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Resección endoscópica submucosa

Evaluación invasión submucosa y tumor budding

Un desafío para el patólogo

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XXIII Congreso Chileno de Anatomía Patológica

Viña del Mar, Chile. 16-18 octubre 2019

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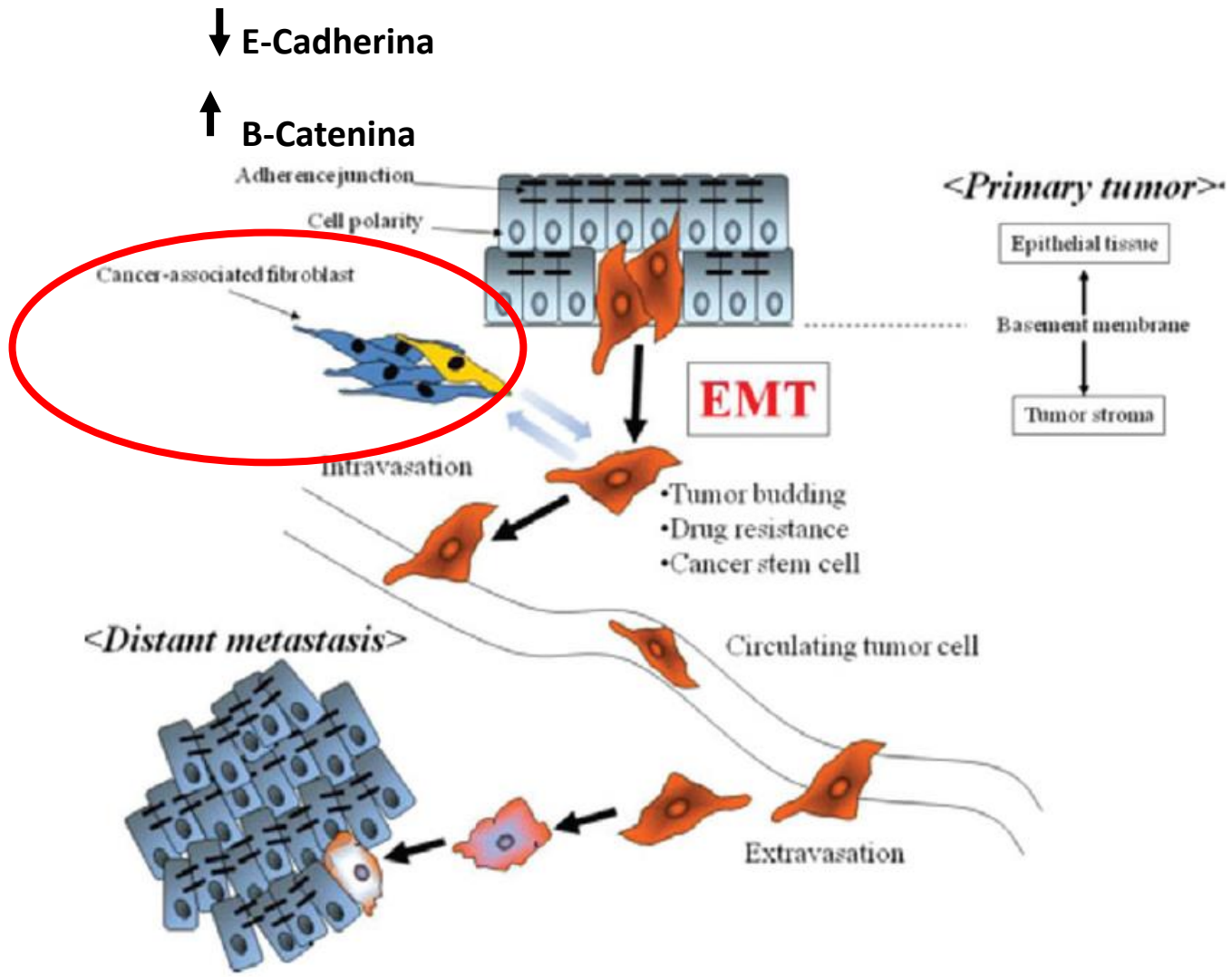
Transición epitelio-mesénquima (EMT)

Manifestaciones morfológicas:

