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WORKSHOP DE PATOLOGIA DIGESTIVA

CÀNCER GÀSTRIC/UEG – NOVA CLASSIFICACIÓ OMS

Stefania Landolfi

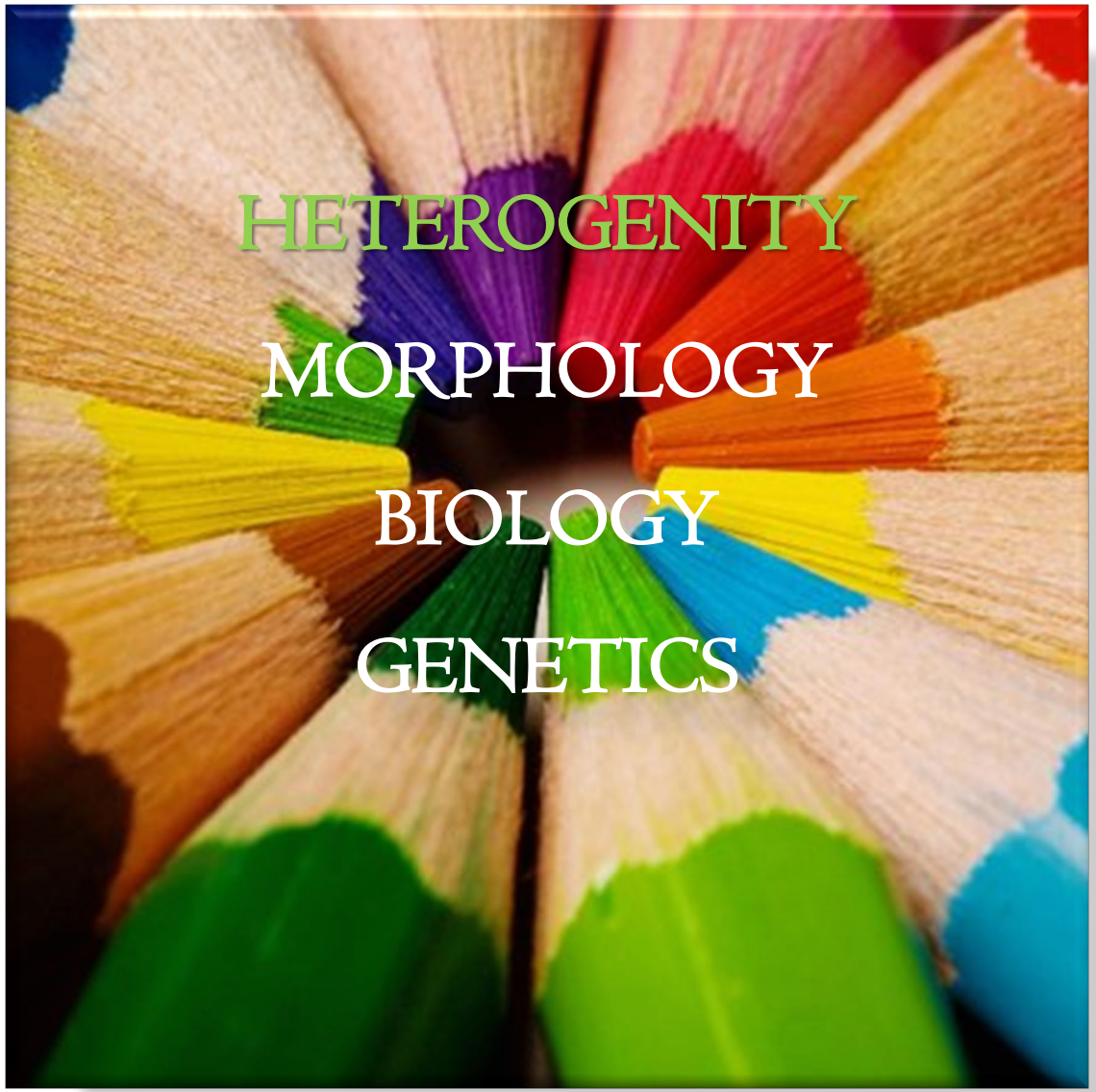
Servei de Anatomia Patologica

Hospital Universitari Vall d'Hebron

NO COI

@steland011

- ✓ Histopathologic classification of gastric cancer
- ✓ Carcinogenesis of gastric cancer
- ✓ Molecular classifications of gastric cancer & predictive biomarkers in gastric cancer: MSI and EBV



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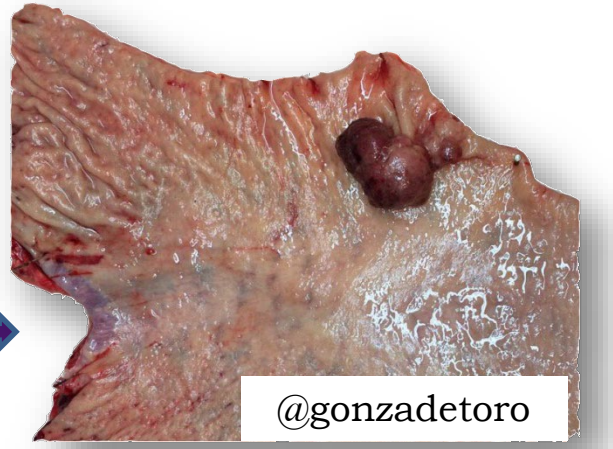
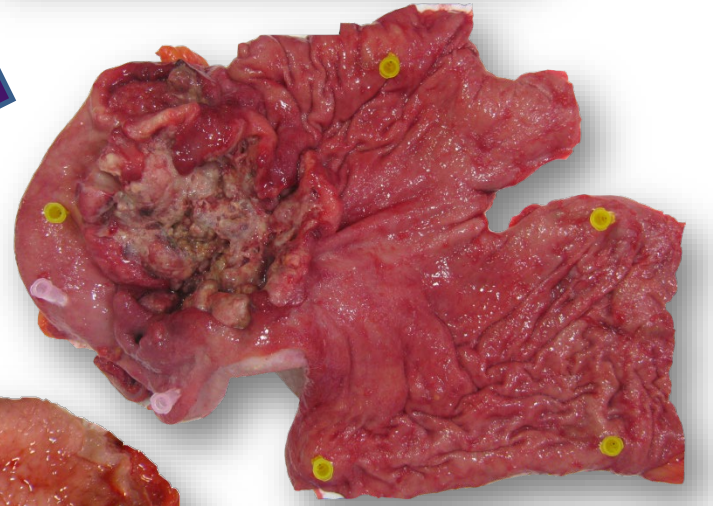
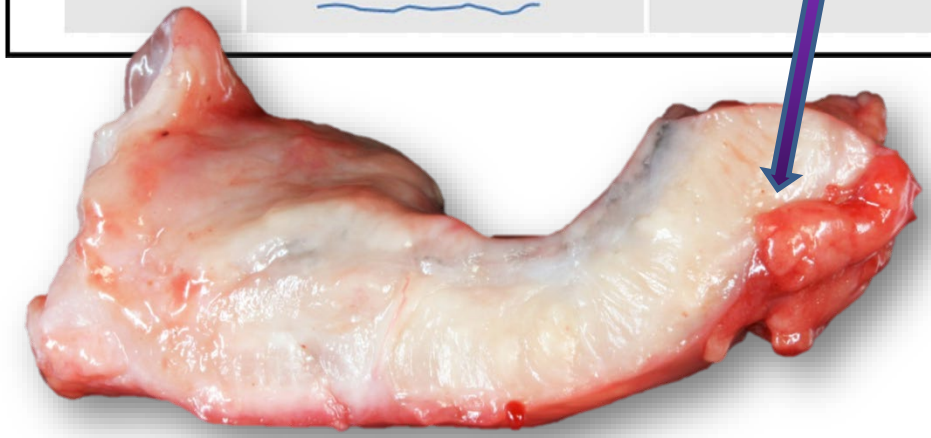
MACROSCOPIC HETEROGENITY

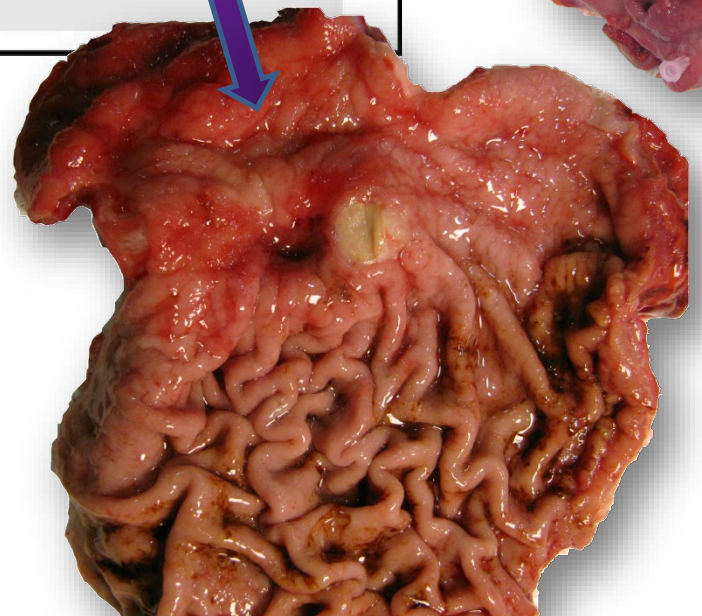
Table 2
The Borrmann classification of advanced gastric cancer (since 1926…)

Type I		Polypoid tumors
Type II		Fungating carcinomas
Type III		Ulcerated carcinomas
Type IV		Infiltrating carcinomas









@ReyesGomezE

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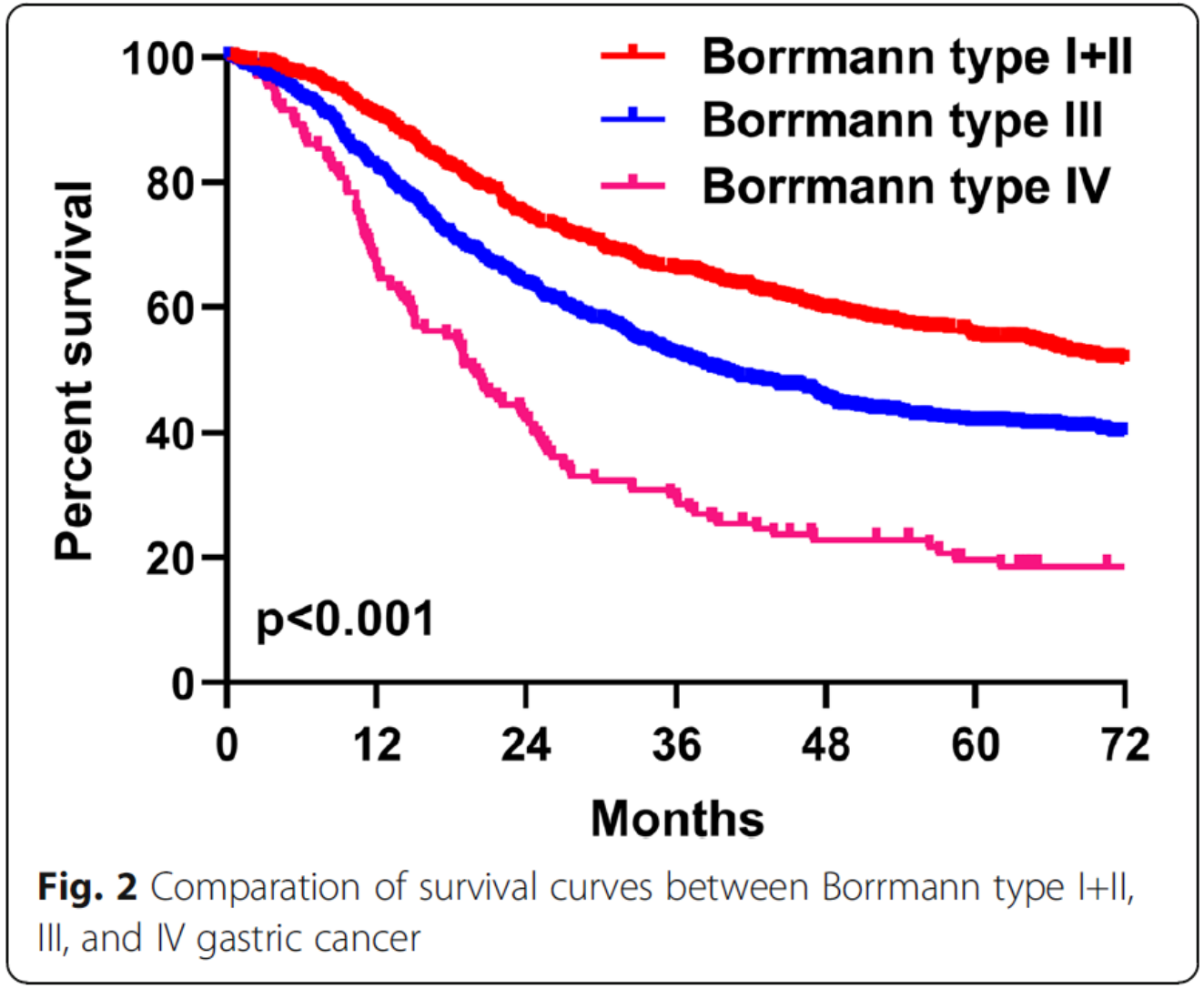
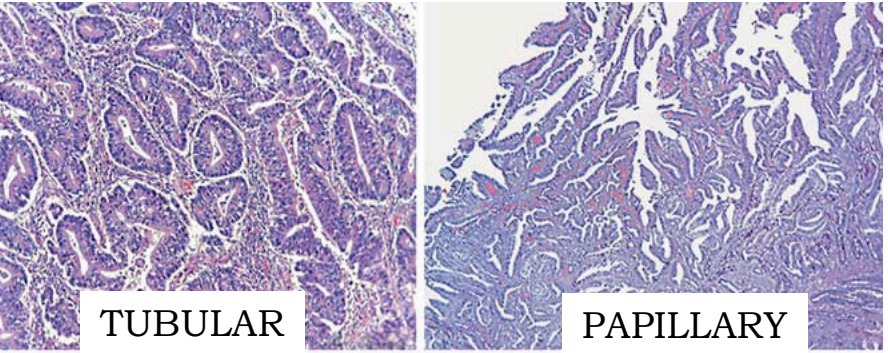
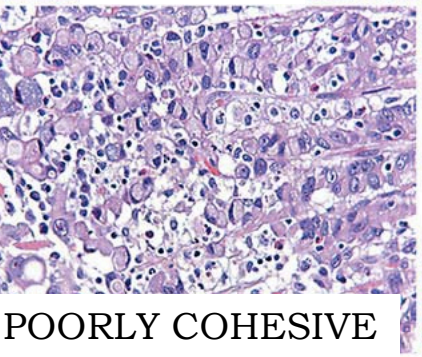


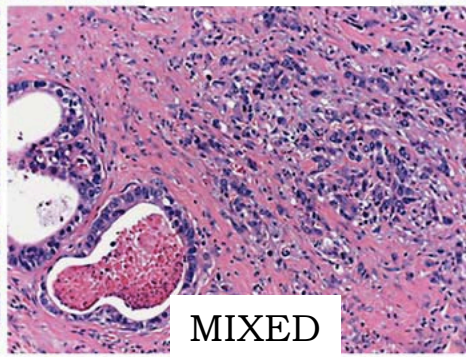
Fig. 2 Comparation of survival curves between Borrmann type I+II, III, and IV gastric cancer

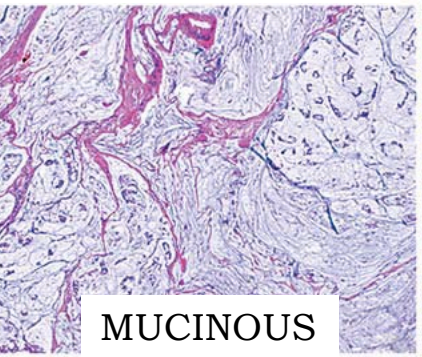
Song *et al. World Journal of Surgical Oncology* (2020) 18:204

