Patologie nádorů v 21. století – problémy a úskalí diagnostiky a úhradového systému

A. Ryška

Fingerlandův ústav patologie
LF UK a FN Hradec Králové

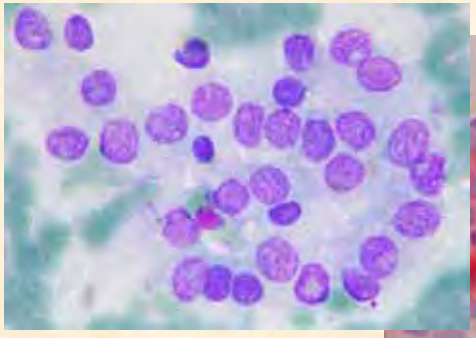
Karel Rokitansky
(1804-1878)

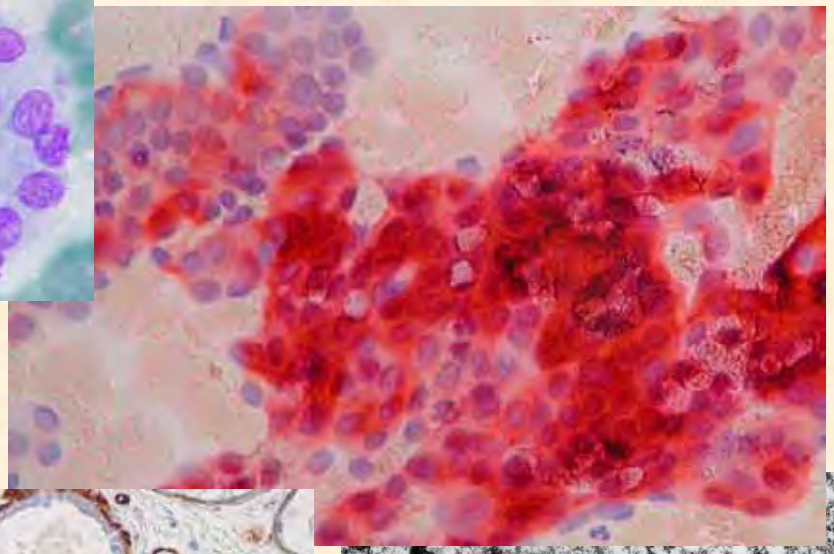
Rudolf Virchow
(1821-1902)

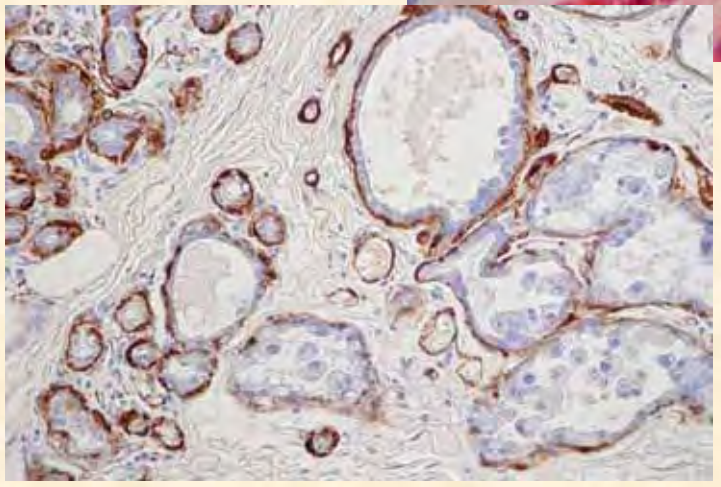
Rozvoj patologie ve 20. století

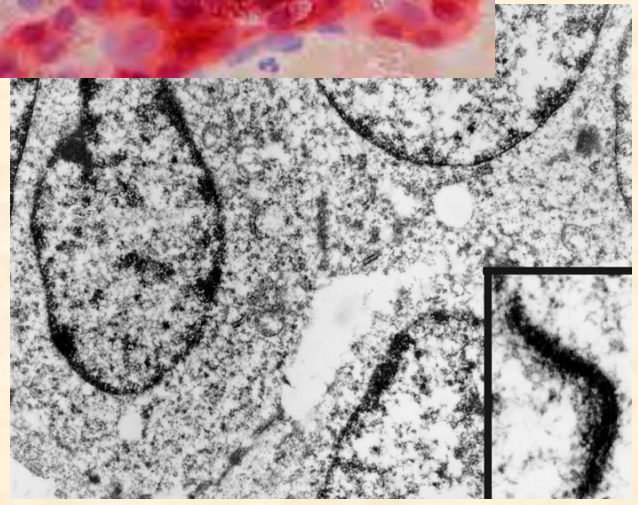
přesun od pitev k biopsiím
nové metody a jejich uplatnění:

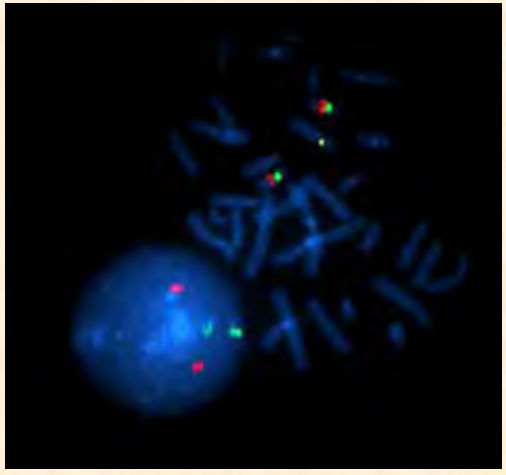
- cytologie
- EM
- histochemie
- imunohistochemie
- cytogenetika
- průtoková cytometrie
- FISH, PCR
- proteomika





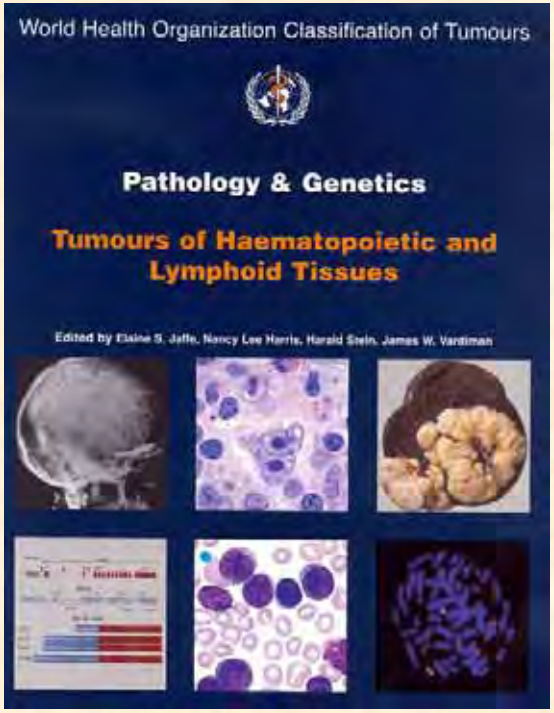


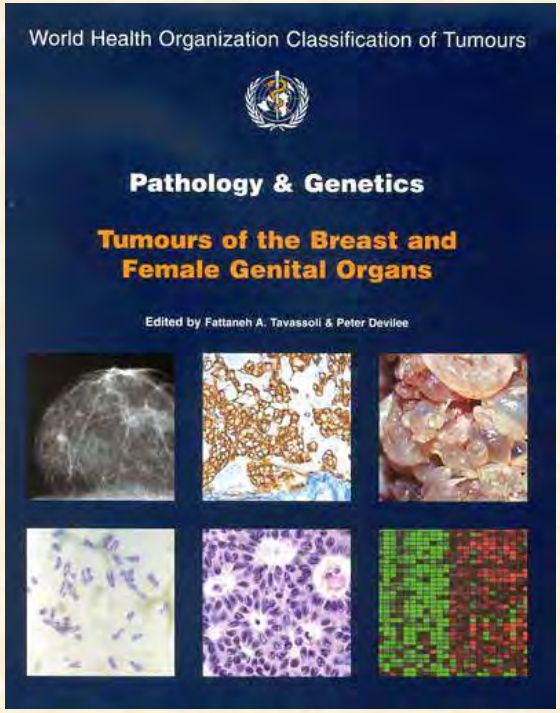


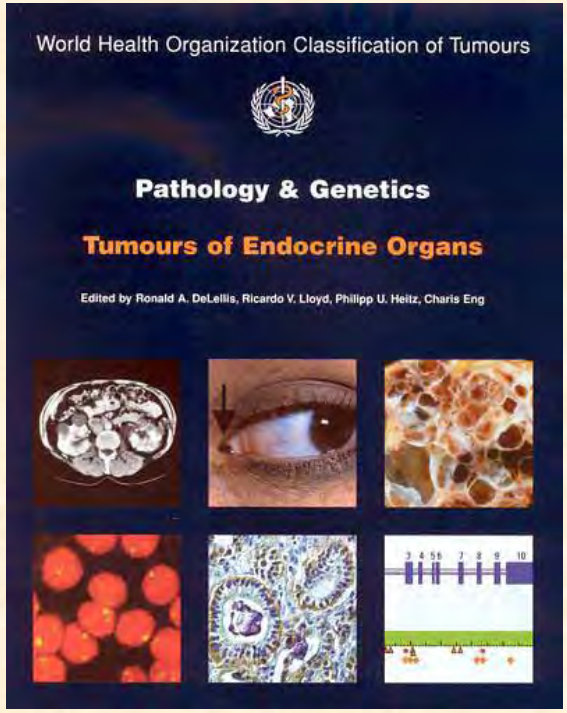


Nové jednotky,
nový pohled na známé choroby

- klasifikace vycházející nikoli výlučně z morfologického vzhledu, ale i z klinického dopadu
- genetické vyšetření – nedílná součást diagnostiky

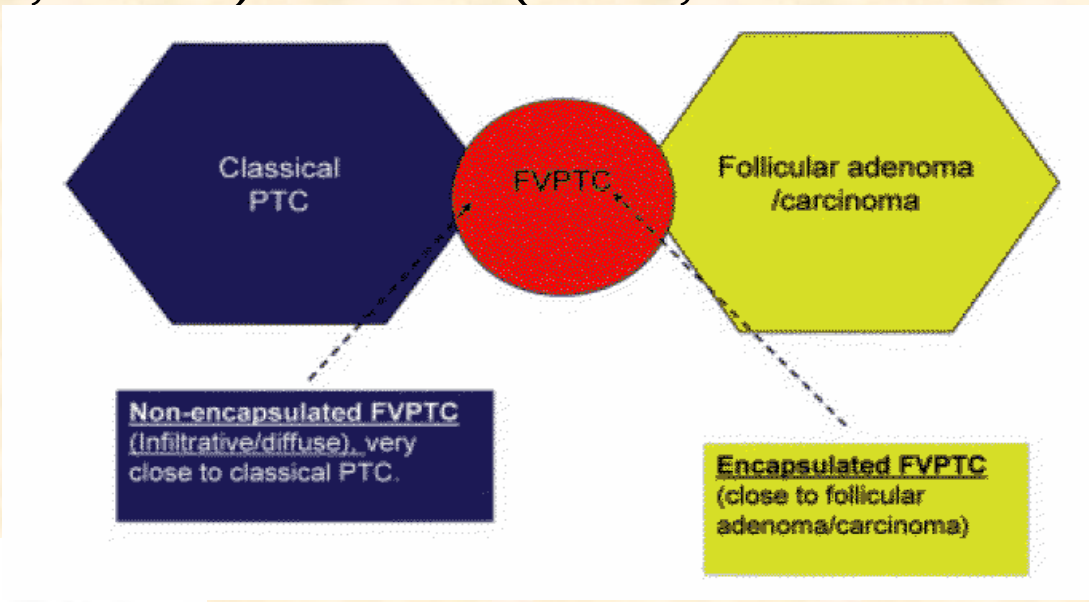






Folikulární varianta PC

- Morfologie PC (jádra) i FA/FC (folikly, pouzdro)
- Genetika PC (RET/PTC, BRAF) i FA/FC (k-ras, PAX8-PPARgamma)
- Variabilní chování



Characteristic	No. of patients (%) Encapsulated FVPTC (n = 61 patients)	Nonencapsulated FVPTC (n = 17 patients)	P*
Lymph node metastases			<.0001
Present	3 (5)	11 (65)	
Absent	58 (95)	6 (35)	

Liu J, Singh B, Tallini G, et al. Follicular variant of papillary thyroid carcinoma - a clinicopathologic study of a problematic entity. Cancer 2006; 107(6): 1255-1264

The American Journal of Surgical Pathology 26(11): 1508–1514, 2002

Observer Variation of Encapsulated Follicular Lesions of the Thyroid Gland

Mitsuyoshi Hirokawa, M.D., J. Aidan Carney, M.D., John R. Goellner, M.D., Ronald A. DeLellis, M.D., Clara S. Heffess, M.D., Ryohei Katoh, M.D., Masahiko Tsujimoto, M.D., and Kennichi Kakudo, M.D.

