Società Medico Chirurgica di Ferrara

Malattia metastatica del carcinoma del grosso intestino
Tecniche e terapie innovative

Ferrara, 29 ottobre 2011

Storia naturale della malattia

Prof. Giovanni Lanza

international union against cancer

uicc global cancer control

Colon - Rectum – 7th edition

T4 Tumour directly invades other organs or structures and/or perforates visceral peritoneum

T4a perforates visceral peritoneum

T4b directly invades other organ or structures

M1 Distant metastasis

M1a one organ

M1b > one organ or peritoneum

Basic categories unchanged

Subdivisions expanded

N1 Metastasis in 1 to 3 regional lymph nodes

N1a 1 node

N1b 2 – 3 nodes

N1c satellites in subserosa, *without* regional nodes*

N2 Metastasis in 4 or more regional lymph nodes

N2a 4 – 6 nodes

N2b 7 or more nodes

Basic categories unchanged

Subdivisions expanded

Changes from 6th edition

www.uicc.org

international union against cancer

uicc global cancer control

Colon - Rectum – 7th edition

Stage 0	Tis	N0
Stage I	T1, T2	N0
Stage II	T3, T4	N0
Stage IIA		T3
N0		
Stage IIB		T4a
N0		
Stage IIC		T4b
N0		

Basic categories unchanged

Subdivisions expanded

Changes from TNM 6

Stage III	Any T N1-2		
Stage IIIA	T1, T2		N1
	T1 N2a		
Stage IIIB	T3, T4a		N1
	T2-T3 N2a		
	T1-T2 N2b		
Stage IIIC	T4a N2a		
	T3-T4a N2b		
	T4b N1-2		
Stage IV	Any T M1	Any N	
Stage IVA	Any T M1a	Any N	
Stage IVB	Any T M1b	Any N	

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TNM classification

	Notes		
No.	**5th Edition**	**6th Edition**	**7th Edition**
1	Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through muscularis mucosae into the submucosa. (Note: the authors of the European Guidelines for quality assurance in pathology in CRC screening and diagnosis recommend not using this category. Respective lesions should be reported as mucosal high-grade neoplasia, see Section 7.3.)		
2	Direct invasion in T4 includes invasion of other segments of the colon or rectum by way of the serosa, e.g. invasion of sigmoid colon by a carcinoma of the cecum.		Direct invasion in T4b includes invasion of other organs or segments of the colon or rectum by way of the serosa, as confirmed on microscopic examination, or for tumours in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria
3		Tumour that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumour is present in the adhesion, microscopically, the classification should be pT3.	Tumour that is adherent to other organs or structures, macroscopically, is classified cT4b. However, if no tumour is present in the adhesion, microscopically, the classification should be pT1-T3, depending on the anatomical depth of wall invasion.
4	A tumour nodule greater than 3 mm in diameter in perirectal or pericolic adipose tissue without histological evidence of a residual lymph node in the nodule is classified as regional lymph node metastasis. However, a tumour nodule up to 3 mm in diameter is classified in the T category as discontinuous extension i.e. T3.	A tumour nodule in the pericolic/perirectal adipose tissue without histological evidence of a residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour it should be classified in the T category and also coded as V1 (microscopic venous invasion) or V2, if it was grossly evident, because there is a strong likelihood that it represents venous invasion.	Tumour deposits (satellites), i.e. macroscopic or microscopic nests or nodules, in the pericolorectal adipose tissue's lymph drainage area of a primary carcinoma without histological evidence of residual lymph node in the nodule, may represent discontinuous spread, venous invasion with extra-vascular spread (V1/2) or a totally replaced lymph node (N1/2). If such deposits are observed with lesions that would otherwise be classified as T1 or T2, then the T classification is not changed, but the nodule is recorded as N1c. If a nodule is considered by the pathologist to be a totally replaced lymph node (generally having a smooth contour), it should be recorded as a positive lymph node and not as a satellite, and each nodule should be counted separately as a lymph node in the final pN determination. (Note of the authors of the European Guidelines for quality assurance in pathology in CRC screening and diagnosis: introduction of N1c category leads to stage shift from II to III for some tumours)

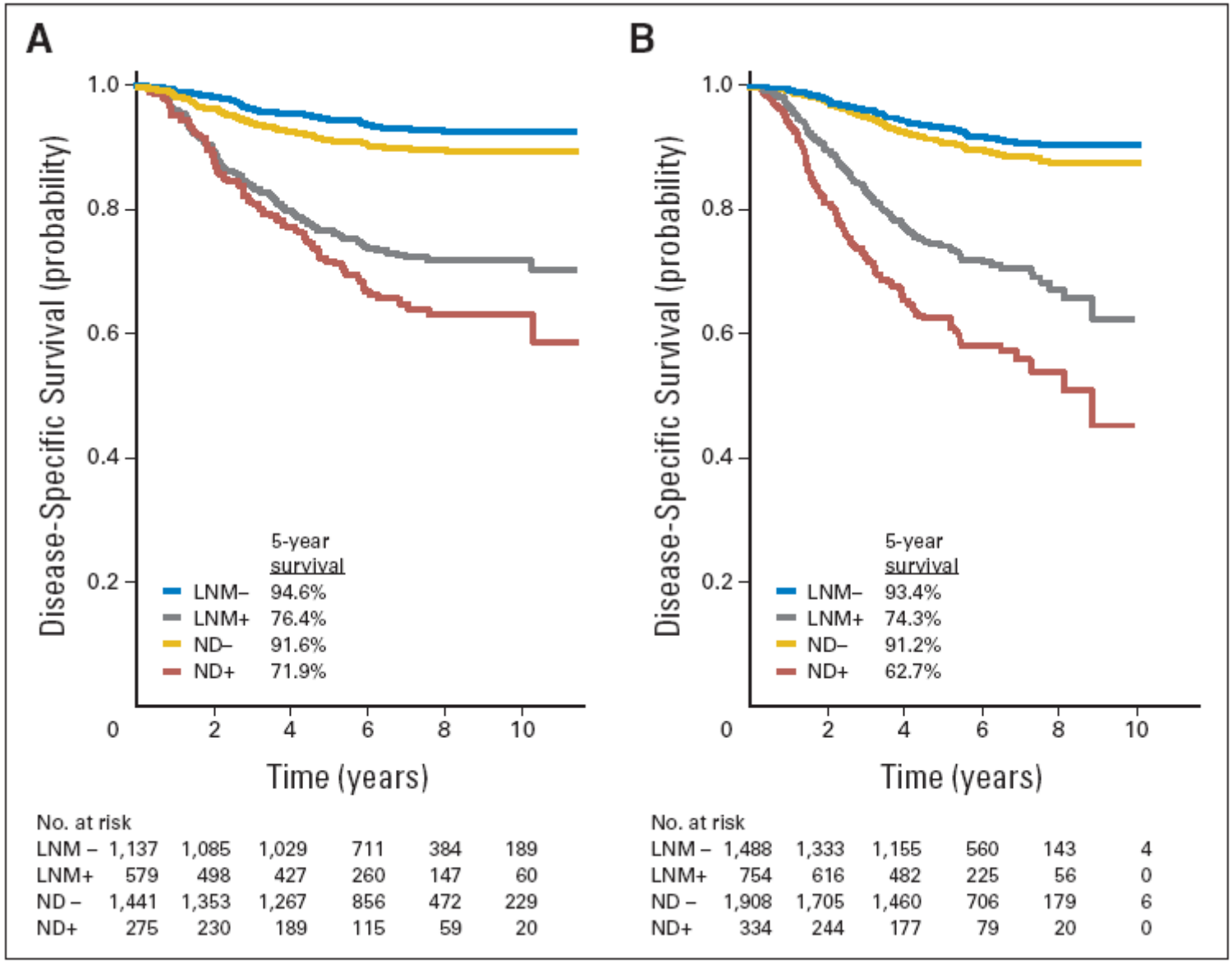
VOLUME 29 · NUMBER 18 · JUNE 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Actual Status of Distribution and Prognostic Impact of Extramural Discontinuous Cancer Spread in Colorectal Cancer

Hideki Ueno, Hidetaka Mochizuki, Kazuo Shirouzu, Takaya Kusumi, Kazutaka Yamada, Masahiro Ikegami, Hiroshi Kawachi, Shingo Kameoka, Yasuo Ohkura, Tadahiko Masaki, Ryoji Kushima, Keiichi Takahashi, Yoichi Ajioka, Kazuo Hase, Atsushi Ochiai, Ryo Wada, Keiichi Iwaya, Takahiro Nakamura, and Kenichi Sugihara



Ueno et al. 2011

Table 1. Incidence and Impact on Survival of LNM and ND

Status	First Cohort (n = 1,716)						Second Cohort (n = 2,242)					
	No. of Patients	%	DSS	*P*	HR	95% CI	No. of Patients	%	DSS	*P*	HR	95% CI
LNM												
Negative	1,137	66.3	94.6	< .001	1		1,488	66.4	93.4	< .001	1	
Positive	579	33.7	76.4		4.53	3.42 to 5.99	754	33.6	74.3		4.14	3.26 to 5.26
ND												
Negative	1,441	84.0	91.6	< .001	1		1,908	85.1	91.2	< .001	1	
Positive	275	16.0	71.9		4.04	3.08 to 5.30	334	14.9	62.7		5.33	4.23 to 6.72
S-ND												
Negative	1,575	91.8	89.7	< .001	1		2,076	92.6	88.8	< .001	1	
Positive	141	8.2	74.7		2.70	1.90 to 3.80	166	7.4	64.5		3.73	2.81 to 4.97
I-ND												
Negative	1,533	89.3	90.9	< .001	1		1,997	89.1	90.4	< .001	1	
Positive	183	10.7	67.9		4.34	3.25 to 5.80	245	10.9	58.7		5.74	4.51 to 7.30
LNM and/or ND												
Both negative	1,067	62.2	95.3	< .001	1		1,432	63.9	94.2	< .001	1	
LNM and/or ND positive	649	37.8	77.2		4.80	3.59 to 6.43	810	36.1	74.2		4.69	3.66 to 6.01

Abbreviations: DSS, disease-specific 5-year survival; HR, hazard ratio; I-ND, irregular-contour ND; LNM, lymph node metastasis; ND, tumor nodules without lymph node structure; S-ND, smooth-contour ND.