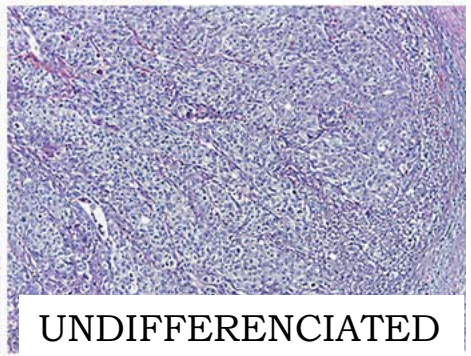

TUBULAR

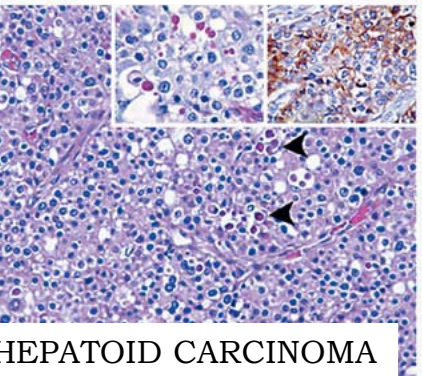
PAPILLARY

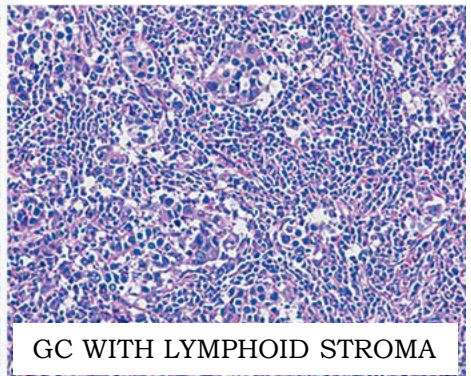

POORLY COHESIVE


MIXED


MUCINOUS


UNDIFFERENCIATED


HEPATOID CARCINOMA


GC WITH LYMPHOID STROMA

MICROSCOPIC HETEROGENITY

Histopathologic classification of gastric cancer

Table 1. Heterogeneity of histopathological classification systems in gastric cancer

Laurén [14], 1965	Carneiro [18], 1995	WHO [20], 2010	Japanese classification [21], 2011	Nakamura [15], 1968	Goseki [17], 1992	Solcia [19], 2009
Intestinal	Glandular	Papillary Tubular	Papillary Tubular 1 (well differentiated) Tubular 2 (moderately differentiated)	Differentiated type	I. Good tubular differentiation, mucin poor	Cohesive, ordinary subtype Cohesive, tubular subtype Cohesive, ordinary subtype
		Mucinous	Mucinous	Undifferentiated type	II. Good tubular differentiation, mucin rich	Mucinous, muconodular subtype Mucinous, infiltrative subtype
Diffuse	Isolated cell	Poorly cohesive, SRC phenotype	SRC carcinoma	Undifferentiated type	IV. Poor tubular differentiation, mucin rich	Diffuse, ordinary subtype
		Poorly cohesive, other cell types	Poorly differentiated, non-solid type		III. Poor tubular differentiation, mucin poor	Diffuse, low-grade desmoplastic subtype
Mixed	Mixed	Mixed				
Indeter-minate	Solid	Undifferentiated	Poorly differentiated, solid type	Undifferentiated type	III. Poor tubular differentiation, mucin poor	Anaplastic
	Rare variants	Rare variants				High lymphoid response

Gullo I et al. Pathobiology. 2018;85(1-2):50-63

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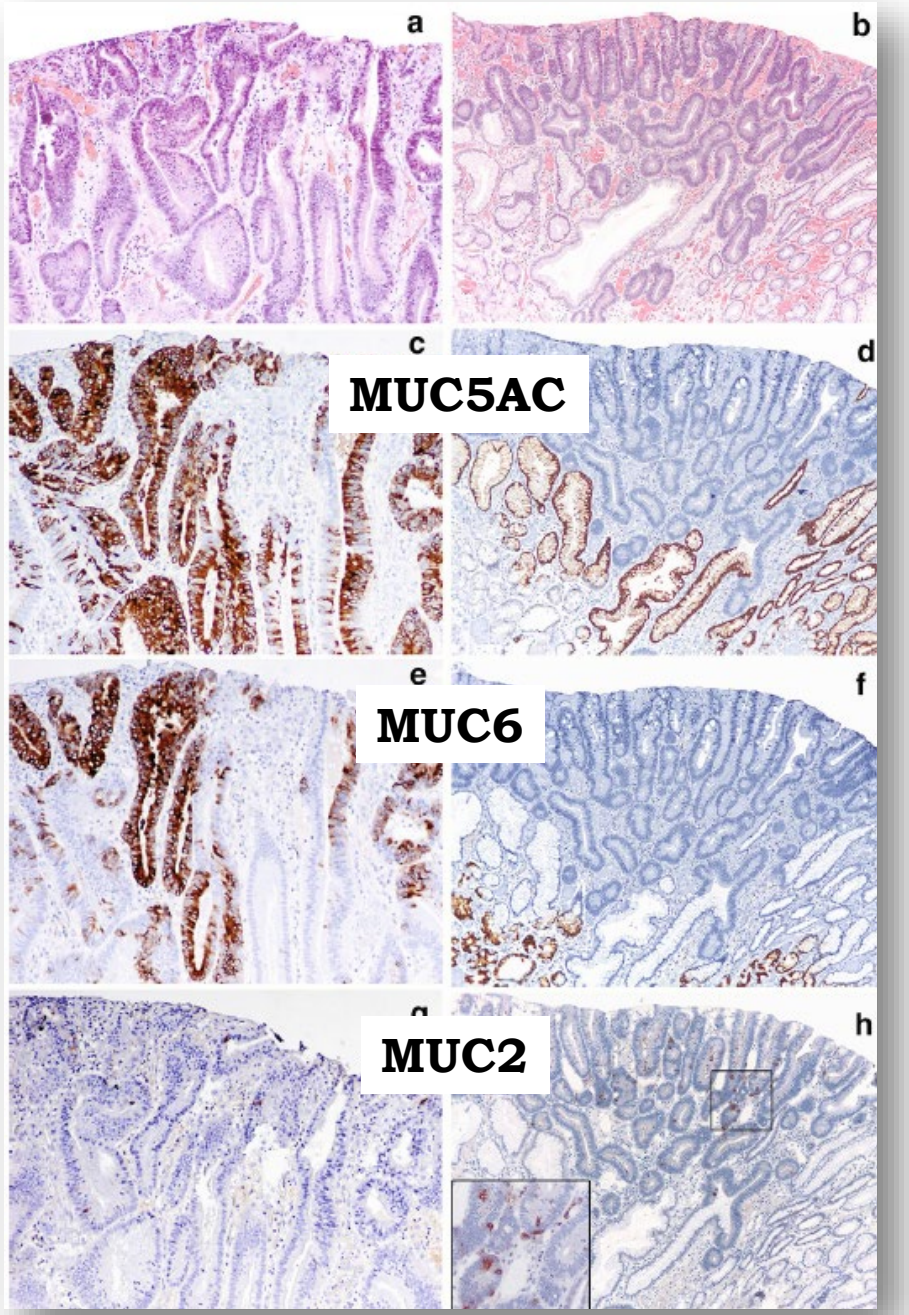
Gastric Cancer (2015) 18:720–728
DOI 10.1007/s10120-014-0416-5

ORIGINAL ARTICLE

Epithelial dysplasia of the stomach with gastric immunophenotype shows features of biological aggressiveness

Gastric (foveolar)-type dysplasia



Intestinal-type dysplasia

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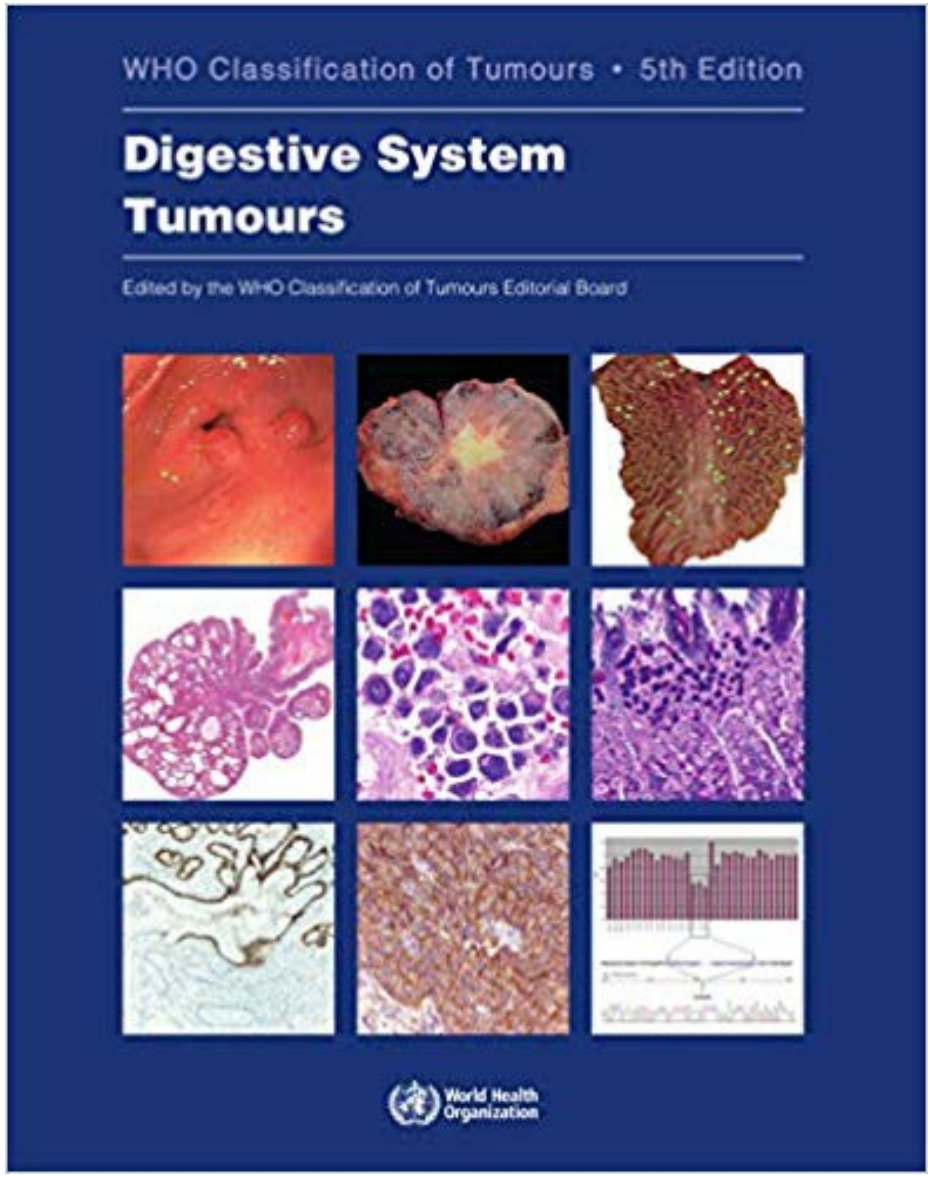

5th ed., 2019

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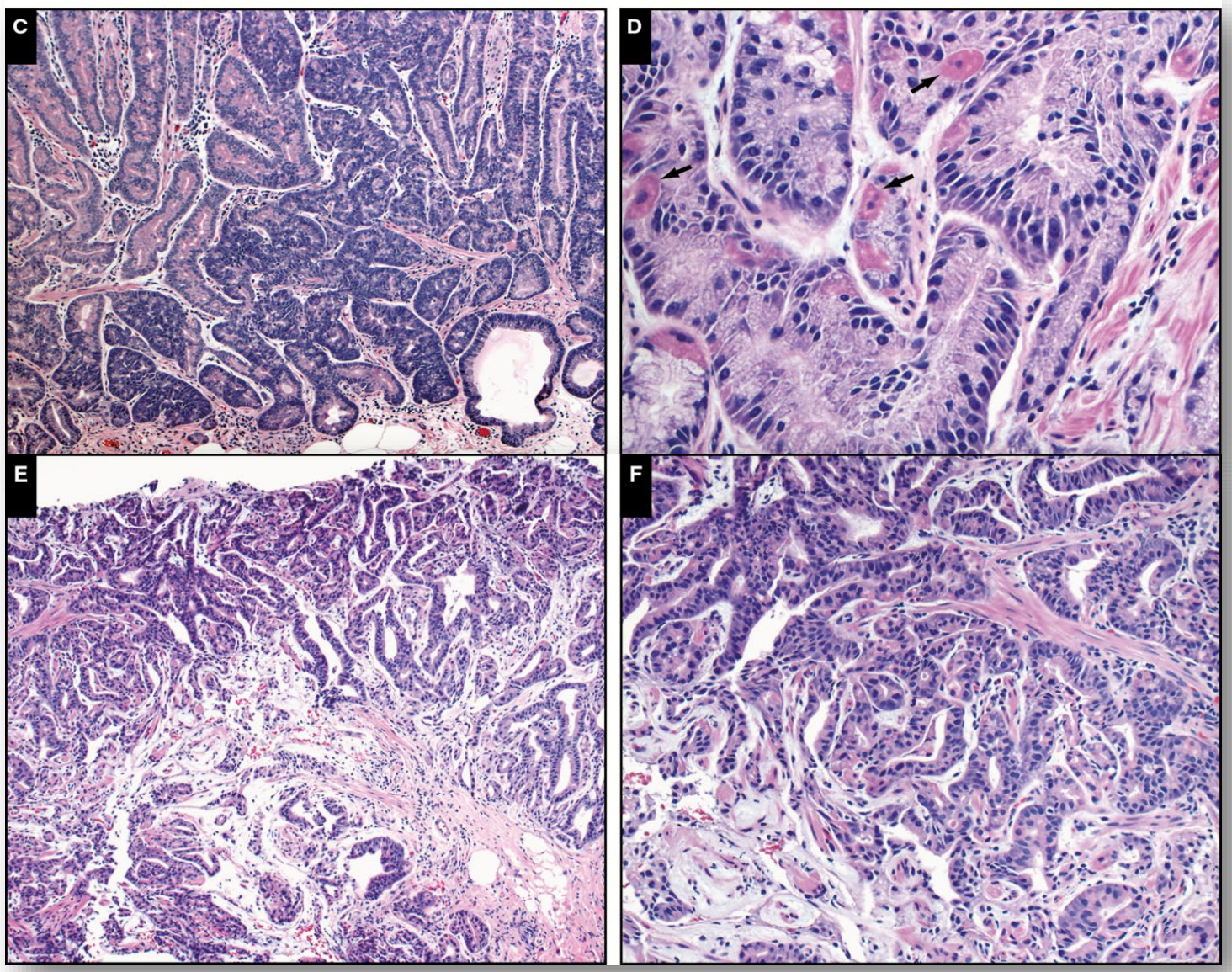
GASTRIC ADENOCARCINOMA OF THE FUNDIC GLAND TYPE

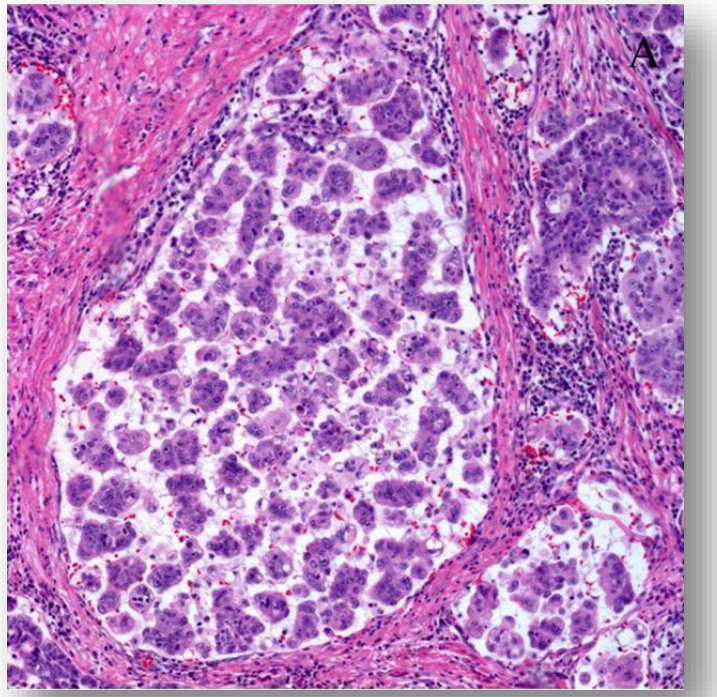


- from oxintyc gland adenoma
- mixed chief and pariental cells
- neoplasic glands more complex than normal oxyntic glands (**anastomosing/"endless glands" pattenr**)
- no desmoplasia
- low-growing
- **very good prognosis**