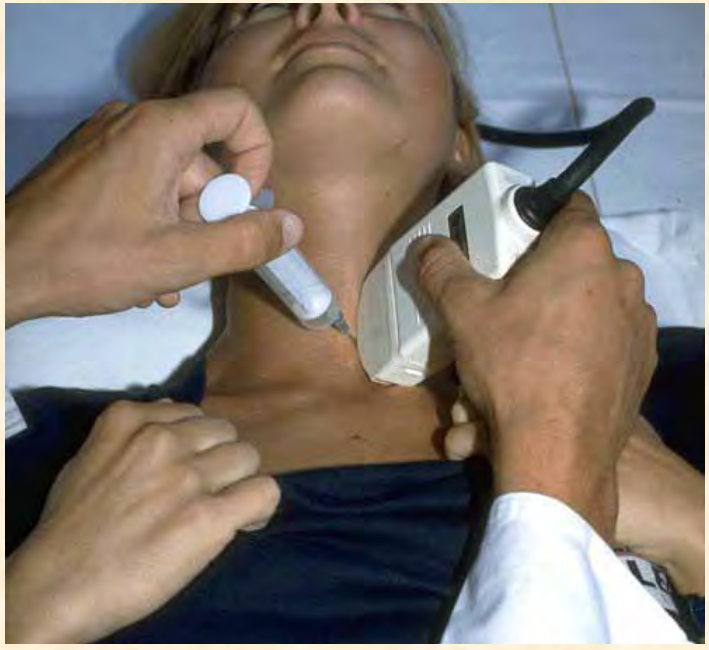
To investigate interobserver variation in assessment of encapsulated follicular lesions, eight pathologists (four American and four Japanese) reviewed the same hematoxylin and eosin-stained slide of each of 21 cases of thyroid lesions showing encapsulation and follicular growth pattern. In 10% of the cases, there was complete agreement. At least seven pathologists agreed on the diagnosis in 29% of the cases, and at least six in 76% of the cases. American and Japanese pathologists agreed among themselves in 33% and 52% of cases, respectively. The frequency of diagnosis of adenomatous goiter among Japanese pathologists (31%) was considerably higher than that among American pathologists (6%). In contrast, the frequency of diagnosis (25%) of papillary carcinoma among American pathologists was considerably higher than that (4%) among Japanese pathologists. Our analysis revealed three main

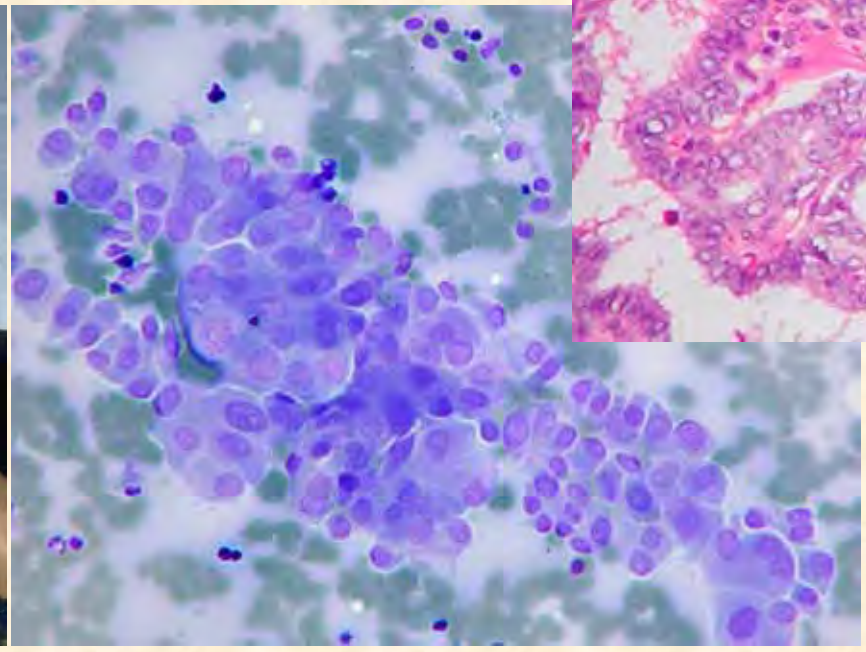
	Pathologists							
	US				Japan			
Case no.	A	B	C	D	E	F	G	H
1	FC	FC	PaC	PaCFo	FC	FC	FC	FC
2	FA	FA	FC	FA	FA	FA	FA	FA
3	FA	FA	PaC	PaCFo	AN	FA	FA	AN
4	FA	FA	FA,	FA	AN	AN	FA	FA
5	FC	FC	PaC	PaCFo	AN	AN	AN	FC
6	FA	FA	PaC	PaCFo	FA	FA	FA	FA
7	FC	FC	PaC	PaCFo	FC	FC	FC	FC
8	FC	FC	FC	PaCFo	FC	FC	FC	FC
9	FA	FA	FA	FA	FA	FA	FA,	FA
10	FA	FA	FA	FA	FA	FA	FA	FA
11	FA	AN	FA	AN	AN	AN	AN	AN
12	FA	FA	FC	PaCFo	FA	FA	FA	FA
13	FA	AN	FA	FA	AN	AN	FA	FA
14	PaC	PaCFo	PaC	PaCFo	PaCFo	PaC	PaCFo	FC
15	FA	FA	AN	FA	AN	AN	FA	AN
16	AN	FA	PaC	PaCFo	AN	AN	AN	AN
17	FA	FA	FA	PaCFo	FA	FA	FA	FA
18	FA	FA	FA	FA	AN	FA	FA	AN
19	FA	FA	FA	FA	AN	FA	FA	AN
20	FA	FA	PaC	PaCFo	FA	FA	FA	FA
21	FA	FA	FA	FA	AN	FA	AN	FA

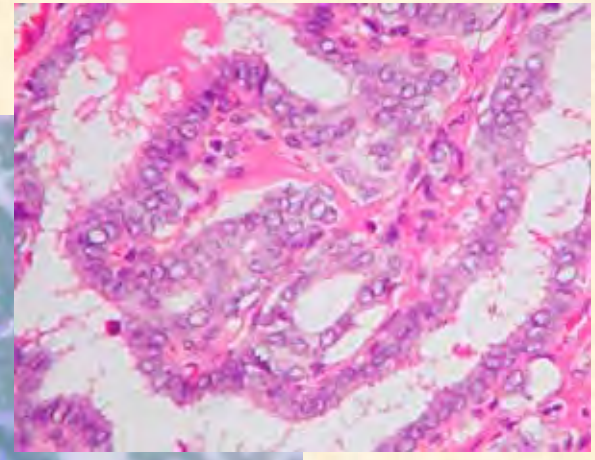
FC, follicular carcinoma; PaC, papillary carcinoma; PaCFo, papillary carcinoma, follicular variant; FA, follicular adenoma; AN, adenomatous nodule.

Patolog partnerem kliniků ve volbě léčby

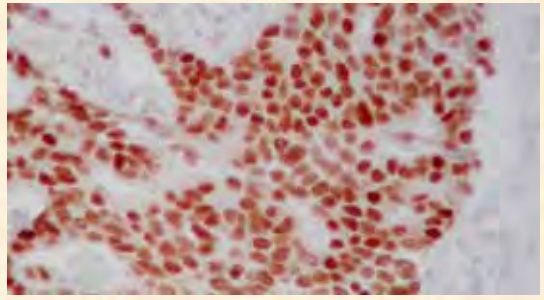
- prostá morfologie



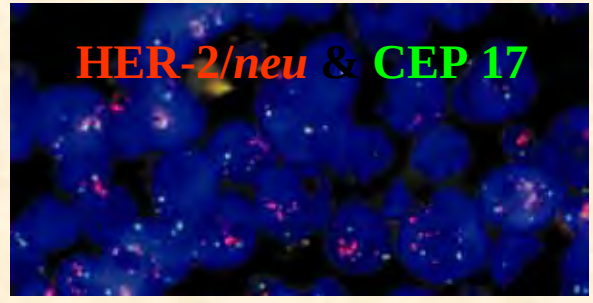




- imunohistochemie



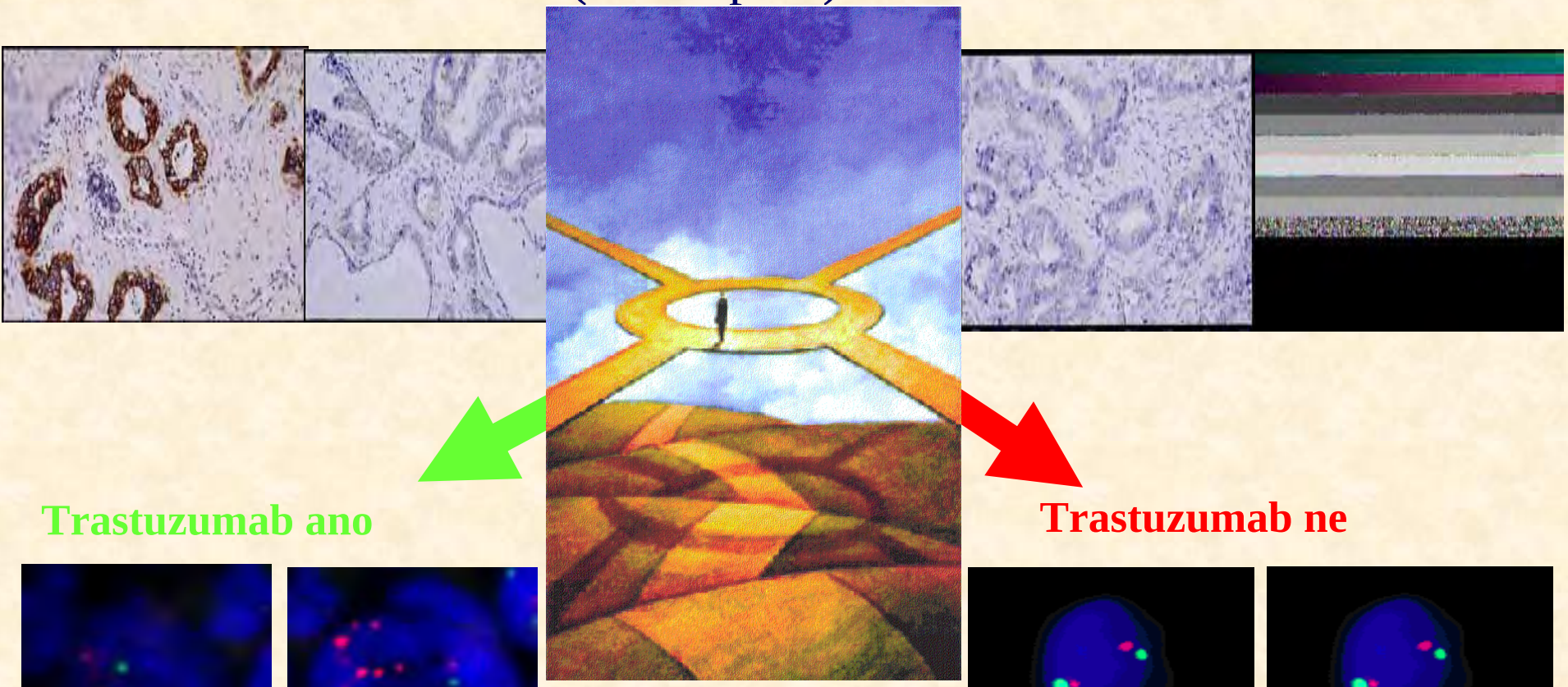
- molekulární biologie



Detekce HER-2/neu

exprese HER-2/neu = významně horší prognóza

1998 – trastuzumab (Herceptin)

