

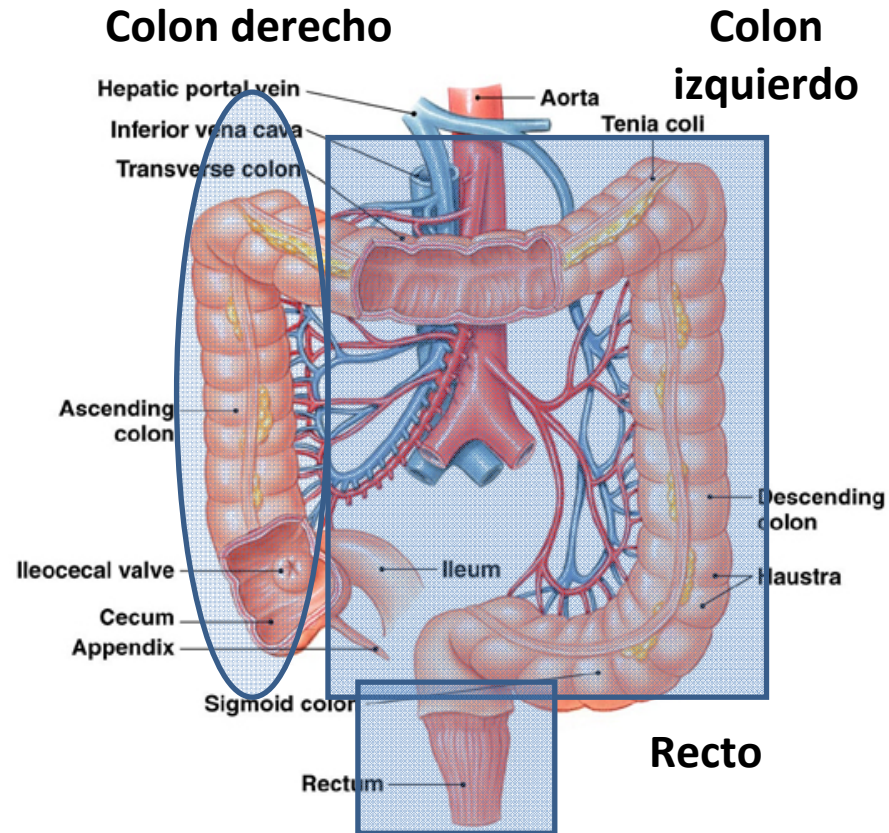
SEMINARIO: CÁNCER COLORRECTAL

**Oncología Molecular, MBMM
2013**

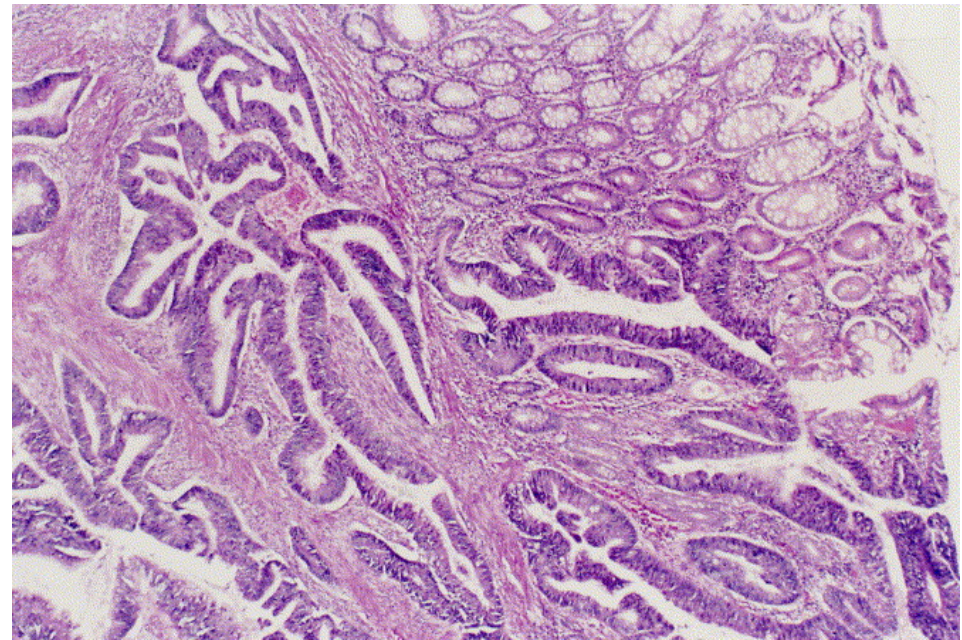
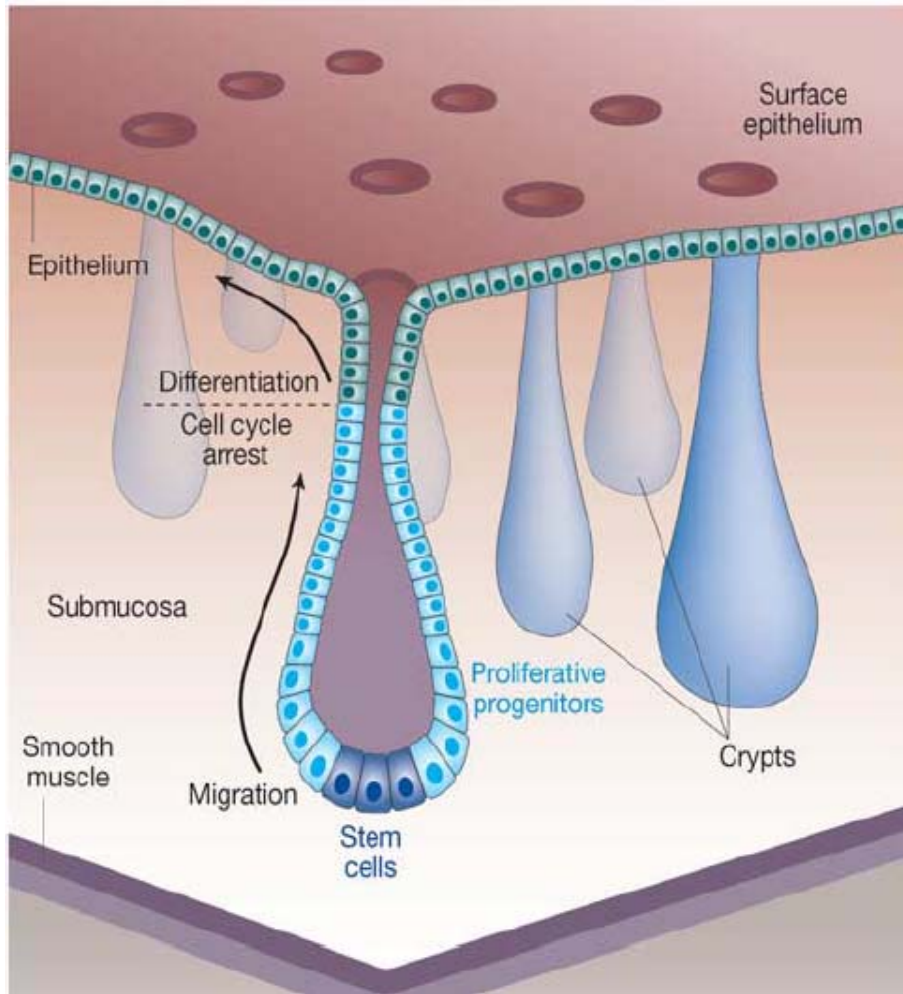
Bioq. Juan Martín Arriaga

Bioq. María Paula Roberti

¿Qué es?

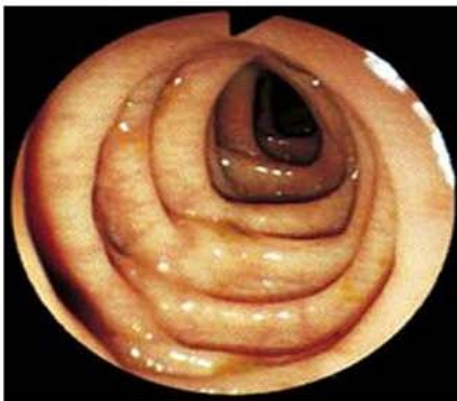
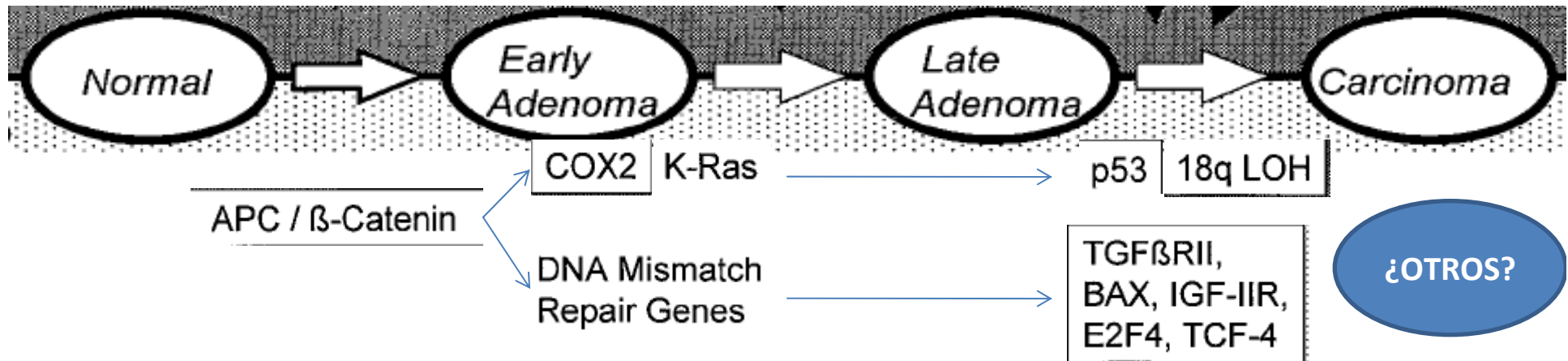
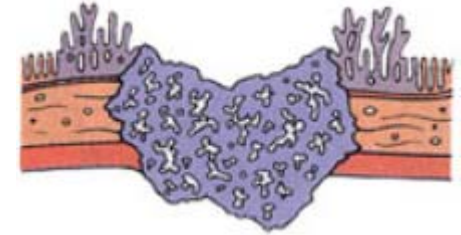
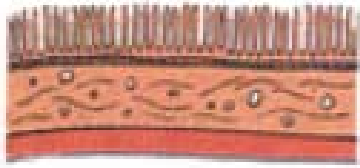