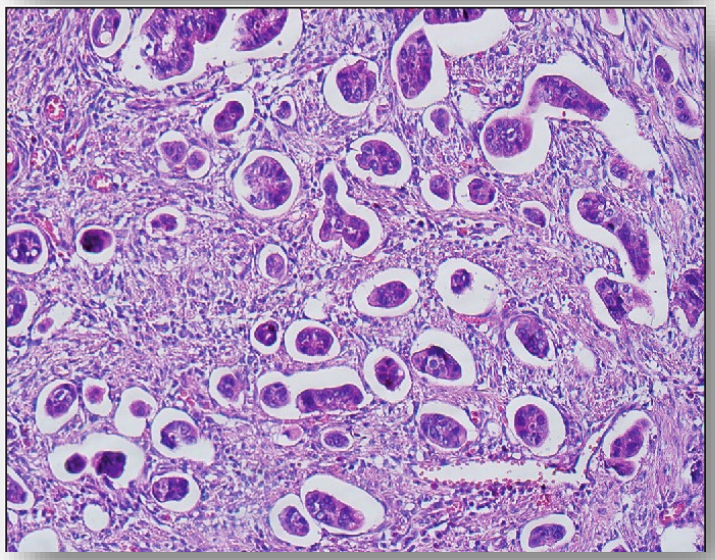
American Journal of Clinical Pathology, Volume 149, Issue 6, June 2018, Pages 461–473

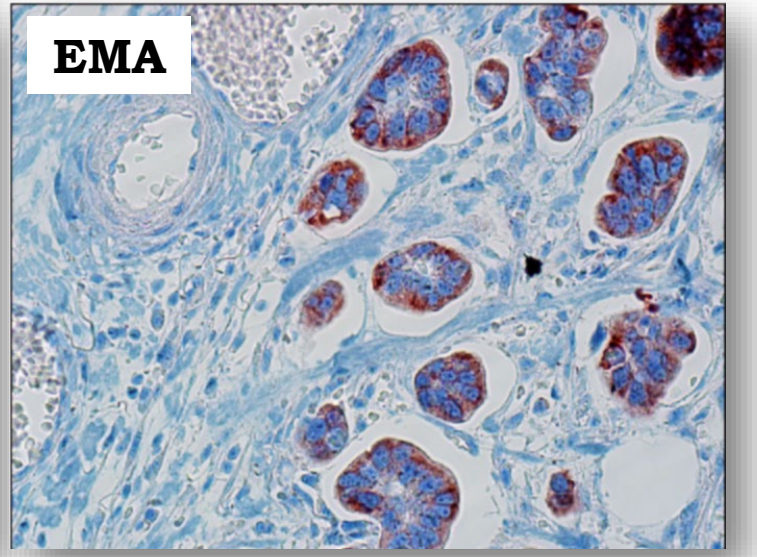
OXFORD UNIVERSITY PRESS

MICROPAPILLARY ADENOCARCINOMA



- Tumor with papillary clusters devoid of fibrovascular cores within lacunar spaces
- High incidence of lymphovascular invasion and lymph node metastasis
- **Worse prognosis** compared to CoA (5-YSR:30%)





Variants of Gastric Carcinoma: Morphologic and Theranostic Importance

Sun-Mi Lee, Kyoung-Mee Kim and Jae Y. Ro

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54342

Vardar, Enver et al. Turk patoloji dergisi 31 3 (2013): 219-22 .

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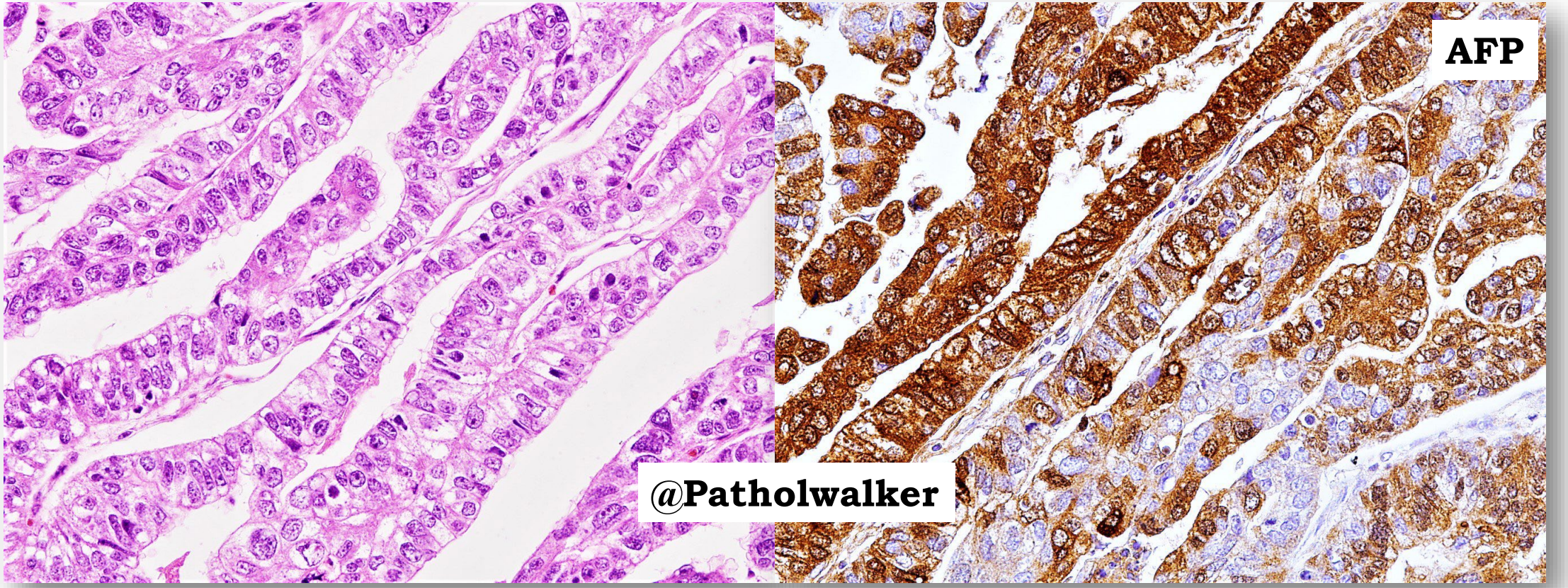


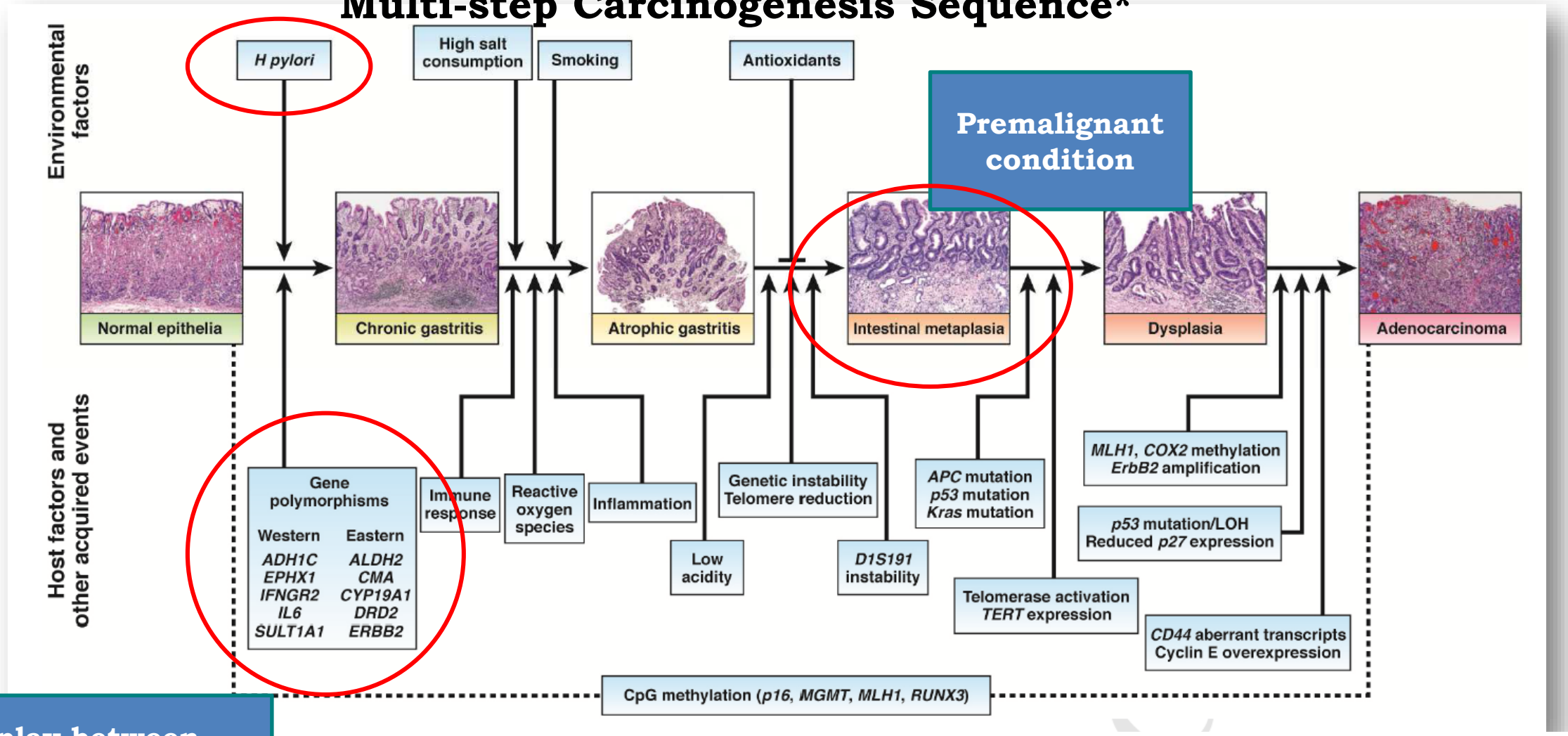
ADENOCARCINOMA WITH ENTEROBLASTIC DIFFERENTIATION (subtype of epatoid carcinoma)

- Tubulopapillary architecture
- Columnar cells with clear cytoplasm (resembling early fetal gut epithelium)
- **Worse prognosis** compared to CoA (5y-SR: 9%)

- ✓ **Histopathologic classification of gastric cancer**
- ✓ **Carcinogenesis of gastric cancer**
- ✓ **Molecular classifications of gastric cancer & predictive biomarkers in gastric cancer: MSI and EBV**

Genetics and Molecular Pathogenesis of Gastric Adenocarcinoma

Multi-step Carcinogenesis Sequence*

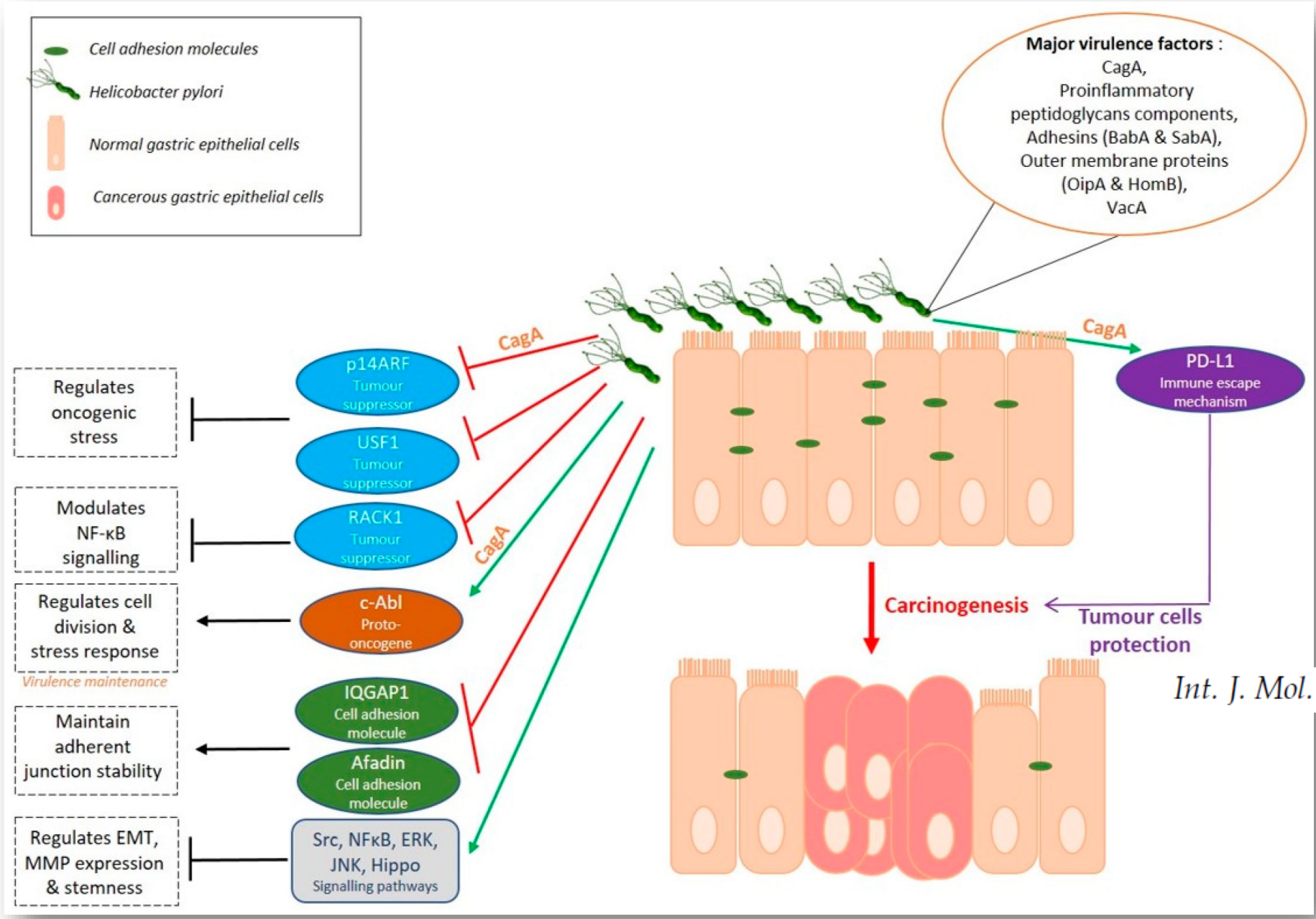


Interplay between environmental and host factors

Gastroenterology 2015;149:1153–1162

*Diffuse-type GC does not involve metaplasia

Gastric Cancer: Advances in Carcinogenesis Research and New Therapeutic Strategies



Int. J. Mol. Sci. **2021**, *22*, 3418.

