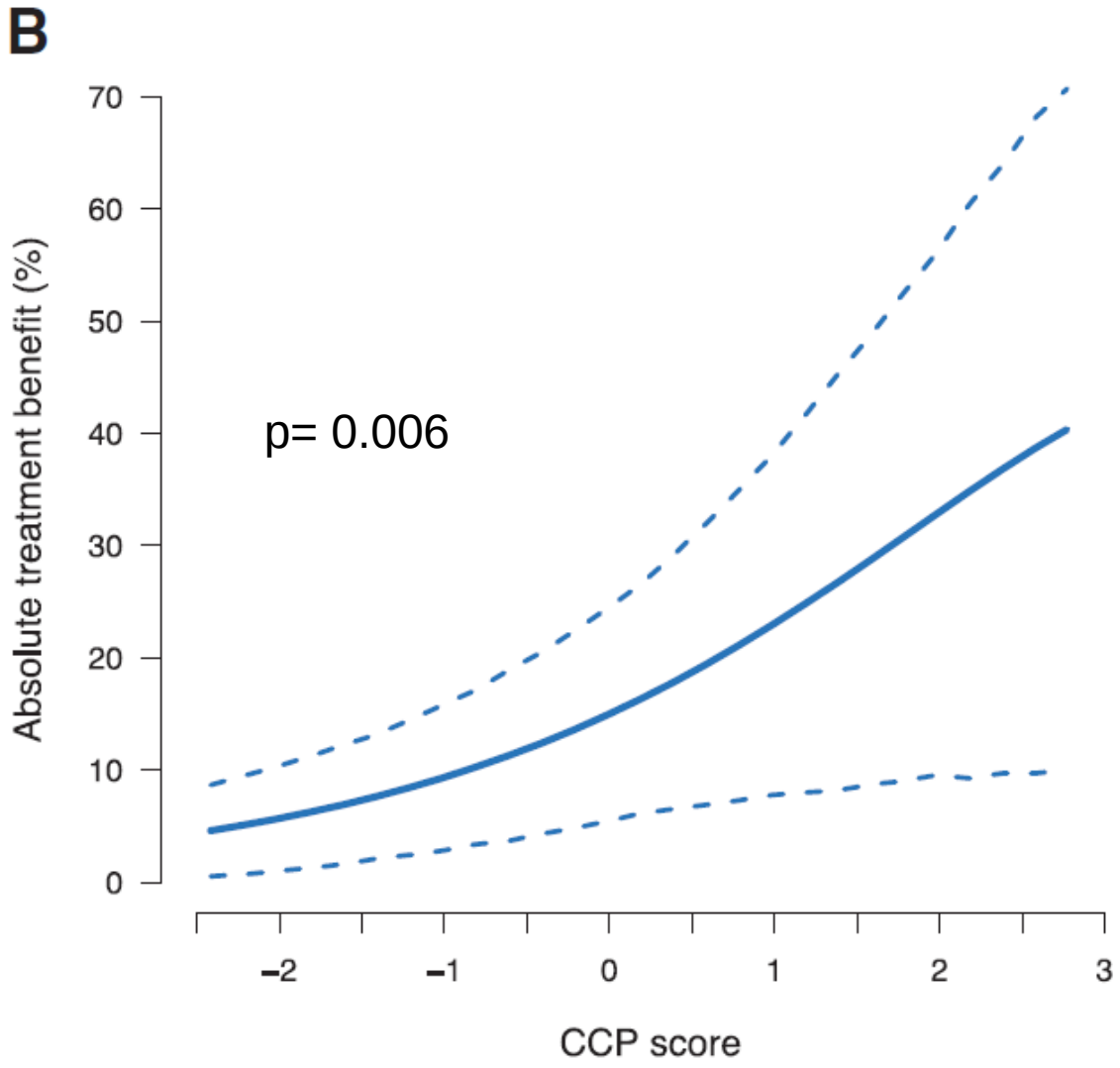
Establishment of the CCP score based on 2 public microarray datasets (DC, GSE31210) and FFPE samples from 2 institutions (n=381 stage I-II adenocarcinomas)



Validation of the CCP score in a series of 650 stage I-II adenocarcinomas

→ The CCP score was the dominant prognostic variable in uni- and multivariate analyses

Predictive Value of the CCP Score



Absolute benefit from adjuvant treatment depending on CCP score (derived from the difference in survival ratios between treated and untreated patients; Zhang and Klein method). CCP high and low was based on the median cut-off point.