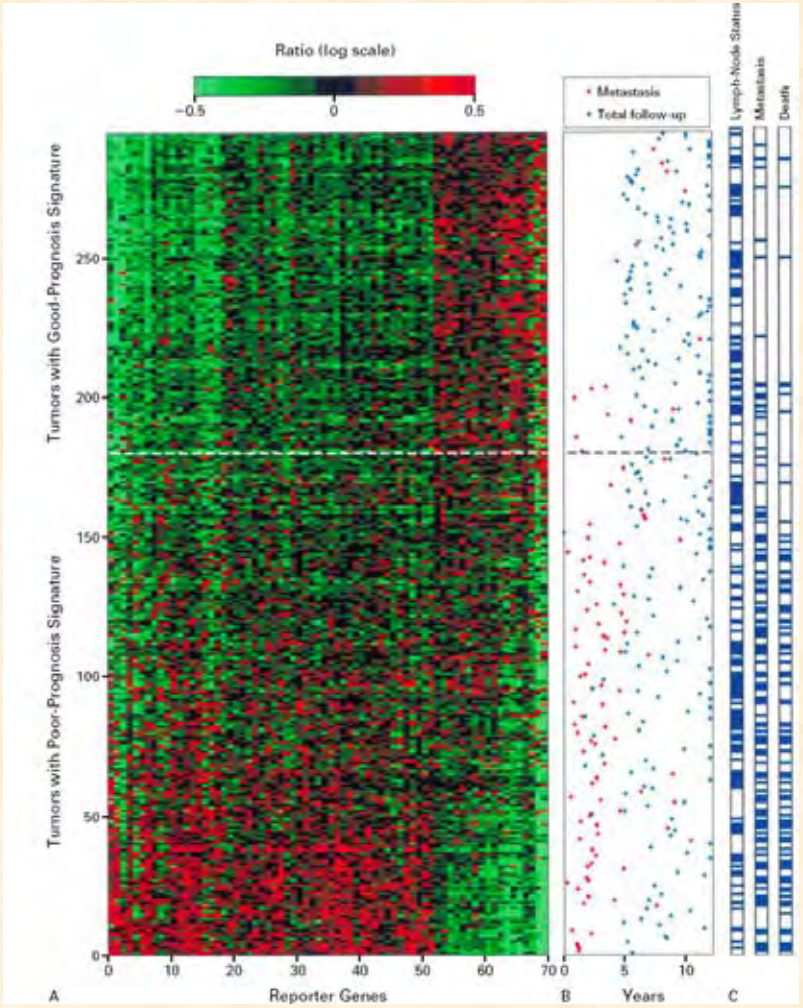


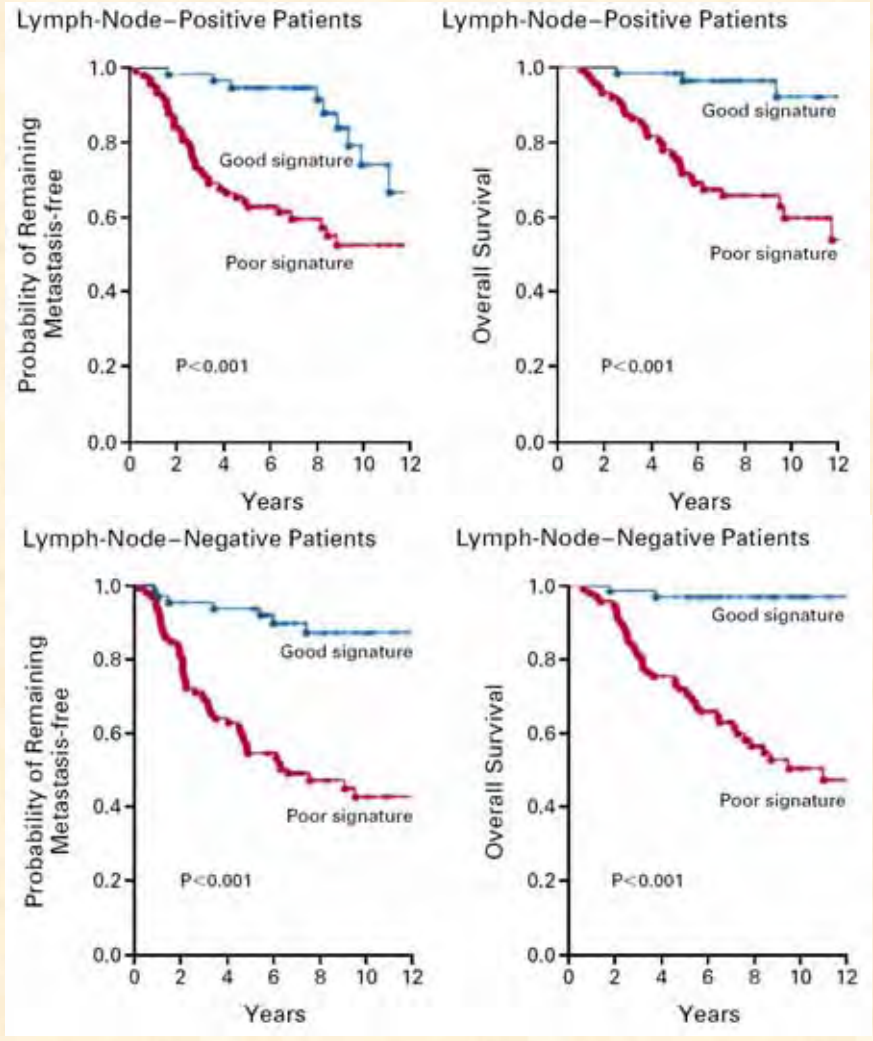
Trastuzumab ano

Trastuzumab ne

Budoucnost patologie

Genetická klasifikace nádorů

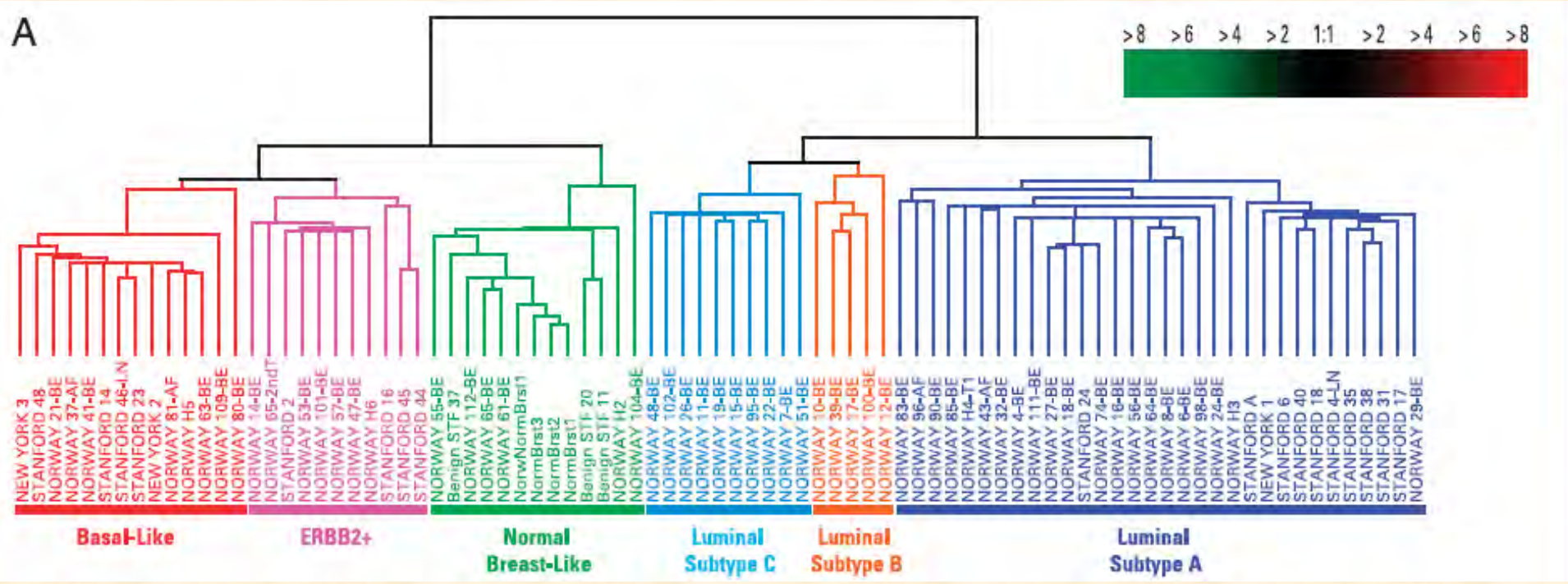




van de Vijver MJ et al: A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 347:1999-2009, 2002

Budoucnost patologie

Genetická klasifikace nádorů



Brenton et al. JCO 23, 2005

Jaká je incidence Her2+ ca prsu?

- Faktory ovlivňující zastoupení jednotlivých fenotypických kategorií
  - podíl ER pozitivních low grade karcinomů starších žen
  - množství černošek v populaci
  - mammografický screening
  - nasazení HRT v minulosti (90. léta)

Jaká je incidence Her2 pozitivity u ca prsu v populaci?

- švýcarská studie - 2197 žen
- soubor z let 1985-1999, odpovídá našemu populačnímu rozložení
- FISH - **17% amplifikací**
- (saudská populace - 33%!)

Al-Kuraya K, Schraml P, Sheikh S, et al. Predominance of high-grade pathway in breast cancer development of Middle East women. Mod Pathol. 2005;18(7):891-7.

- polská populační studie (842 případů z let 2000-2003)
- IHC - **14% overexprese**

Yang et al. Differences in risk factors for breast cancer molecular subtypes in a population-based study. Cancer Epidemiol Biomark Prev. 2007 Mar;16(3):439-43.

Jaká je incidence Her2 pozitivity u ca prsu v populaci?

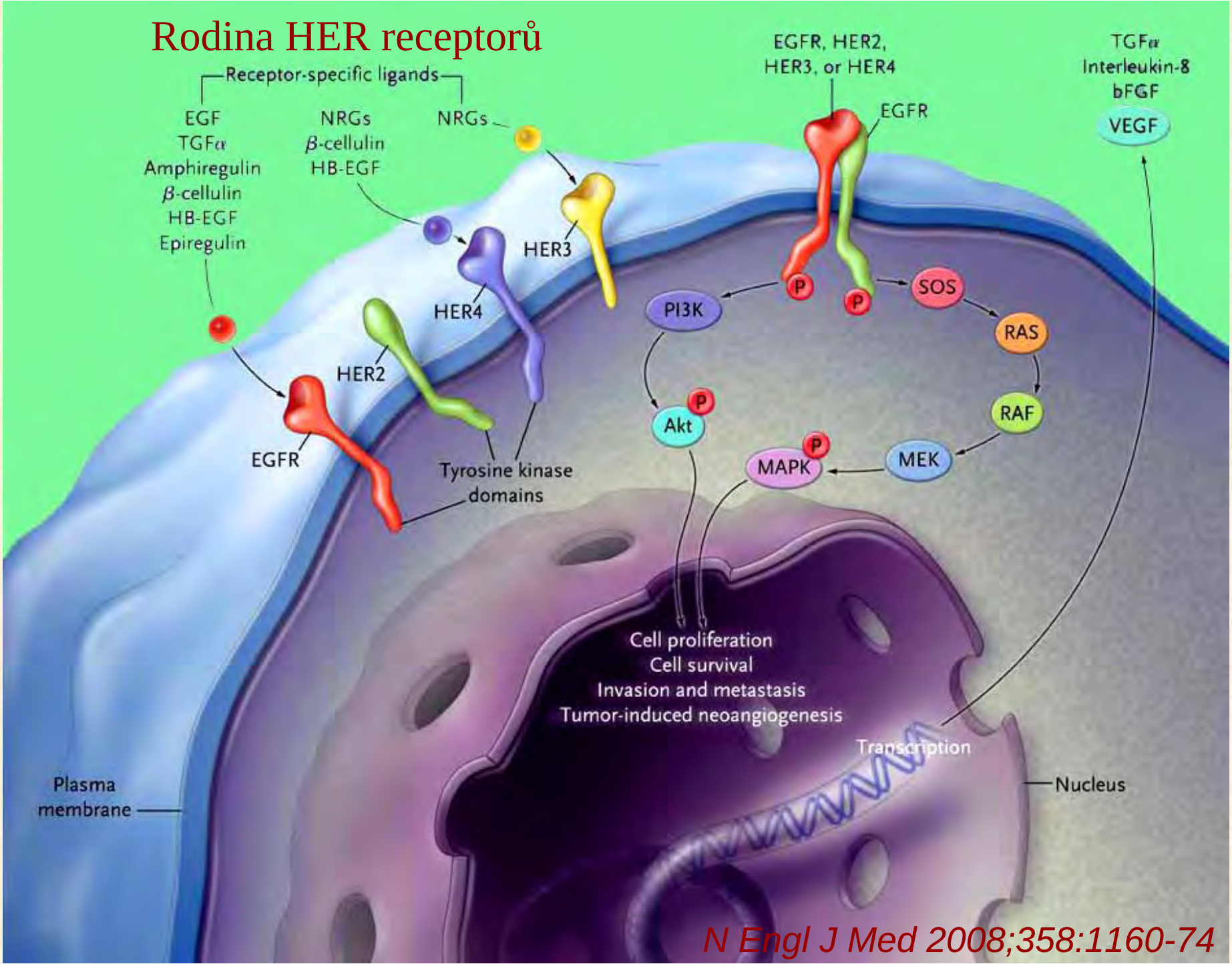
- USA - MG screenovaná populace (n=2898)
- IHC frekvence HER-2 **overexprese 12%** (2+, 3+)

Tamimi RM et al.: Her2 status in a US population based cohort: results from a tissue microarray based analysis of 2898 breast cancers from women enrolled in the nurses health study. Breast Cancer Reserch and Treatment Vol.106, S263 (2007).