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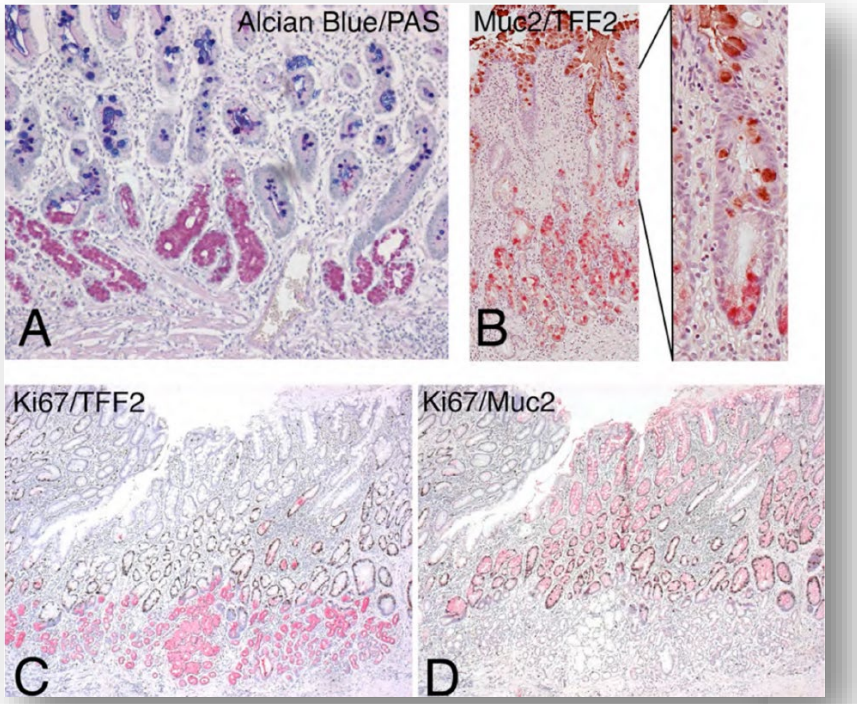
Spasmolytic Polypeptide-Expressing Metaplasia (SPEM)

isthmal stem cells

mucous neck cells

parietal cells

chief cells



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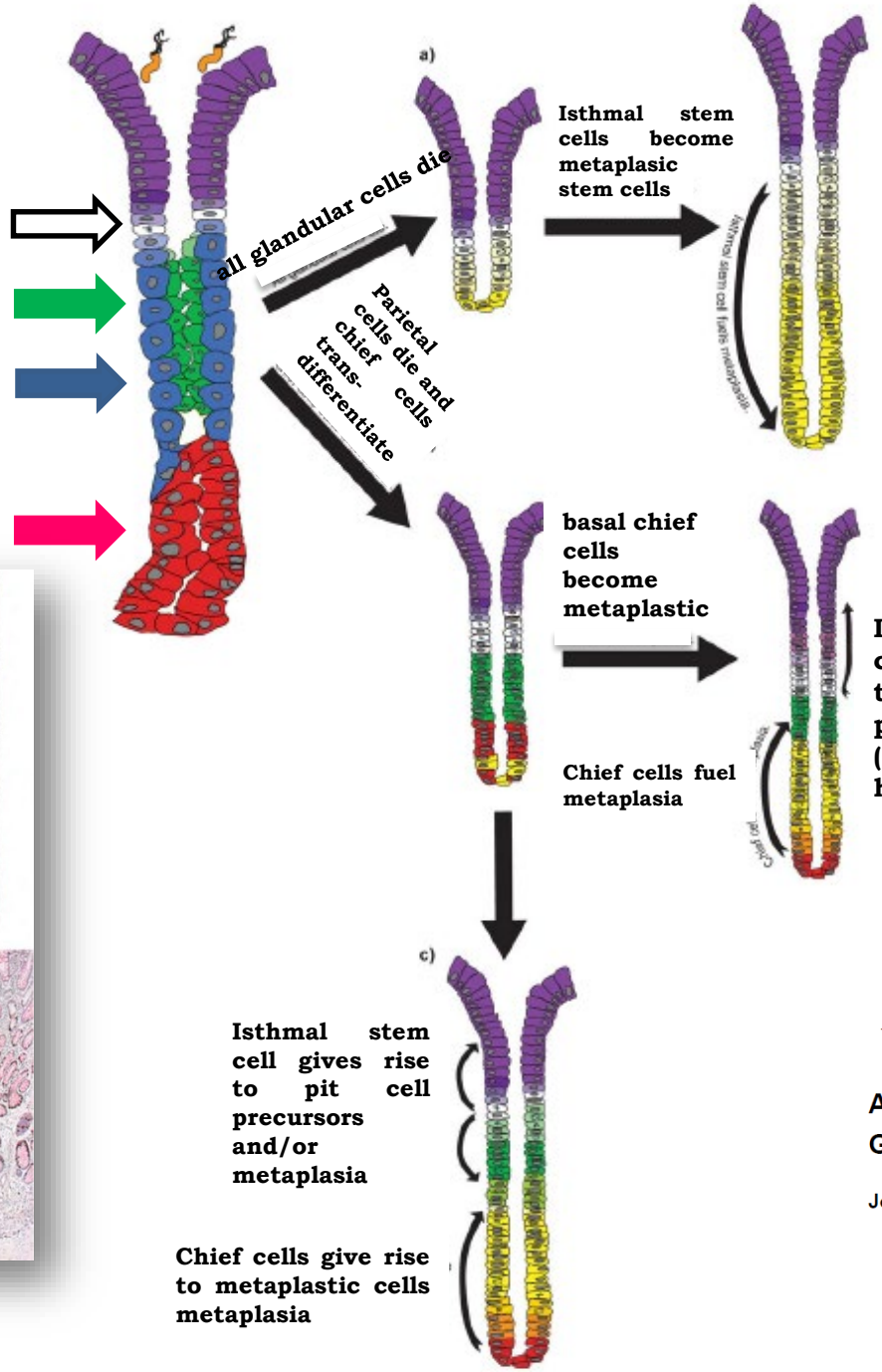

Gastroenterology. 2010 June ; 138(7): 2207–2210.e1. doi:10.1053/j.gastro.2010.04.023.

SPEM and IM: Time for re-evaluation of metaplasias and the origins of gastric cancer

James R. Goldenring[1,#], Ki Taek Nam[1], Timothy C. Wang[2], Jason C. Mills[3], and Nicholas A. Wright[4]

Nat Rev Gastroenterol Hepatol. 2018 May ; 15(5): 257–273. doi:10.1038/nrgastro.2018.5.

Acid and the Basis for Cellular Plasticity and Reprogramming in Gastric Repair and Cancer

José B. Sáenz, MD, PhD[1] and Jason C. Mills, MD, PhD[1,2,3]

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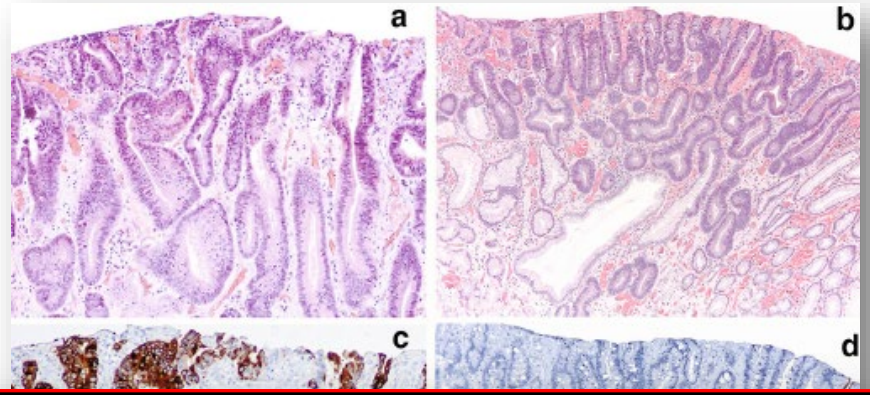
Gastric Cancer (2015) 18:720–728
DOI 10.1007/s10120-014-0416-5

ORIGINAL ARTICLE

Epithelial dysplasia of the stomach with gastric immunophenotype shows features of biological aggressiveness

Gastric (foveolar)-type dysplasia

Intestinal-type dysplasia



‘Singapore-Duke’ classification

Genomic Subtype	Histological Features	Associated Genes/Pathways	Drug sensitivity (Preclinical)
Mesenchymal	• Diffuse subtype	• EMT pathways • CSC pathways • *TGFβ* • mTOR signalling	• Sensitive to PI3K/AKT/mTOR inhibitors
Proliferative	• Intestinal subtype	• Genomic instability • *TP53* mutations • Cell cycle • DNA replication • Mitosis • Copy number alterations (*ERBB2/HER2* and *KRAS*)	• Unresponsive to 5-FU
Metabolic	• Gastric subtype	• Metabolic processes • Digestion • Secretion • SPEM	• Increased sensitivity to 5-FU

GASTROENTEROLOGY 2013;145:554–565

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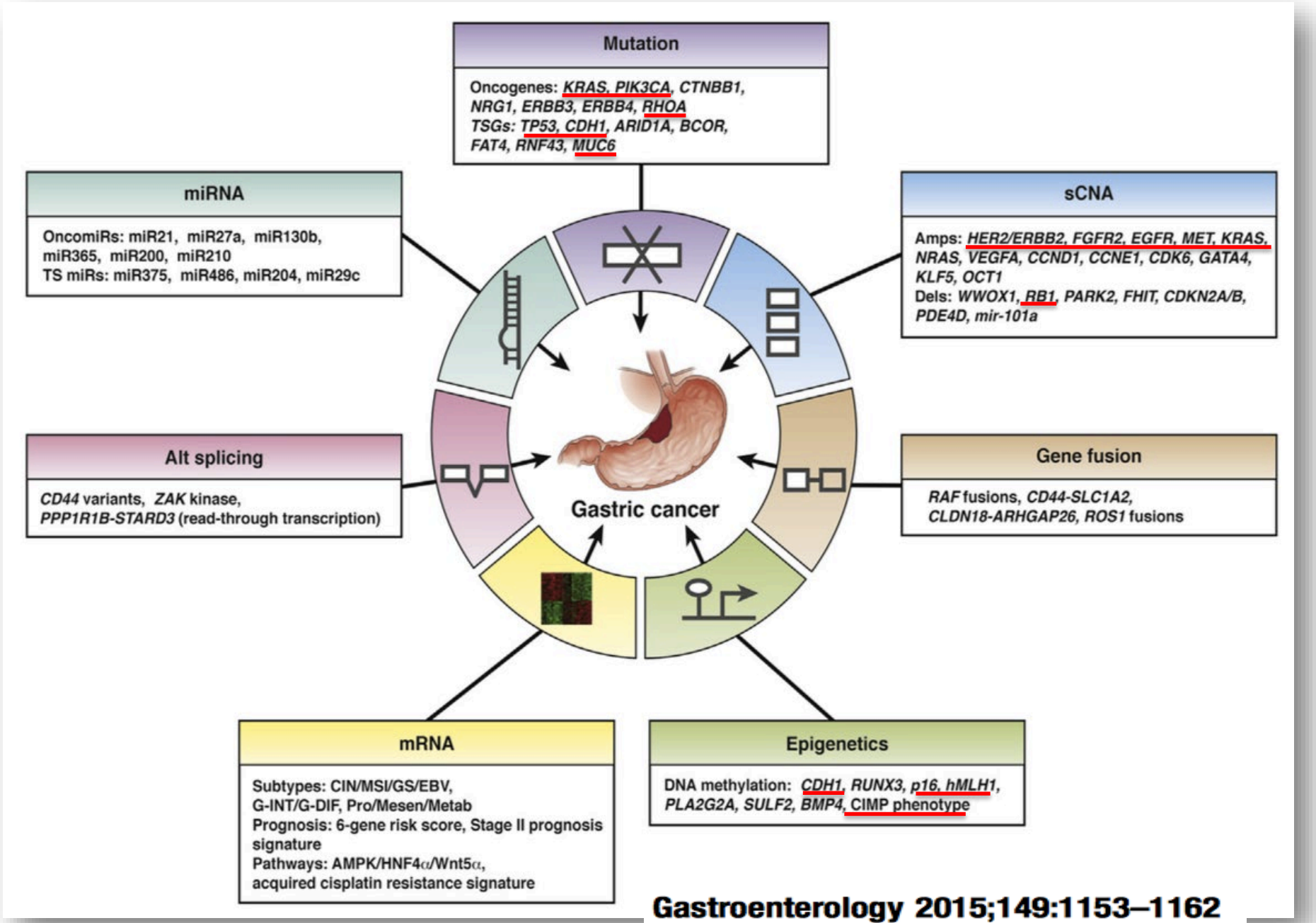
- ✓ **Histopathologic classification of gastric cancer**
- ✓ **Carcinogenesis of gastric cancer**
- ✓ **Molecular classifications of gastric cancer & emerging predictive biomarkers in gastric cancer: MSI and EBV**



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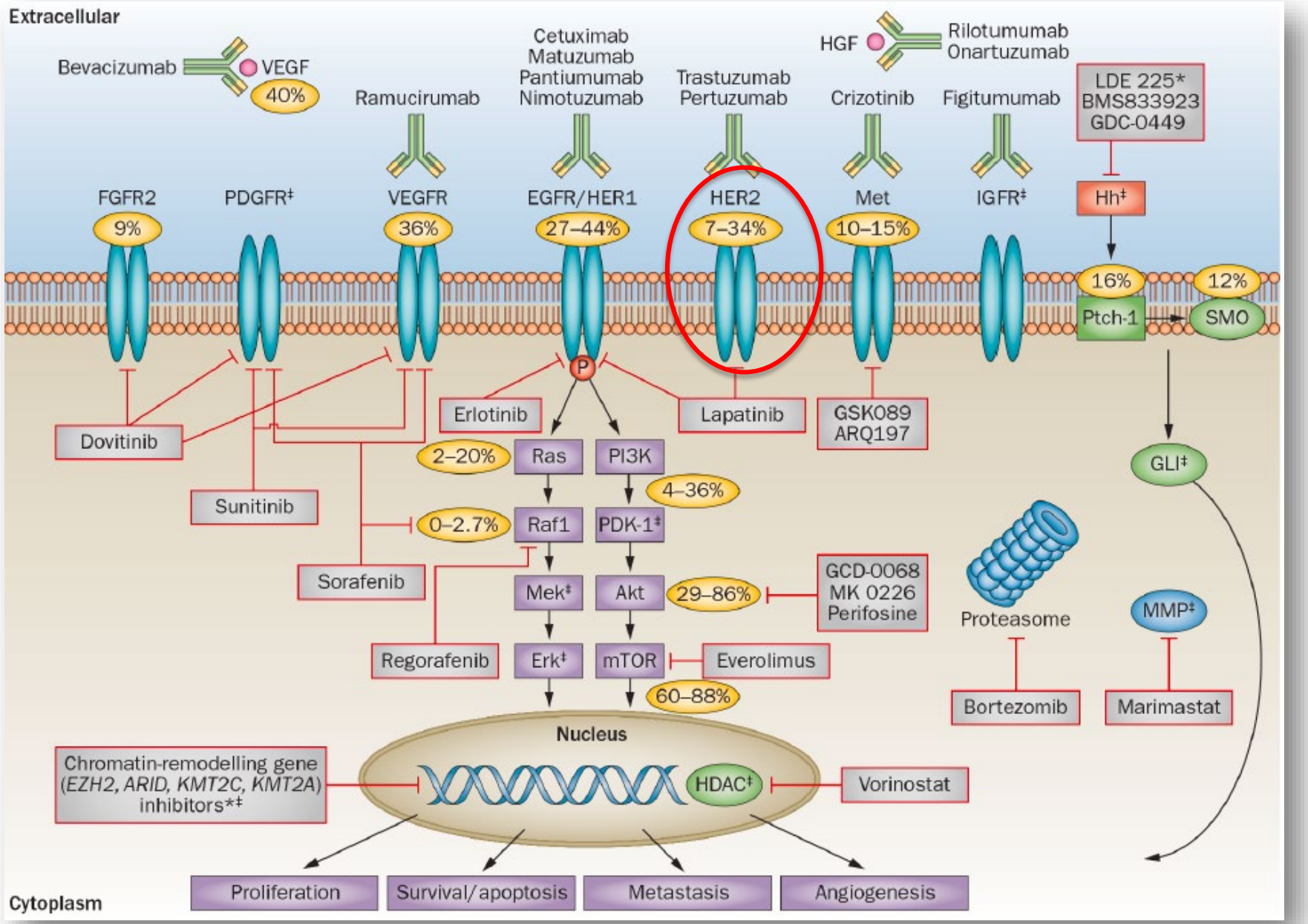