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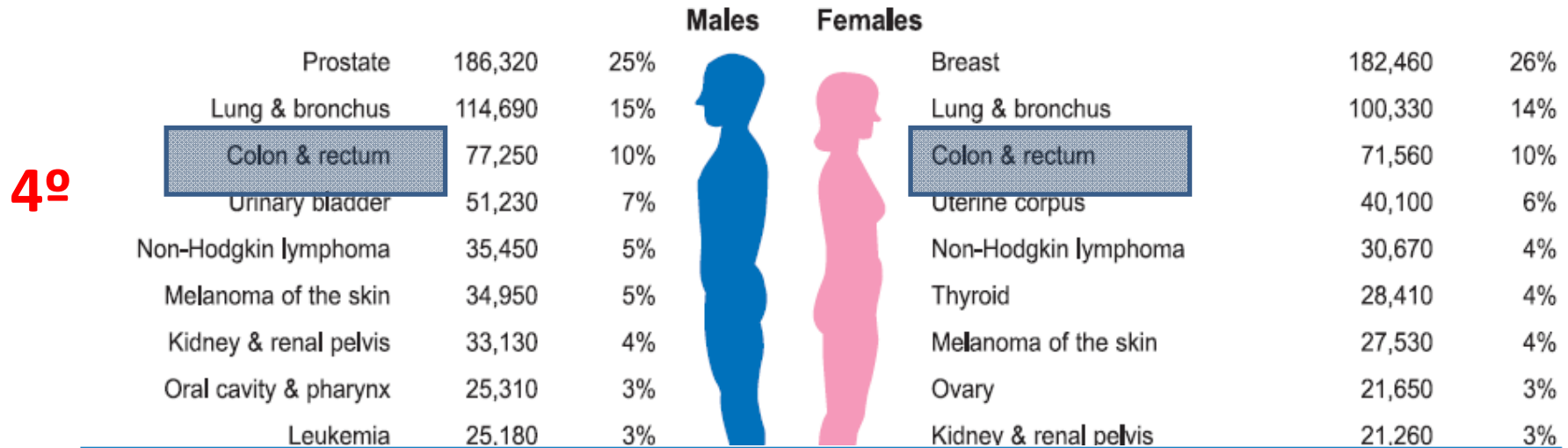
Secuencia Adenoma Carcinoma

Luz intestinal

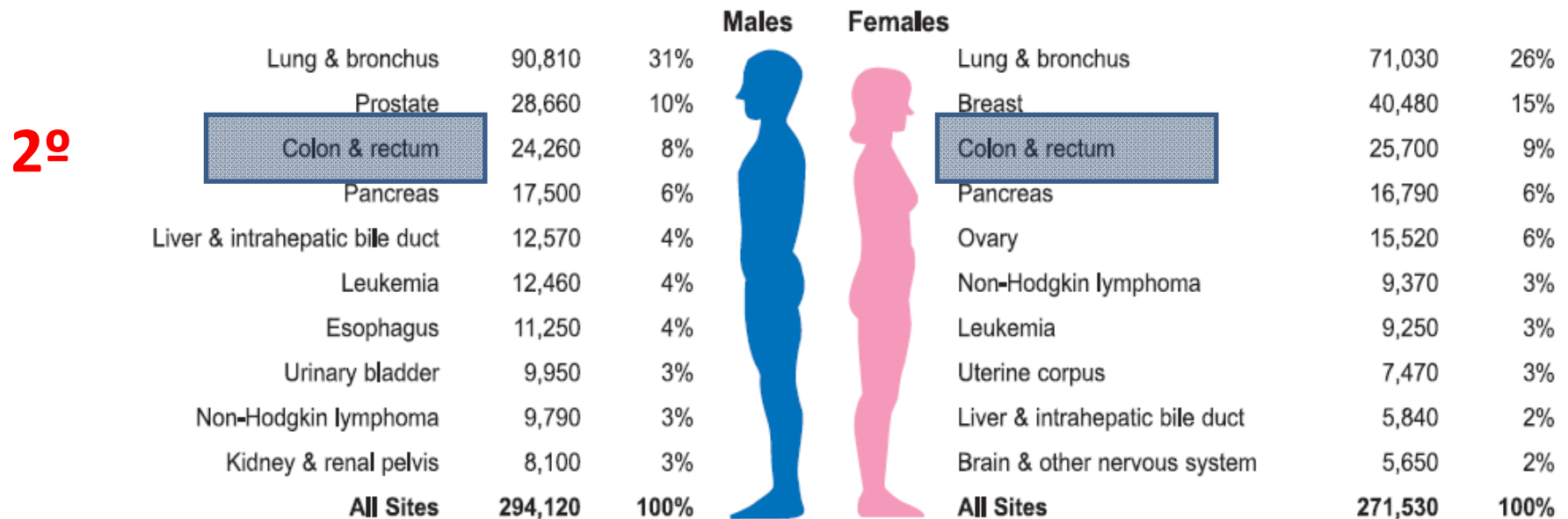


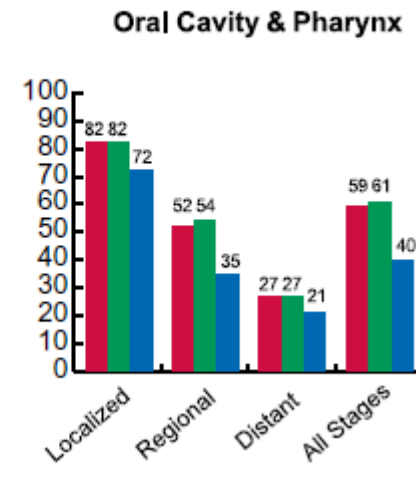
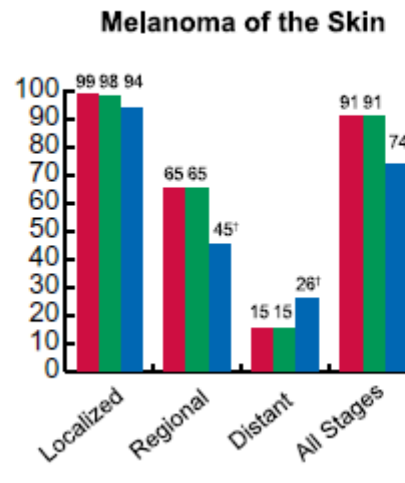
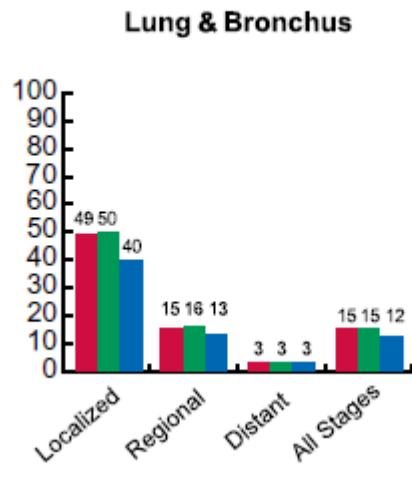
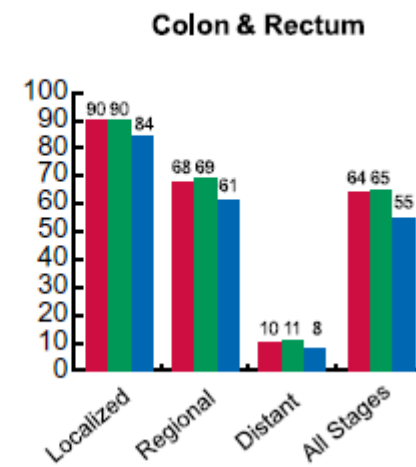
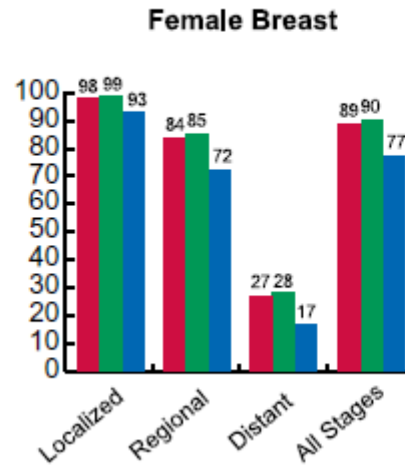
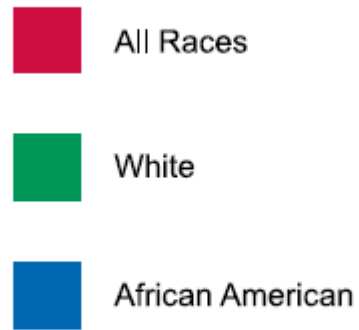
Epidemiología

Estimated New Cases*



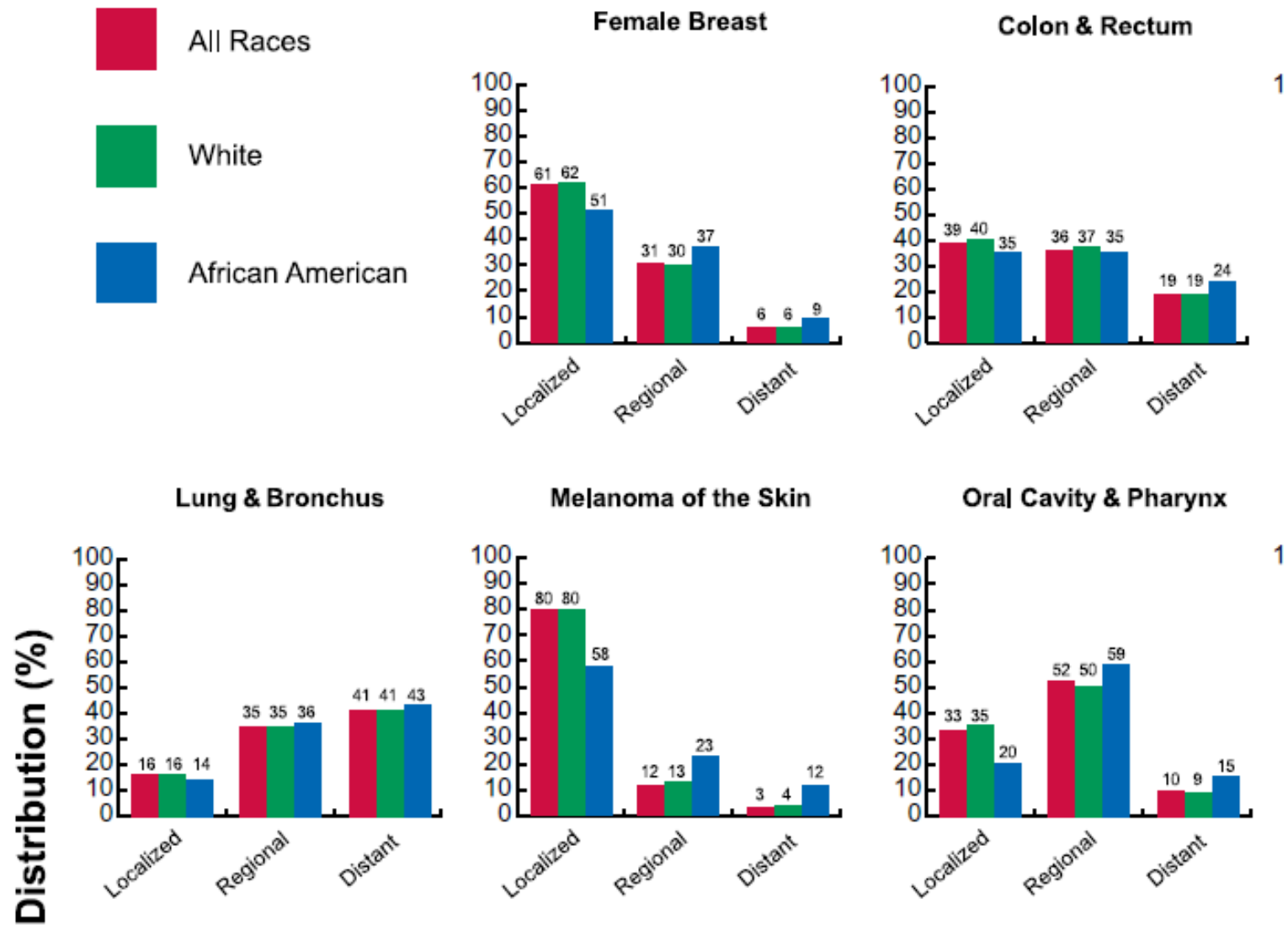
Estimated Deaths





Survival (%)