- **Tumor Budding (TB)** células aisladas o en pequeños grupos ≤4 cels. en el frente invasivo del tumor
- **Poorly Differenciated Clusters (PDC)** agregados de ≥5 células neoplásicas en el estroma que no forman estructuras glandulares
- **Tumor-Stroma Ratio (TSR)** relación del % de tumor respecto al estroma en el frente invasivo del tumor

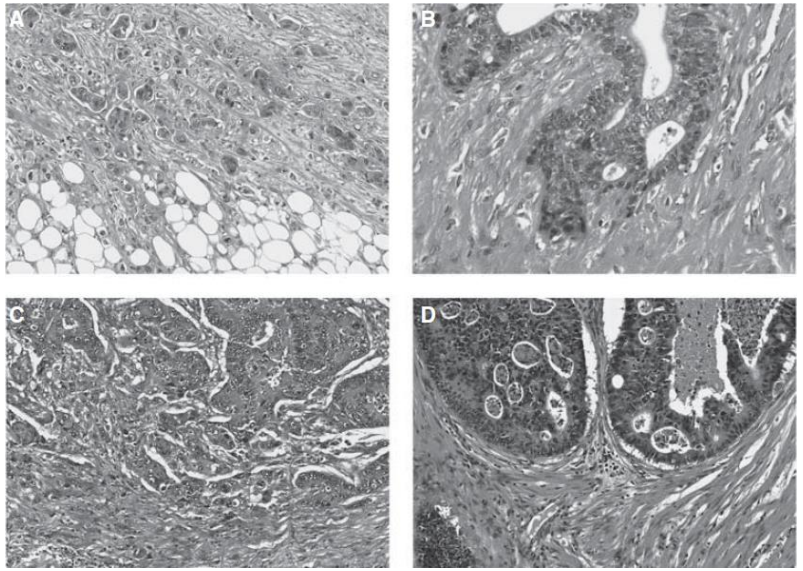
Factores pronósticos independientes en estadio II CCR

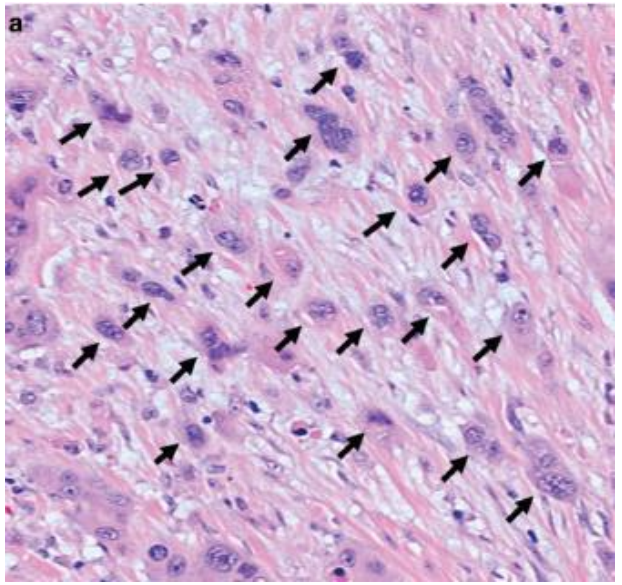


Tumor budding en CCR

- **Tumor Budding:** presencia de células aisladas o en pequeños grupos de ≤4 células en el margen infiltrante del tumor

- Tumor Budding se gradúa en:
  - Budding **bajo**; Bd1: 0-4 buds
  - Budding **intermedio**: Bd2: 5-9 buds
  - Budding **alto**; Bd3: ≥10 buds





Betge J, et al. Ann Surg Oncol 2012; 19:3706-3712
Ueno H, et al. Histopathology 2002; 40:127-32
Prall F. Histopathology 2007; 50:151-62
Modern Pathology (2017), 1–13
Lugli A. BrJournal Cancer 2012
Ueno et al. 2002

UNIVERSITÄT BERN

CLÍNIC BARCELONA Hospital Universitari

April 27–29, 2016
Kursaal Bern, www.kursaal-bern.ch

International Tumor Budding Consensus Conference ITBCC 2016

MODERN PATHOLOGY (2017), 1–13

Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016

Alessandro Lugli[1,22], Richard Kirsch[2,22], Yoichi Ajioka[3], Fred Bosman[4], Gieri Cathomas[5], Heather Dawson[1], Hala El Zimaity[6], Jean-François Fléjou[7], Tine Plato Hansen[8], Arndt Hartmann[9], Sanjay Kakar[10], Cord Langner[11], Iris Nagtegaal[12], Giacomo Puppa[13], Robert Riddell[2], Ari Ristimäki[14], Kieran Sheahan[15], Thomas Smyrk[16], Kenichi Sugihara[17], Benoît Terris[18], Hideki Ueno[19], Michael Vieth[20], Inti Zlobec[1] and Phil Quirke[21]