Interobserver Agreement

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ARTICLE

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An International Ki67 Reproducibility Study

Mei-Yin C. Polley, Samuel C. Y. Leung, Lisa M. McShane, Dongxia Gao, Judith C. Hugh, Mauro G. Mastropasqua, Giuseppe Viale, Lila A. Zabaglo, Frédérique Penault-Llorca, John M.S. Bartlett, Allen M. Gown, W. Fraser Symmans, Tammy Piper, Erika Mehl, Rebecca A. Enos, Daniel F. Hayes, Mitch Dowsett, Torsten O. Nielsen, on behalf of the International Ki67 in Breast Cancer Working Group of the Breast International Group and North American Breast Cancer Group

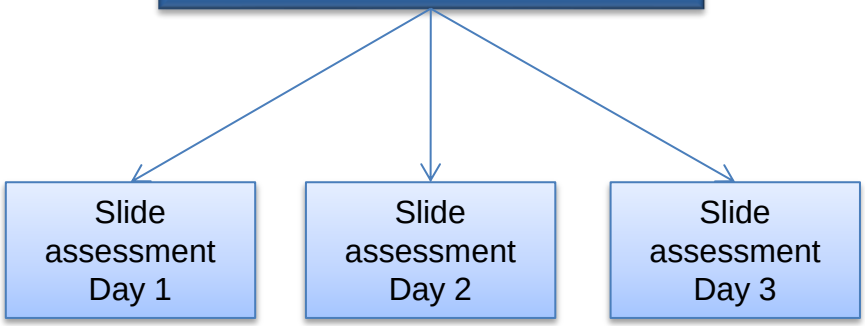
- Participation of 8 experienced laboratories from the US and Europe.
  - All participants used the MIB-1 clone but with different local staining protocols and scoring methods.
- Analysis of 100 breast cancer cases based on a TMA.
- Assessment of intra- and interlaboratory agreement based on the intraclass correlation coefficient (ICC) ranging from 0 (lowest) to 1 (highest agreement).