Stage distribution



Etiología

- **Esporádicos: 70-80%**
 - Factores ambientales + edad
- **Hereditarios: 5%**
 - FAP: 1%
 - HNPCC / Lynch: 3%
 - Otros
- **Síndromes predisponentes / Familiar: 20-25%**

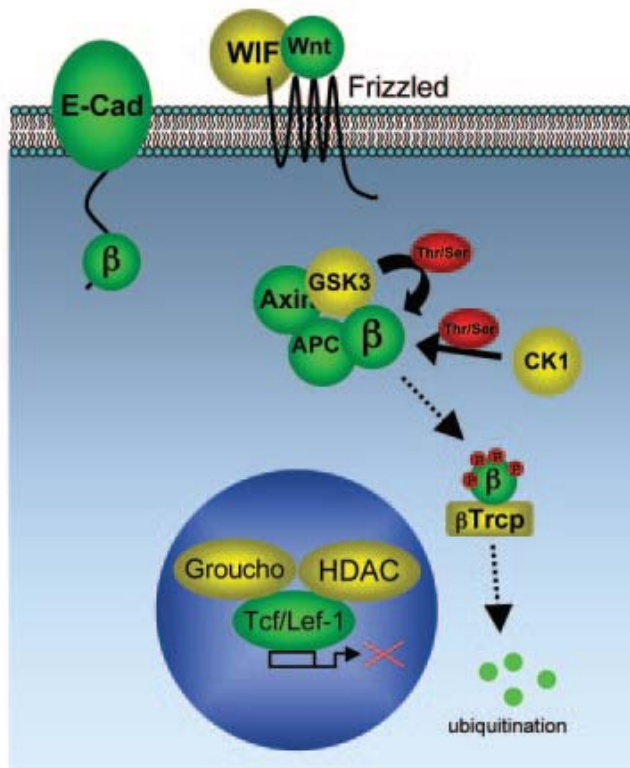
Factores Ambientales

Increased Incidence	Decreased Incidence
High-caloric diet	High-fiber diet
High red meat consumption	Antioxidant vitamins
Overcooked red meat	Fresh fruit/vegetables
High saturated fats	Nonsteroidal anti-inflammatories
Excess alcohol consumption	
Cigarette-smoking	High calcium
Sedentary lifestyle	
Obesity	
No effect on incidence with coffee or tea	

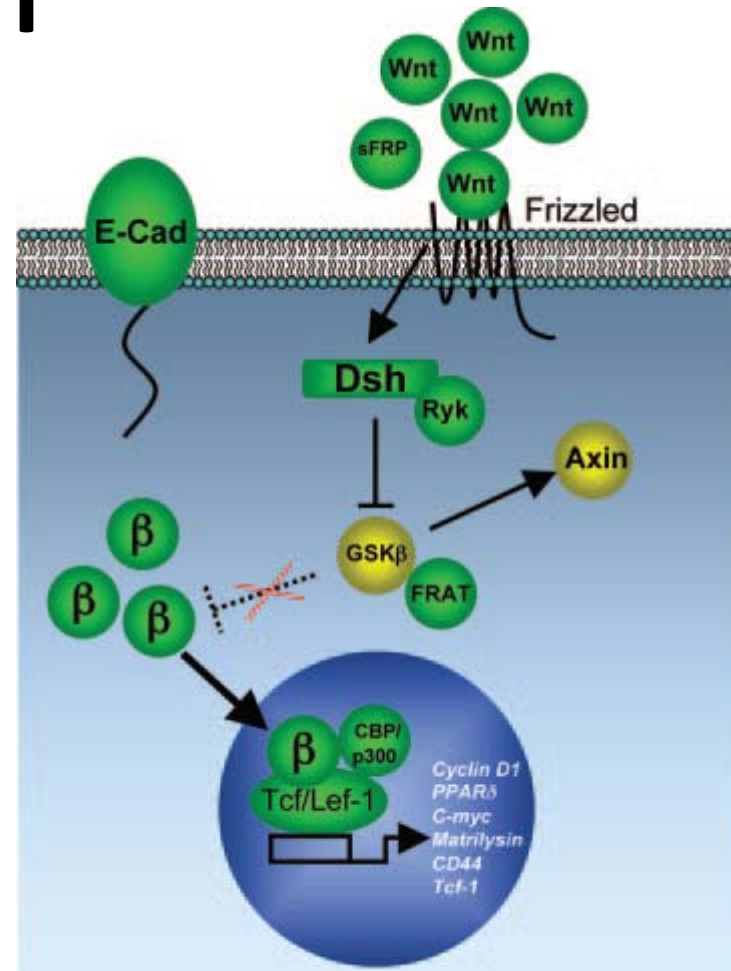
Alteraciones moleculares

- **Inestabilidad cromosómica (CIN): 85%**
 - Hay pocos defectos génicos específicos
 - Muchas alteraciones
- **Inestabilidad de microsatélites (MSI): 15%**
 - Euploides
 - Alteraciones es “mismatch repair” (MMR)
 - “Fenotipo mutador”
- **Fenotipo metilador de islas CpG (CIMP):30%**
 - Asociado a MSI
 - Alteraciones epigenéticas
 - Se discute si es un subtipo diferente de CCR