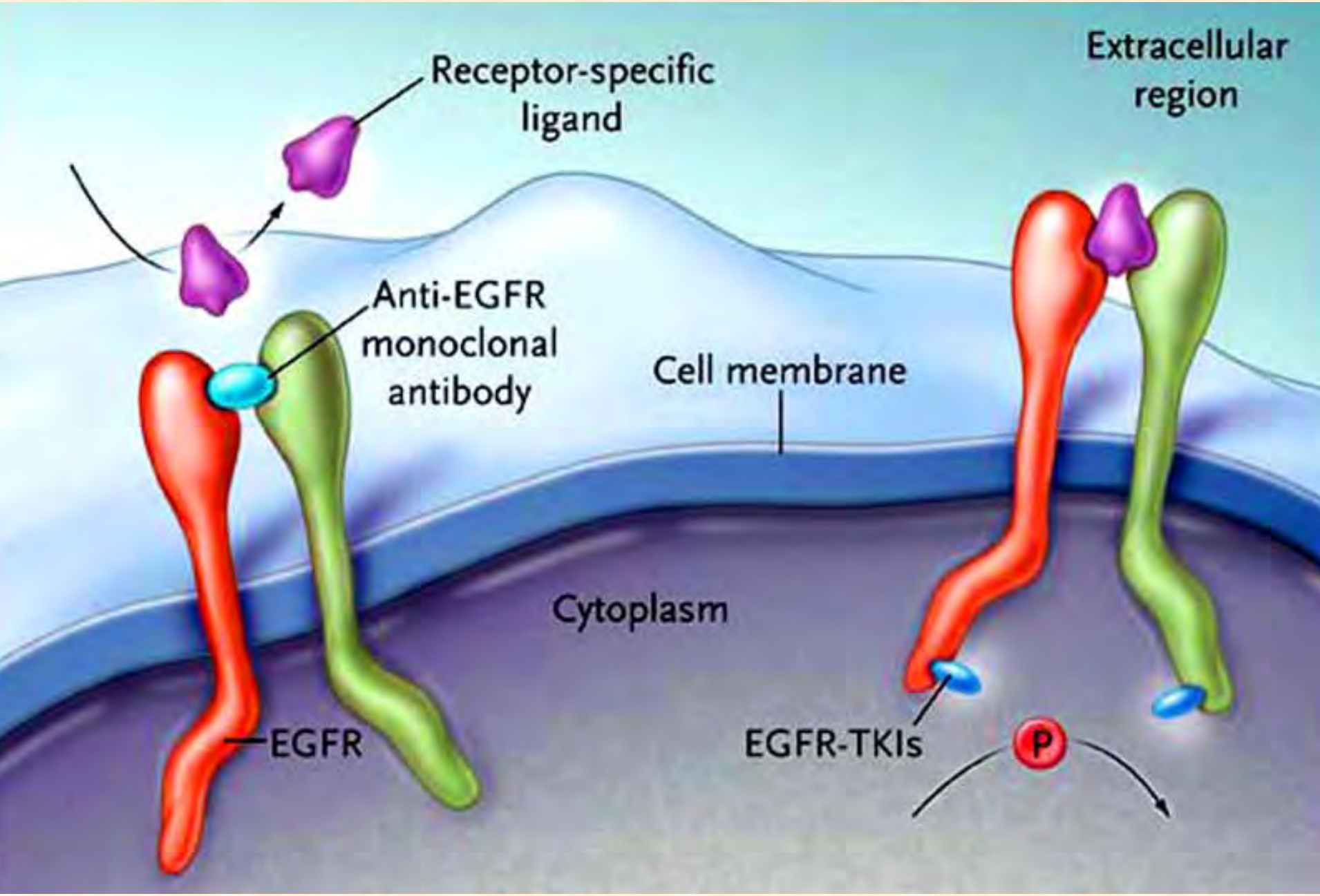
- česká série 522 konsekutivních případů MOÚ z let 2004-2005
- IHC, s validací 2+ a 3+ pomocí FISH - **14,2%**

Fabian P. et al. Incidence Her-2 amplifikace u mammárního karcinomu a její korelace s klinicko-patologickými parametry. Sestava 500 konsekutivních mammárních karcinomů MOÚ. XXX. Brněnské onkologické dny. 2006;153

Rodina HER receptorů



N Engl J Med 2008;358:1160-74



N Engl J Med 2008;358:1160-74

Detekce EGFR

- Nepřímá imunohistochemie
- Cytoplazmatická a membránová pozitivita
  - Intenzita
  - Distribuce
  - % buněk

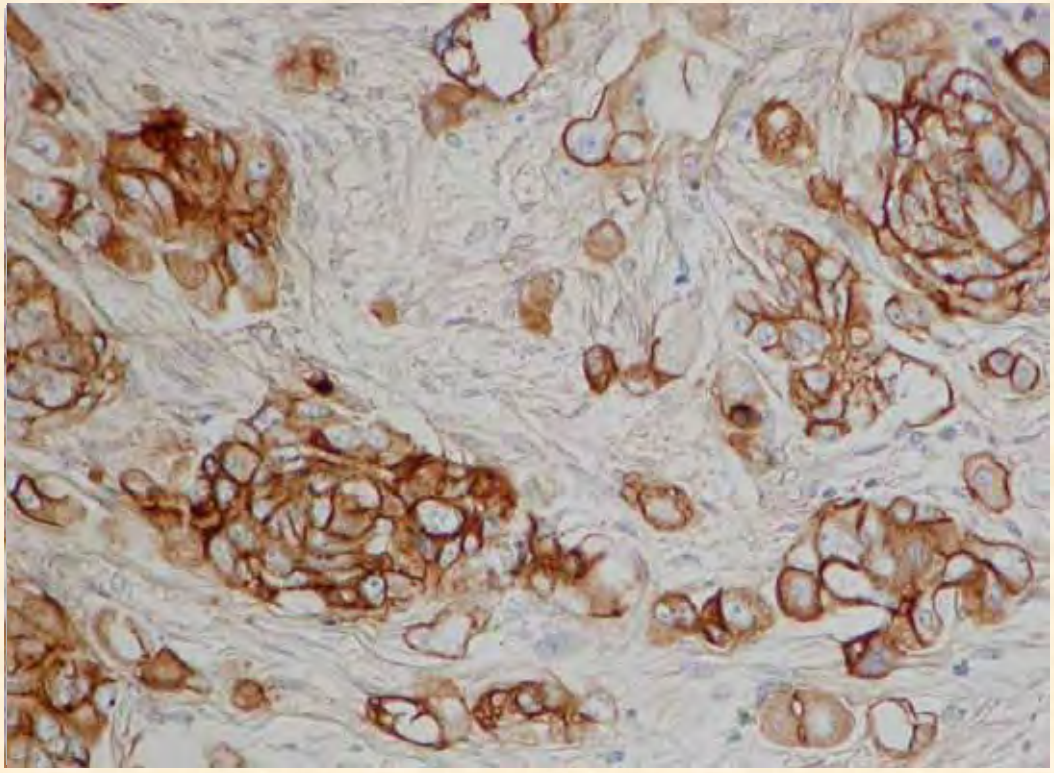


Table 3. Patient Data

Patient No.	EGFR Status	No. of Cetuximab Treatments	Concurrent Irinotecan	Radiographic Response	CEA Trend		Skin Rash Grade
					Status	Values (ng/mL)	
1	0/3+	14	Yes	PR, 73% reduction	Decline	3,000 → 60	1
2	0/3+	17	Yes	PR, 73% reduction	Decline	12,914 → 16	0
3	0/3+	16	Yes	PR, 60% reduction	Decline	12 → 3	1
4	0/3+	8	Yes	PR, 54% reduction	Decline	4,803 → 2,403	0
5	0/3+	16	Yes	MR, 39% reduction	Decline	1,432 → 206	2
6	0/3+	14	Yes	MR, 32% reduction	Decline	11 → 7	1
7	0/3+	10	No	SD	Stable	619 → 712	1
8	0/3+	13	Yes	POD	Stable	8 → 7	0
9	0/3+	7	Yes	POD	Stable	29 → 30	1
10	0/3+	15	Yes	POD	Stable	832 → 374 → 613	1
11	0/3+*	12	Yes	POD	NA	—	1
12	0/3+	9	Yes	POD	Decline	18 → 12	1
13	0/3+	8	Yes	POD	NA	—	0
14	0/3+†	2	No	Early POD	NA	—	1
15	0/3+	1	Yes	Early POD	NA	—	0
16	0/3+	1	Yes	Early POD	NA	—	0

Abbreviations: EGFR, epidermal growth factor receptor; CEA, carcinoembryonic antigen; PR, partial response; MR, minor response; SD, stable disease; POD, progression of disease; NA, not available.

*Upon rereview of pathology (1/3+).

†Upon pathology rereview, the specimen tested for EGFR was not adequate for assessment.

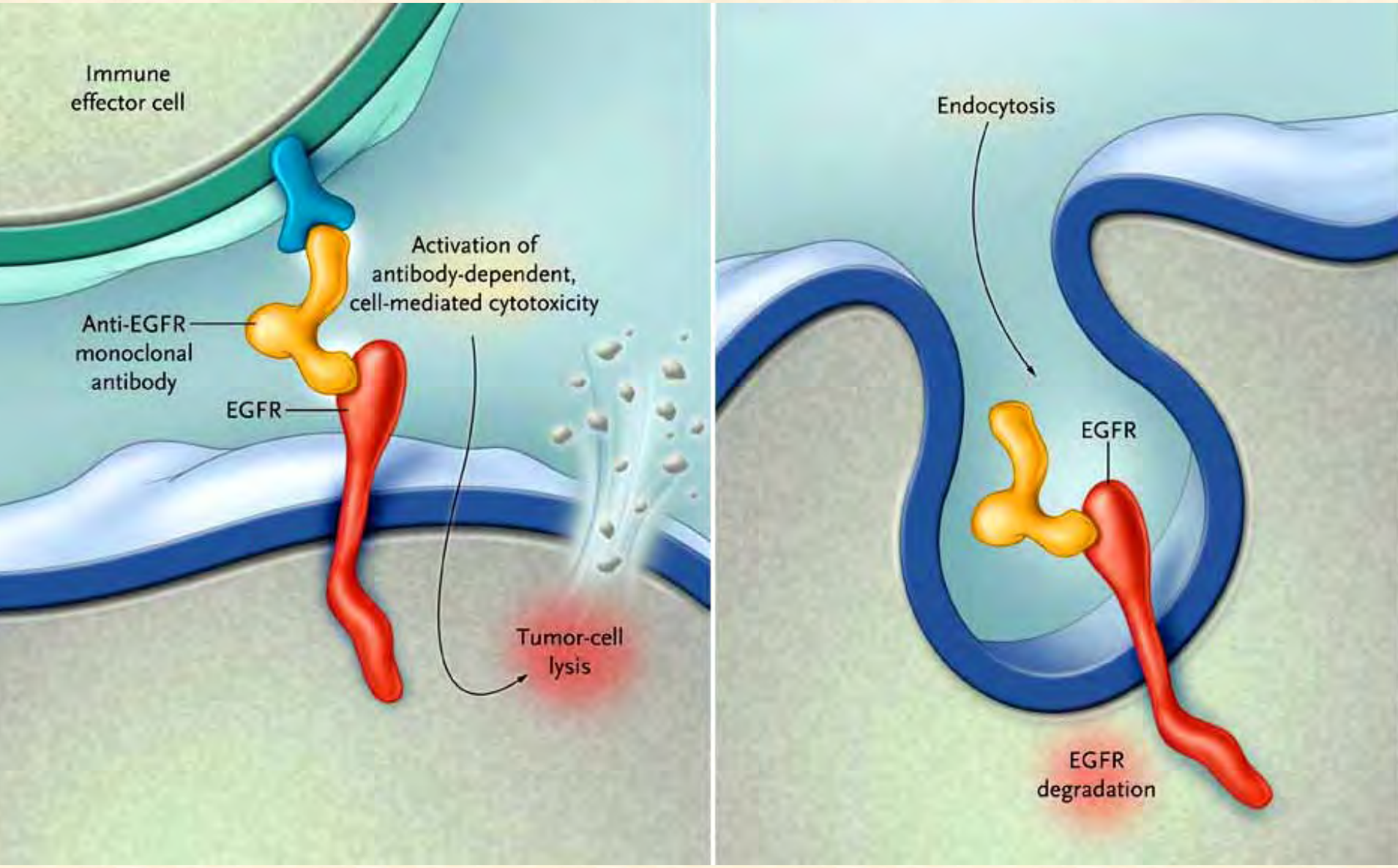
ONCOLOGY REPORTS 16: 1173-1179, 2006

Is there an immunohistochemical technique definitively valid in epidermal growth factor receptor assessment?