Nat Rev Clin Oncol. 2013 November ; 10(11): 643–655

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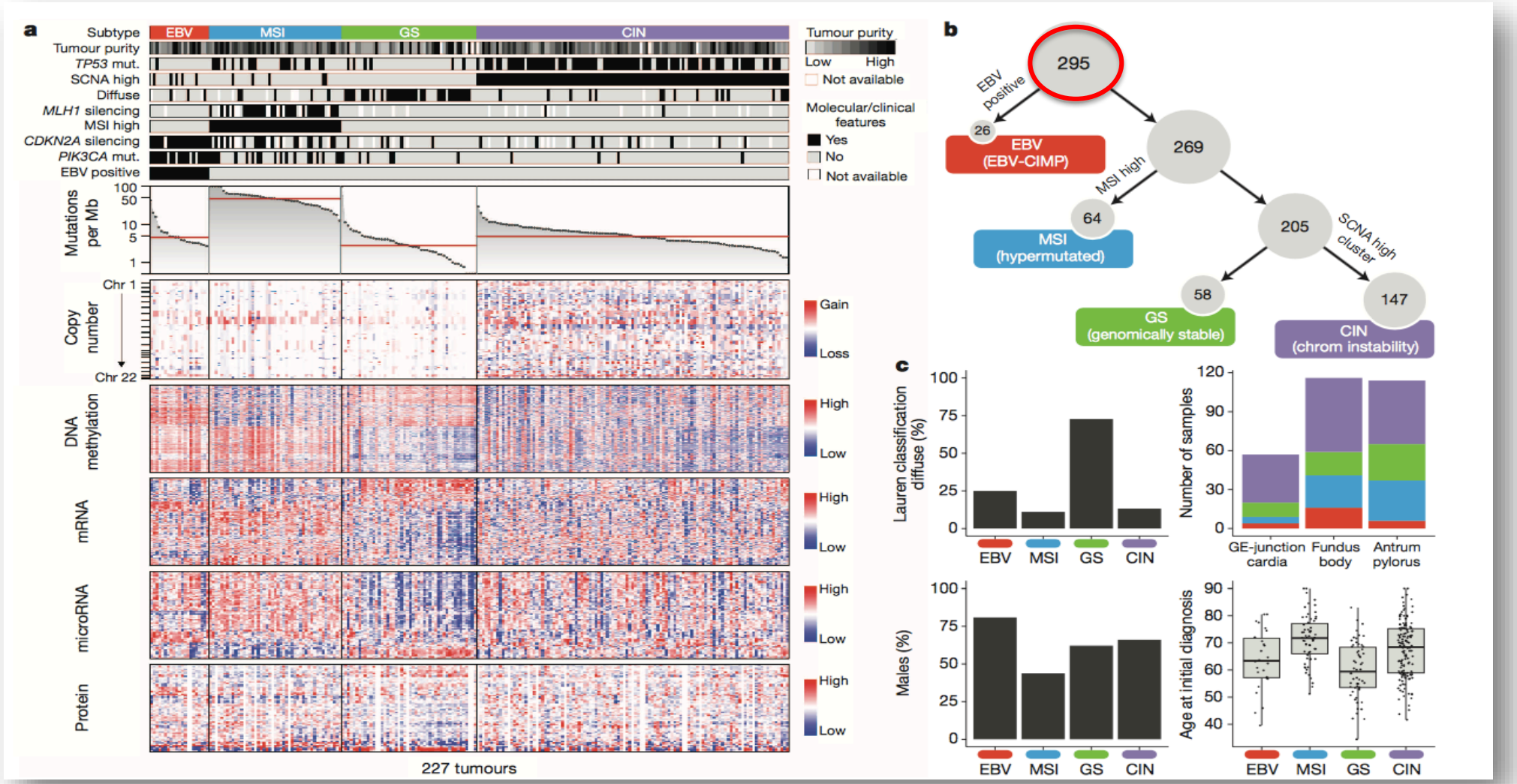
Comprehensive molecular characterization of gastric adenocarcinoma

Nature. 2014 Sep 11;513(7517):202-9

The Cancer Genome Atlas Research Network*



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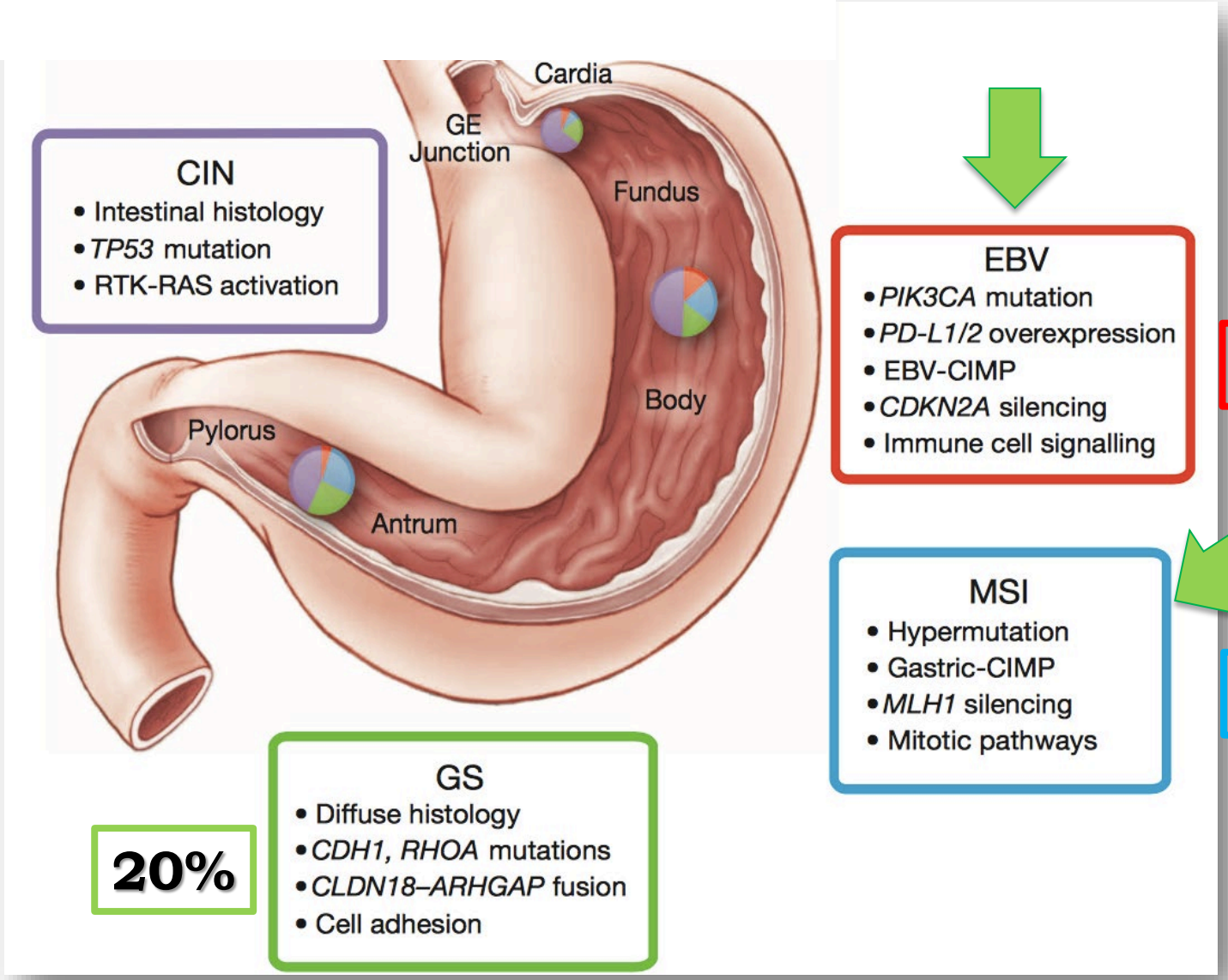

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Table 2. Molecular Classification Systems for Gastric Cancer

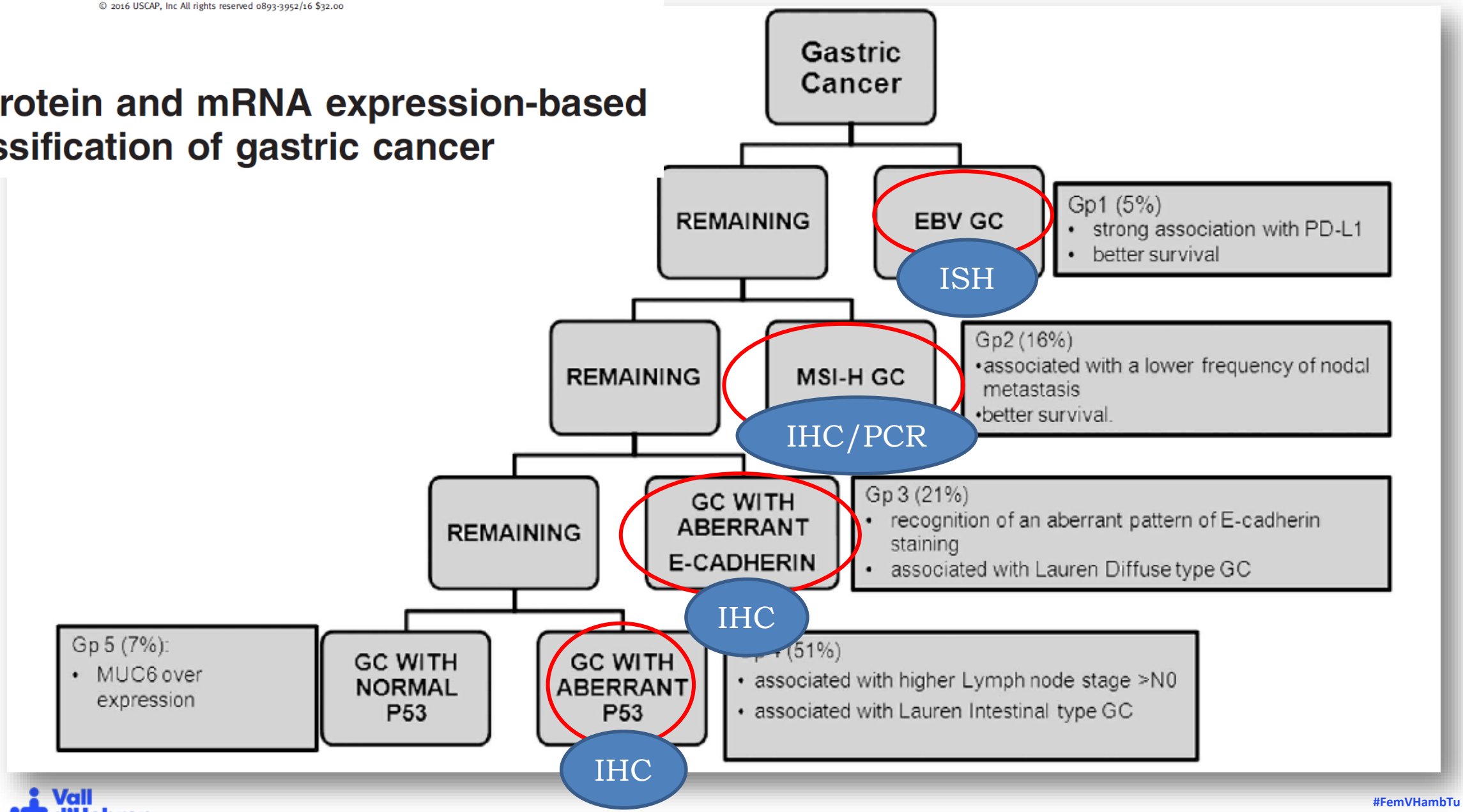
GC Subtype	The Cancer Genome Atlas Research Network[57] (N = 295)	Asian Cancer Research Group[58] (N = 300)
Subtype 1	**MSI** Hypermutation Gastric-CIMP *MLH1* gene silencing Mitotic pathways	**MSI (best prognosis)** Predominantly intestinal subtype by Lauren classification (> 60%) Located in antrum Often diagnosed at early stage (I/II) Hypermutation
Subtype 2	**EBV** *PIK3CA* mutation PD-L1 and PD-L2 overexpression EBV-CIMP *CDKN2A* silencing Immune cell signaling	**MSS/*TP53*-positive (intermediate prognosis)** EBV infection more frequent Intact *TP53* tumor suppressor gene activity
Subtype 3	**CIN** Intestinal histology by Lauren classification *TP53* mutation Receptor tyrosine kinase-Ras activation	**MSS/*TP53*-negative (intermediate prognosis)** Loss of functional *TP53* tumor suppressor gene activity
Subtype 4	**GS** Diffuse histology by Lauren classification *CDH1* (E-cadherin) and *RHOA* tumor suppressor gene mutations *CLDN18-ARHGAP* fusion Cell adhesion	**MSS/EMT (worst prognosis)** Younger age Predominantly diffuse subtype by Lauren classification (> 80%) Often diagnosed at later stage (III/IV)

CIMP = CpG island methylator phenotype; CIN = chromosomal instability; EBV = Epstein-Barr virus; EMT = epithelial-to-mesenchymal transition; GC = gastric cancer; GS = genomically stable; MSI = microsatellite instability; MSS = microsatellite stable; PD-L = programmed death ligand.

Oncology (Williston Park). 2016 Jul;30(7):635-45.