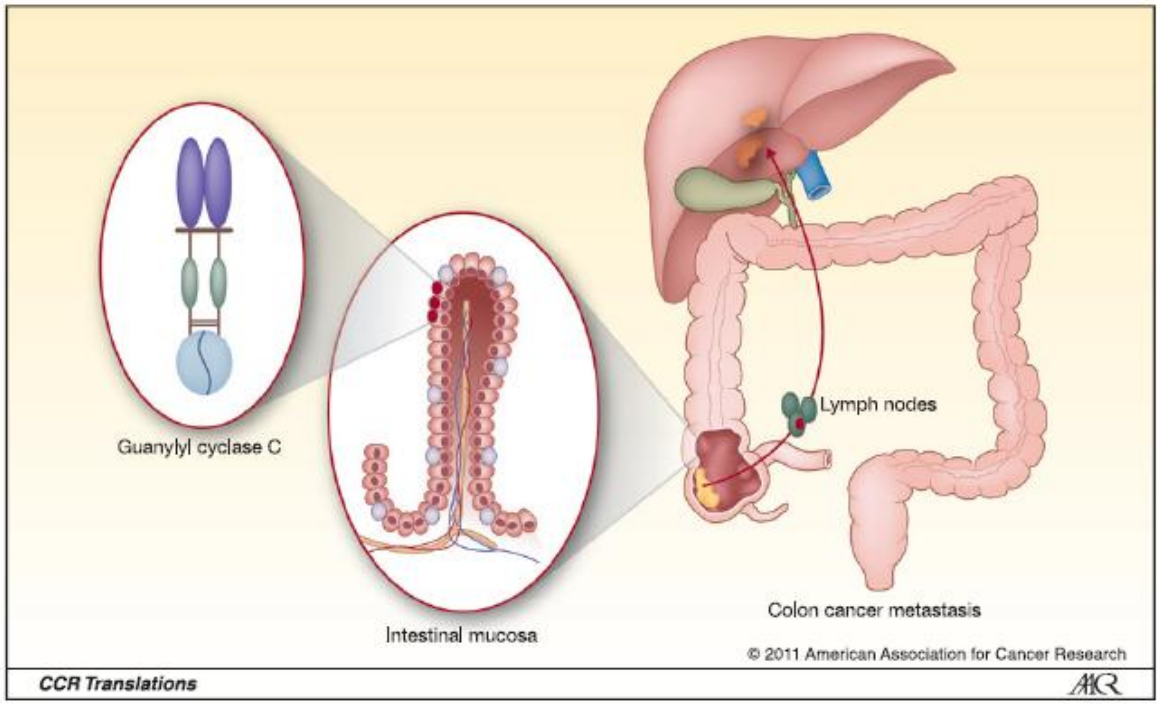
Ueno et al. 2011

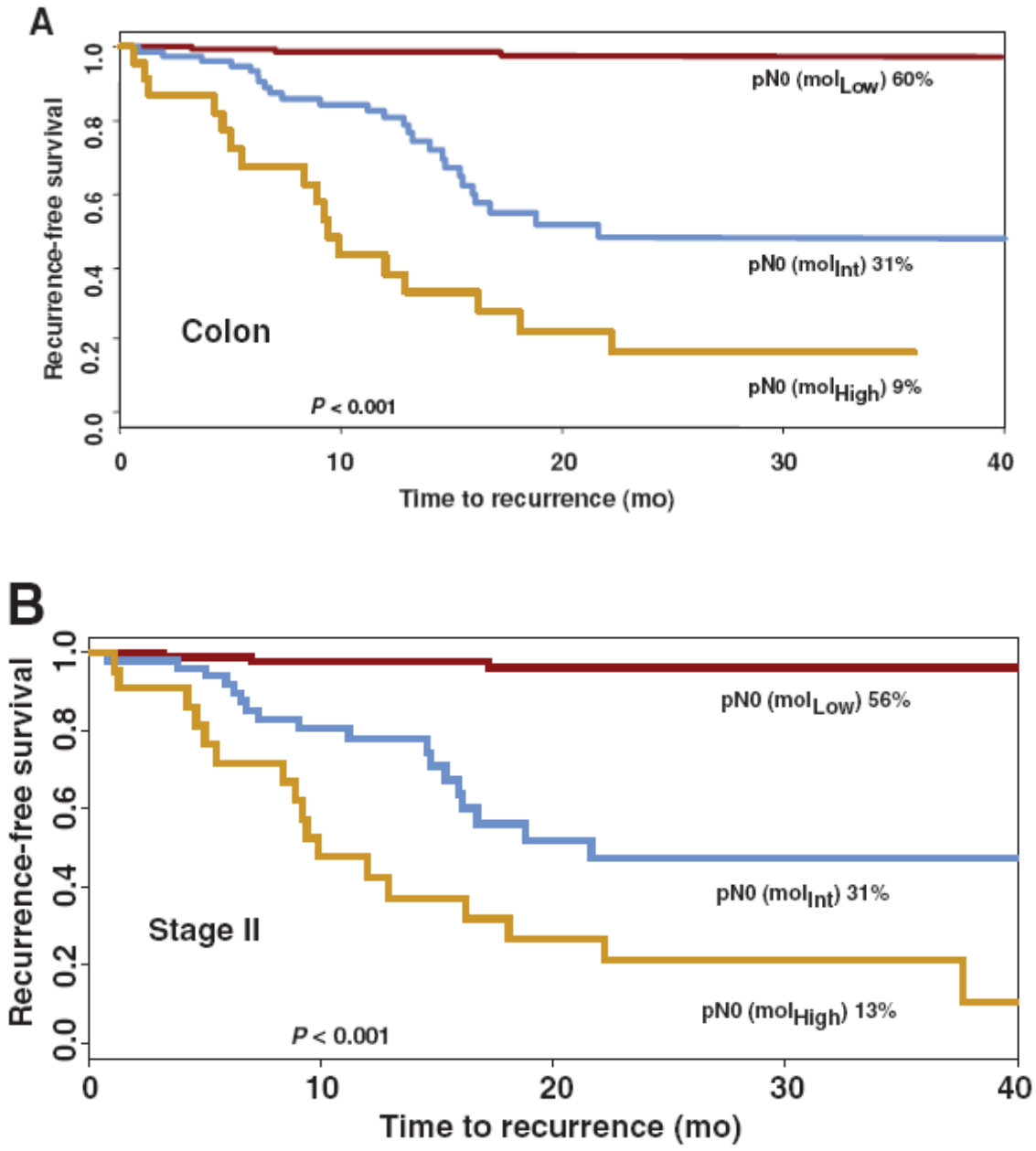
Clinical Cancer Research

Occult Tumor Burden Predicts Disease Recurrence in Lymph Node –Negative Colorectal Cancer

Terry Hyslop, David S. Weinberg, Stephanie Schulz, et al.

Clin Cancer Res 2011;17:3293-3303. Published OnlineFirst February 9, 2011.





Hyslop et al. 2011

VOLUME 29 · NUMBER 1 · JANUARY 1 2011

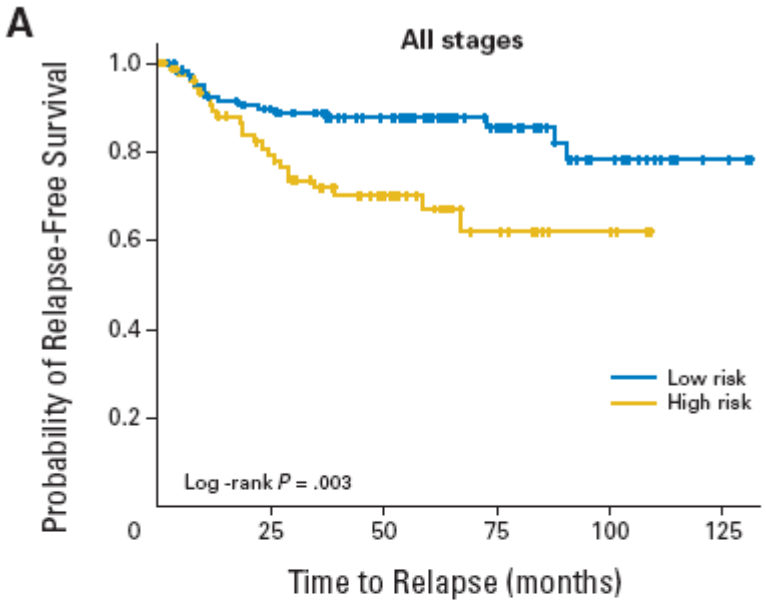
JOURNAL OF CLINICAL ONCOLOGY

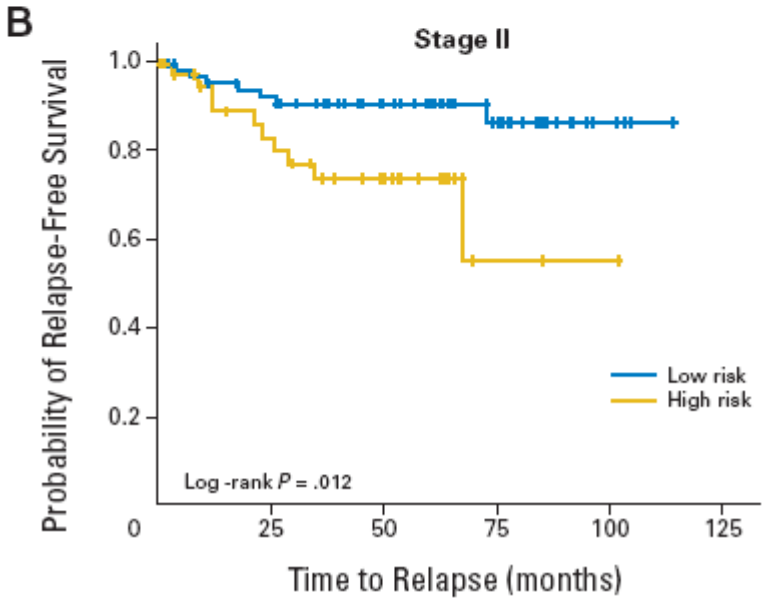
ORIGINAL REPORT

Gene Expression Signature to Improve Prognosis Prediction of Stage II and III Colorectal Cancer

Ramon Salazar, Paul Roepman, Gabriel Capella, Victor Moreno, Iris Simon, Christa Dreezen, Adriana Lopez-Doriga, Cristina Santos, Corrie Marijnen, Johan Westerga, Sjoerd Bruin, David Kerr, Peter Kuppen, Cornelis van de Velde, Hans Morreau, Loes Van Velthuysen, Annuska M. Glas, Laura J. Van't Veer, and Rob Tollenaar

ColoPrint





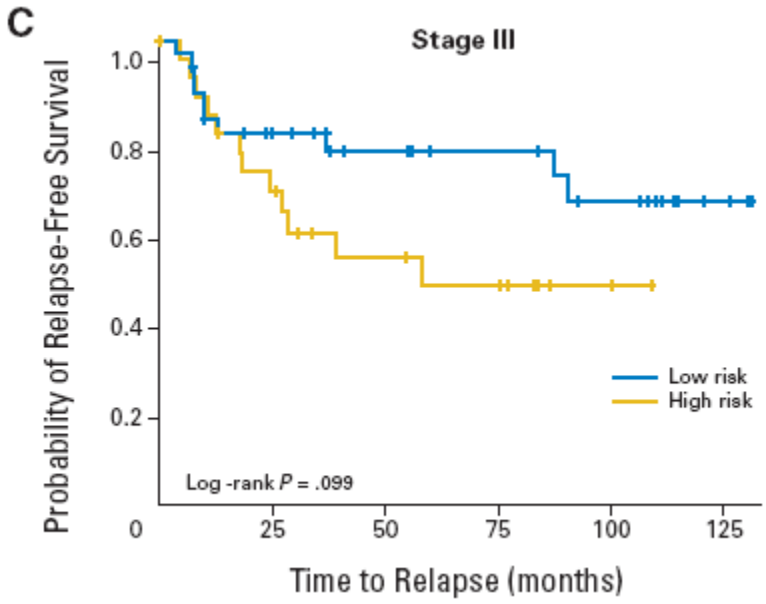
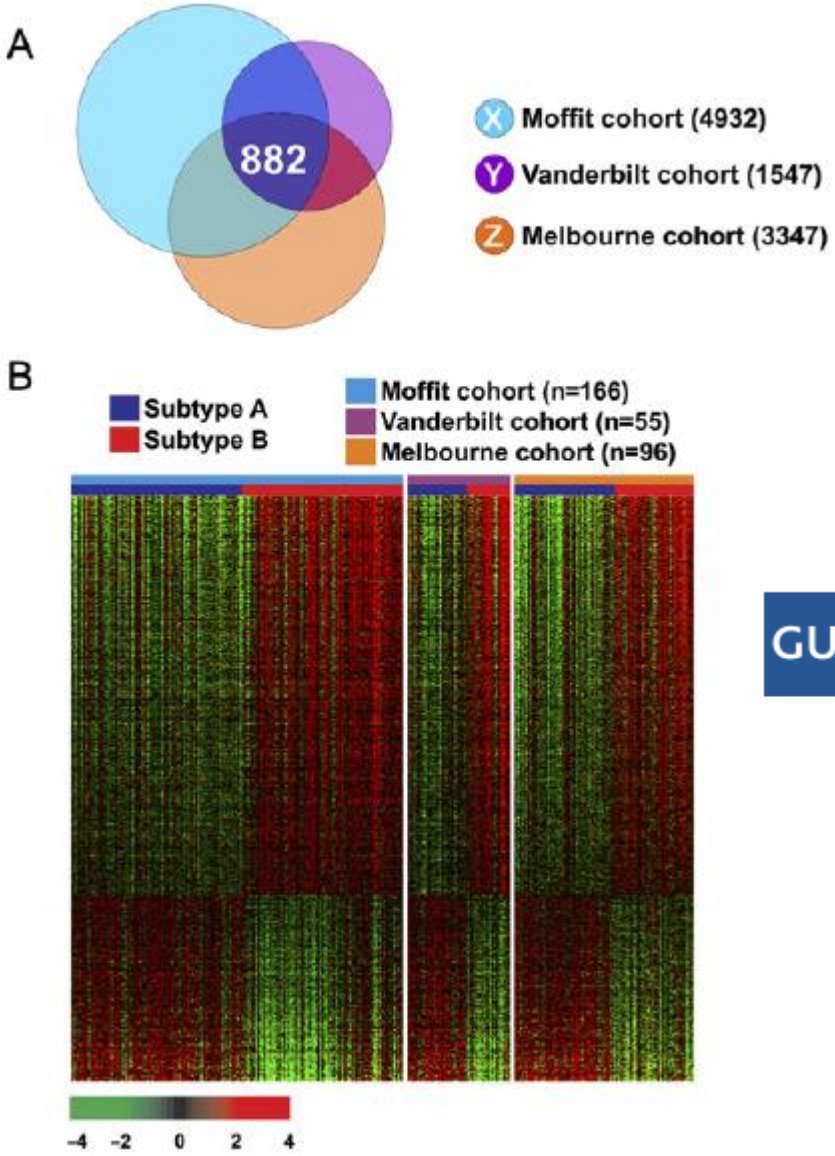


Table 4. Multivariate Analysis for Relapse-Free Survival in Validation Set

Variable	*P*	HR	95% CI
All stages, N = 206			
ColoPrint, high *v* low	.003	2.69	1.41 to 5.14
pT			
T2	.000		
T3 *v* T2	.038	0.19	0.04 to 0.91
T4 *v* T2	.960	1.05	0.19 to 5.88
Stage, continuous	.021	0.05	0.00 to 0.063
pN			
No positive LNs	.000		
1-3 positive LNs *v* no positive LNs	.327	1.52	0.66 to 3.52
> 3 positive LNs *v* no positive LNs	.000	5.97	2.62 to 13.63
No. of LNs assessed, continuous	.059		
Lymphatic, venous, or perineural invasion, any	.491		
Stage II only, n = 114			
ColoPrint, high *v* low	.018	3.29	1.24 to 8.83
pT, T4 *v* T3	.051	3.06	0.99 to 9.44

NOTE. Multivariate analysis includes only variables that were significant ($P < .05$) in the univariate analysis.
Abbreviations: HR, hazard ratio; LN, lymph node.