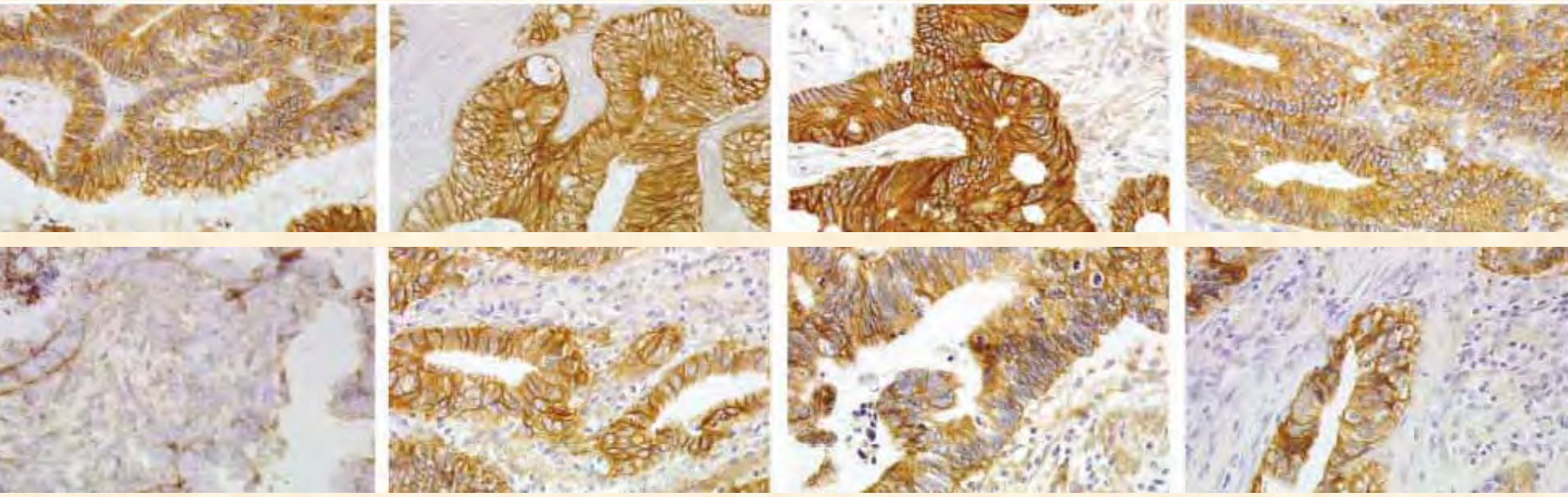
FRÉDÉRIQUE PENAULT-LLORCA[1], ANNE CAYRE[1], LAURENT ARNOULD[2], FRÉDÉRIC BIBEAU[3], MARIE-PIERRE BRALET[4], PHILIPPE ROCHAIX[5], JACQUELINE SAVARY[6] and JEAN-CHRISTOPHE SABOURIN[7]

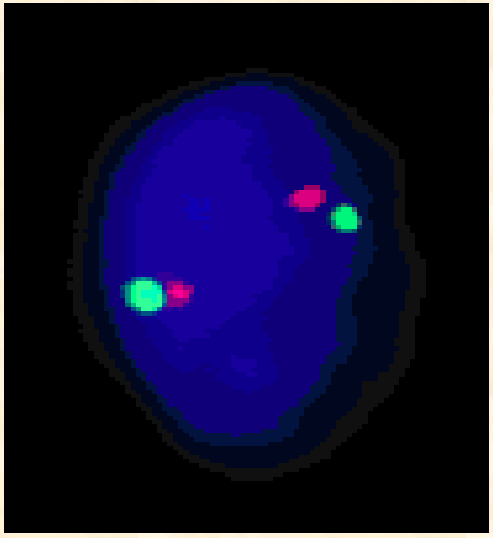
specimens). Our data showed a higher percentage of positive cells detected by Ventana and Zymed tests, whatever the cut-off value for positivity. No scoring system showed, to date, its accuracy, and more studies have to be conducted with an evaluation of the response to cetuximab, possibly with a correlation with FISH amplification in colorectal carcinoma.

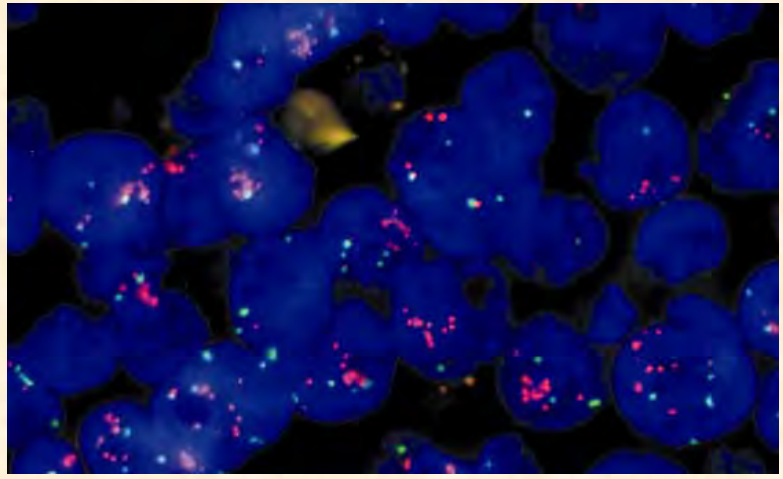
ONCOLOGY REPORTS 16: 1173-1179, 2006

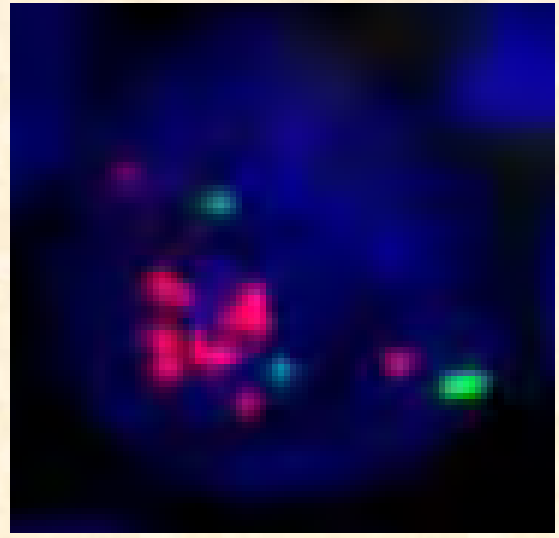


N Engl J Med 2008;358:1160-74







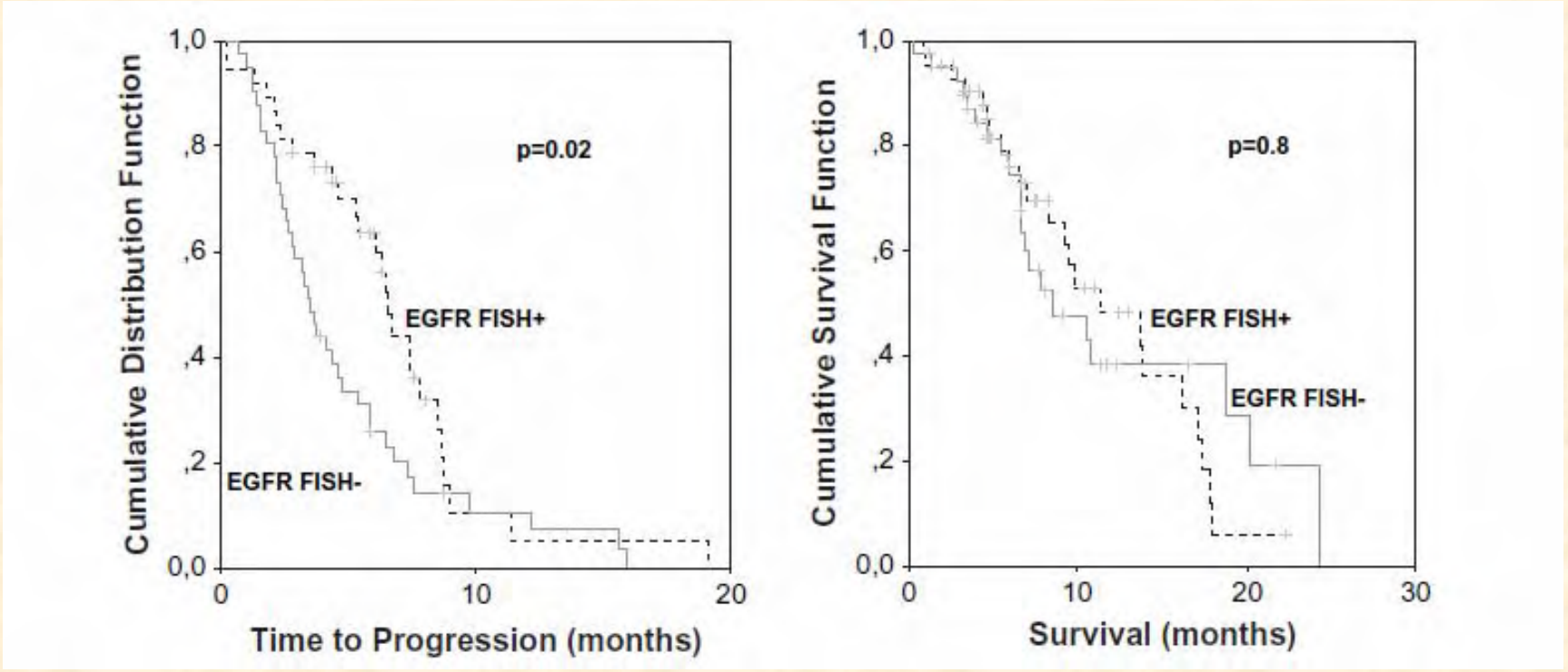


original article

Annals of Oncology 19: 717–723, 2008
doi:10.1093/annonc/mdm492
Published online 31 December 2007

EGFR FISH assay predicts for response to cetuximab in chemotherapy refractory colorectal cancer patients

F. Cappuzzo[1*], G. Finocchiaro[1,2], E. Rossi[3], P.A. Jänne[4], C. Carnaghi[5], C. Calandri[6], K. Bencardino[7], C. Ligorio[1], F. Ciardiello[7], T. Pressiani[1], A. Destro[1,8], M. Roncalli[1,8], L. Crino[9], W. A. Franklin[2], A. Santoro[1] & M. Varella-Garcia[1]