Modern Pathology (2016) 29, 772–784

A protein and mRNA expression-based classification of gastric cancer



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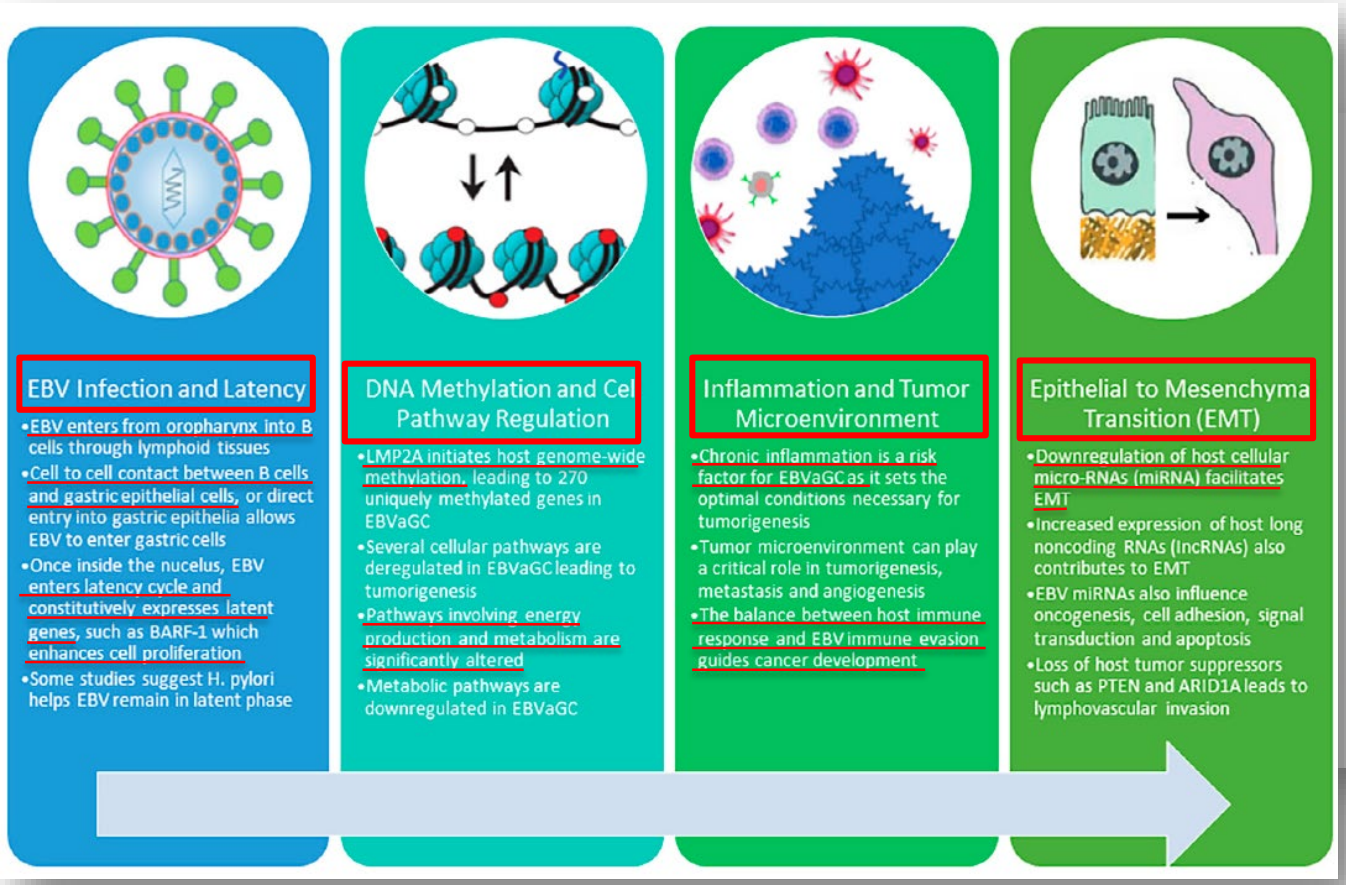
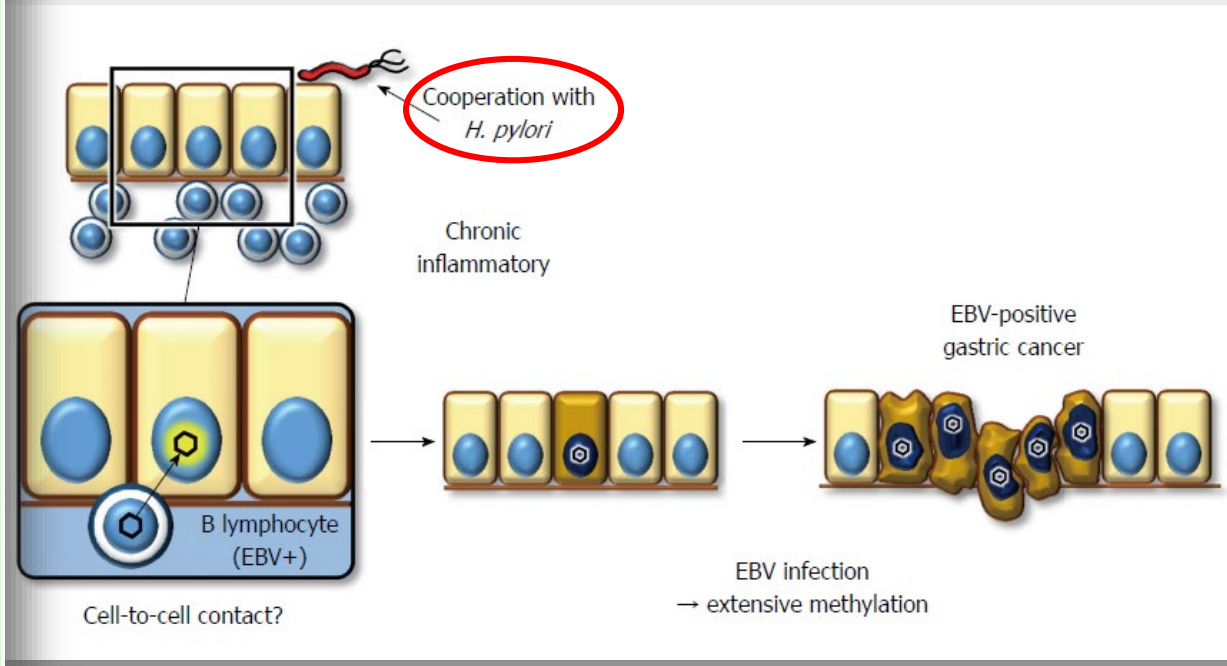
Pathogenesis of EBV-associated





Cancer Treatment Reviews 66 (2018) 15–22

World J Gastroenterol 2014 April 14; 20(14): 3916-3926

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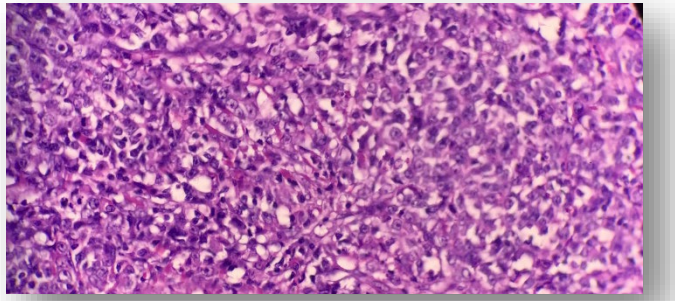
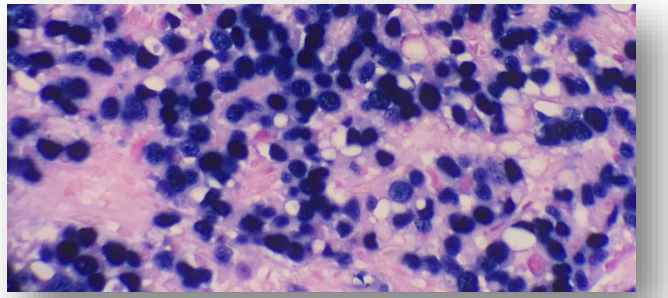
Clinical-pathological features EBV-associated GC

- predominantly proximal stomach
- associated with lower T and N stages
- well-delineated tumors with pushing bordes
- moderade-poor degree of differentation
  - ✓ 63,4% tubular type
  - ✓ 4,9% poorly cohesive type
- associated with prominent immune infiltrate
- Lower HER2 expression

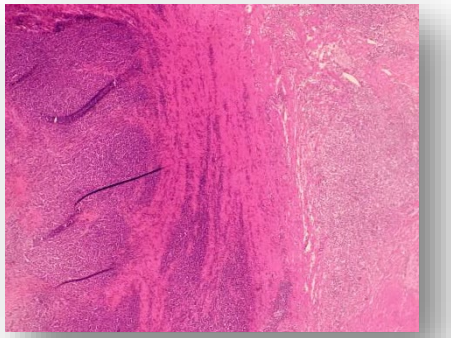
Morphology of EBV-associated GC

- ✓ **GC with lymphoid stroma** (lymphoepithelioma-like/medullary carcinoma)

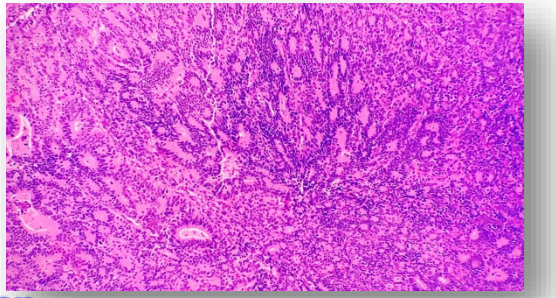


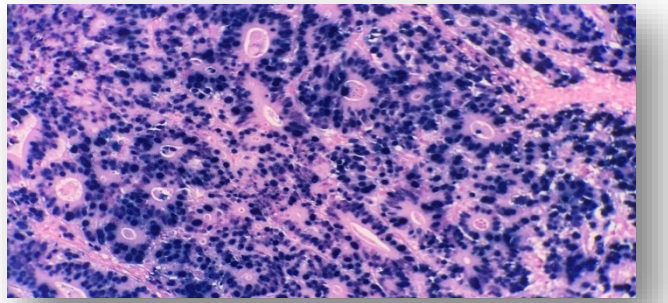


- ✓ **Carcinoma with Crohn's disease-like lymphoid reaction** (3 or more follicles in the invasion edge of the tumor)



- ✓ **Conventional-type adenocarcinoma** (scattered lymphocytes with prominent desmoplasia wo or less 3 follicles)





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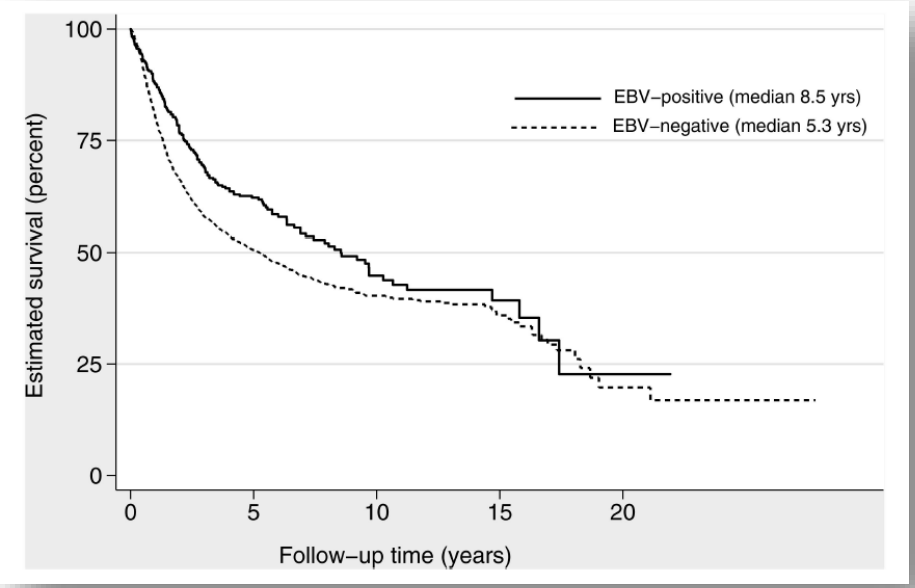
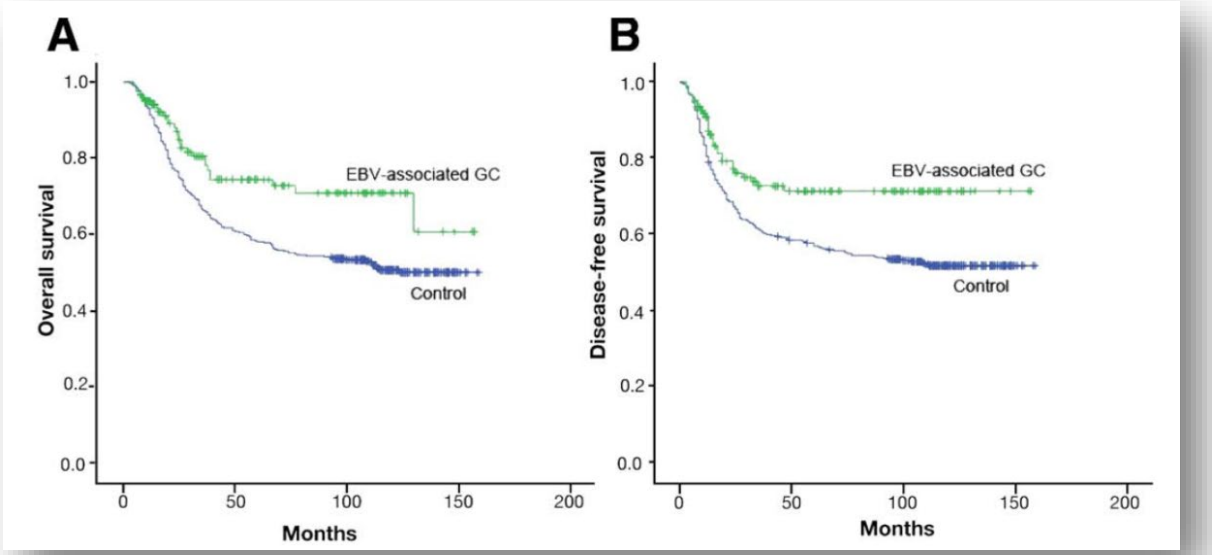
Cancer Sci 2008; 99: 195–201

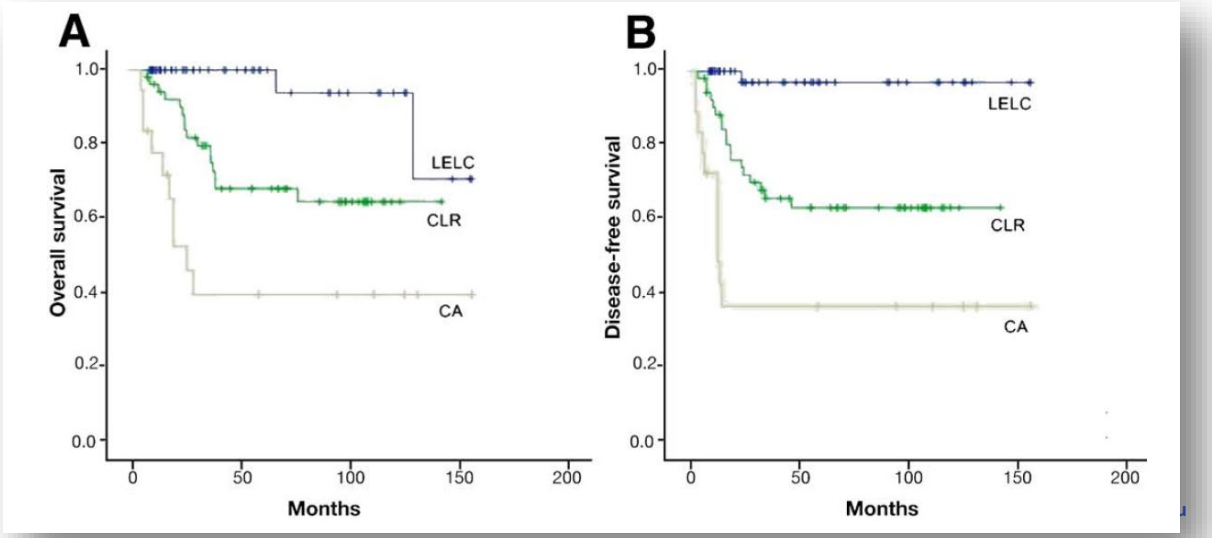
Gut and Liver, Vol. 5, No. 2, June 2011, pp. 143-148

Prognosis of EBV-associated GC



Camargo MC, *et al*. *Gut* 2014;**63**:236–243

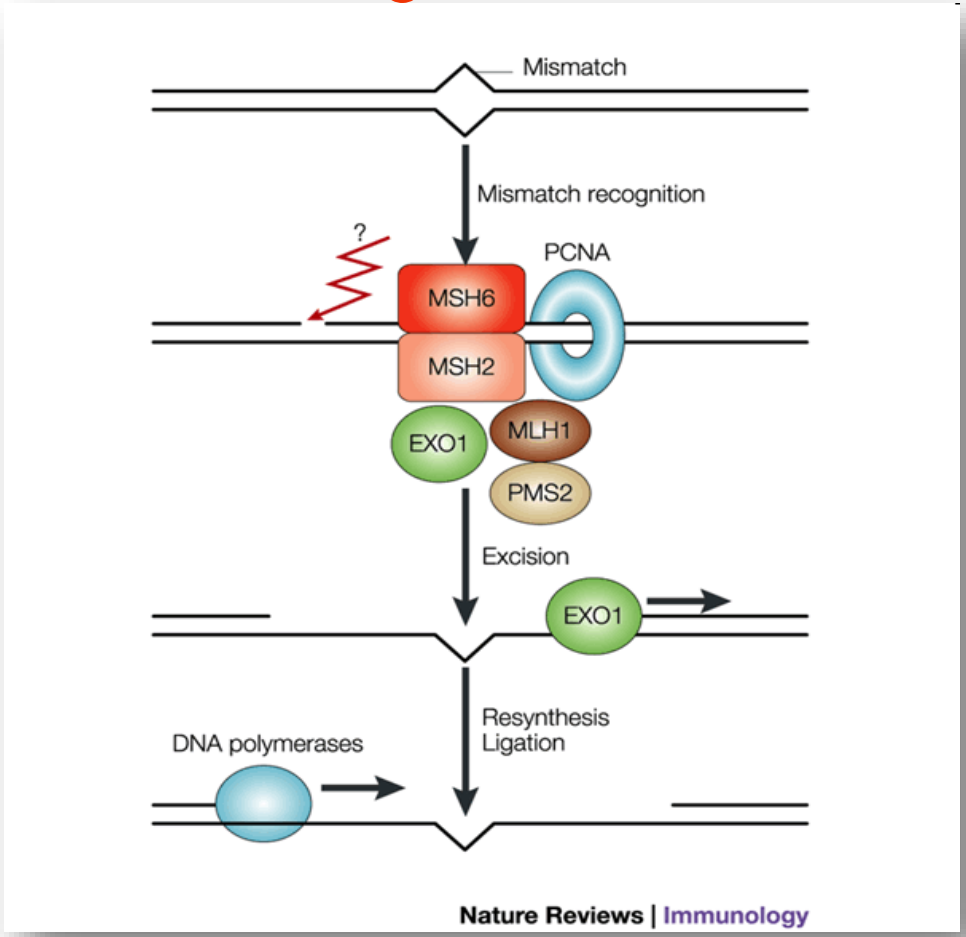




GASTROENTEROLOGY 2010;139:84–92

REPLICATIVE ERRORS REPAIR (MMR) PROTEINS

Puntual	Insertion	Deletion
G	AAAA	CACACACACA
T	TTTTT	GTGTGTGT



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MSI GASTRIC CANCER

- MSI in about 15-20% of cases
- usually associated with:
  - female sex
  - older age
  - antral location
  - intestinal histology
  - earlier stage
  - considered a favorable prognostic indicator for both early and advanced stages
- The incidence of gastric cancer in HNPCC is low