Salazar et al. 2011

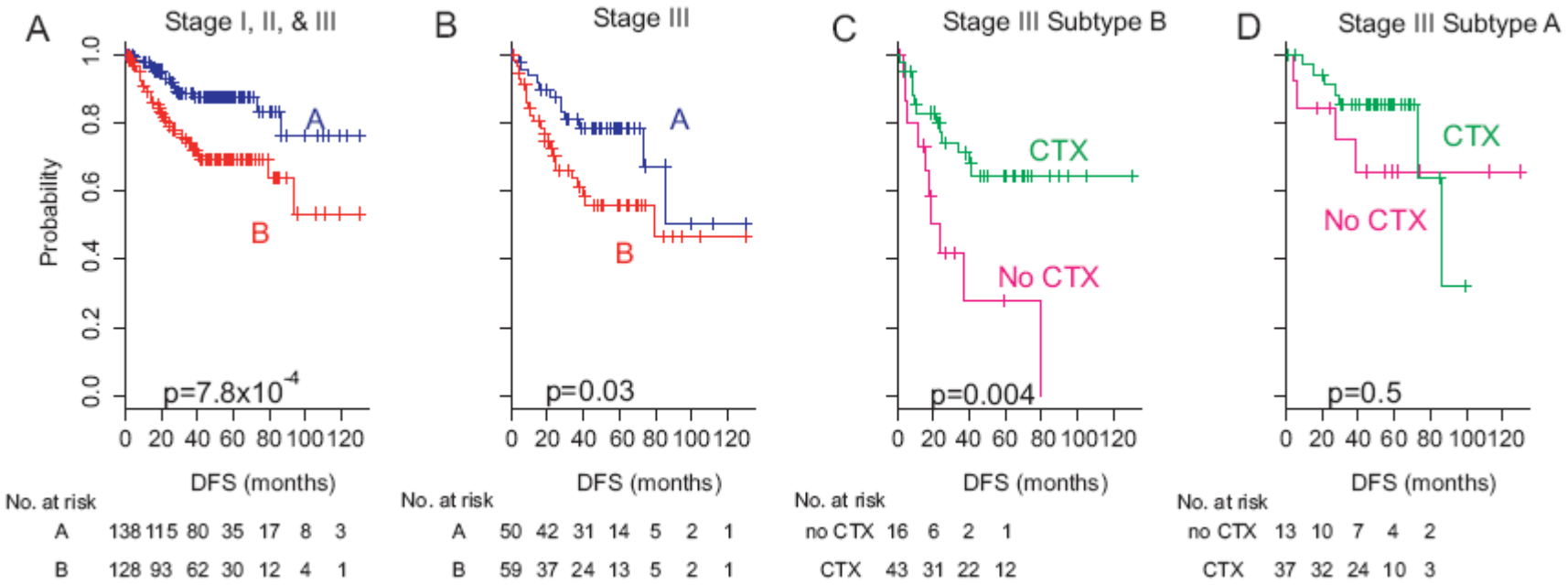


GUT

Prognostic gene expression signature associated with two molecularly distinct subtypes of colorectal cancer

Sang Cheul Oh, Yun-Yong Park, Eun Sung Park, et al.

Gut published online October 13, 2011
doi: 10.1136/gutjnl-2011-300812


A
Stage I, II, & III
Probability
1.0
0.8
0.6
0.4
0.2
0.0
A
B
p=7.8x10^-4
0 20 40 60 80 100 120
DFS (months)
No. at risk
A 138 115 80 35 17 8 3
B 128 93 62 30 12 4 1
B
Stage III
A
B
p=0.03
0 20 40 60 80 100 120
DFS (months)
No. at risk
A 50 42 31 14 5 2 1
B 59 37 24 13 5 2 1
C
Stage III Subtype B
CTX
No CTX
p=0.004
0 20 40 60 80 100 120
DFS (months)
No. at risk
no CTX 16 6 2 1
CTX 43 31 22 12
D
Stage III Subtype A
CTX
No CTX
p=0.5
0 20 40 60 80 100 120
DFS (months)
No. at risk
no CTX 13 10 7 4 2
CTX 37 32 24 10 3

Oh et al. 2011

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

La linea giusta è prevenire.

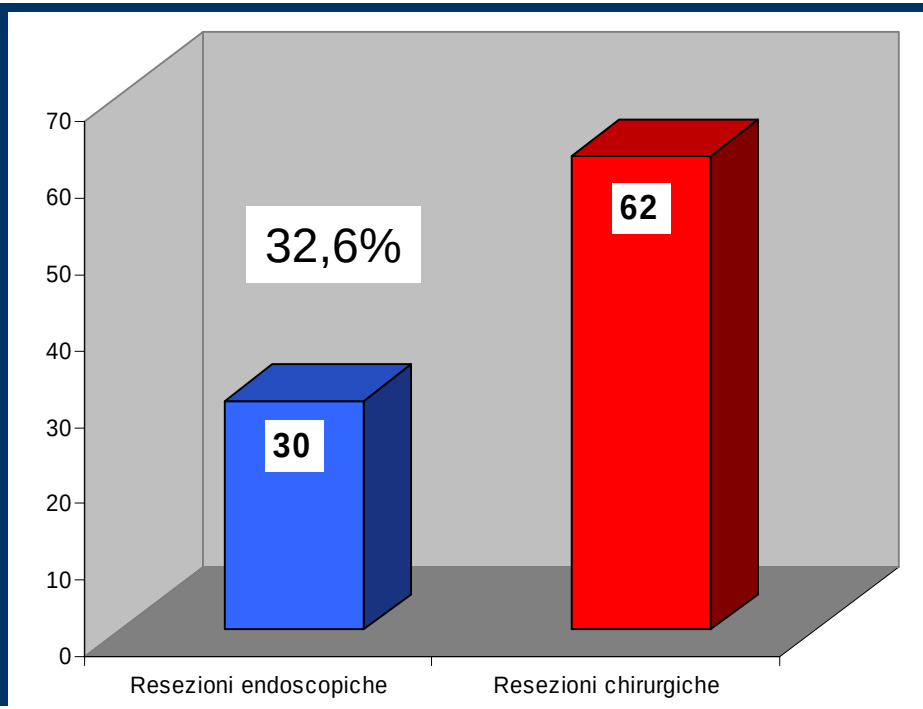
CAVA

PROGRAMMA DI SCREENING PER LA PREVENZIONE DEI TUMORI DEL COLON-RETTO

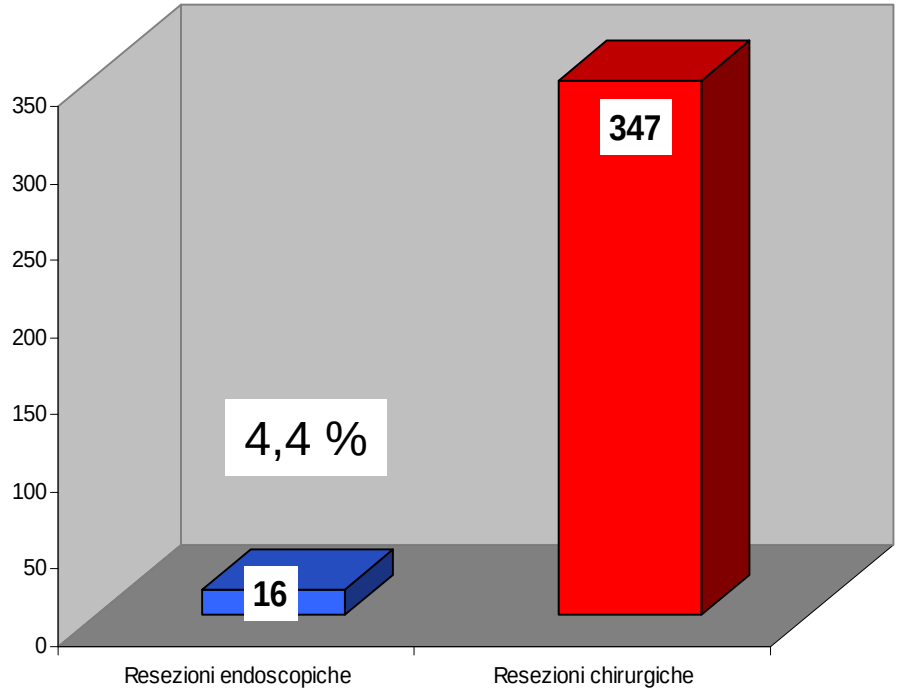
SCREENING. vuol dire salute

I.P.

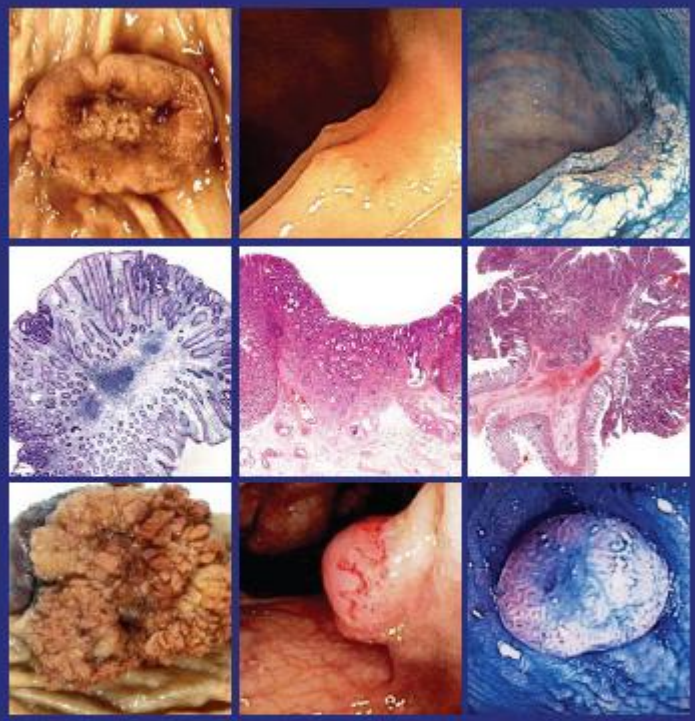
RegioneEmilia-Romagna



Screening



Casistica 2004



European guidelines for quality assurance in colorectal cancer screening and diagnosis