Vías de señalización alteradas: WNT

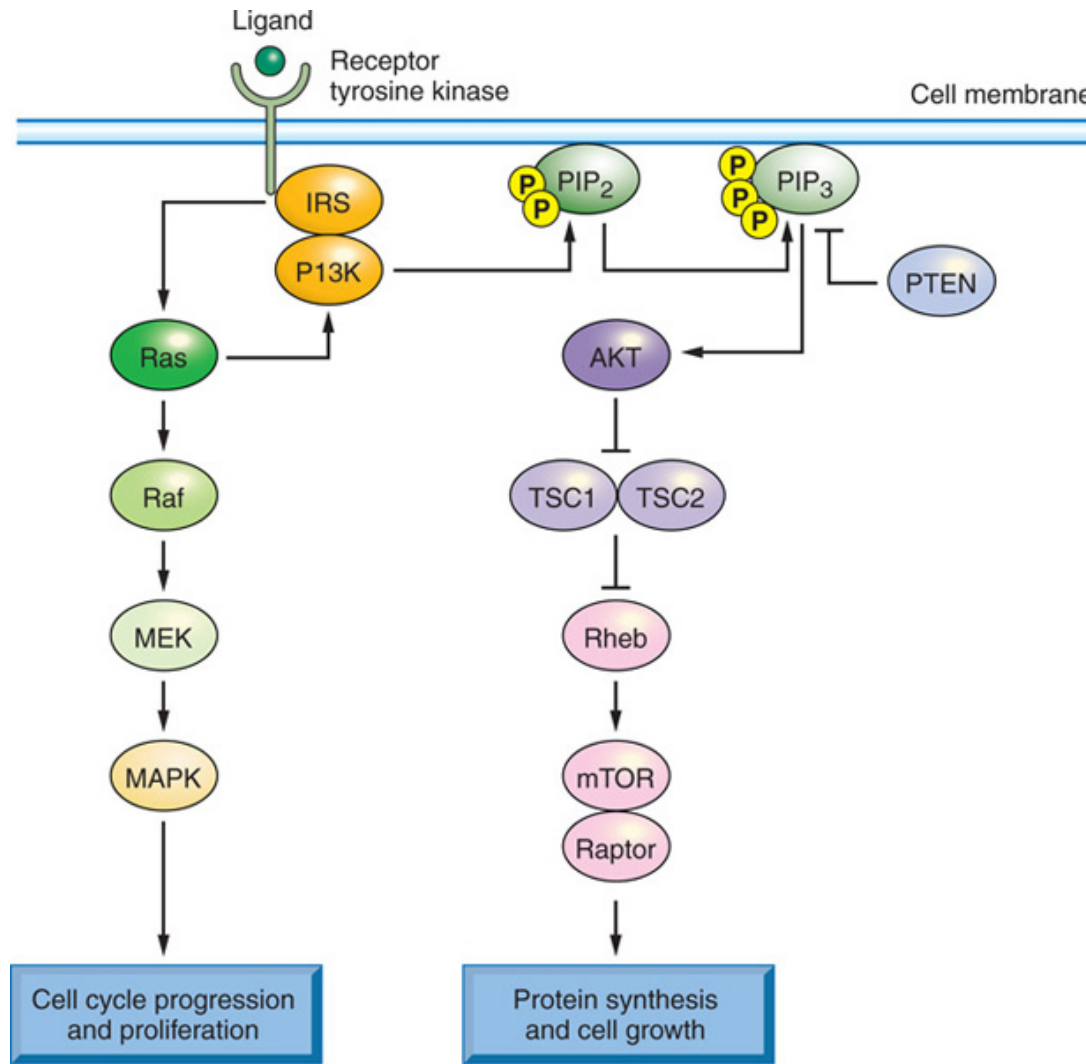


B In-activated Canonic Wnt Signalling



A Activated Canonic Wnt Signalling

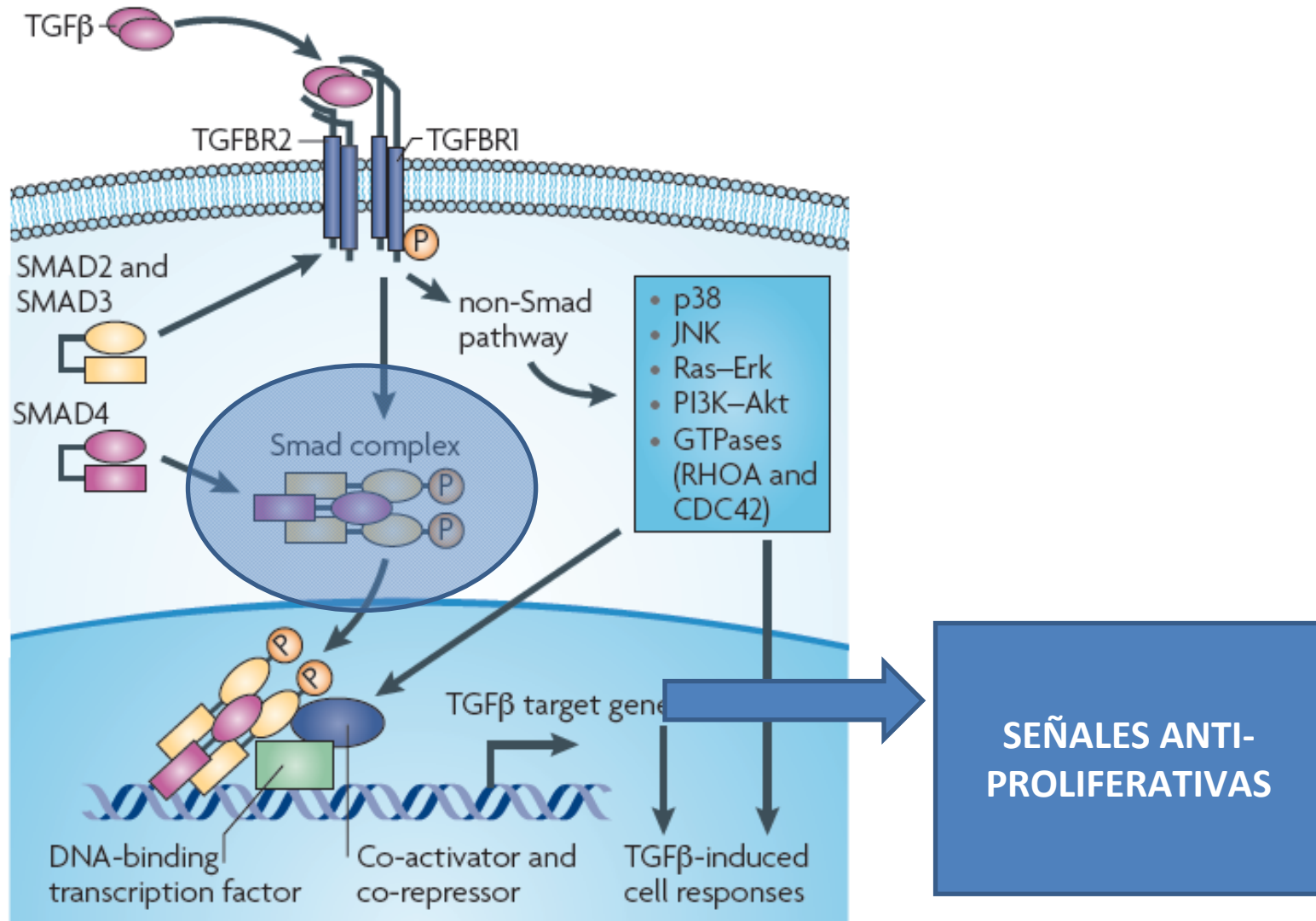
Vías de señalización alteradas: RAS/RAF + AKT



Source: DeVita VT, Lawrence TS, Rosenberg SA: *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, 9th Edition*:
www.lwwoncology.com

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Vías de señalización alteradas: TGF- β /SMAD



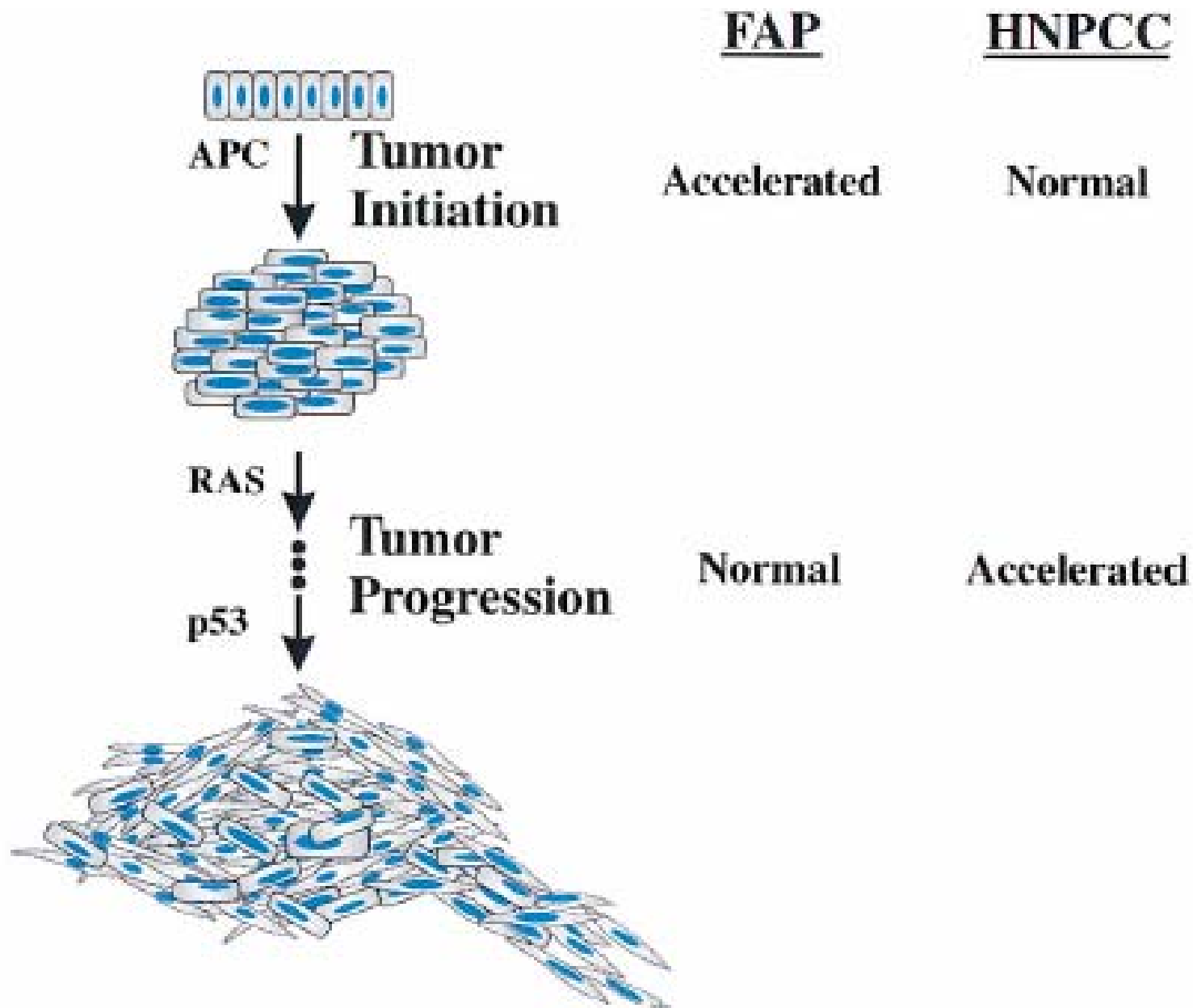
ONCOGENES

Gene	Type of Mutation	Frequency of Alterations (%)
<i>KRAS</i>	Point mutation (codons 12, 13, 61)	40% (majority at codon 12)
<i>PIK3CA</i>	Point mutations activating kinase activity	14%–35%
<i>BRAF</i>	Point mutation (V600E)	5%–8%
<i>CTNNB1</i>	Point mutation and in-frame deletions (amino-terminus)	~5%
<i>HER-2/ERBB2</i>	Amplification	<5%

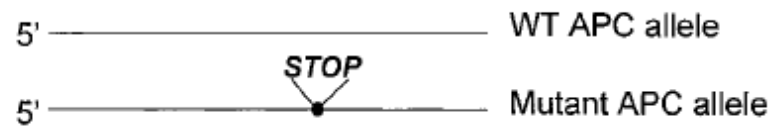
SUPRESORES	Type of Mutation	Frequency of Alterations (%)
<i>p53</i>	Point mutation, LOH	>60% (most are missense mutations)
<i>APC</i>	Small insertion or deletion, point mutation, LOH	>80% (most result in a truncated protein)
<i>SMAD4</i>	LOH, point mutation	60% LOH; 10%–15% missense, nonsense mutations
<i>SMAD2</i>	LOH, point mutation, small deletion,	60% LOH; <5% missense mutations, small deletions
<i>TGF-βRII</i>	Small insertion or deletion	10%–15%; higher (>90%) in MSI-Hi disease
<i>DCC</i>	LOH, insertion, deletion	~60% LOH; 10%–15% microsatellite insertions

CCR HEREDITARIO

	FAP	HNPCC
Modo herencia		
Número de pólipos por individuo (pocos / miles)		
Riesgo de desarrollar cáncer en toda la vida (80% o 100%)		
% aproximado de todos los casos de CCR (1 o 3%)		
Edad mediana de diagnóstico (/ 39)		
Gen(es) afectados		
Inestabilidad asociada (CIN/MSI)		
Tests de diagnóstico usados		