DFS and OS analysis of MSI gastric cancer

MAGIC and CLASSIC trials

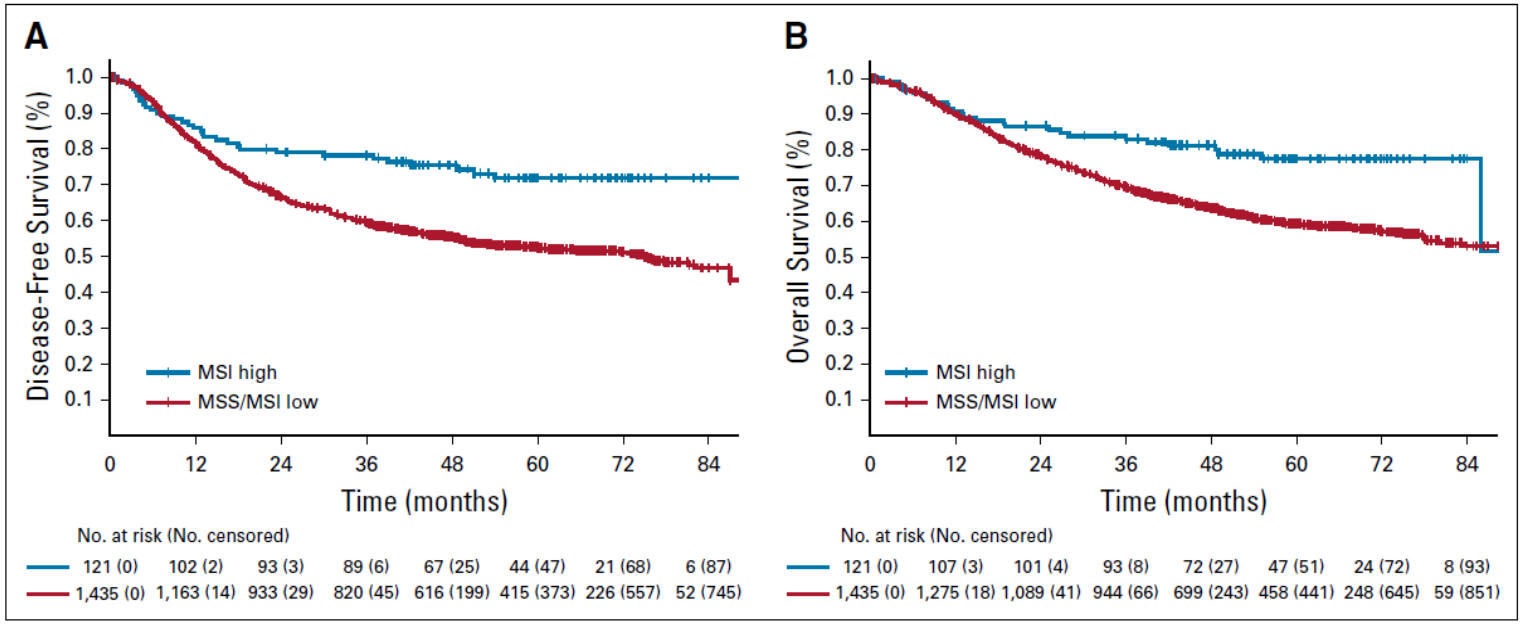
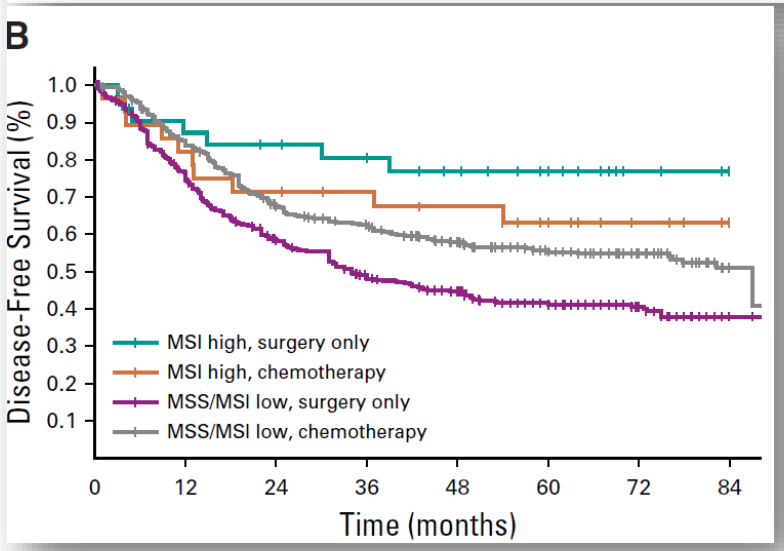
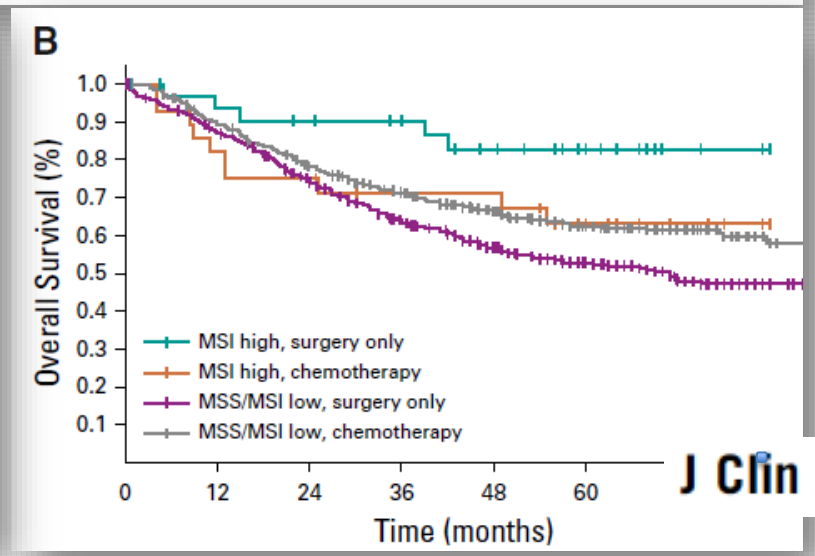


FIG 2. Kaplan-Meier curves of (A) disease-free survival and (B) overall survival according to microsatellite-instability (MSI) status (microsatellite stable [MSS]/MSI-low *v* MSI-high).





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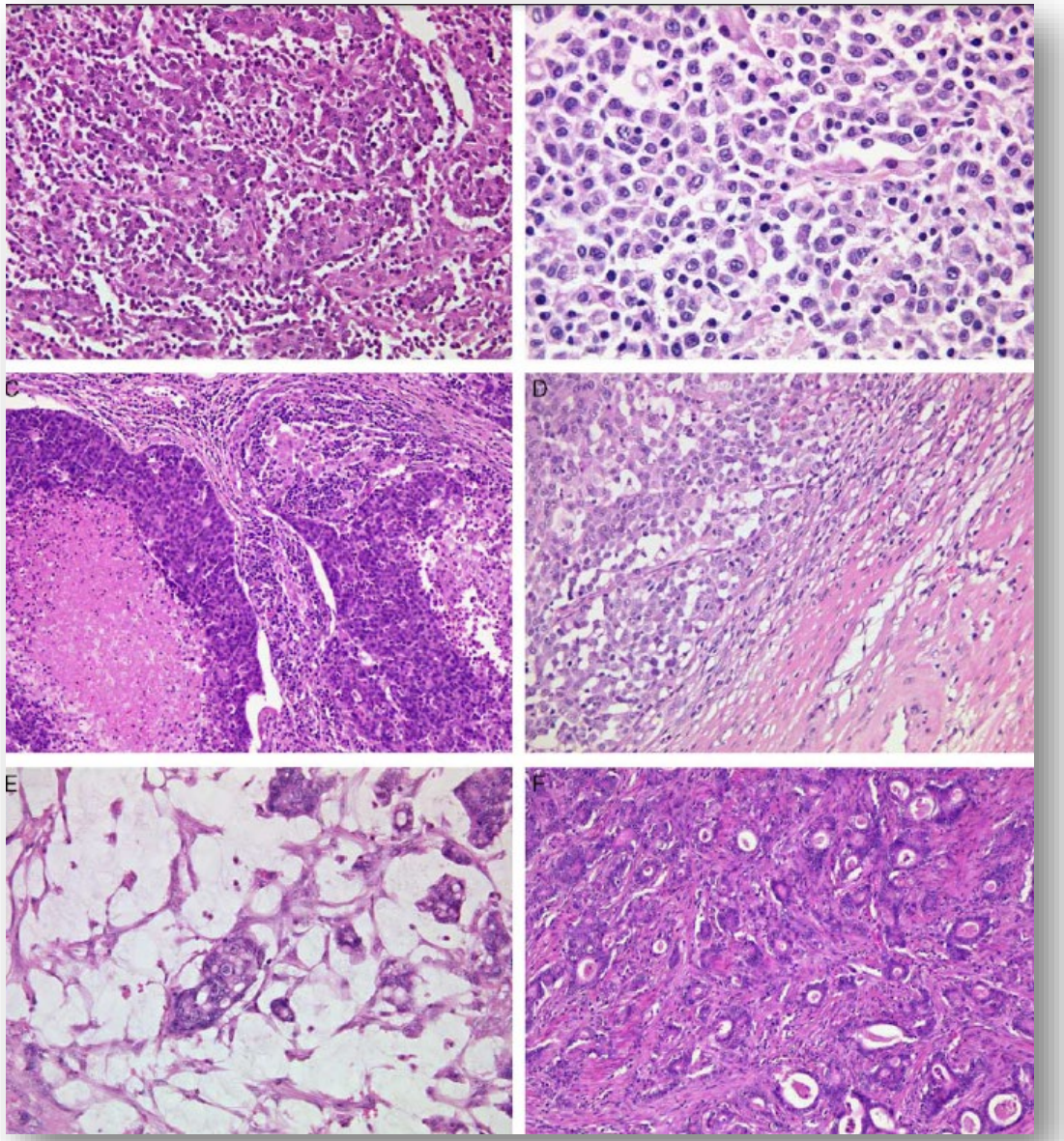
J Clin Oncol 37:3392-3400.

Histomorphology of MSI gastric cancers



Appl Immunohistochem Mol Morphol 2017;25:12–24

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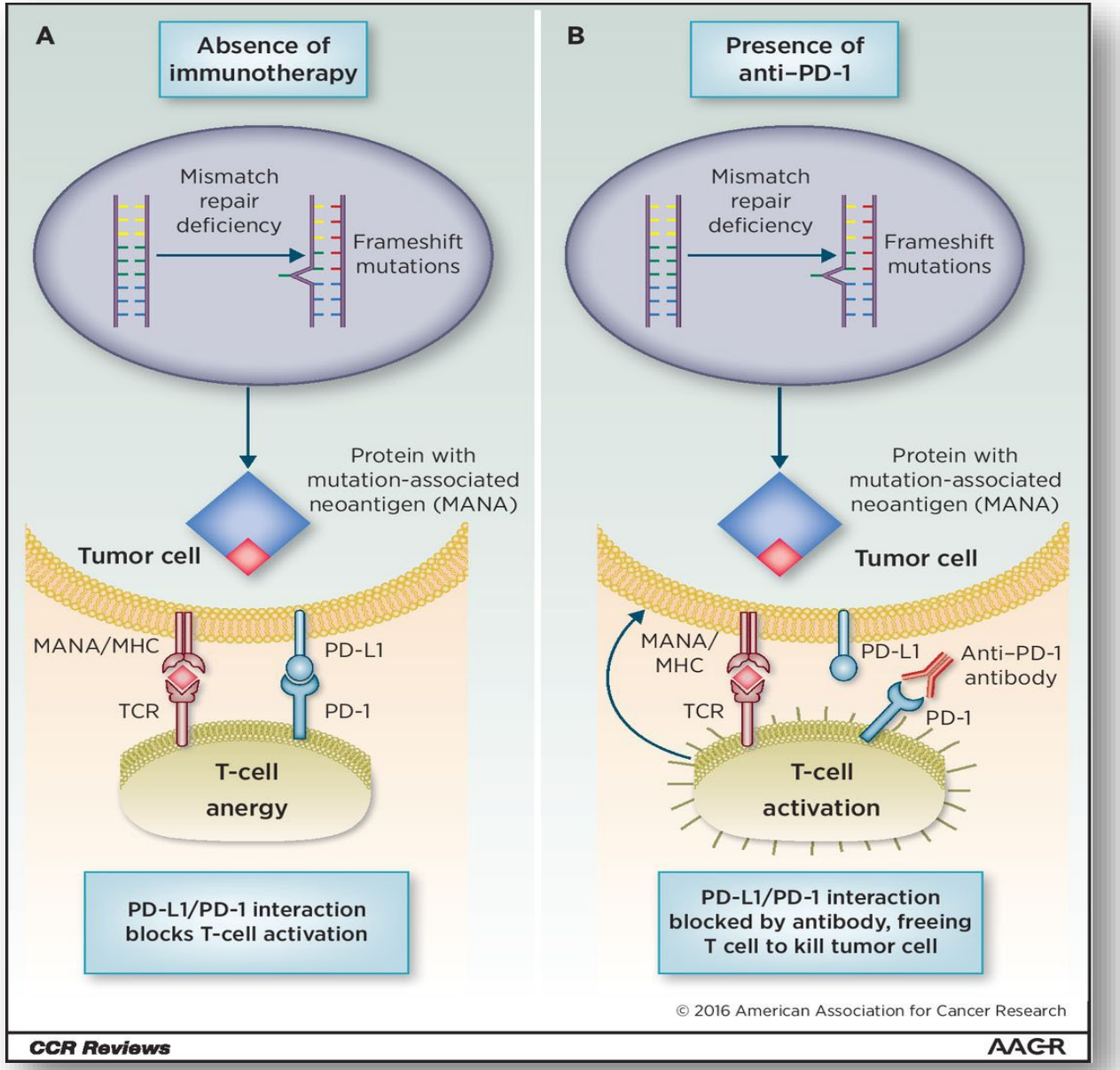
Proposed relationship between MSI status and immunologic response