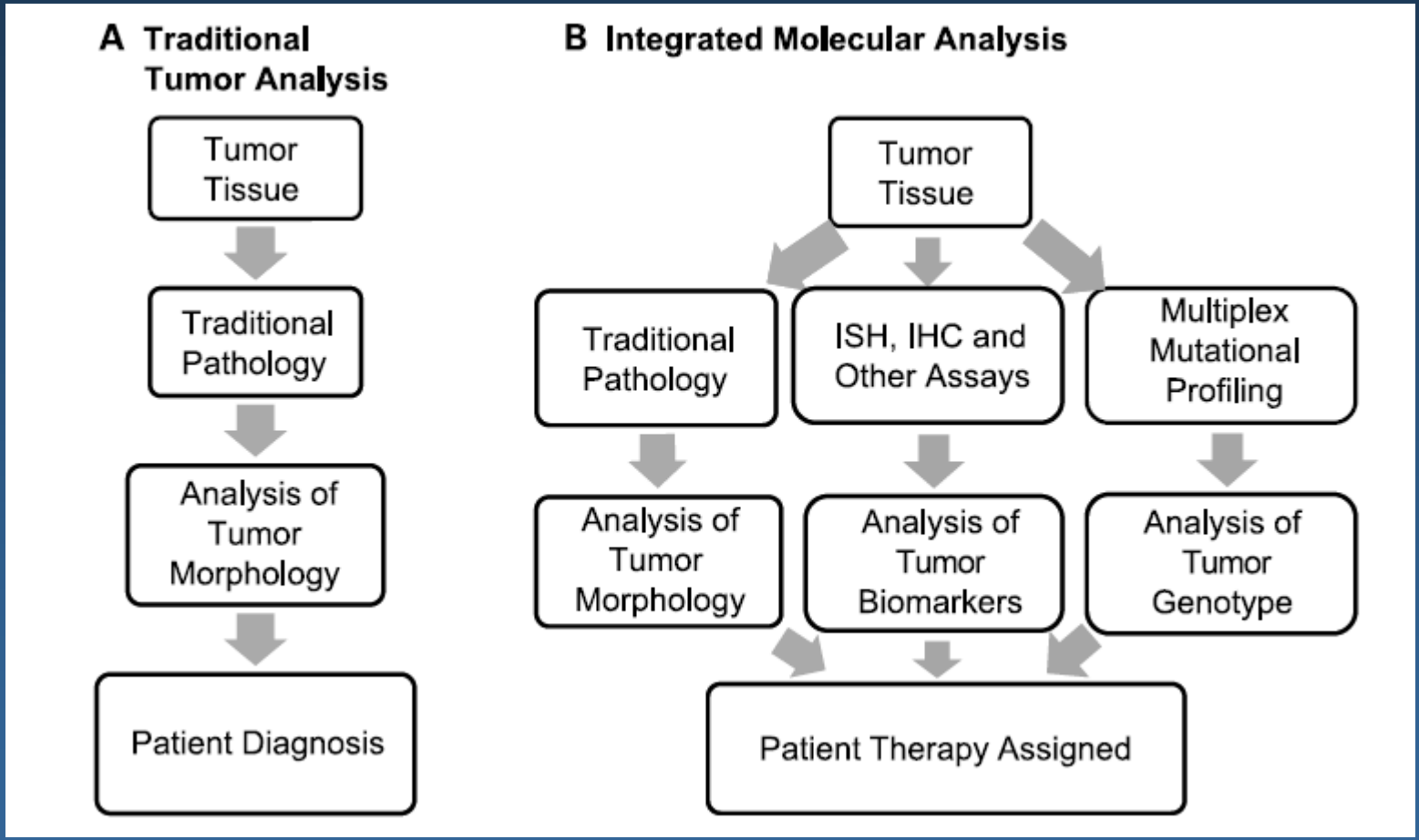
First Edition

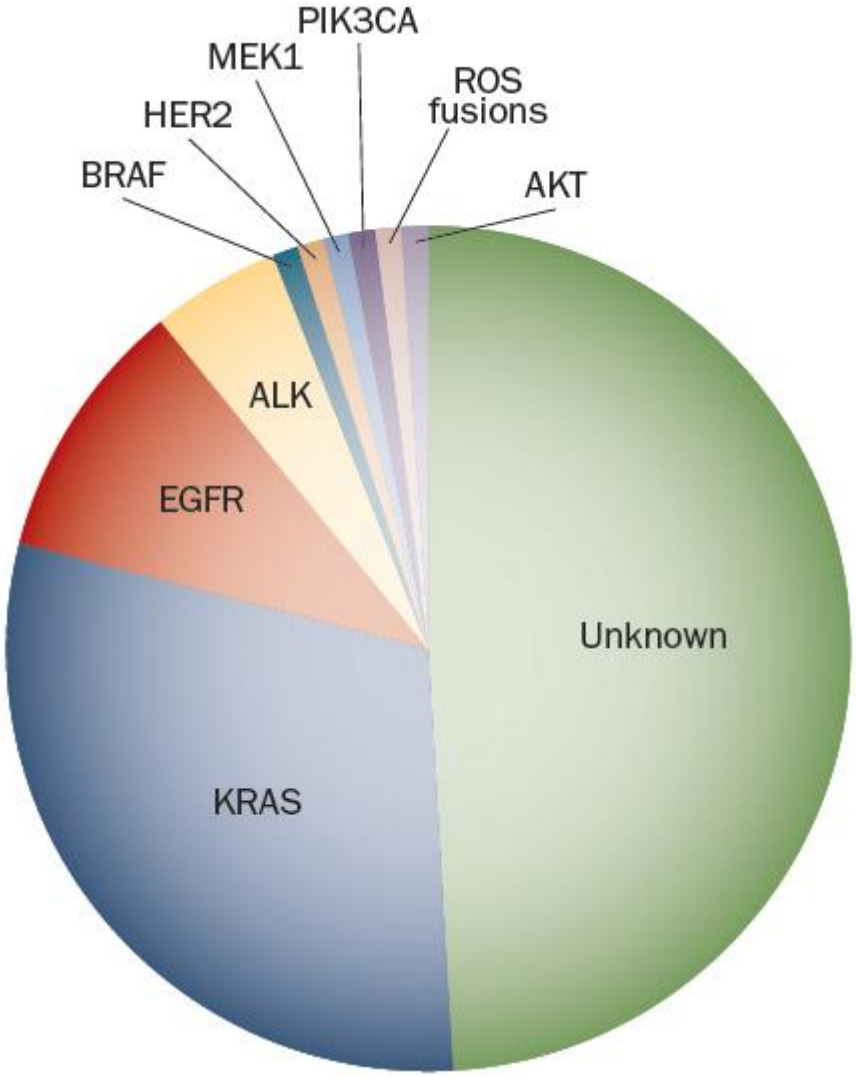
European Commission

Carcinoma colorettale avanzato
Diagnosi istopatologica

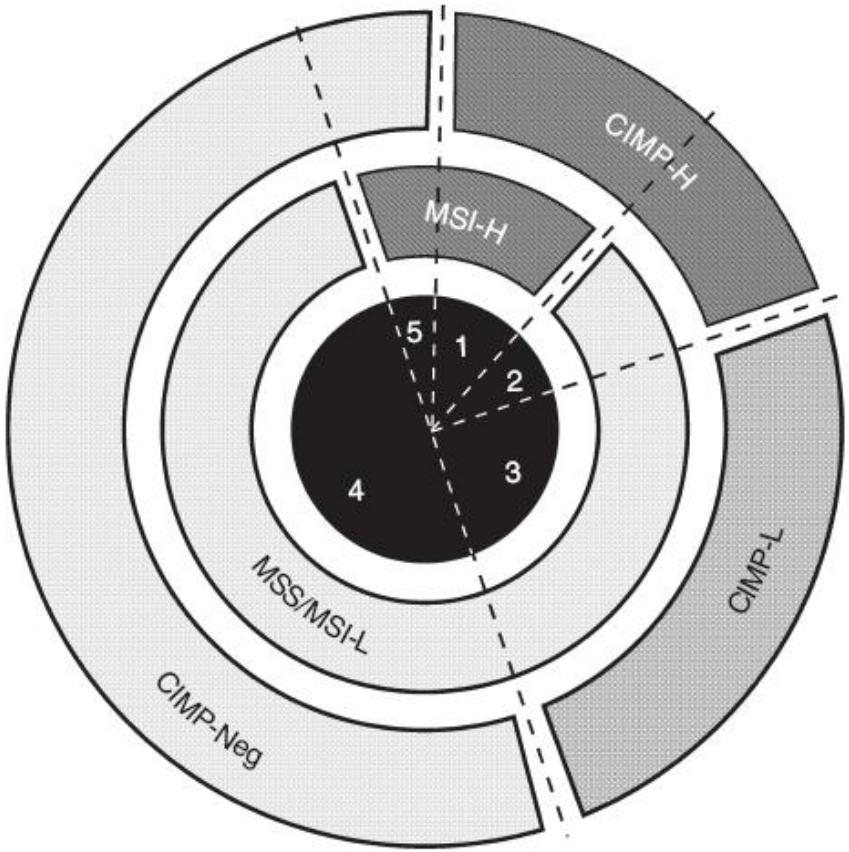
- **Istotipo**
- **Grado di differenziazione**
- **Livello di infiltrazione (pT)**
- **Stato linfonodale (pN)**
  - **linfonodi metastatici, linfonodi esaminati, noduli satelliti peritumorali**
- **Metastasi a distanza (pM)**
- **Invasione venosa**
- **Margini di resezione**
  - **prossimale/distale, circonferenziale, mesenterico**
- **Risposta alla terapia neoadiuvante (retto)**
- **Patologia associata**
  - **numero e tipo di polipi, altro**