Annals of Surgical Oncology **15**(2):649–654
DOI: 10.1245/s10434-007-9667-2

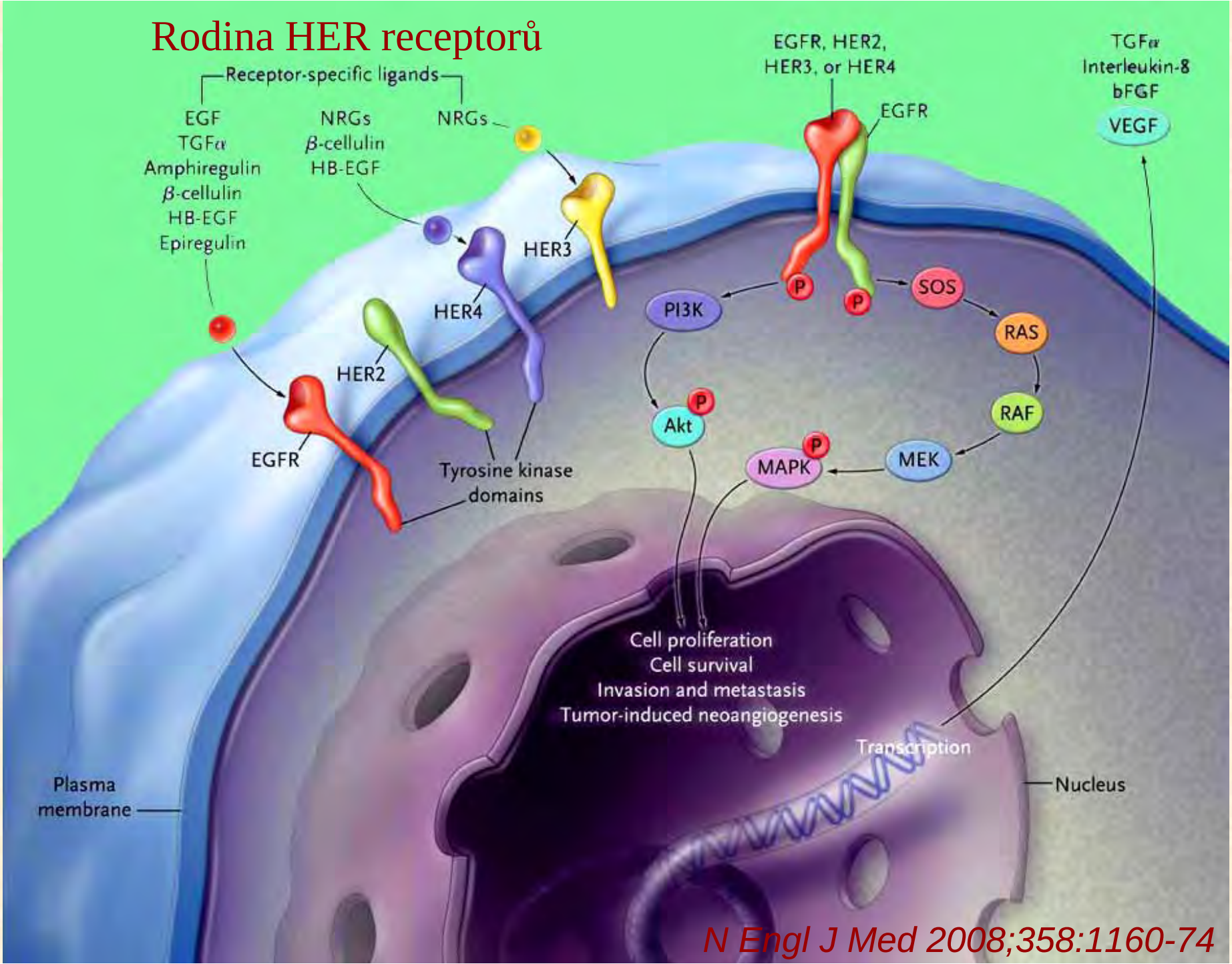
Cetuximab Shows Activity in Colorectal Cancer Patients With Tumors for Which FISH Analysis Does Not Detect an Increase in *EGFR* Gene Copy Number

Antoine Italiano, MD,[1,2] Philippe Follana, MD,[1] François-Xavier Caroli, MD,[3] Jean-Luc Badetti, MD,[4] Daniel Benchimol, MD,[3] Georges Garnier, MD,[5] Jean Gugenheim, MD,[3] Juliette Haudebourg, MD,[6] Frédérique Keslair, MS,[2] Gérard Lesbats, MD,[7] Gérard Lledo, MD,[8] Jean-Francois Roussel, MD,[9] Florence Pedeutour, PharmD, PhD,[2] and Eric François, MD[1]

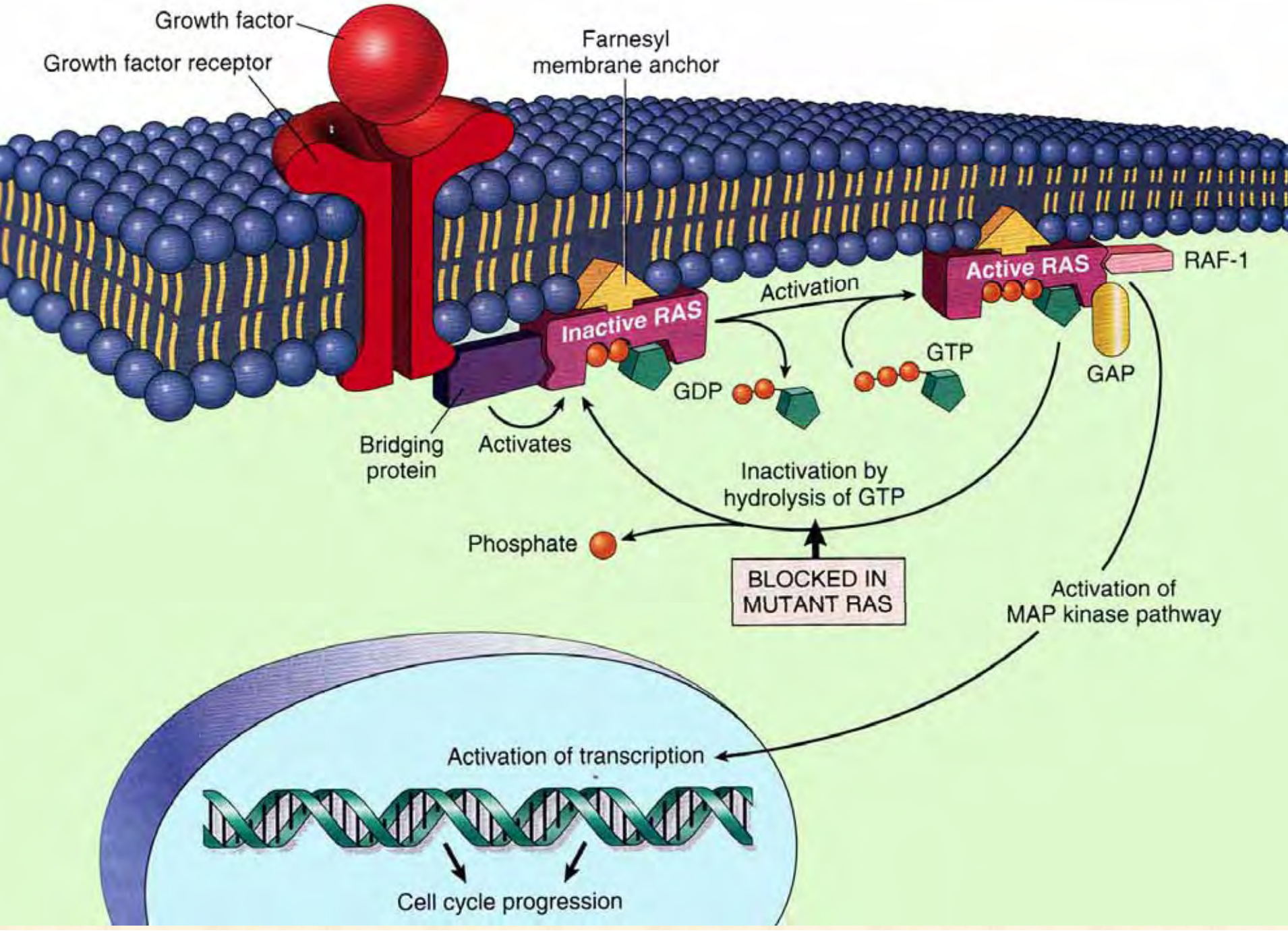
Results: By IHC (n = 47), 39 patients (83%) had EGFR-positive tumors. *EGFR* gene copy gain was detected in 8 (19.5%) of 41 tumors. Neither EGFR expression assessed by IHC nor *EGFR* gene copy gain assessed by FISH were statistically significantly correlated with objective response rate, disease control rate, progression-free survival, and overall survival. Of the 33 patients whose tumors were FISH negative, 8 patients (24.2%) had a partial response, and 10 (30.3%) had stable disease.

Conclusions: *EGFR* FISH analysis does not seem to be a sufficiently robust test for selecting candidate CRC patients for cetuximab therapy.

Rodina HER receptorů



N Engl J Med 2008;358:1160-74

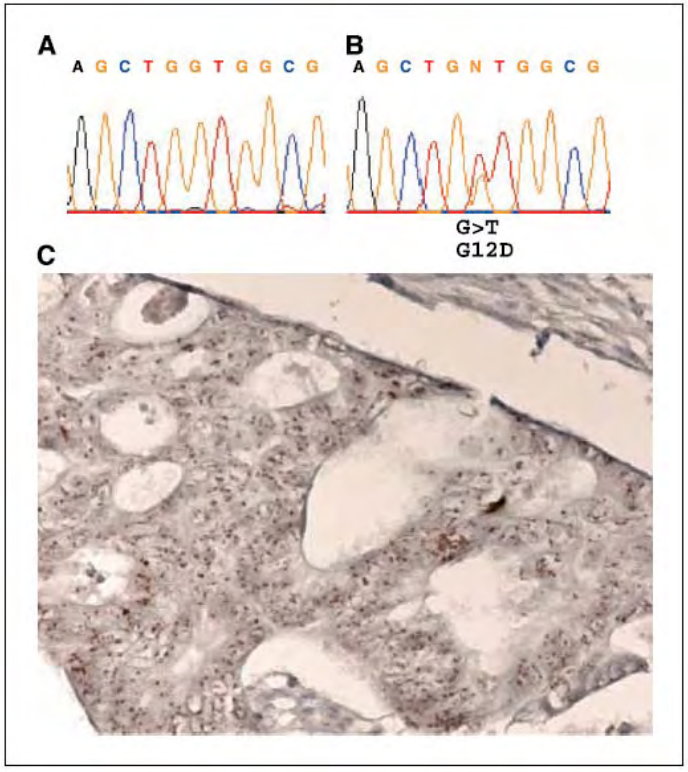

Growth factor
Growth factor receptor
Farnesyl membrane anchor
Inactive RAS
Activation
Active RAS
RAF-1
GTP
GDP
GAP
Bridging protein
Activates
Inactivation by hydrolysis of GTP
Phosphate
BLOCKED IN MUTANT RAS
Activation of MAP kinase pathway
Activation of transcription
Cell cycle progression

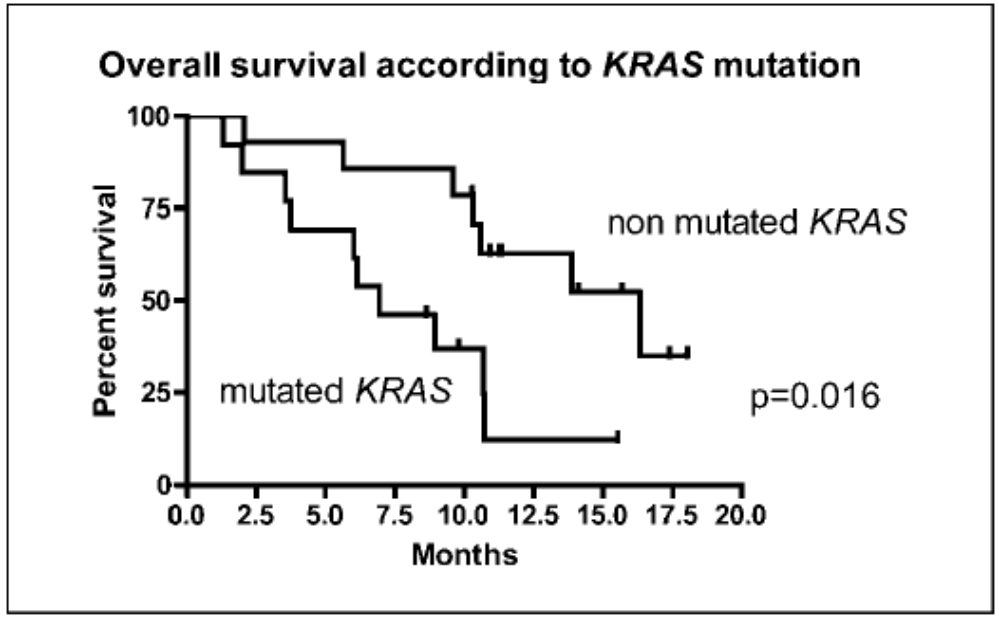
Priority Report

KRAS Mutation Status Is Predictive of Response to Cetuximab Therapy in Colorectal Cancer