Test de la proteína truncada

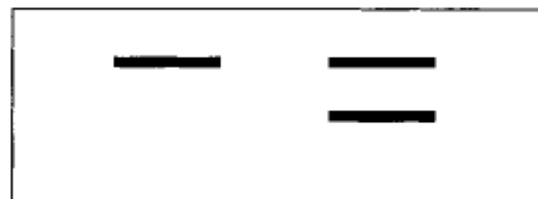


Amplify with PCR

Transcribe *in vitro* into mRNA

Translate *in vitro* into protein

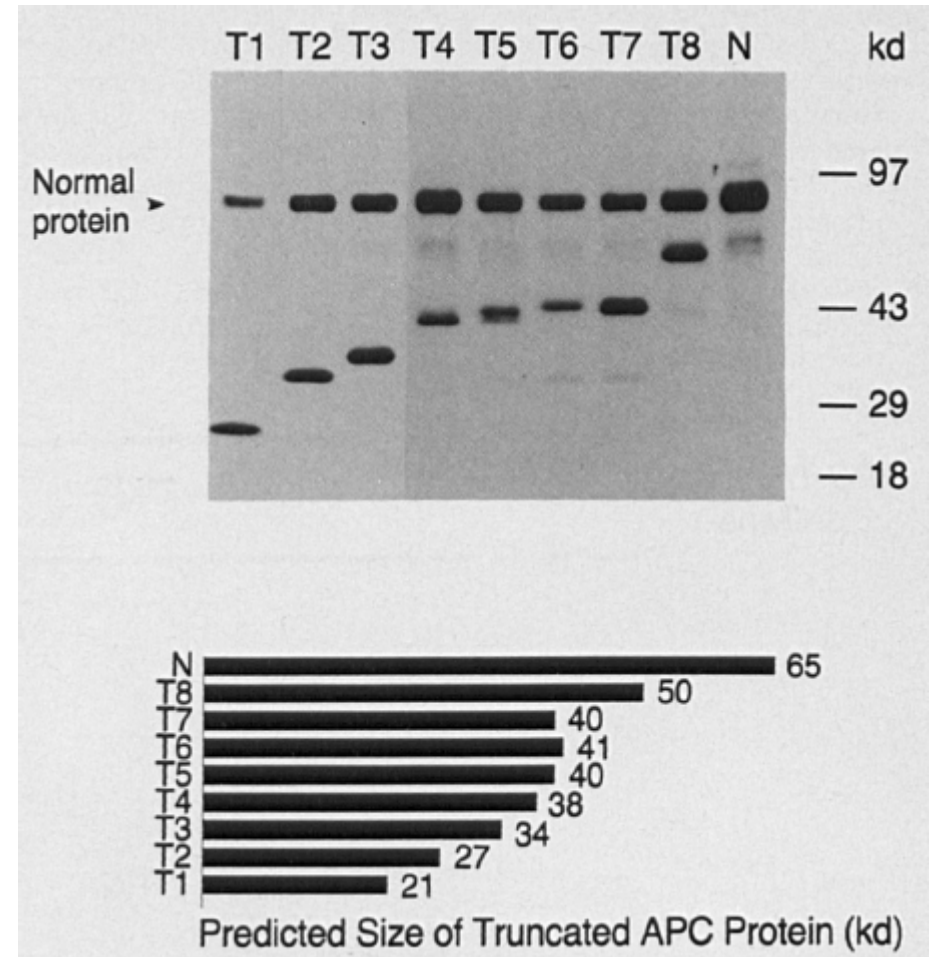
Visualize products with gel electrophoresis



← WT APC protein

← Truncated APC protein product

Normal subject FAP patient

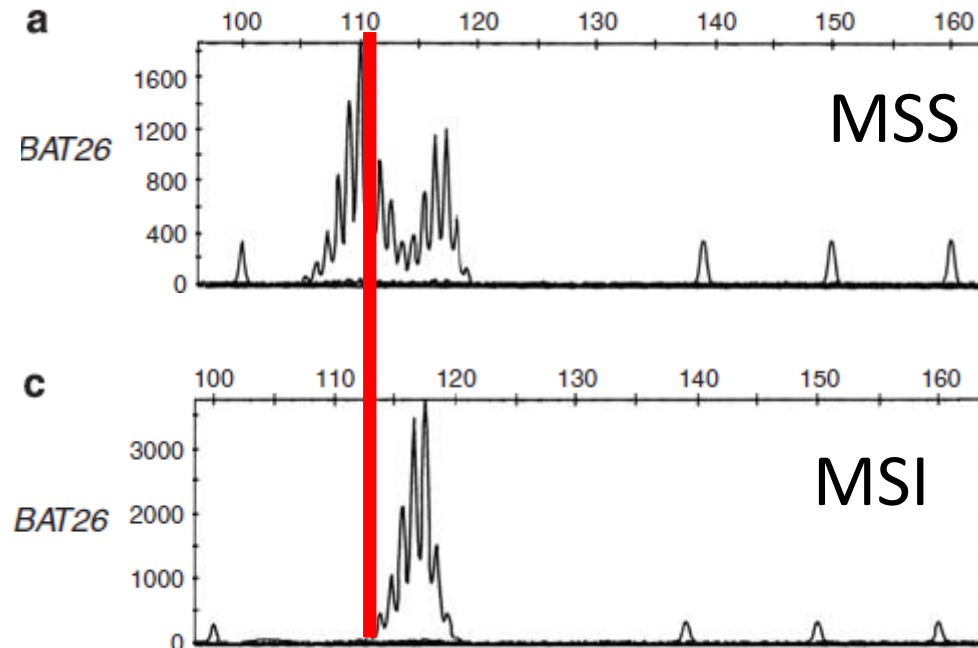
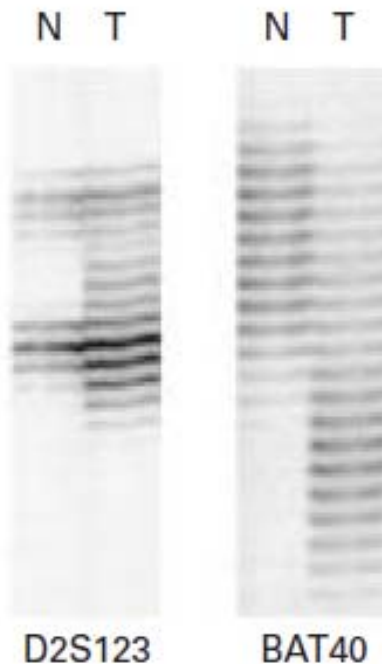


MSI: inestabilidad de microsatélites

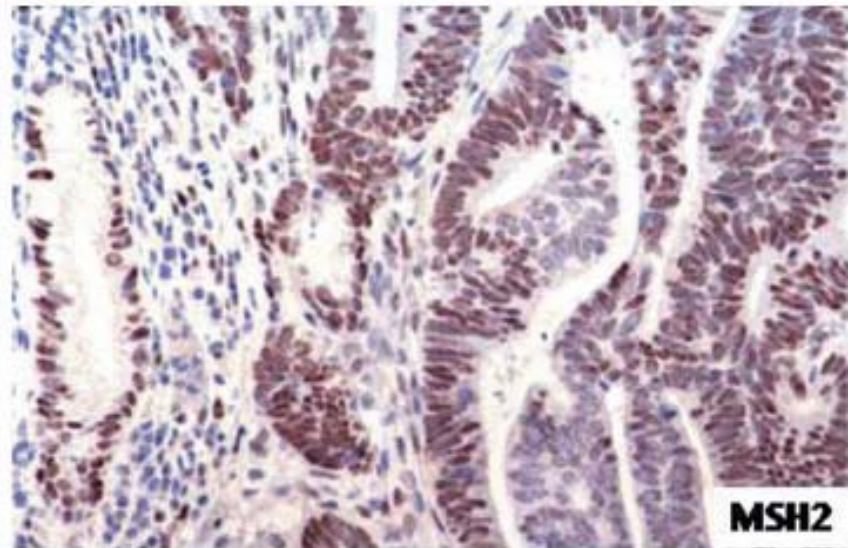
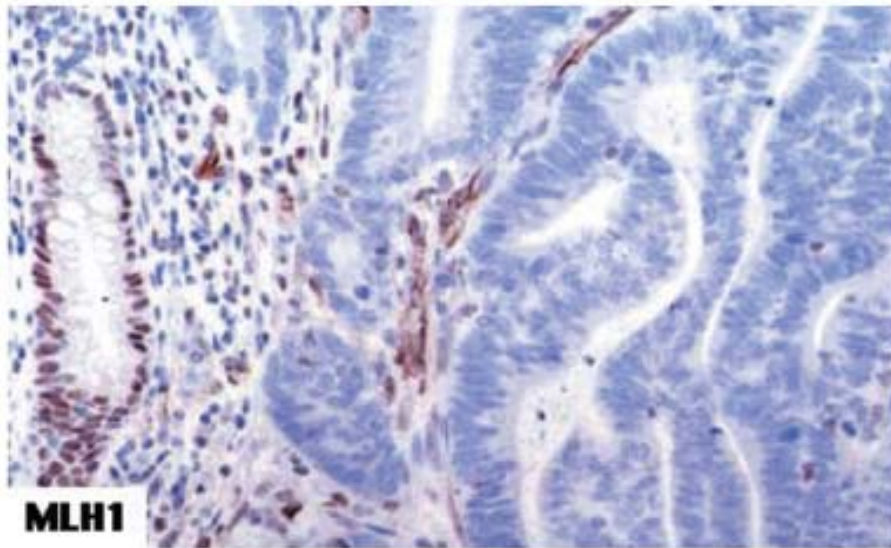
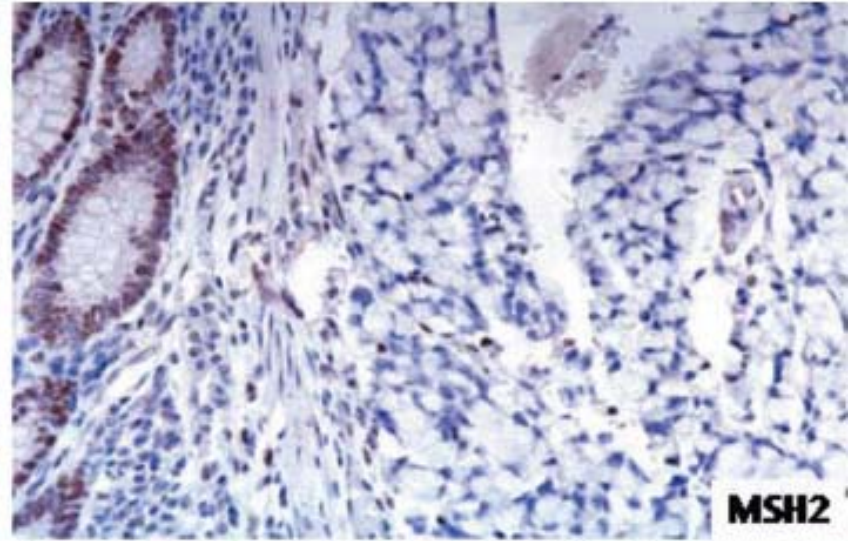
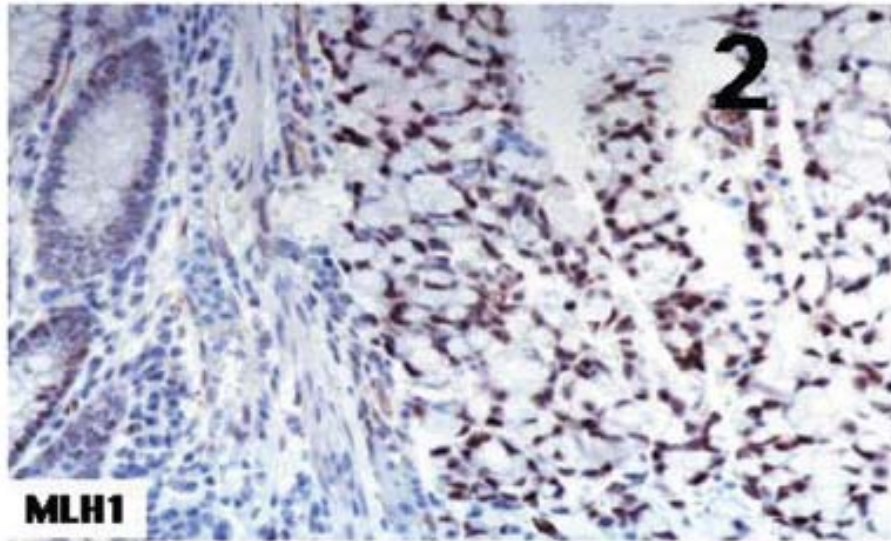
- “MSI is defined as a change of any length due to either insertion or deletion of repeating units, in a microsatellite within a tumor when compared to normal tissue”
- Si >30-40% locus tienen MSI = “MSI-H”
- Si 0-30-40% locus tienen MSI = “MSI-L”
- 0% = “MSS”