Integration of molecular pathology into cancer clinic

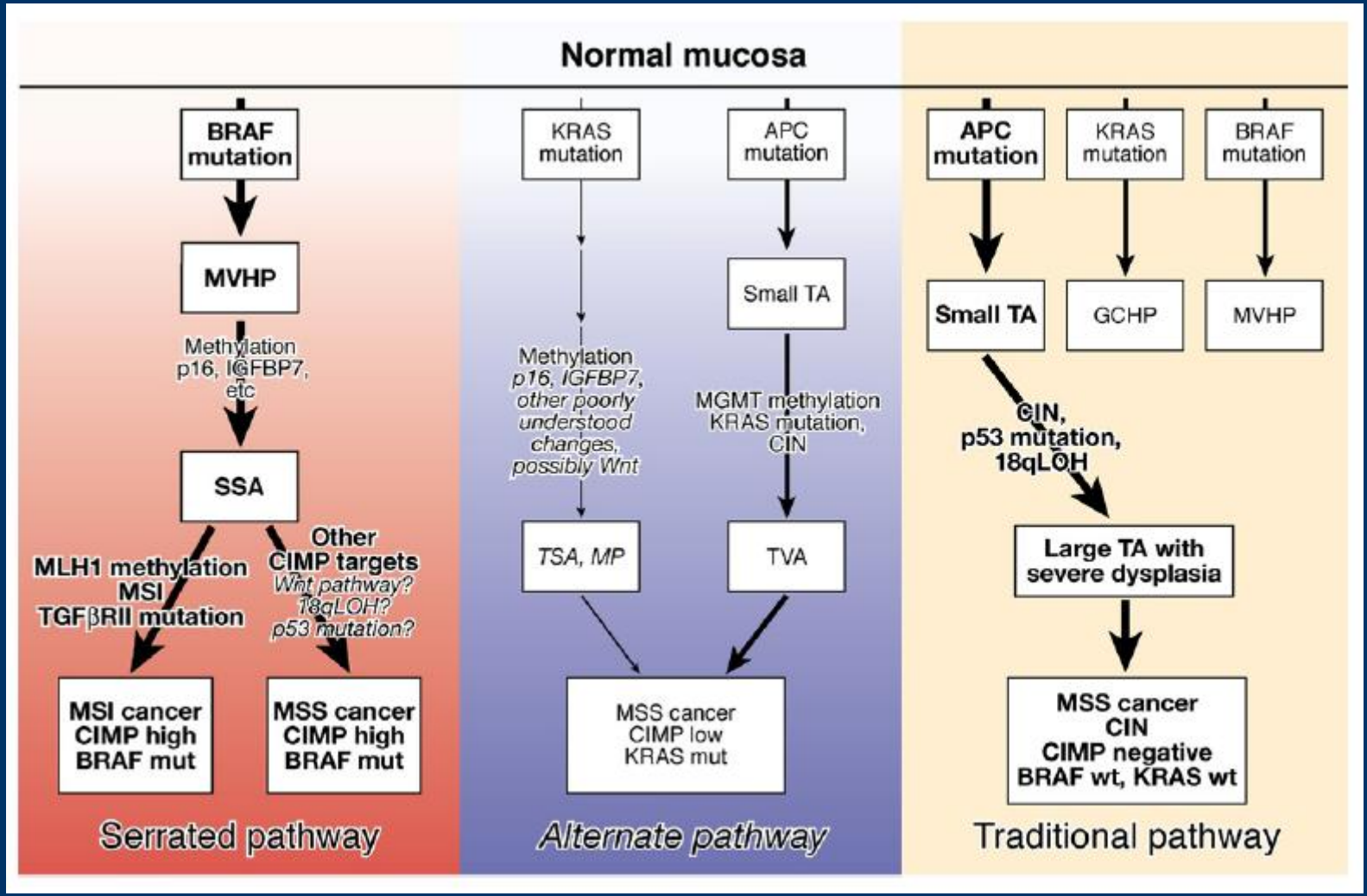


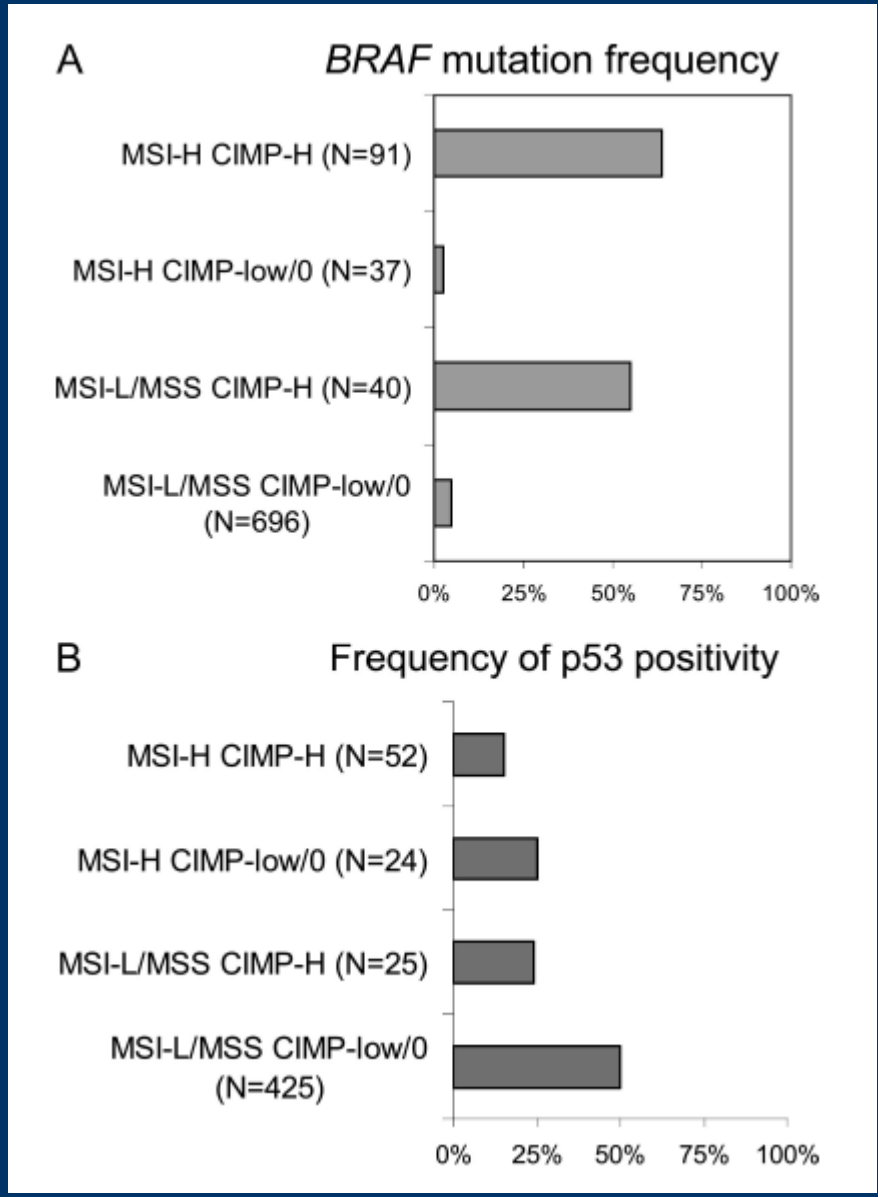


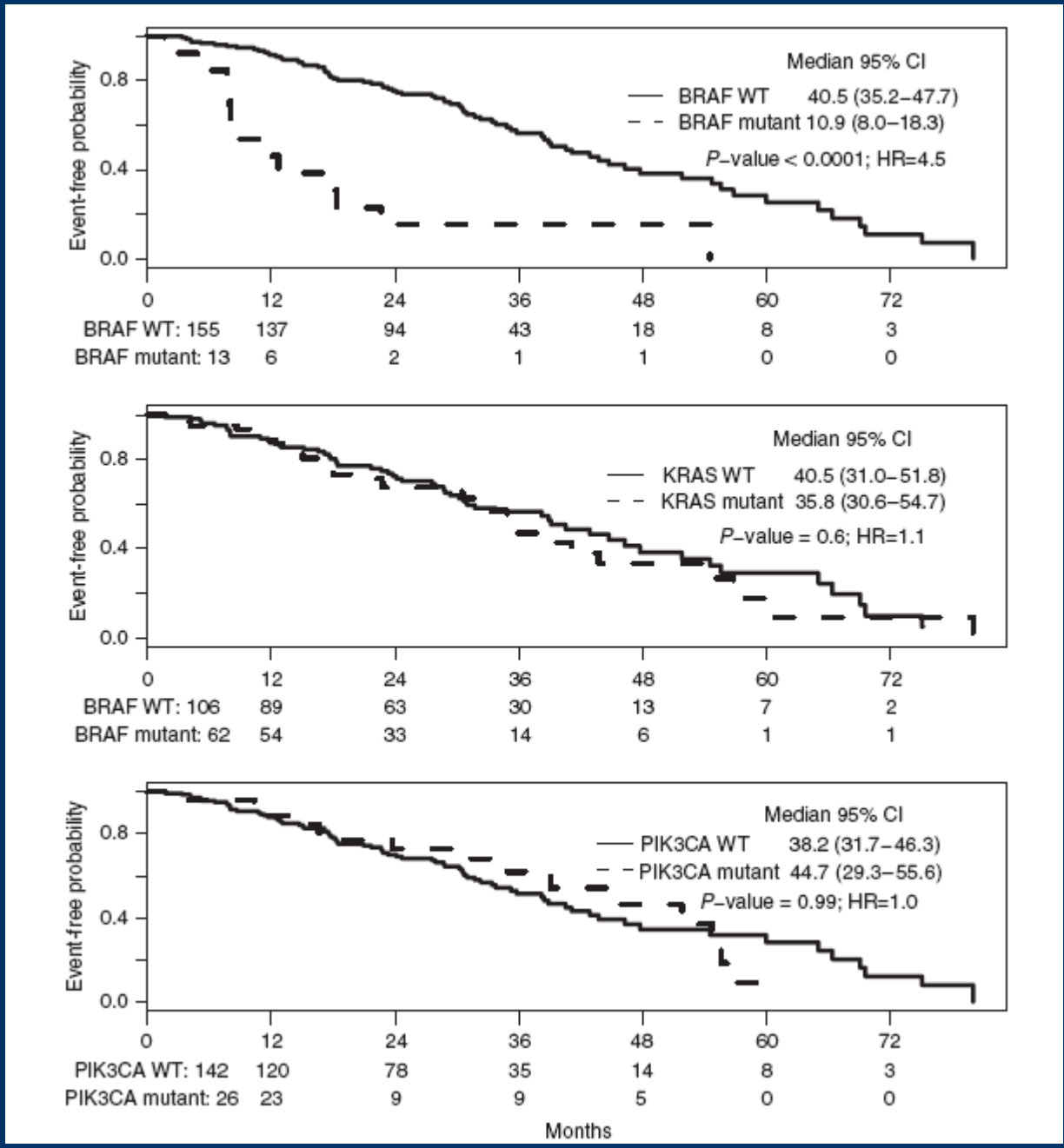
Molecular subsets of lung cancer



Molecular classification of colorectal cancer


Normal mucosa
BRAF mutation
MVHP
Methylation p16, IGFBP7, etc
SSA
MLH1 methylation MSI TGFβRII mutation
Other CIMP targets Wnt pathway? 18qLOH? p53 mutation?
MSI cancer CIMP high BRAF mut
MSS cancer CIMP high BRAF mut
Serrated pathway
KRAS mutation
APC mutation
Small TA
Methylation p16, IGFBP7, other poorly understood changes, possibly Wnt
MGMT methylation KRAS mutation, CIN
TSA, MP
TVA
MSS cancer CIMP low KRAS mut
Alternate pathway
APC mutation
KRAS mutation
BRAF mutation
Small TA
GCHP
MVHP
CIN, p53 mutation, 18qLOH
Large TA with severe dysplasia
MSS cancer CIN CIMP negative BRAF wt, KRAS wt
Traditional pathway


A
BRAF mutation frequency
MSI-H CIMP-H (N=91)
MSI-H CIMP-low/0 (N=37)
MSI-L/MSS CIMP-H (N=40)
MSI-L/MSS CIMP-low/0 (N=696)
0%
25%
50%
75%
100%
B
Frequency of p53 positivity
MSI-H CIMP-H (N=52)
MSI-H CIMP-low/0 (N=24)
MSI-L/MSS CIMP-H (N=25)
MSI-L/MSS CIMP-low/0 (N=425)
0%
25%
50%
75%
100%



CRC metastatico

Souglakos et al. 2009

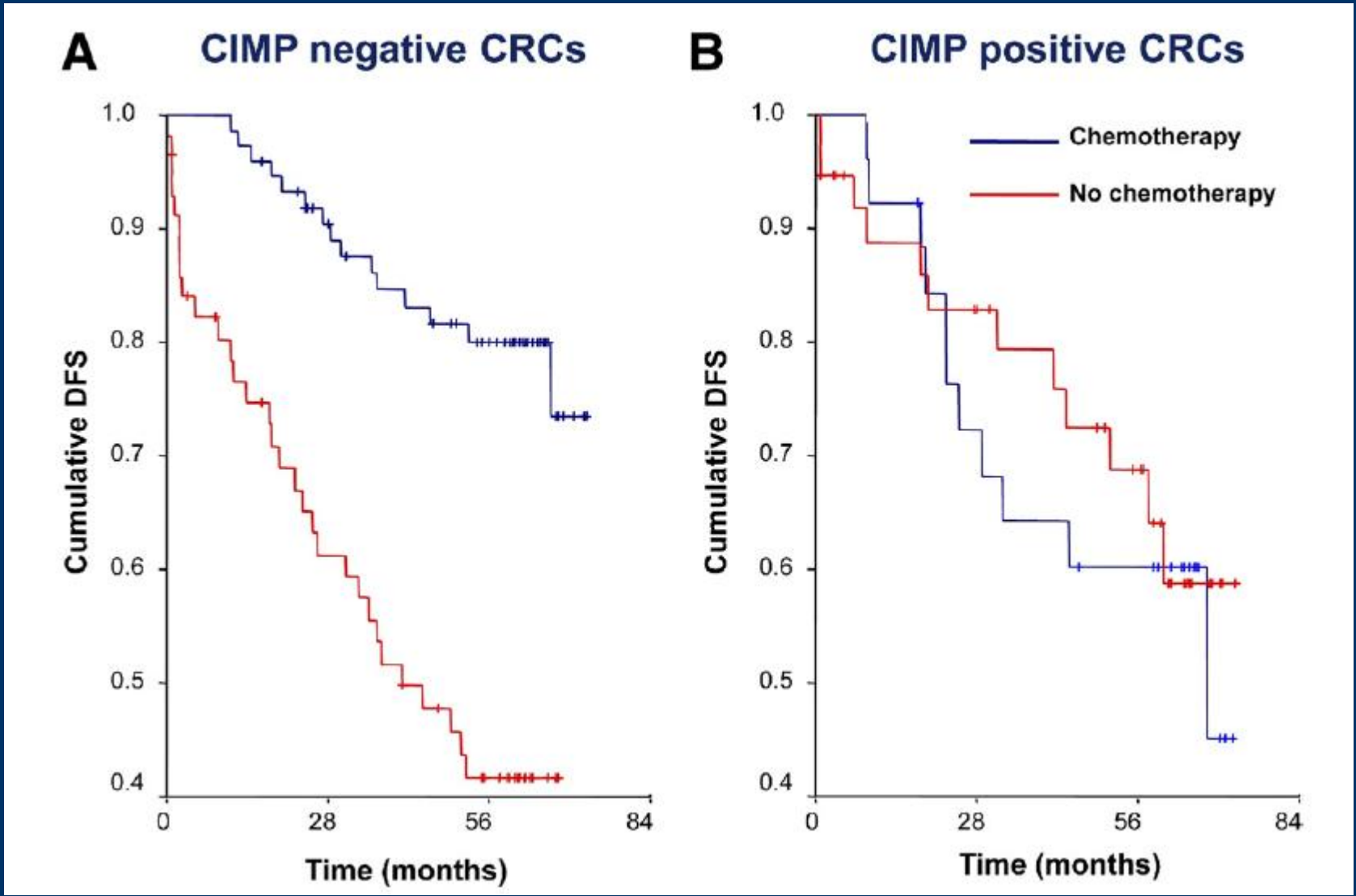
GASTROENTEROLOGY 2011;140:1174–1181

5-Fluorouracil Adjuvant Chemotherapy Does Not Increase Survival in Patients With CpG Island Methylator Phenotype Colorectal Cancer

RODRIGO JOVER,[*,‡] THUY–PHUONG NGUYEN,[§] LUCÍA PÉREZ–CARBONELL,[‡] PEDRO ZAPATER,[‖] ARTEMIO PAYÁ,[‡,¶] CRISTINA ALENDA,[‡,¶] ESTEFANÍA ROJAS,[‡] JOAQUÍN CUBIELLA,[#] FRANCESC BALAGUER,[§,**] JUAN D. MORILLAS,[‡‡] JUAN CLOFENT,[§§] LUIS BUJANDA,[‖‖] JOSEP M. REÑÉ,[¶¶] XAVIER BESSA,[##] ROSA M. XICOLA,[***] DAVID NICOLÁS–PÉREZ,[‡‡‡] ANTONI CASTELLS,[**] MONTSERRAT ANDREU,[##] XAVIER LLOR,[***] C. RICHARD BOLAND,[§] and AJAY GOEL[§]

[*]Unidad de Gastroenterología, [‡]Unidad de Investigación, [‖]Departamento de Farmacología Clínica, and [¶]Department of Pathology, Hospital General Universitario de Alicante, Alicante, Spain; [§]Division of Gastroenterology, Department of Internal Medicine, Baylor University Medical Center, Dallas, Texas; [#]Gastroenterology Department, Complexo Hospitalario de Ourense, Ourense, Spain; [**]Gastroenterology Department, Hospital Clinic, CIBERehd, IDIBAPS, University of Barcelona, Barcelona, Spain; [‡‡]Gastroenterology Department, Hospital Clínico de Madrid, Madrid, Spain; [§§]Gastroenterology Department, Hospital Meixoeiro, Vigo, Spain; [‖‖]Gastroenterology Department, Hospital Donostia, CIBERehd, Universidad del País Vasco, San Sebastián, Spain; [¶¶]Gastroenterology Department, Hospital Arnau de Vilanova, Lleida, Spain; [##]Gastroenterology Department, Hospital del Mar, Barcelona, Spain; [***]Department of Medicine and Cancer Center, University of Illinois at Chicago, Chicago, Illinois; and [‡‡‡]Gastroenterology Department, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain

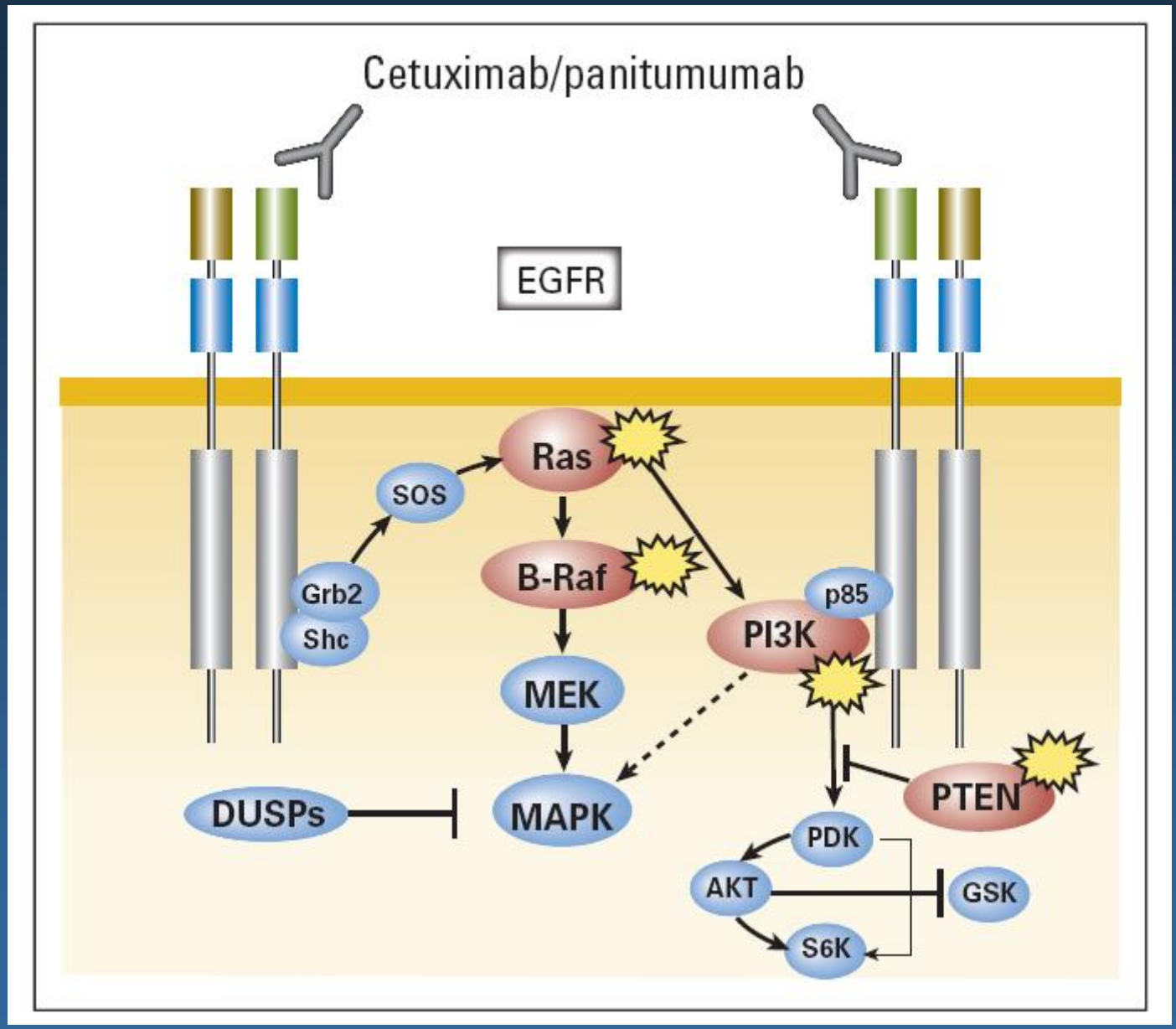
Pazienti stadio II e III

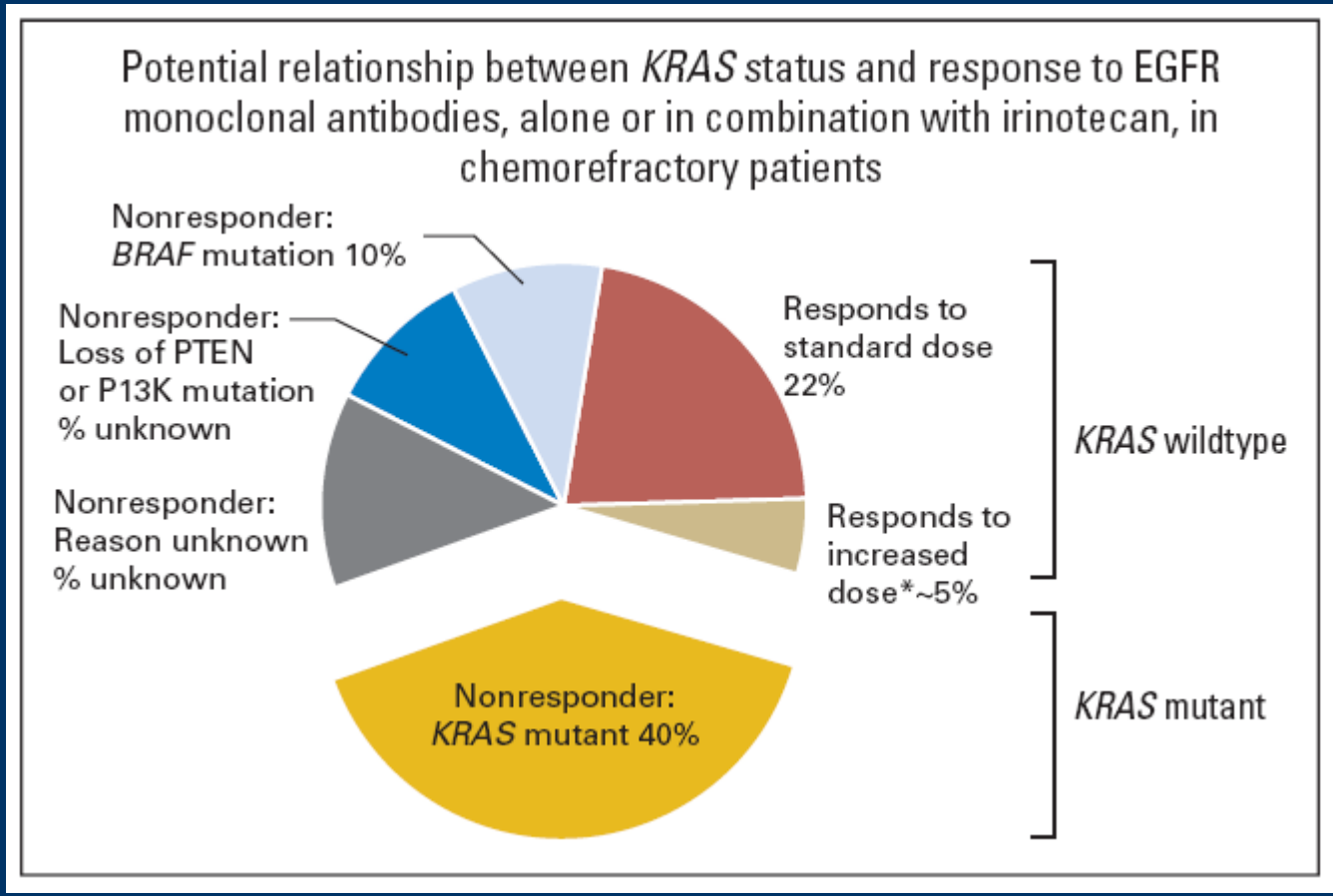


Jover 2011

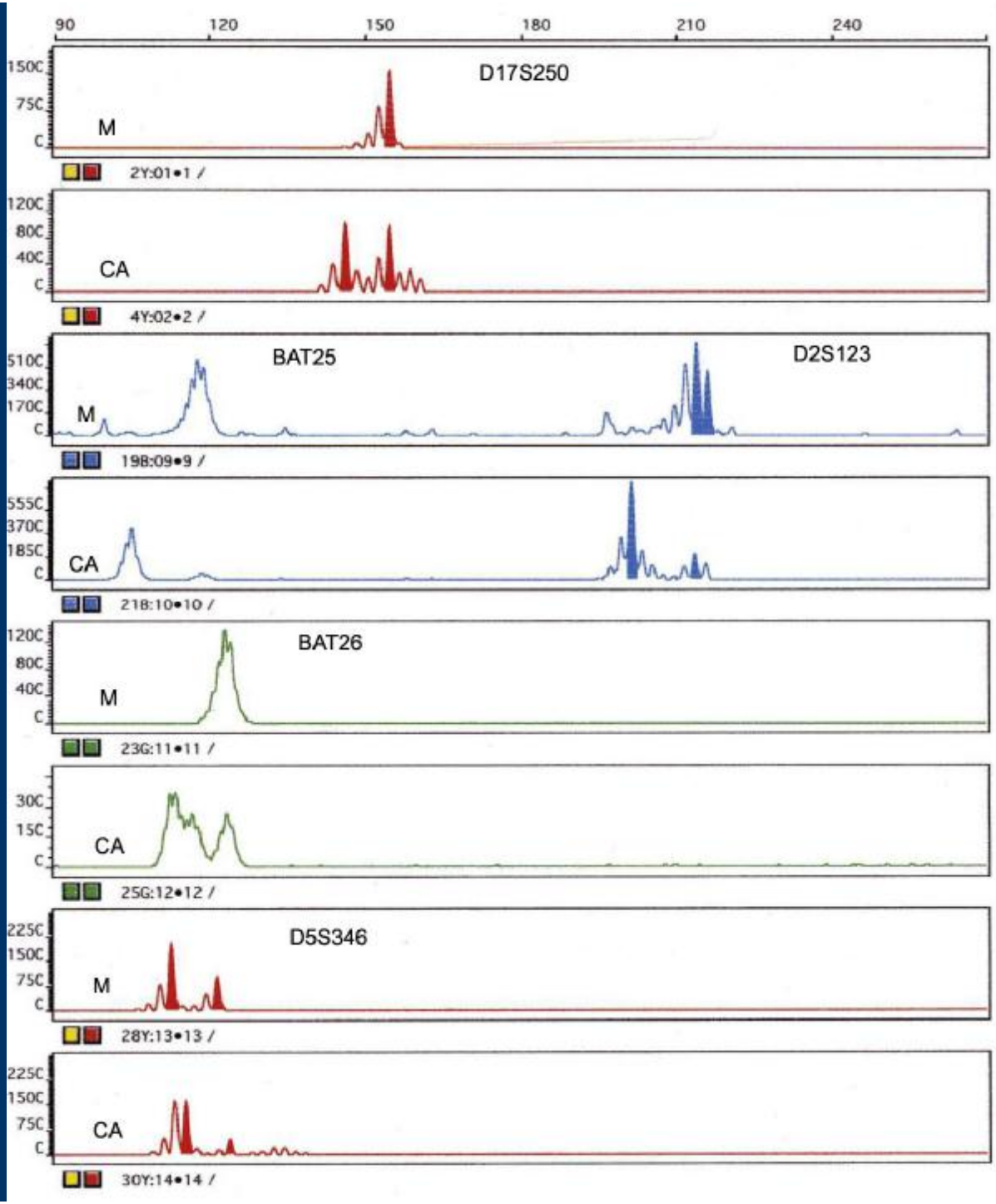
Carcinoma colorettale
Marcatori biologici e molecolari

- **Parametri prognostici e predittivi**
  - **mutazione di KRAS**
  - **Instabilità dei microsatelliti**
- **Identificazione sindromi ereditarie**
  - **Instabilità dei microsatelliti**


Cetuximab/panitumumab
EGFR
Ras
SOS
B-Raf
Grb2
Shc
p85
PI3K
MEK
DUSPs
MAPK
PTEN
PDK
AKT
GSK
S6K