Astrid Lièvre,[1,3] Jean-Baptiste Bachet,[3] Delphine Le Corre,[1] Valérie Boige,[4] Bruno Landi,[2] Jean-François Emile,[3] Jean-François Côté,[1,2] Gorana Tomasic,[4] Christophe Penna,[3] Michel Ducreux,[4] Philippe Rougier,[3] Frédérique Penault-Llorca,[5] and Pierre Laurent-Puig[1,2]

Cancer Res 2006; 66: (8). April 15, 2006





K-ras mutace u 0/11 s pozitivní odpovědí na léčbu vs. 13/19 bez odpovědi p=0,0003

original article

Annals of Oncology 19: 508–515, 2008
doi:10.1093/annonc/mdm496
Published online 12 November 2007

KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab

W. De Roock[1], H. Piessevaux[2], J. De Schutter[1], M. Janssens[3], G. De Hertogh[4], N. Personeni[5], B. Biesmans[1], J.-L. Van Laethem[6], M. Peeters[7], Y. Humblet[8], E. Van Cutsem[5] & S. Tejpar[1,5*]

Results: OR was seen in 27 of 66 KRAS wild-type (WT) patients versus 0 of 42 in KRAS mutants. Median OS was significantly better in KRAS WT versus mutants (43.0 versus 27.3 weeks; $P = 0.020$). Decrease in tumor sizes was significantly larger at all time points in WT patients. KRAS WT patients with an initial relative decrease of tumor size >9.66% at week 6 had a significantly better median OS compared with all other patients (74.9 versus 30.6 weeks; $P = 0.0000025$). Within KRAS WT patients OS was significantly better in patients with an initial decrease compared with those without [median OS: 74.9 versus 30.6 weeks ($P = 0.00000012$)].

Mutace K-ras jako prediktor odpovědi u anti-EGFR terapie

Citace	Terapie (panitumumab nebo cetuximab)	N (WT:mut)	Odpověď (%)	
			WT	mut
Laurent-Puig[12]	ERBITUX ± CT	76 (49:27)	49%	0%
Benvenuti[2]	ERBITUX n. Panitumumab n. ERBITUX + CT	48 (32:16)	31%	6%
De Roock[5]	ERBITUX n. ERBITUX + irinotecan	113 (67:46)	40%	0%
Finocchiaro[7]	ERBITUX ± CT	81 (49:32)	26%	6%
Di Fiore[6]	ERBITUX + CT	59 (43:16)	28%	0%
Khambata-Ford[9]	ERBITUX	80 (50:30)	10%	0%

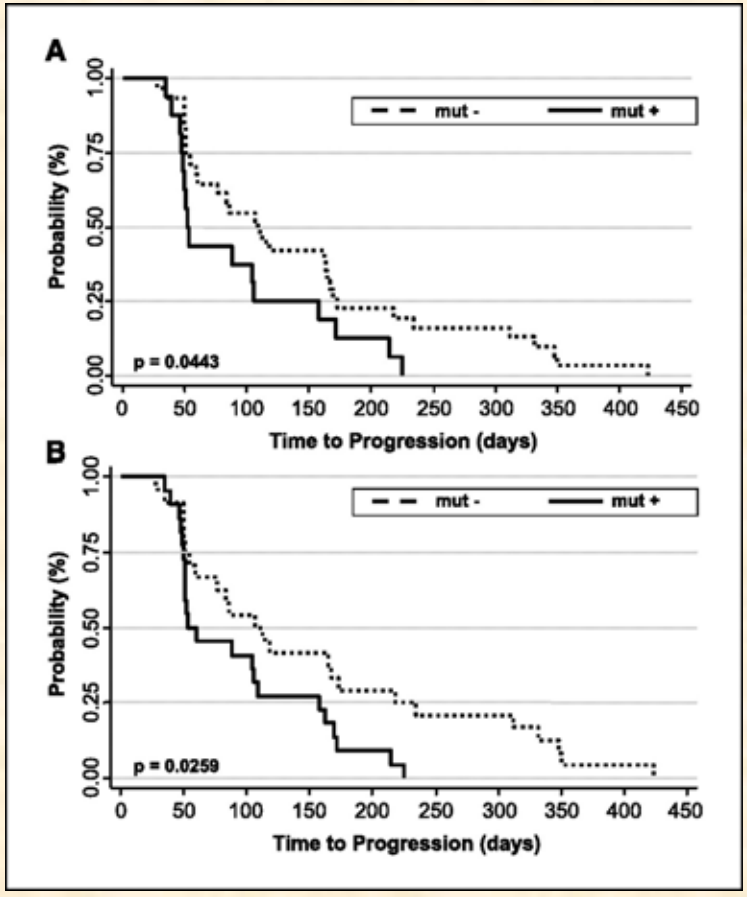
[2]Benvenuti S et al. Cancer Res 2007; 67:2643-48 [5]De Roock W et al. Ann Oncol Nov 12, 2007; epub
[6]Di Fiore F, et al. Br J Cancer 2007;96:1166–69 [7]Finocchiaro G et al. J Clin Oncol 2007; 25(18s):Abstract 4021
[9]Khambata-Ford S, et al. J Clin Oncol 2007; 25:3230-37 [12]Laurent-Puig P et al. Ann Oncol 2007; 18(S 7):Abstract 0194

WT = wild type; mut = mutace k-ras; CT = chemoterapie

Oncogenic Activation of the RAS/RAF Signaling Pathway Impairs the Response of Metastatic Colorectal Cancers to Anti–Epidermal Growth Factor Receptor Antibody Therapies

Silvia Benvenuti,[1] Andrea Sartore-Bianchi,[2] Federica Di Nicolantonio,[1] Carlo Zanon,[1] Mauro Moroni,[2] Silvio Veronese,[2] Salvatore Siena,[2] and Alberto Bardelli[1,3]

Cancer Res 2007; 67: (6). March 15, 2007



$P = 0.017$). These results suggest that patients carrying either *K-RAS* or *BRAF* mutations are less likely to achieve partial response to therapy with anti-EGFR mAbs. Our data also indicate that signaling pathways rather than single genes should be the focus of genetic studies aimed at dissecting the molecular basis of targeted therapies.

mCRC – antiEGFR terapie

- Mechanismy účinku molekulární léčby jsou komplexní
- Funkční signální dráhy
- Vzájemné interakce - síť
- Heterogenita nádorové populace
- IHC detekce je obsolétní
- K-ras WT – nejdůležitější molekulární prediktor pozitivní odpovědi

Co nás čeká v nejbližší budoucnosti?

- Zavádění detekce nových prediktivních markerů
- Zavádění nových technologií
- Zlepšení diagnostiky
- Standardizace metod
- Zavedení systému externí kontroly kvality

Imunohistochemie

- Dobrý sluha, ale zlý pán.
- Vnitřní kontrola kvality:
  - pozitivní
  - negativní
- Externí kontrolu kvality (EKK) zajišťuje nezávislá instituce
- Běžné v zahraničí, v ČR zatím 0

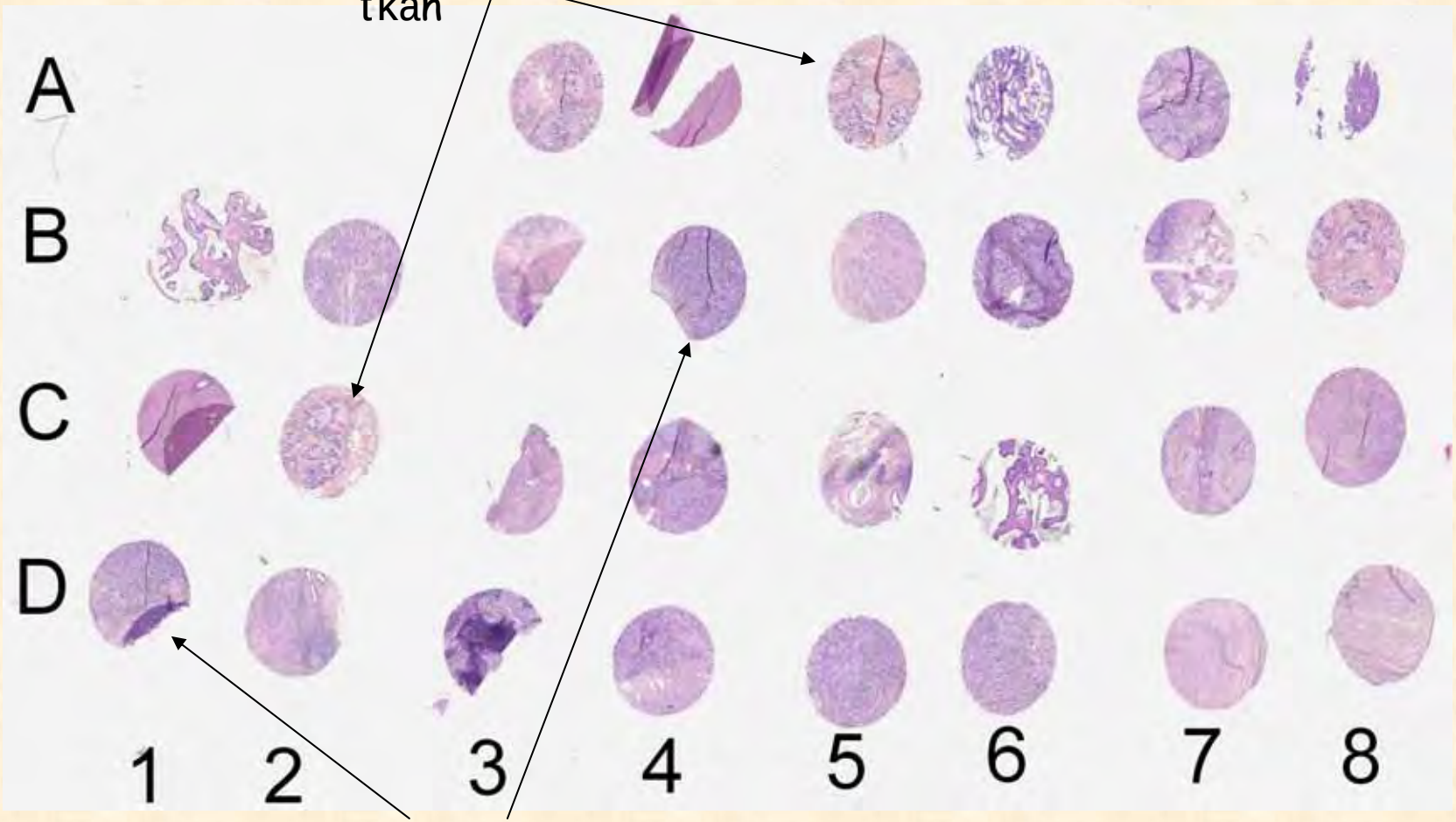
Externí Kontrola Kvality

- EKK - běžná a nezbytná (biochemické laboratoře (v ČR cca 300 subjektů)), zajišťuje SEEK s.r.o. nebo CAP. Za všechno se platí.
- Nezbytná i u imunohistochemie, FISH, zejména u prediktivních faktorů s navazující závažnou/nákladnou léčbou (c-kit, CD 20, EGFR, HER-2, VEGF, karcinoid /octreotid/ atd.).
- Zatím povinná účast referenčních laboratoří – do budoucna by mělo jít o standard