Testeo para MSI

- PCR para un panel de microsatélites
 - PCR con [^{33}P]dATP + PAGE
 - Electroforesis capilar con primers fluorescentes

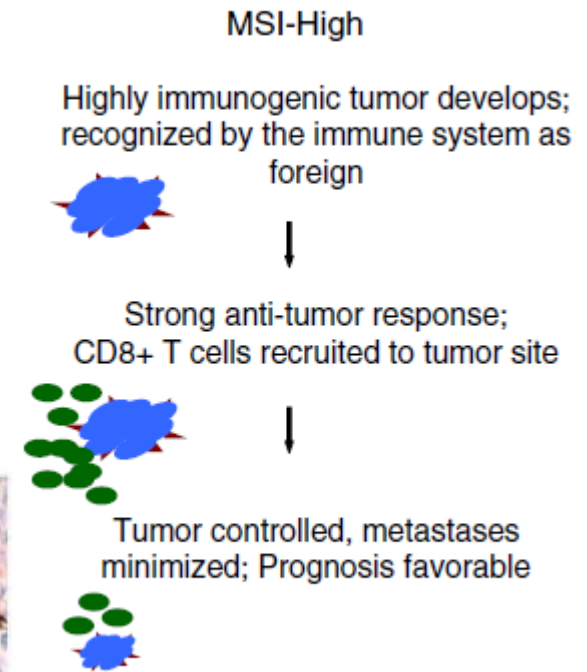
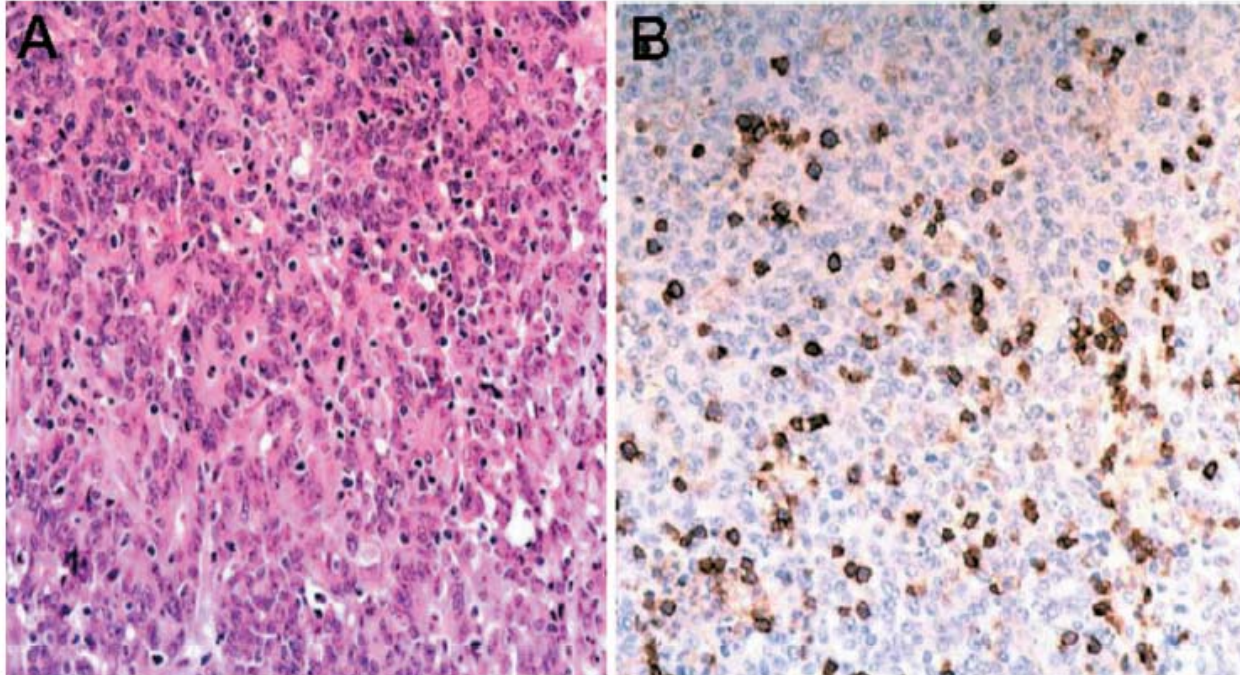


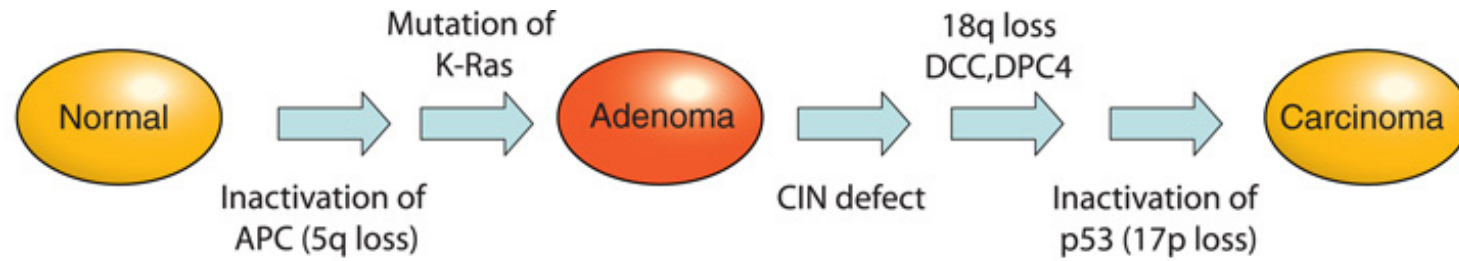
Testeo MSI: IHQ



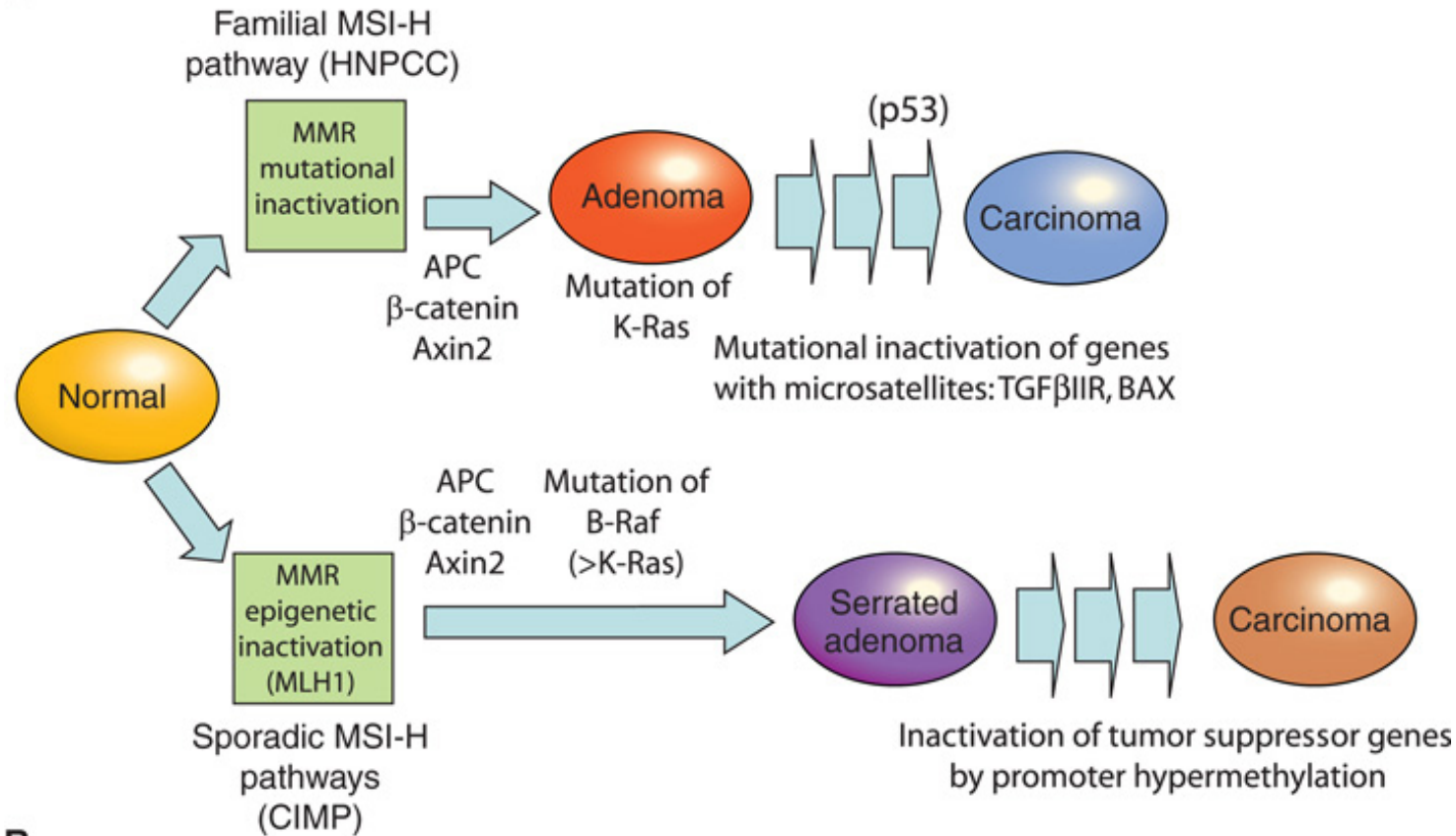
Tumores MSI-H

- Fenotipo mutador
- Euploides
- Mayor infiltrado leucocitario
- Mejor pronóstico
- Falta de respuesta a 5FU