Modern Pathology (2017), 1–13

1 Define the field (specimen) area for the 20x objective lens of your microscope based on the eyepiece field number (FN) diameter

Objective magnification: 20		
Eyepiece FN Diameter (mm)	Specimen Area (mm2)	Normalization Factor
19	0.636	0.810
19	0.709	0.903
20	0.785	1.000
21	0.866	1.103
22	0.950	1.210
23	1.038	1.323
24	1.131	1.440
25	1.227	1.563
26	1.327	1.690

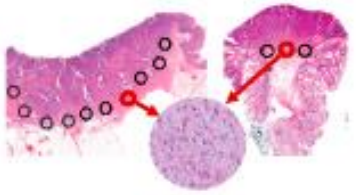
2 Select the H&E slide with greatest degree of budding at the invasive front

3 Scan 10 individual fields at medium power (10x objective) to identify the "hotspot" at the invasive front

For surgical resection specimens, scan 10 fields

For pT1 endoscopic resections (usually <10 fields available), scan all

4 Count tumor buds in the selected "hotspot" (20x objective)



Selected hotspot indicated in red

5 Divide the bud count by the normalization factor (figure 2) to determine the tumor bud count per 0.785mm²

Select the budding [Bd] category based on bud count and indicate the absolute count per 0.785mm² (see reporting example)

Tumor bud count per 0.785 mm² = Bud count (20x objective) / Normalization factor*

Bd1 (low):	0-4 buds	per 0.785 mm²
Bd2 (intermediate):	5-9 buds	
Bd3 (high):	≥10 buds	

Reporting example:
Tumor budding: Bd3 (high), count 14 (per 0.785 mm²)

Figure 4 Procedure proposed by the ITBCC 2016 for reporting tumor budding in colorectal cancer in daily diagnostic practice.

1

Define the field (specimen) area for the 20x objective lens of your microscope based on the eyepiece field number (FN) diameter