Jonathan C. Dudley et al. Clin Cancer Res 2016;22:813-820

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Clinical Cancer Research

AACR American Association for Cancer Research

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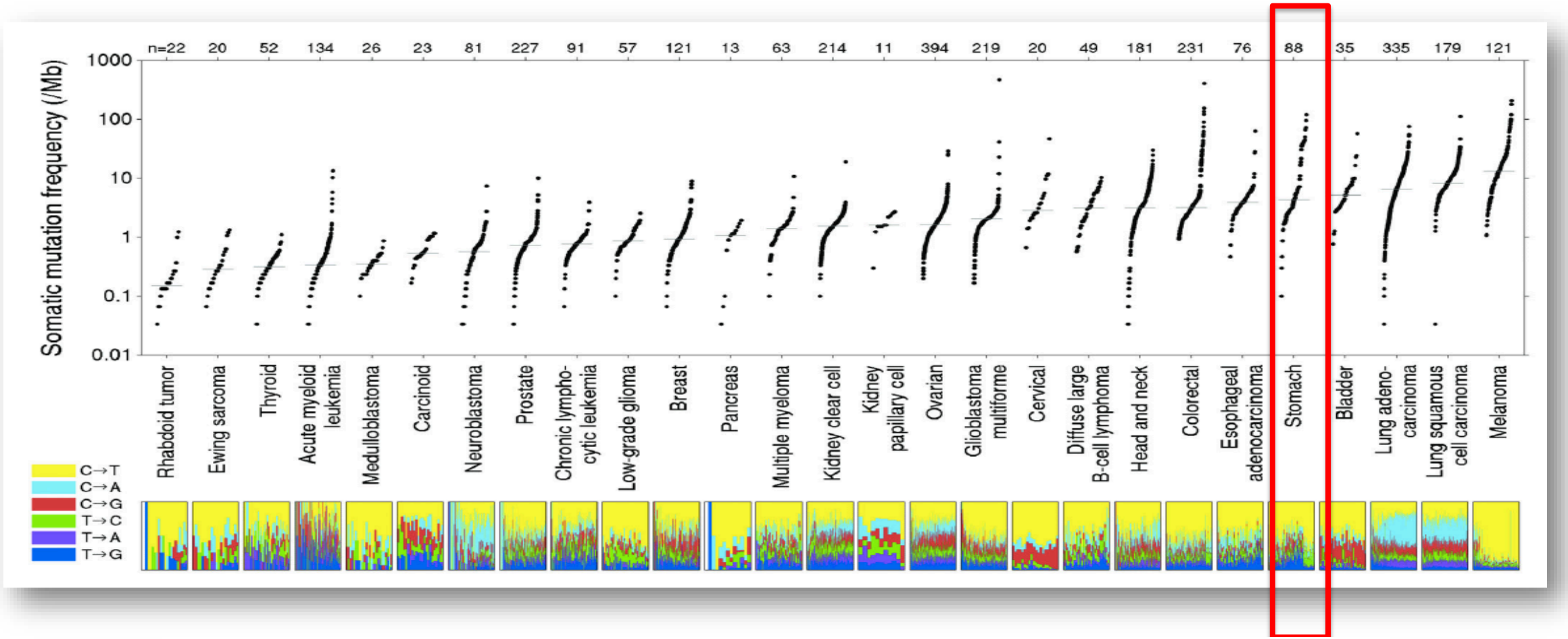
Frecuency of genetic somatic mutations in cancer



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Nature. 2013 July 11; 499(7457): 214–218

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Programmed Death-Ligand 1 Expression Is Common in Gastric Cancer Associated With Epstein-Barr Virus or Microsatellite Instability

Am J Surg Pathol 2016;40:1496–1506

Changqing Ma, MD, PhD, Krishna Patel, MD,† Aatur D. Singhi, MD, PhD,* Bing Ren, MD, PhD,* Benjamin Zhu, BA,* Fyza Shaikh, MD,† and Weijing Sun, MD†*

TABLE 2. PD-L1 Expression and Tumor Immune Microenvironment Stratified by EBV and MSI Status

	All (N = 44)	EBV + (N = 7)	MSI (N = 16)	EBV −/MSS (N = 21)	*P*
Pattern of PD-L1 staining (n [%])					
Diffuse	10 (23)	4 (57)	5 (31)	1 (5)	< 0.001
Invasive front	14 (32)	2 (29)	9 (56)	3 (14)	
Immune infiltrates	8 (18)	1 (14)	0	7 (33)	
Negative	12 (27)	0	2 (13)	10 (48)	
Portion of cells in tumor with PD-L1 staining (n [%])					
0% (PD-L1 −)	12 (27)	0	2 (13)	10 (48)	0.013
> 0% (PD-L1 +)	32 (72)	7 (100)	14 (87)	11 (52)	
> 0, < 5%	16	2	5	9	
≥ 5%, < 10%	6	1	4	1	
≥ 10%, < 20%	3	1	2	0	
≥ 20%, < 30%	3	1	2	0	
≥ 30%, < 40%	1	1	0	0	
≥ 40%	3	1	1	1	
T cells at the invasive front (mean/high-power field [range])					
CD3	436 (112-865)	580 (265-865)	527 (149-780)	318 (112-654)	< 0.001
CD4	249 (51-516)	310 (164-516)	287 (51-489)	200 (52-514)	0.011
CD8	246 (35-640)	366 (129-512)	306 (63-640)	161 (35-338)	< 0.001
PD-1	97 (5-331)	137 (48-230)	127 (5-331)	60 (17-178)	0.002
CD4/CD8 ratio (n [%])					
CD4 ≥ CD8	29 (66)	3 (43)	8 (50)	18 (86)	0.028
CD4 < CD8	15 (34)	4 (57)	8 (50)	3 (14)	
Portion of immune cells expressing PD-1 (n [%])					
< 5%, > 0%	3 (7)	0	2 (13)	1 (5)	0.481
≥ 5%	41 (93)	7 (100)	14 (87)	20 (95)	

100%

87%

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Possibility of using PD-1/PD-L1 immune checkpoint inhibitors in EBV+/MSI GCs

- PD-L1 amplification is frequent in EBV+ GC

- Studies and clinical trials proved that **MSI-high GCs** treated with **pembro** are associated with a higher rate of response and disease control compared with MSS

KEYNOTE 059 Cohort 1

Response by MSI Status (n = 174)

4.0% of patients were MSI-High

Response[a]	MSI-High (n = 7)		Non–MSI-High (n = 167)	
	%	95% CI	%	95% CI
ORR	57.1	18.4-90.1	9.0	5.1-14.4
CR	14.3	0.4-57.9	2.4	0.7-6.0
PR	42.9	9.9-81.6	6.6	3.3-11.5
DCR[b]	71.4	29.0-96.3	22.2	16.1-29.2

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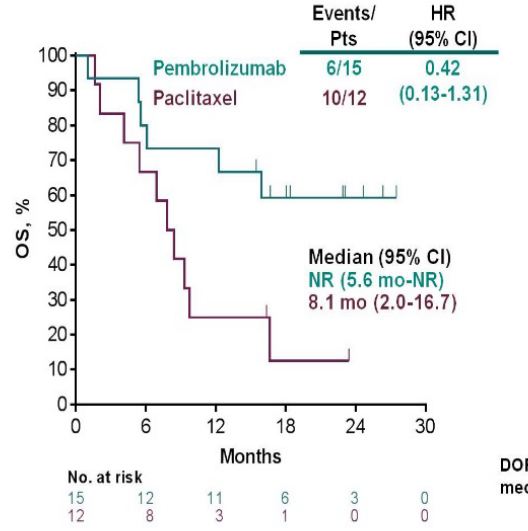
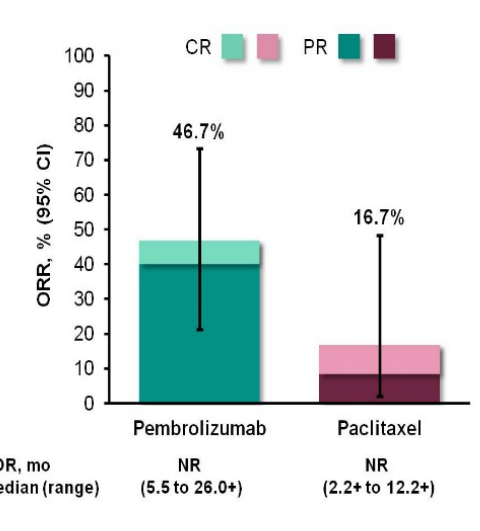
[a]Only confirmed responses were included
[b]CR + PR + SD≥2 months
Data cutoff: January 16, 2017

Fuchs ASCO 2017

KEYNOTE-061 (phase 3)

OS, ORR, and DOR for MSI-H Tumors[a]





[a]Post-hoc subgroup analysis. Data cutoff date: Oct 26, 2017.

Shitara ASCO 2018

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Table 1 Selected active clinical trials involving molecular targeted therapies for specific gastric cancer subtypes

GC subtype	Molecular target	Therapeutic agents	Clinical trial name (ID)	Phase	Patients	Aditional treatments	ESCD	Clinical efficiency			Condition	Study (citation)
								ORR	mOS	mPFS		
EBV	PD-1	Pembrolizumab	KEYNOTE-059 (NCT02335411)	II	316	Cis+5-FU	May-19	11.60%	5.6	2	Rec/Met GC	[37]
			KEYNOTE-061 (NCT02370498)	III	592	Paclitaxel	Jul-19		Failed		Adv GC	[38]
			KEYNOTE-062 (NCT02494583)	III	764	Cis+5-FU(X)	Jun-20				Adv GC	
			KEYNOTE-585 (NCT03221426)	III	860	Cis+X(5-FU) or FLOT	Jul-23				GC	
		Nivolumab +/-Ipilimumab (CTLA4 inhibitor)	ONO-4538-38 (NCT03006705)	III	700	S-1 or XOX	Jun-10				Stage III GC	
			CheckMate649 (NCT02872116)	III	1266	XOX or FOLFOX	Oct-21				Adv/Met GC	
			ONO-4538-37 (NCT02746796)	II/III	680	SOX or XOX	Aug-20				Adv/Rec GC	
			ONO-4538-12 (NCT02267343)	III	480	Nivolumab *vs* Placebo	Aug-17	11.20%	5.32/4.14 *P* < 0.0001	1.61/1.45	Adv/Rec GC	[40]
	PD-L1	Avelumab	JAVELIN Gastric 300 (NCT02625623)	III	371	Avelumab + BSC *vs* Irinotecan + Paclitaxel	Sep-20				Rec/Met GC	
			JAVELIN Gastric 100 (NCT02625610)	III	466	*vs* OX + 5-FU(X)(LV)	Mar 202 4				Adv/Met GC	
		Durvalumab	NCT02572687	I	114	Ramucirumab	Sep-18	36%		2.6	Adv/Met GC	[43,45]
			NCT02340975	Ib/II	135	+/- Tremelimumab (CTLA4 inhibitor)	Aug-19				Rec/Met GC	[46]
			NCT02678182	II	770	Cis, X	Aug-10				Adv/Met HER2 neg. GC	
		Atezolizumab	DANTE (NCT03421288)	II	295	FLOT	Feb-25				Adv GC	
			ICONIC (NCT03399071)	II	40	FLOT-A	Aug-25				T1-T3 GC	
	PIK3CA	BYL719	NCT01613950	I	18	AUY922	Mar-14	NA			Adv/Met GC	
		AZD5363	NCT02451956	II	25	Paclitaxel	Dec-18				Adv GC with PIK3CA mutation	
	ARID1A	PLX2853	NCT03297424	II	166		May-21				ARID1A mutations	
		AZD2281 (Olaparib)	NCT02576444	II	64		Sep-18				PIK3CA, AKT, or ARID1A mutations	
MSI	PD-1	Pembrolizumab	KEYNOTE-016 (NCT01876511)	II	171		Jun-21	40%	Not reached	5.4	MSI	[47]
GS	CDH1	NA	-			Prophylactic gastrectomy						
	RHOA	NA				NA						
	CLDN18-ARHGAP fusion	NA				NA						
CIN	EGFR	Cetuximab	NCT00183898	II	75	XOX	Jun-18				Adv GC	
		Panitumumab	NEOPECX (NCT01234324)	II	171	ECX, placebo	Aug-17				Adv GC incl. GEJ	
			MEGA (NCT01443065)	II	162	FOLFOX/FOLFOX + panitumumab/FOLFOX + AMG102	Jan-19		13.1/8.3/11.5	5.8/5.2/7.6	Adv GC	[48]
		Nimotuzumab	NCT01813253	III	400	Irinotecan, placebo	Jan-18				EGFR overexpr. Adv GC or GEJ	
			NIEGA (NCT03400592)	II	55	Irinotecan	Jun-18				Rec/Met GC with overexpr. EGFR	

EUROPEAN MEDICINES AGENCY

Keytruda
pembrolizumab

19 May 2022
EMA/CHMP/237136/2022
Committee for Medicinal Products for Human Use (CHMP)

KEYTRUDA as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

Oesophageal carcinoma

KEYTRUDA, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma, in adults whose tumours express PD-L1 with a CPS ≥ 10 (see section 5.1).

Opdivo (*nivolumab*)

Gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.

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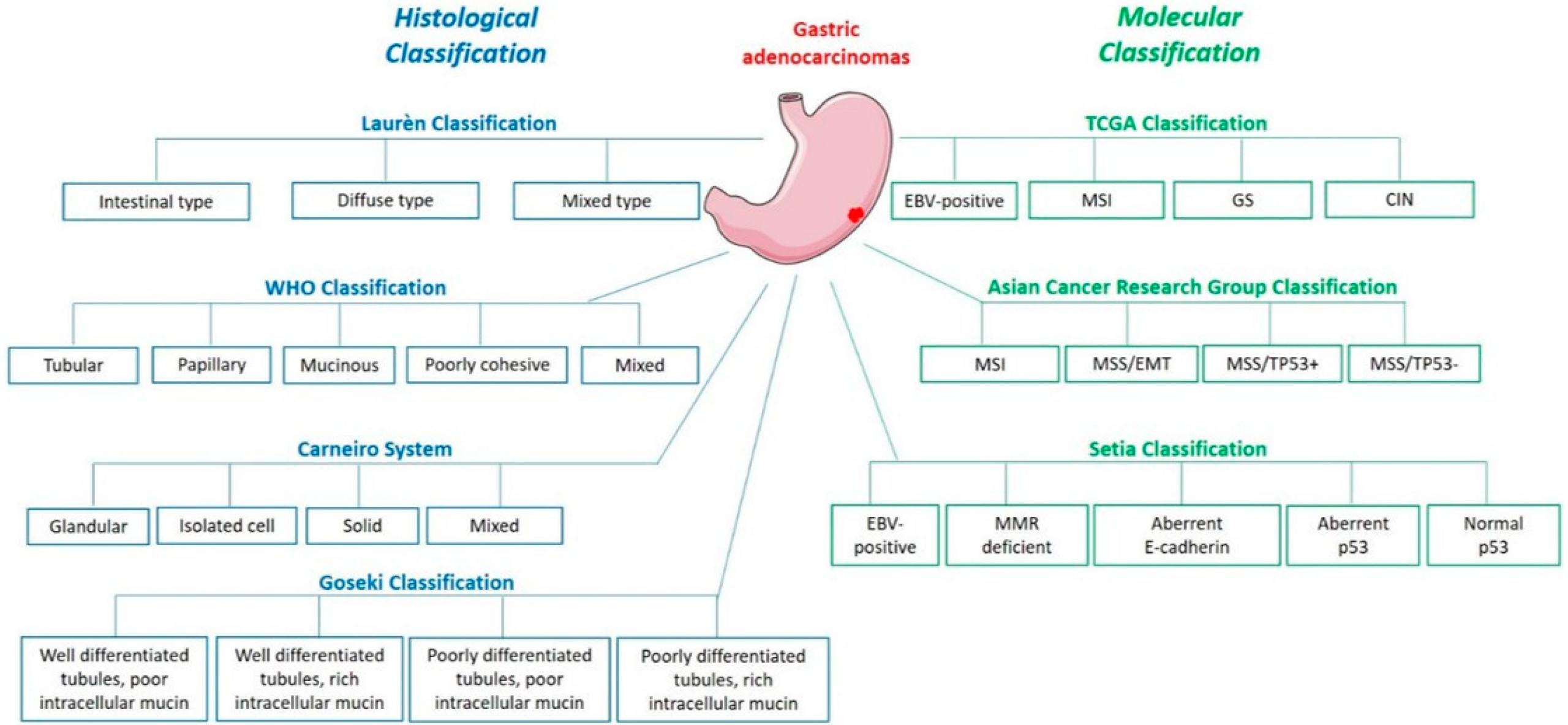

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Int. J. Mol. Sci. **2021**, *22*, 3418.


Gràcies