Pilotní projekt EKK ER

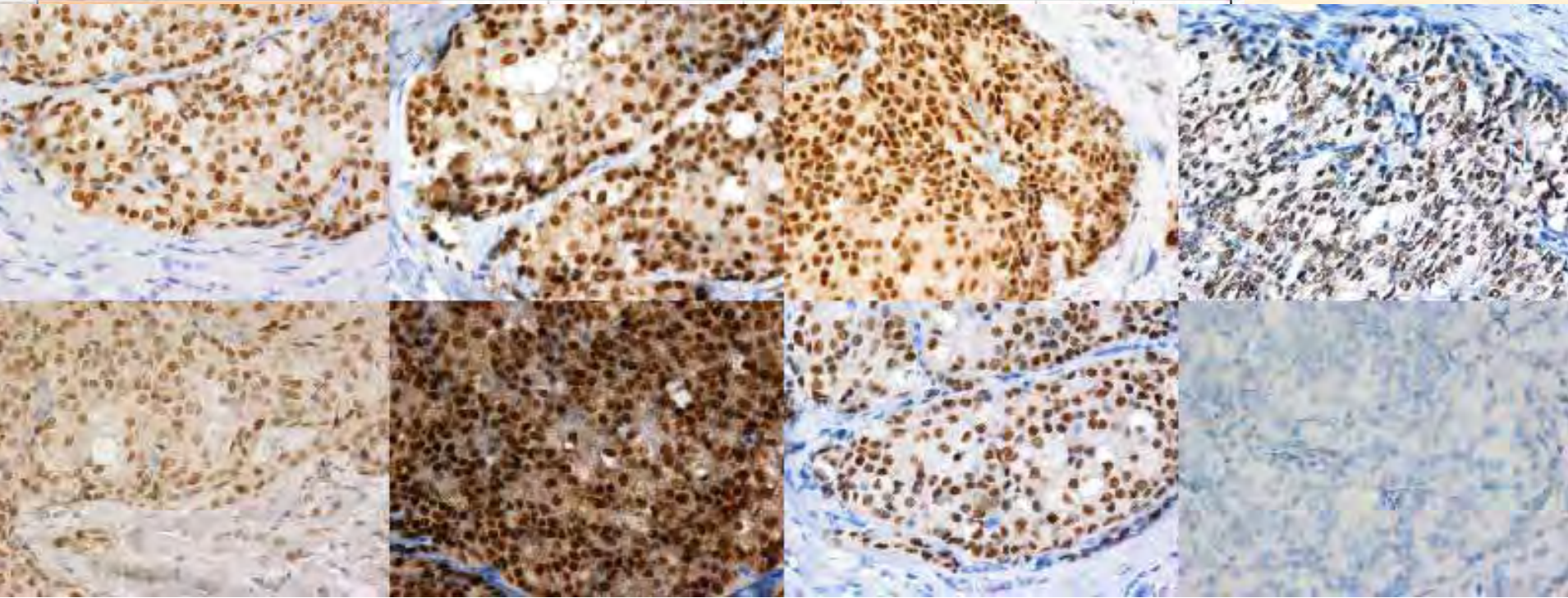
- 8 laboratoří (převážně FN a větší nemocnice)
- IHC laboratoře provedly reakci stejně jako v běžném provozu.
- Řezy vyhodnotil lékař a stanovil „%“ pozitivních buněk, zaznamenal do tabulky a tu spolu se skly a s „barvicím“ protokolem vrátil.
- Sumarizace v tabulce, fotodokumentace.

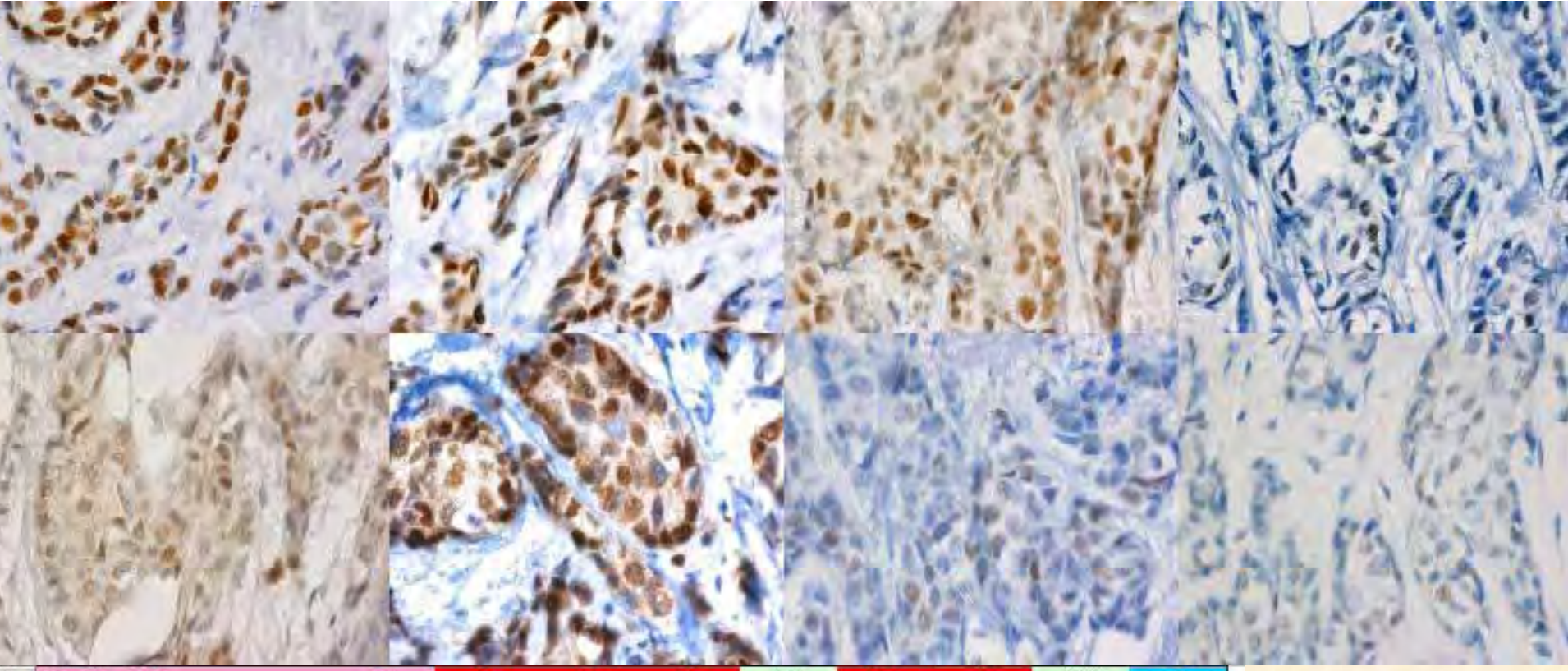
HE - přehled arraye



	A	B	C	D	E	F	G	H	I	J	K	L
1	**Pracoviště**		2107	2208	9235	8906	1042	2191	6688	1234		
2	**Materiál**		ER	ER	ER	ER	ER	ER	ER	ER		
3	B6, D3 C 50	D3	0	0	0	0	0	0	0	0		
4	B6, D3 C 50	B6	0	0	0	0	0	0	0	0		
5	B7, D4 C50	D4	0	0	0	0	0	0	0	0		
6	B7, D4 C50	B7	0	0	0	0	0	0	0	0		
7	B5, D2 C50	D2	0	0	0	0	0	0	0	0		
8	B5, D2 C50	B5	0	0	0	0		0	0	0		
9	A7, C4 C50	A7	100	100	100	100	99	80	95	0		
10	A7, C4 C50	C4	100	100	100	100	99	100	99	95		
11	B3, C8 C50	B3	90	85	90	100	95	90	70	0		
12	B3, C8 C50	C8	100	80	85	50	80	100	30	0		
13	D5, D6 C 50	D5	95	100	95	80	90	80	70	95		vysoká shoda
14	D5, D6 C 50	D6	90	95	95	90	70	100	70	95		střední shoda
15	D7, D8 C50	D7	90	80	80	30	65	60	50	95		neshoda
16	B1, C6 C56	B1	100	100	70	80	80	25	40	0		
17	B1, C6 C56	C6	100	95	90	80	60	10	40	30		
18	B2, C7 C50	B2	95	90	75	30	60	50	30	5		
19	B2, C7 C50	C7	80	40	30	0	10	25	10	50		
20	D7, D8 C50	D8	80	80	70	0	0	25	5	95		
21	A3, B8 mammární hamartom	B8	20	15	10	0	0	5	1	0		
22	A3, B8 mammární hamartom	A3	15	20	10	5	5	5	0	0		
23	A5, C2 mammární tkáň	C2	70	20	15	10		5	3	0		
24	A5, C2 mammární tkáň	A5	30	15	30	0	2	5	5	0		
25	B4, D1 C50	B4	40	35	5	0	0	5	3	0		
26	B4, D1 C50	D1	25	20	0	0	0	10		0		
27	A4, C1 jaterní tkáň	A4	5	0	0	0	10	0	0	0		
28	A4, C1 jaterní tkáň	C1	5	5	0	0	10	0	0	0		
29	**Protilátka**		SP1	6F11	1D5	1D5	1D5	1D5	6F11	1D5		
30			SP1	ENV	ENV+	LSAB2	x	x	ENV	x		
31			DAB+	DAB	DAB+				DAB			
32												

101	Pracoviště		2107	2208	9235	8906	1042	2191	6688	1234
102	Materiál		ER	ER	ER	ER	ER	ER	ER	ER
103	B6, D3 C 50	D3	0	0	0	0	0	0	0	0
104	B6, D3 C 50	B6	0	0	0	0	0	0	0	0
105	B7, D4 C50	D4	0	0	0	0	0	0	0	0
106	B7, D4 C50	B7	0	0	0	0	0	0	0	0
107	B5, D2 C50	D2	0	0	0	0	0	0	0	0
108	B5, D2 C50	B5	0	0	0	0		0	0	0
109	A7, C4 C50	A7	100	100	100	100	99	80	95	0
110	A7, C4 C50	C4	100	100	100	100	99	100	99	95
111	B3, C8 C50	B3	90	85	90	100	95	90	70	0
112	B3, C8 C50	C8	100	80	85	50	80	100	30	0
113	D5, D6 C 50	D5	95	100	95	80	90	80	70	95
114	D5, D6 C 50	D6	90	95	96	90	70	100	70	96
115	D7, D8 C50	D7	90	80	80	30	65	50	50	95





153	B2, C7 C50	B2	95	90	75	30	60	50	30	5
154	B2, C7 C50	C7	80	40	30	0	10	25	10	50
155	D7, D8 C50	D8	80	80	70	0	0	25	5	95
156	A3, B8 mammární hamartom	B8	20	15	10	0	0	5	1	0
157	A3, B8 mammární hamartom	A3	15	20	10	5	5	5	0	0
158	A5, C2 mammární tkáň	C2	70	20	15	10		5	3	0
159	A5, C2 mammární tkáň	A5	30	15	30	0	2	5	5	0
160	B4, D1 C50	B4	40	35	5	0	0	5	3	0
161	B4, D1 C50	D1	25	20	0	0	0	10		0
162	A4, C1 jaterní tkáň	A4	5	0	0	0	10	0	0	0
163	A4, C1 jaterní tkáň	C1	5	5	0	0	10	0	0	0
164	**Protilátka**		SP1	6F11	1D5	1D5	1D5	1D5	6F11	1D5
165			SP1	ENV	ENV+	LSAB2	x	x	ENV	x
166			DAB+	DAB	DAB+				DAB	

NordiQC

- Nekomerční, placený a sponzorovaný systém skandinávských zemí, od r. 2003.
- General module (800 euro)
  - 4x ročně cca 6 antigenů v jednom kole
- Breast module (250 euro)
  - 2x ročně Her-2, ER, PgR

http://www.nordiqc.org

UK NEQAS

- Nekomerční, placený a sponzorovaný systém UK, od r. 1988 (!)
- 4x ročně 3-14 skel
- 1. General Pathology Immunocytochemistry
  2. Breast Pathology Immunocytochemistry
  3. Neuropathology Immunocytochemistry
  4. Lymphoma Pathology Immunocytochemistry
  5. Non gynae cytology

http://www.ukneqas.org.uk/

UK NEQAS

- Rozeslání nebarvených skel z „centrálního“ (složeného) tkáňového bloku.
- Nabarvit zaslaná skla a vrátit zpět se svou kontrolou a s protokolem.
- Hodnotí 4 zkušené osoby, skórování 1-5.
  - 13-20 optimální
  - 10-12 borderline
  - pod 12 - nevyhovující

http://www.ukneqas.org.uk/


CzeQC
nebo
Czech NEQAS?