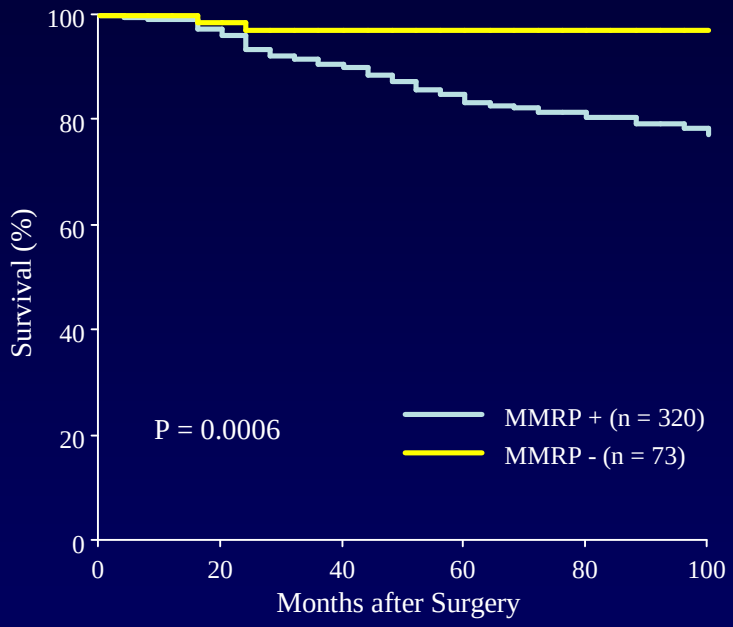


Wong & Cunningham 2008

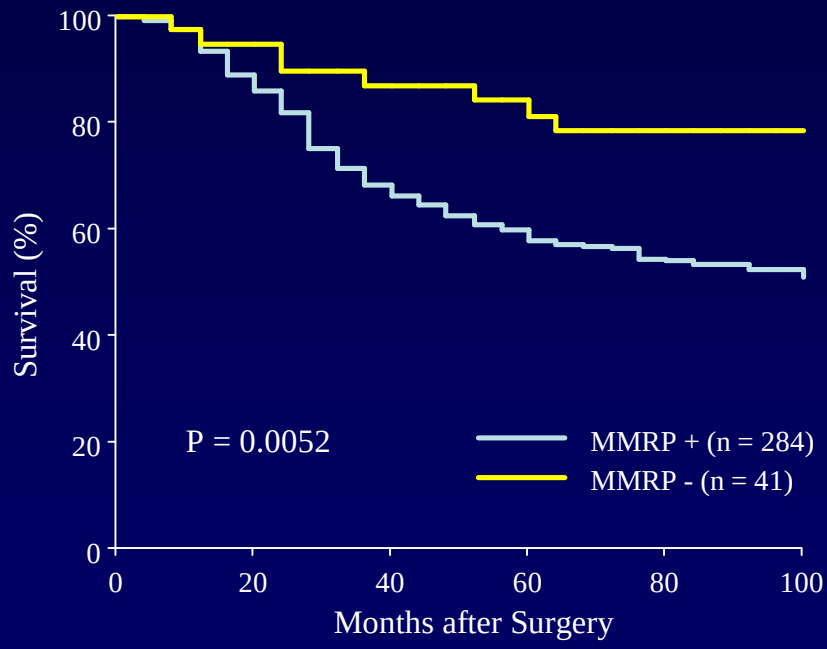


Carcinoma del colon con instabilità dei microsatelliti

MMR status and clinical outcome in CRC



Stage II patients



Stage III patients

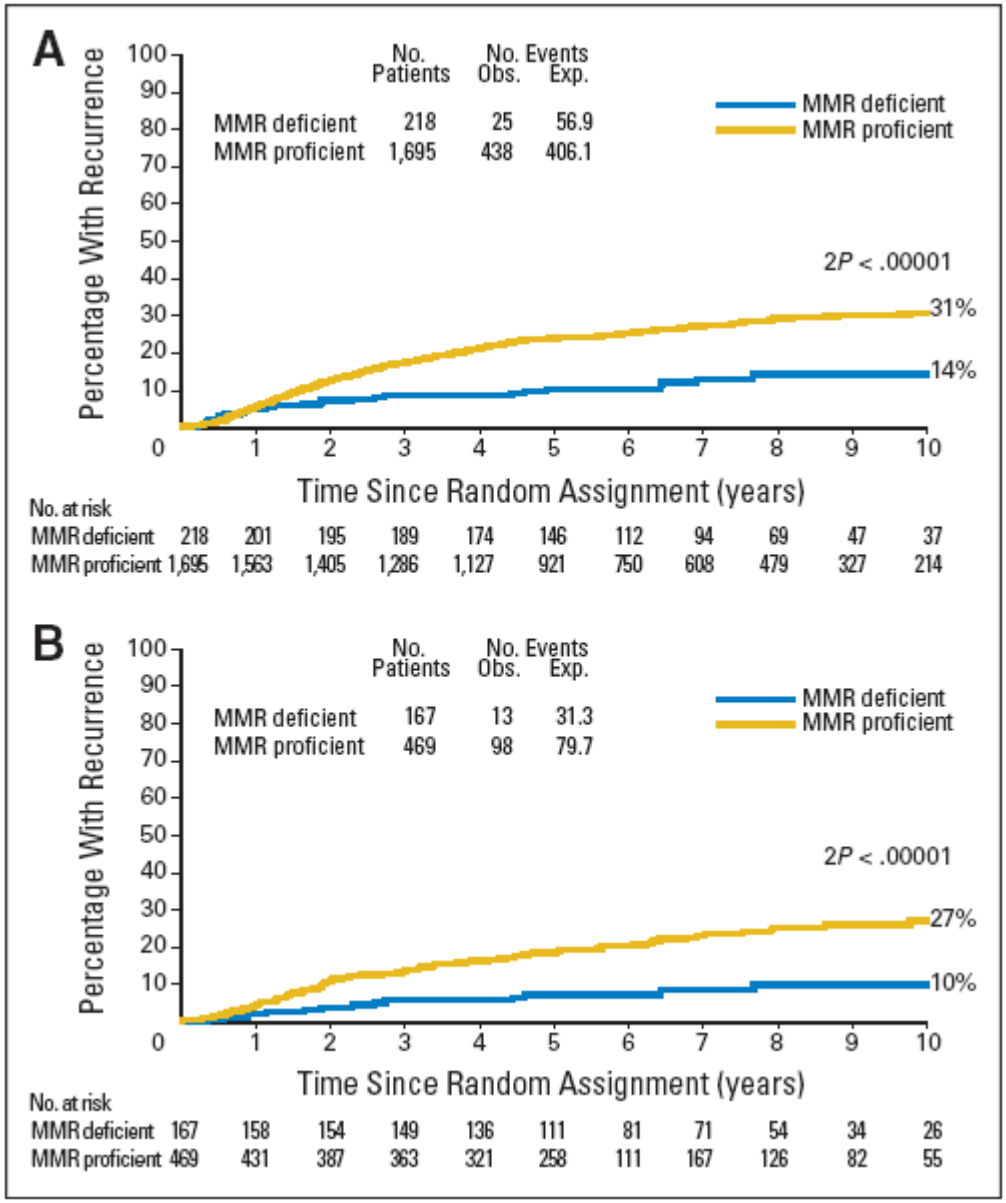
VOLUME 29 · NUMBER 10 · APRIL 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Value of Mismatch Repair, *KRAS*, and *BRAF* Mutations in Predicting Recurrence and Benefits From Chemotherapy in Colorectal Cancer

Gordon Hutchins, Katie Southward, Kelly Handley, Laura Magill, Claire Beaumont, Jens Stahlschmidt, Susan Richman, Philip Chambers, Matthew Seymour, David Kerr, Richard Gray, and Philip Quirke



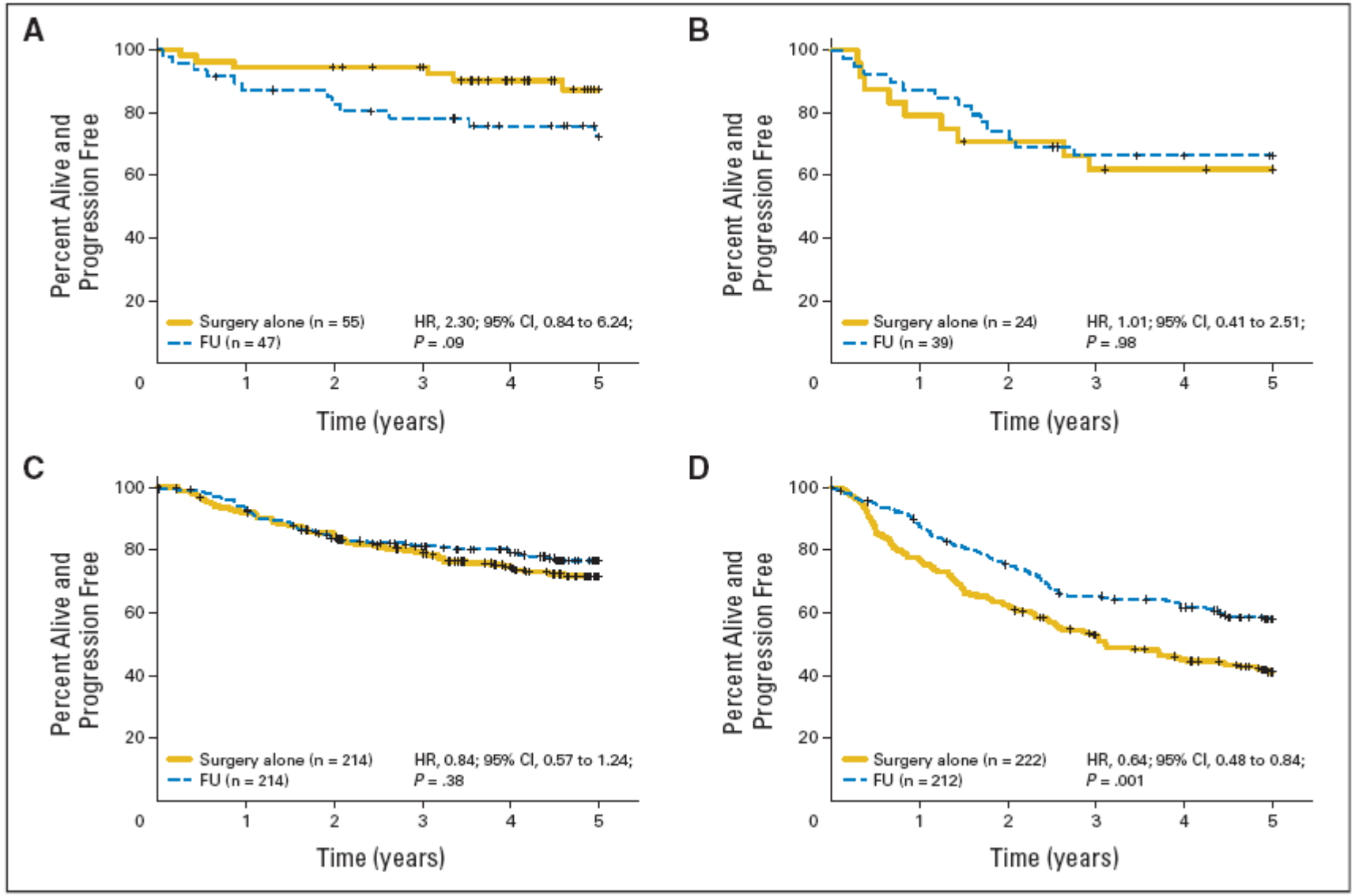
All patients

Stage II

Hutchins et al. 2011

Stage II dMMR

Stage III dMMR



Stage II pMMR

Stage III pMMR

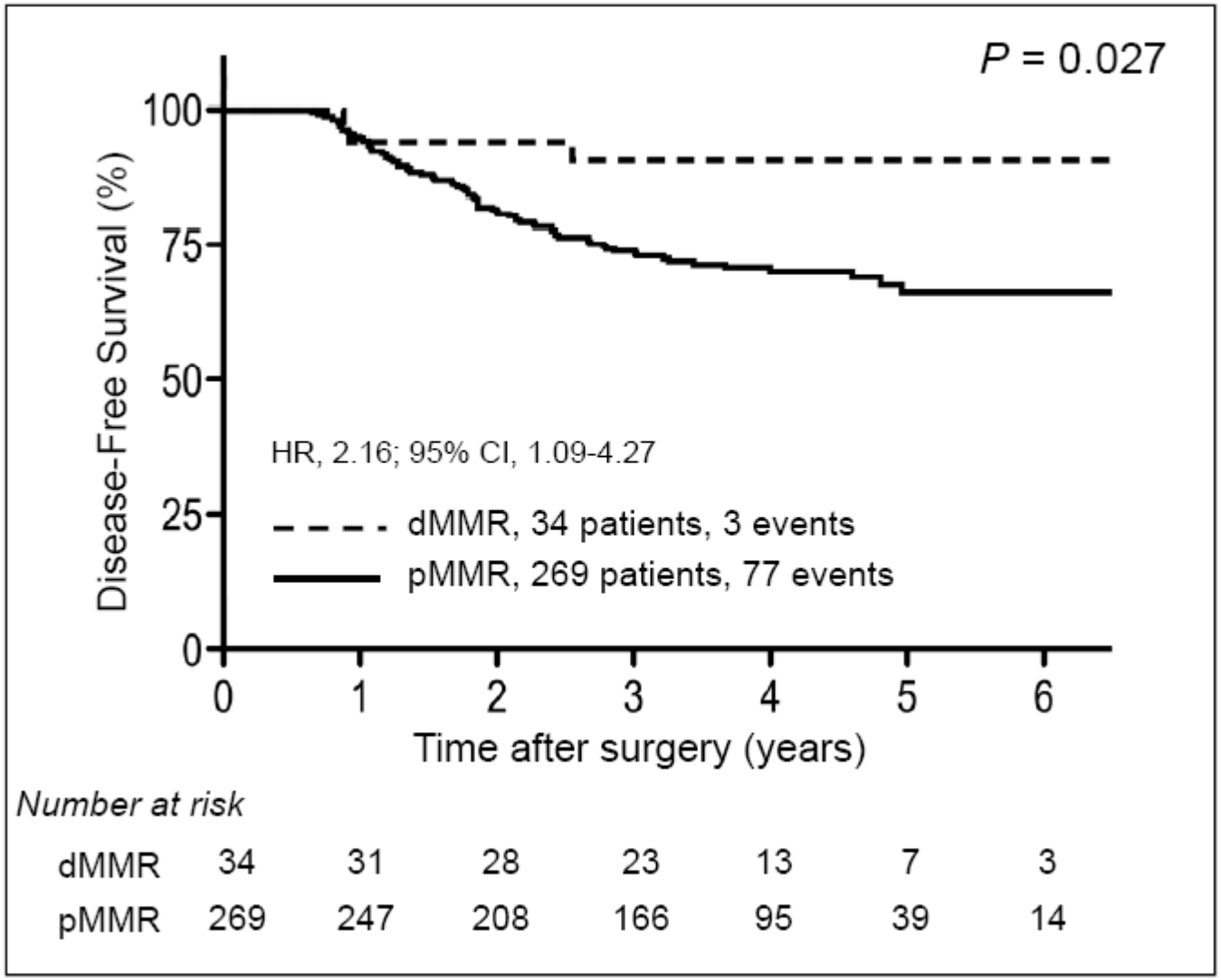
Sargent et al 2010

Clinical Cancer Research

Defective Mismatch Repair status as a prognostic biomarker of disease-free survival in stage III colon cancer patients treated with adjuvant FOLFOX chemotherapy