Experiments

Intralaboratory Reproducibility

Experiment 1

- Local staining protocol
- Local scoring method



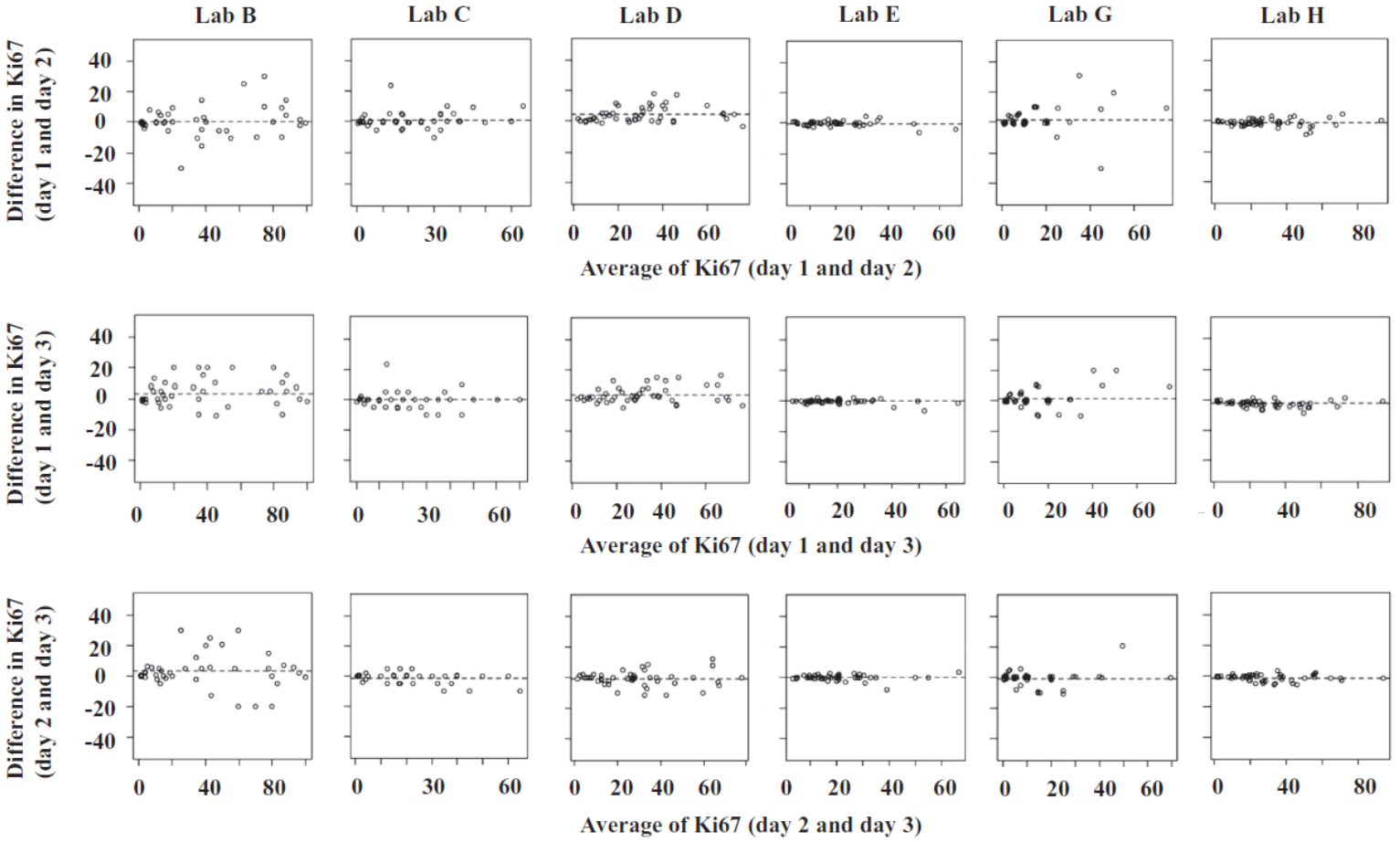
Interlaboratory Reproducibility

Experiment 2

- A: central staining, local scoring
- B: local staining, local scoring

Results Experiment 1

Intralaboratory Reproducibility

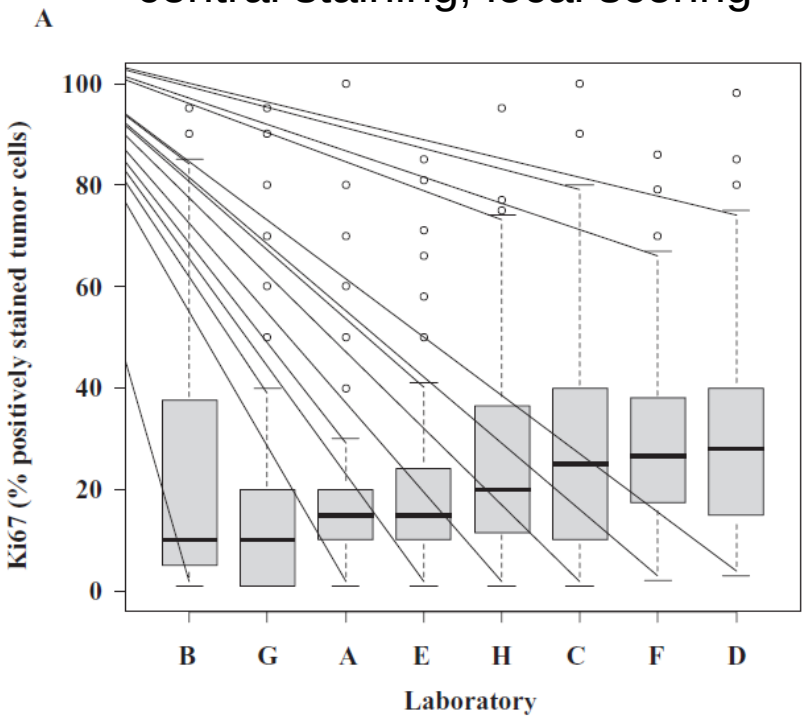


Intraclass Correlation Coefficient (ICC) = 0.94

Results Experiment 2

Interlaboratory Reproducibility

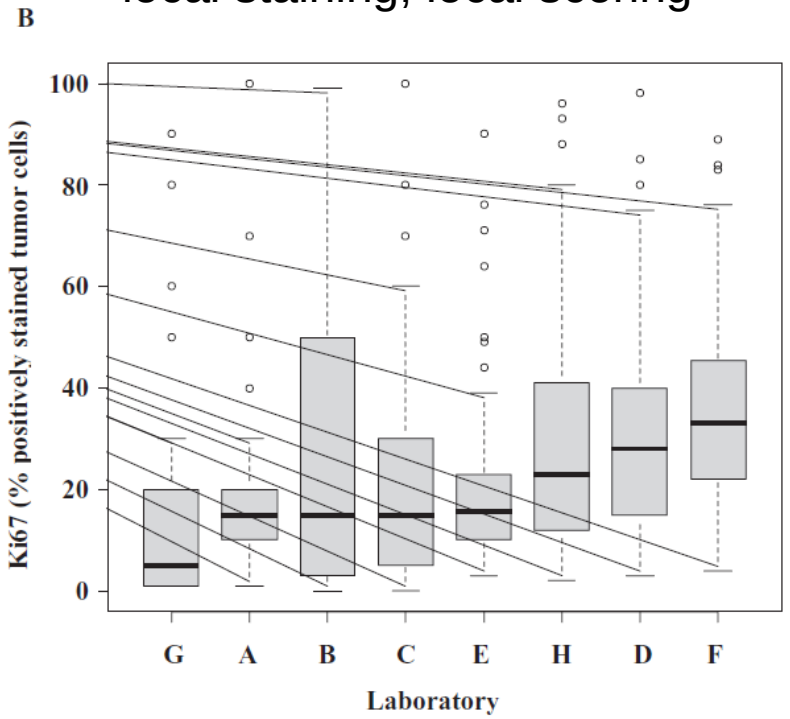
central staining, local scoring



ICC = 0.71

Range of the geometric mean: 10% - 28%

local staining, local scoring



ICC = 0.59

Range of the geometric mean: 6.1% - 30.1%

Conclusions

- Significant lack of standardized methodology of proliferation assessment (time/type of fixation, storage, antibody, staining, evaluation, cut-off definition, …).
  → difficult to compare studies and to draw definitive conclusions.

- There is accumulating evidence that assessment of proliferation is of prognostic value for early stage adenocarcinomas.
  → further studies required (mitosis vs. Ki-67).

- No sufficient evidence to support proliferation assessment in squamous cell carcinomas.