A



B

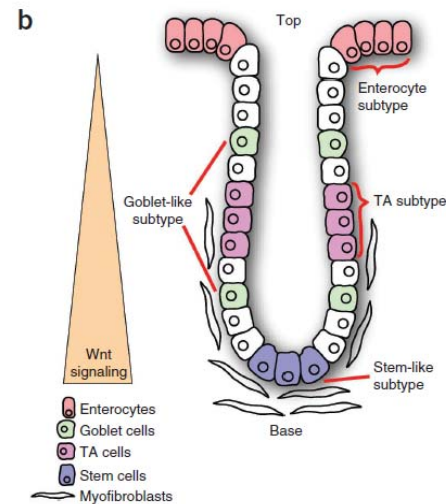
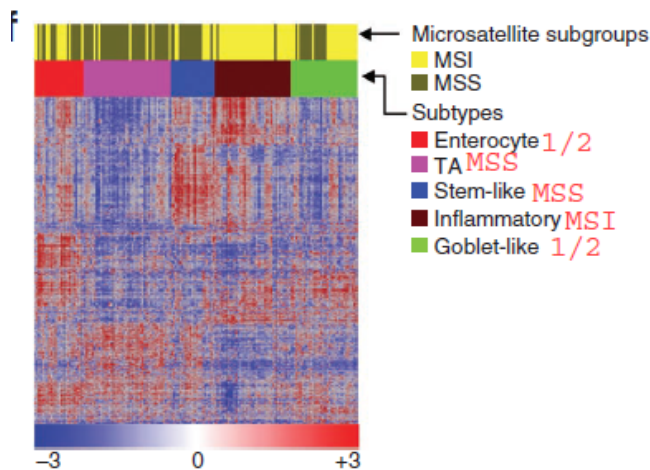
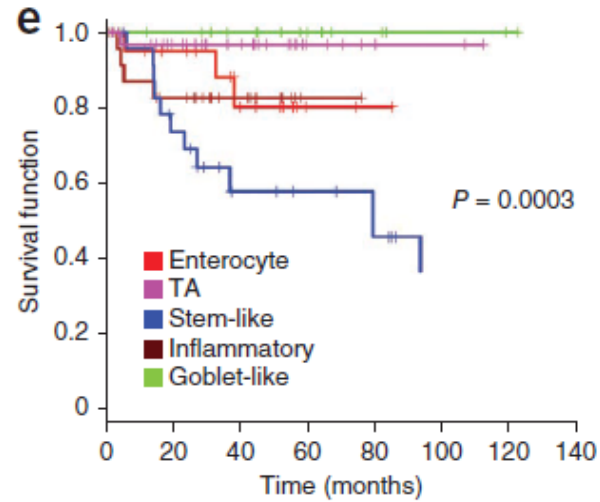
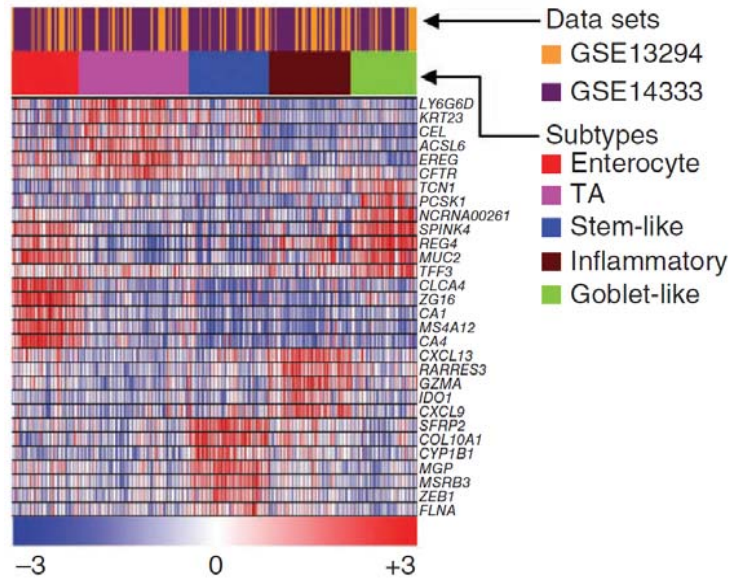
Source: DeVita VT, Lawrence TS, Rosenberg SA: *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, 9th Edition*: www.lwwoncology.com

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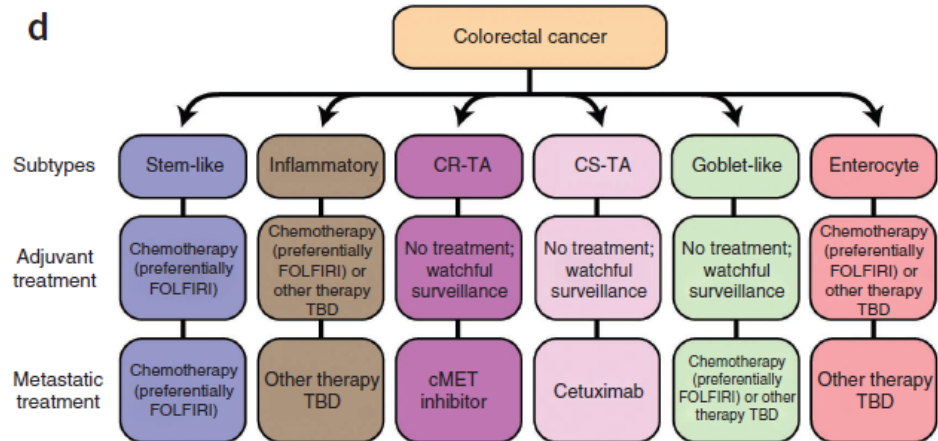
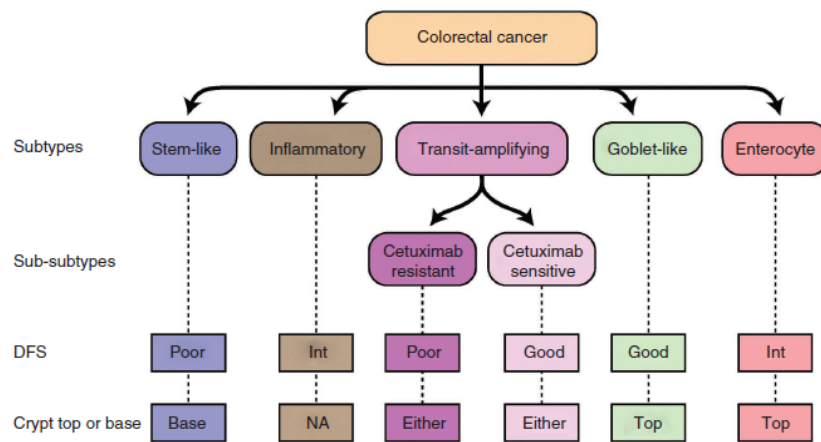
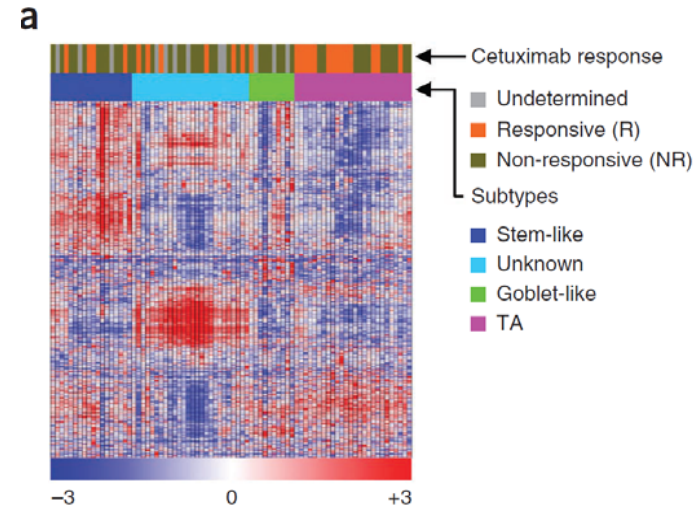
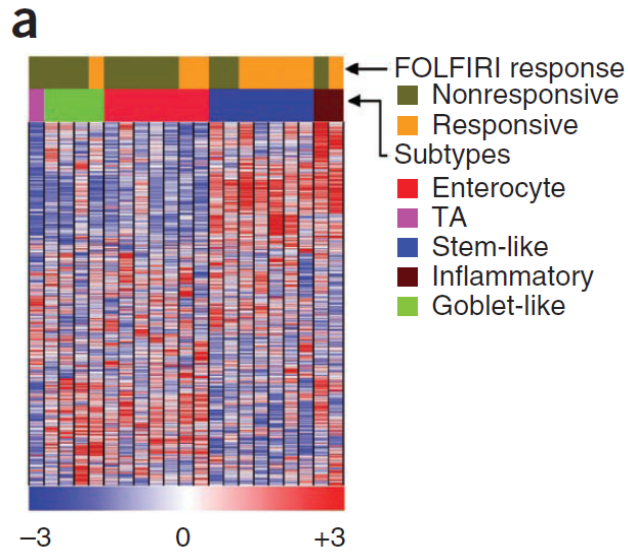
Clasificación Molecular: I

A colorectal cancer classification system that associates cellular phenotype and responses to therapy

Anguraj Sadanandam^{1,2}, Costas A Lyssiotis^{3,4,14,15}, Krisztian Homicsko^{2,5,15}, Eric A Collisson⁶, William J Gibb⁷, Stephan Wullschlegler², Liliane C Gonzalez Ostos², William A Lannon^{3,14}, Carsten Grotzinger⁸, Maguy Del Rio⁹, Benoit Lhermitte¹⁰, Adam B Olshen^{11,12}, Bertram Wiedenmann⁸, Lewis C Cantley^{3,4,14}, Joe W Gray¹³ & Douglas Hanahan²