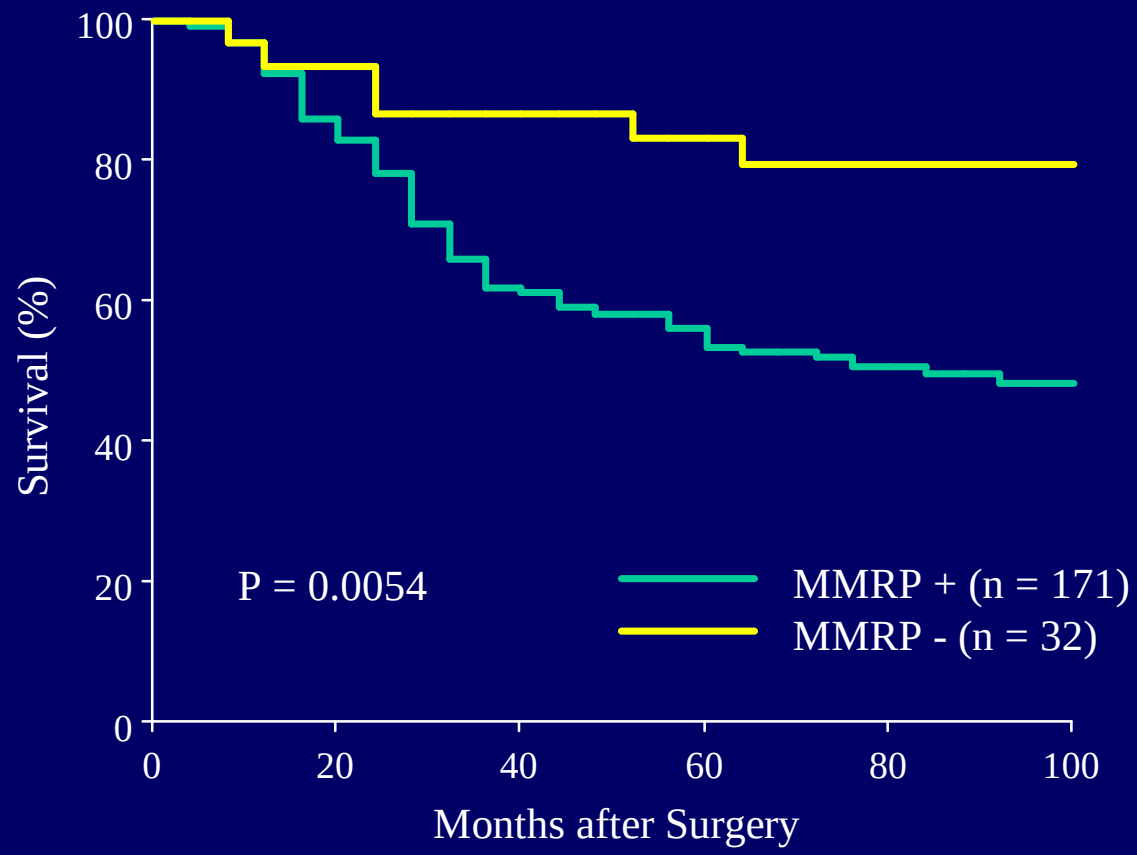
Aziz Zaanan, Jean-François Fléjou, Jean-François Emile, et al.

Clin Cancer Res Published OnlineFirst October 13, 2011.

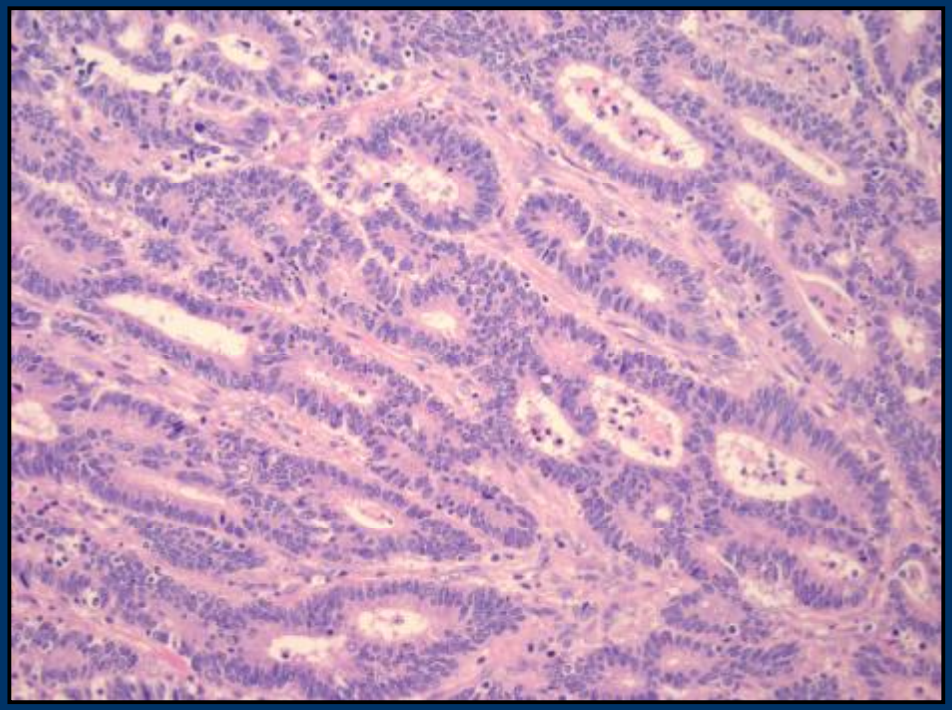


Zaanan et al. 2011

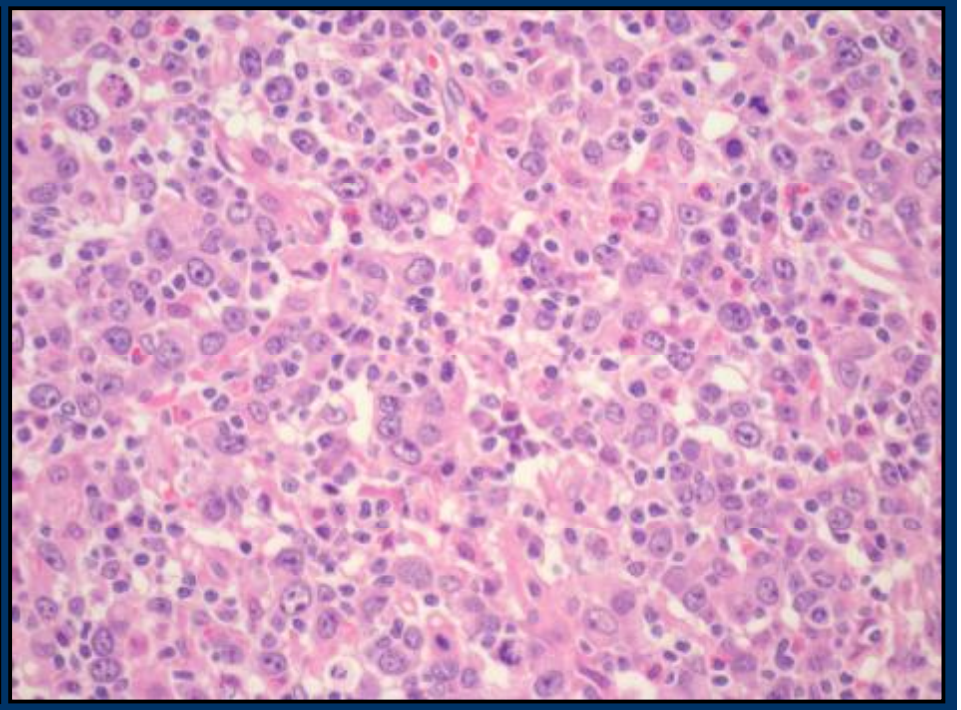
MMR status and clinical outcome in CRC



Stage III patients - no adjuvant chemotherapy

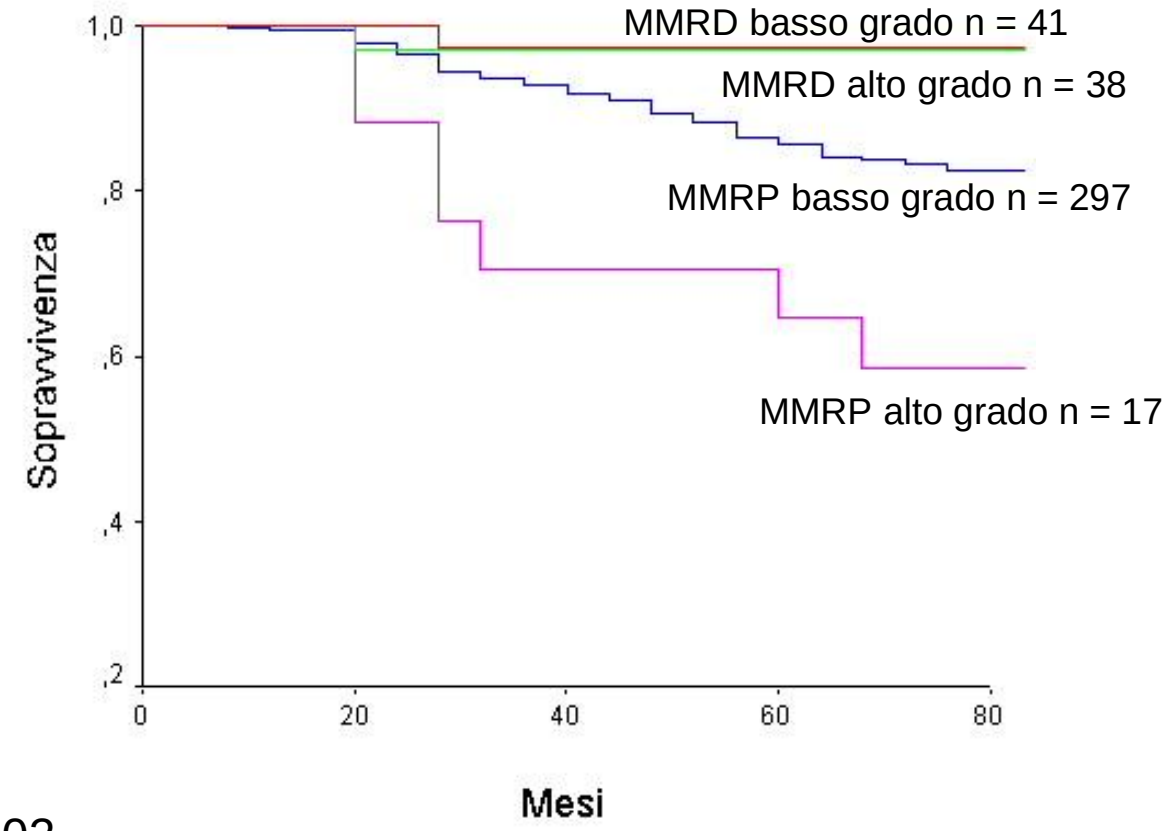


Adenocarcinoma bene differenziato
(basso grado)



Adenocarcinoma poco differenziato
di tipo midollare (alto grado)

Stadio II



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