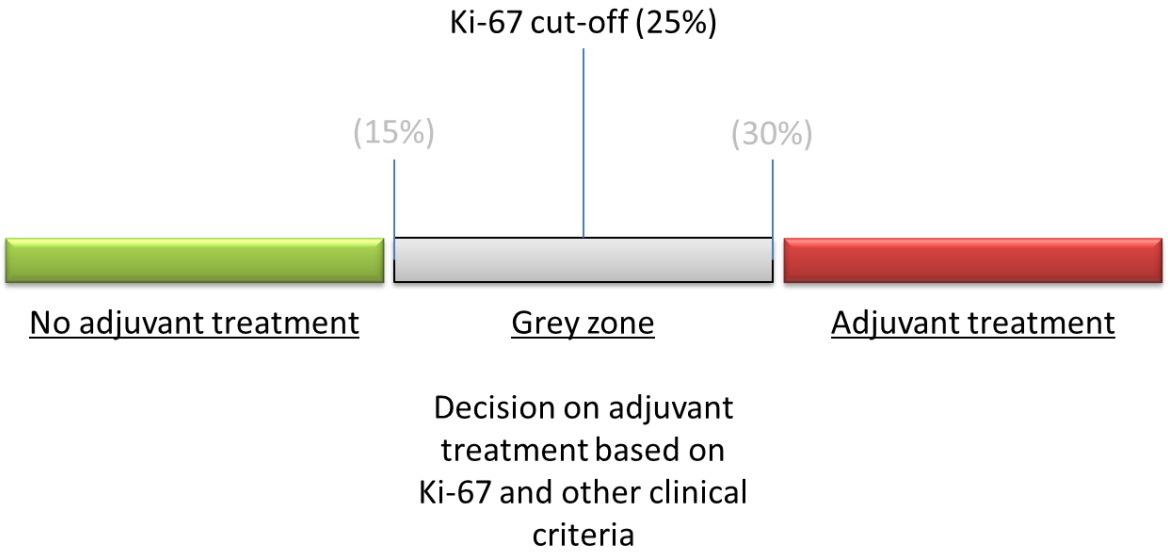
- No sufficient evidence to support microscopic proliferation assessment as a predictive biomarker.
  → gene expression profiles are promising.

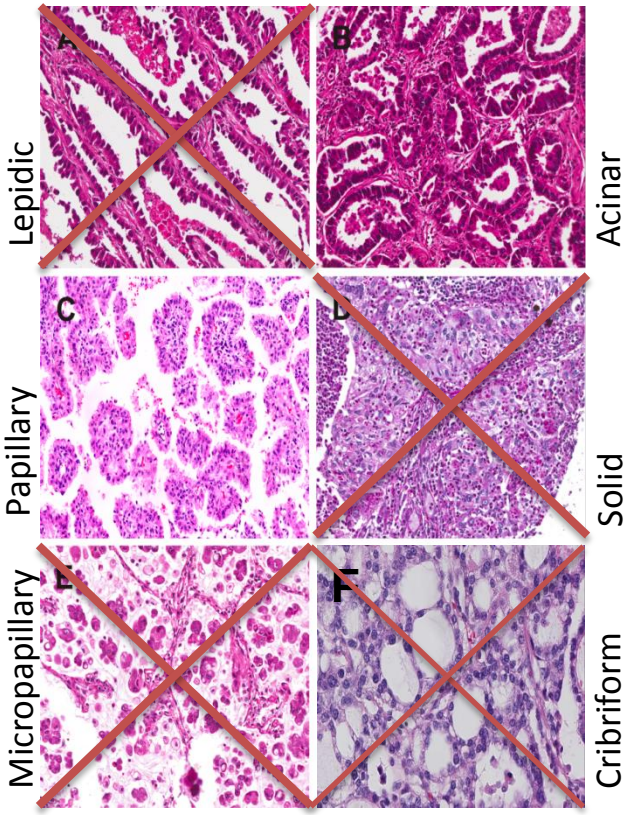
Perspective: Implementation of Proliferation Assessment into Routine Diagnosis of Adenocarcinoma

1. Clinical consequences.
2. Integration of staging and morphology.
3. International establishment of reliable and reproducible staining/evaluation protocols.
4. Integration of morphology and proliferation.

Stage I micropapillary predominant:	60.2 months OS
Stage I papillary predominant:	62.9 months OS
Stage I solid predominant:	78.6 months OS
adjuvant therapy	
Stage II acinar predominant:	58.6 months OS
Stage II lepidic predominant:	84.7 months OS

Warth A et al. J Clin Oncol. 2012,30:1438-46.





Thank you…

……. for your attention!