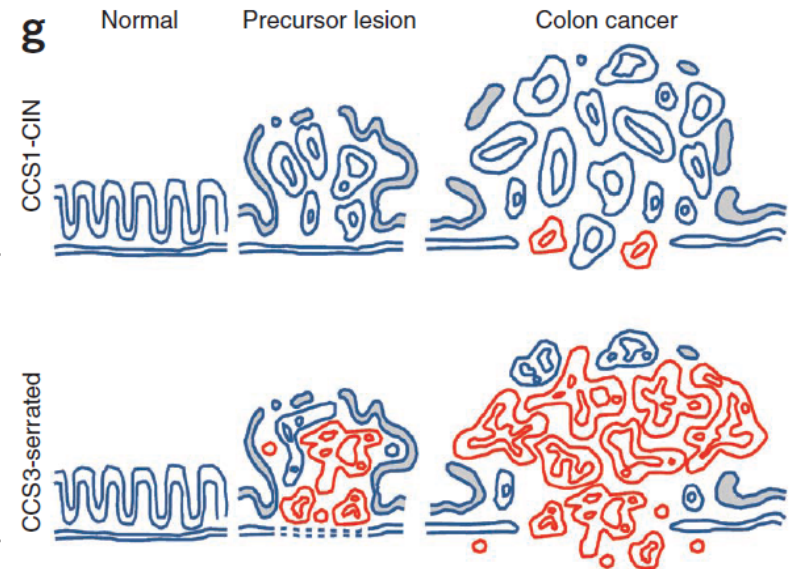
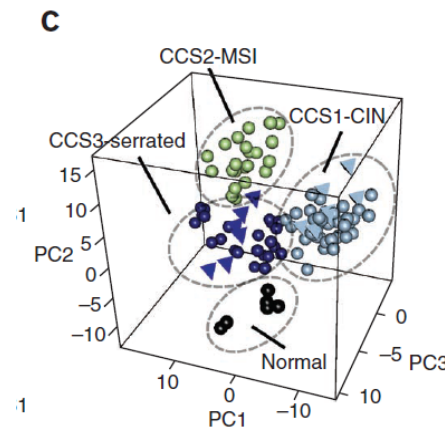
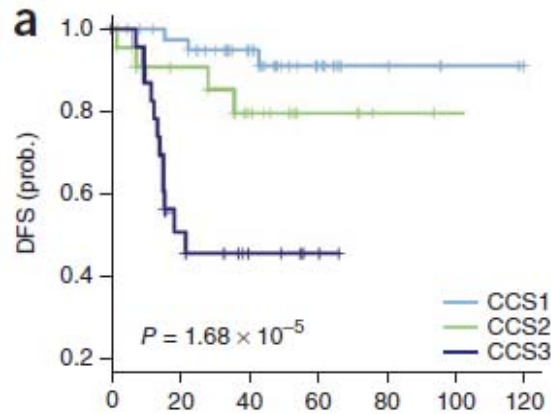
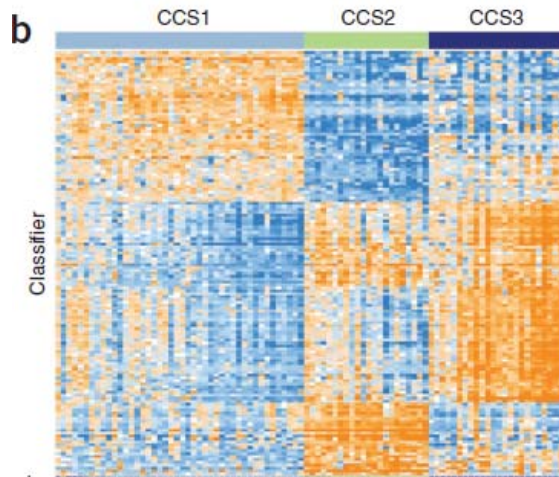
Clasificación Molecular: I



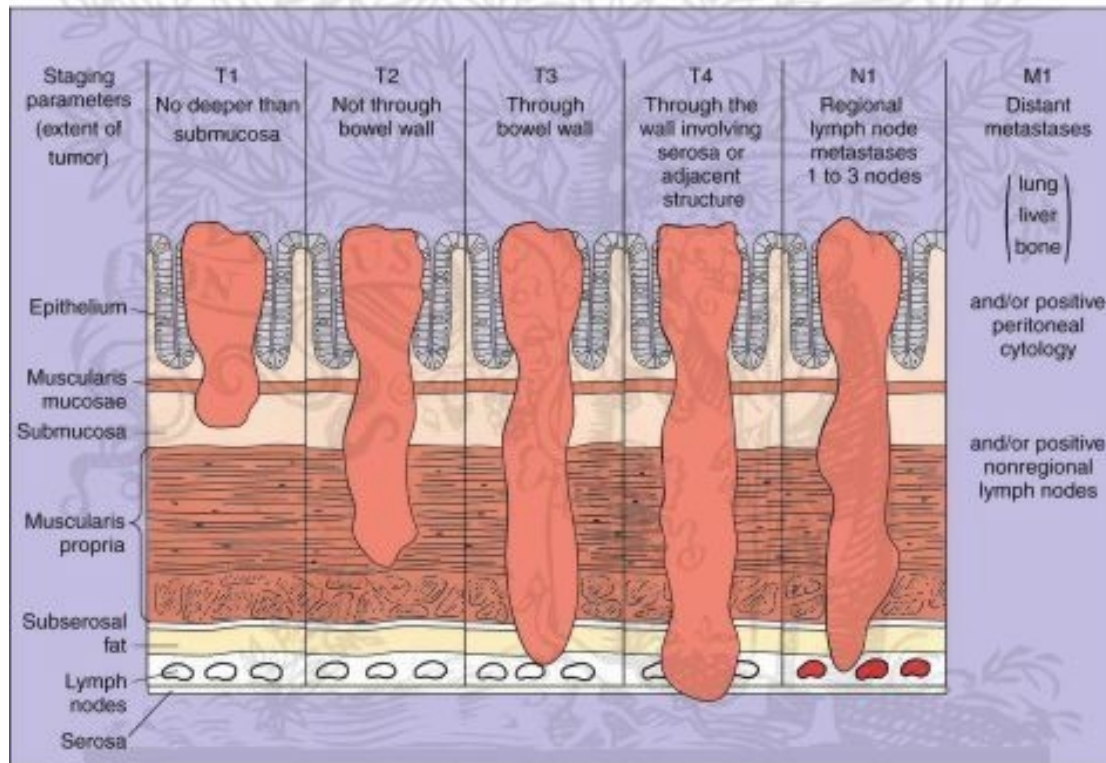
Clasificación Molecular: II

Poor-prognosis colon cancer is defined by a molecularly distinct subtype and develops from serrated precursor lesions

Felipe De Sousa E Melo^{1,7}, Xin Wang^{2,7}, Marnix Jansen³, Evelyn Fessler¹, Anne Trinh², Laura P M H de Rooij¹, Joan H de Jong¹, Onno J de Boer³, Ronald van Leersum¹, Maarten F Bijlsma¹, Hans Rodermond¹, Maartje van der Heijden^{1,4}, Carel J M van Noesel³, Jurriaan B Tuynman⁵, Evelien Dekker⁶, Florian Markowitz², Jan Paul Medema^{1,7} & Louis Vermeulen^{1,4,7}



ESTADIFICACIÓN: TNM

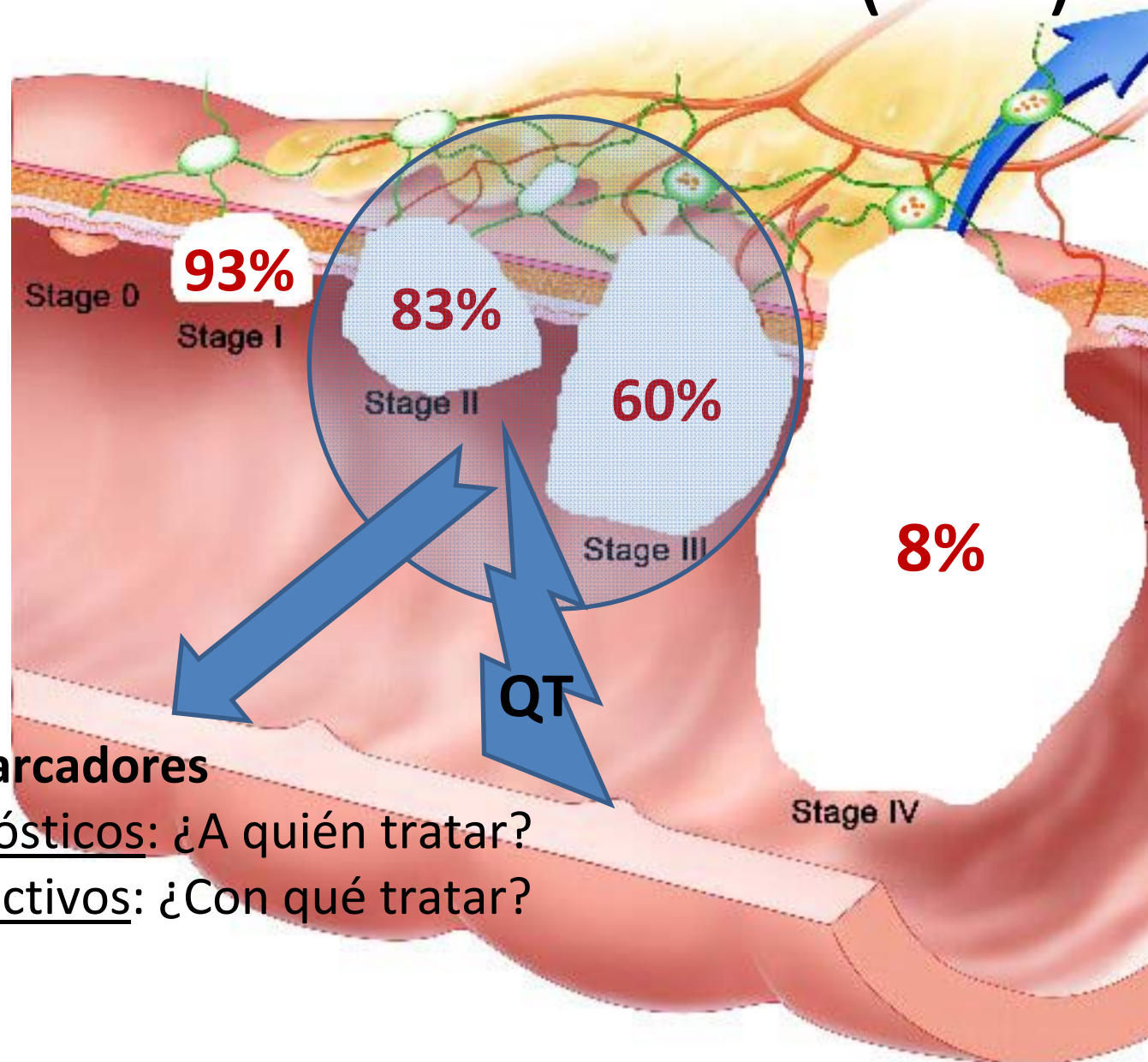


Tasas sobrevida a 5 años

- Stage I (T1, T2, N0): 97.1%
- Stage IIA (T3, N0): 87.5%
- Stage IIB (T4, N0): 71.5%
- Stage IIIA (T1, T2, N1): 87.7%
- Stage IIIB (T1, T2, N2): 75.0%
- Stage IIIB (T3, N1): 68.7%
- Stage IIIC (T3, N2): 47.3%
- Stage IIIC (T4, N1): 50.5%
- Stage IIIC (T4, N2): 27.1%

ELSEVIER

Cáncer colorrectal (CCR)



Biomarcadores

- Pronósticos: ¿A quién tratar?
- Predictivos: ¿Con qué tratar?

CEA: Antígeno carcinoembrionario

- Proteína de membrana específica de intestino
- Se determina en suero
- USOS:
 - PRE-OPERATORIO: pronóstico
 - POST-OPERATORIO: monitoreo metástasis
 - MONITOREO TRATAMIENTO METASTÁSICO

TRATAMIENTOS

- CIRUGÍA
- 5-FLUOROURACILO
- OXALIPLATINO
- IRINOTECAN
- RAYOS (RECTO)
- CETUXIMAB/PANITUMUMAB
- BEVACIZUMAB

Cetuximab

- Efectivo en 40% pacientes con KRAS salvaje
- No es efectivo en pacientes con **KRAS mutado**
- Mutaciones potencialmente predictivas:
 - BRAF
 - PI3KCA
 - PTEN
 - pAKT
- El número de copias de EGFR **NO es predictivo**