Objective magnification: 20		
Eyepiece FN Diameter (mm)	Specimen Area (mm2)	Normalization Factor
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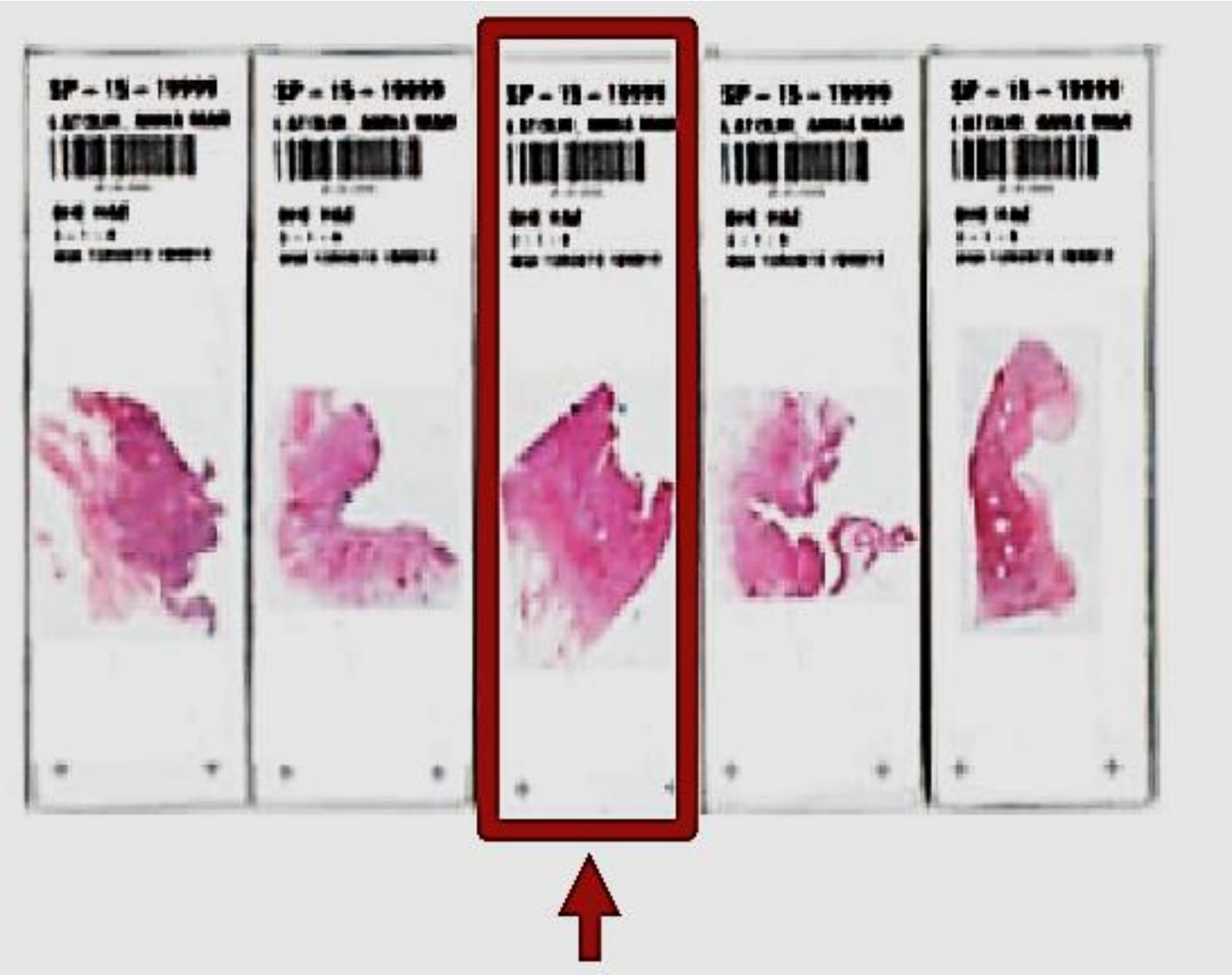
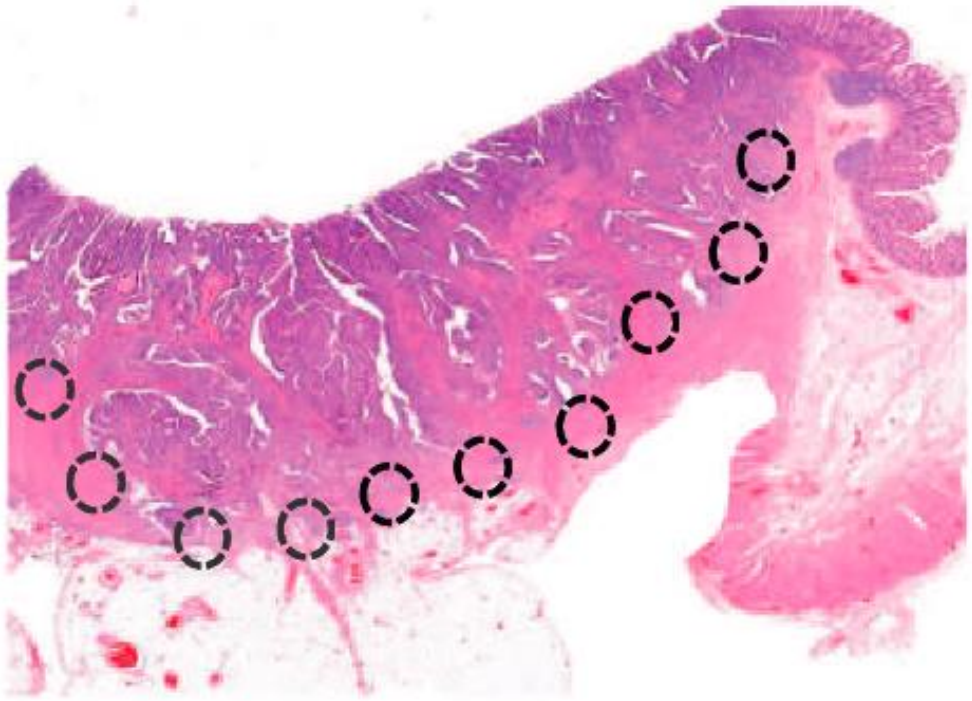
2

Select the H&E slide with greatest degree of budding at the invasive front



3

Scan 10 individual fields at medium power (10x objective) to identify the "hotspot" at the invasive front



For surgical resection specimens, scan 10 fields

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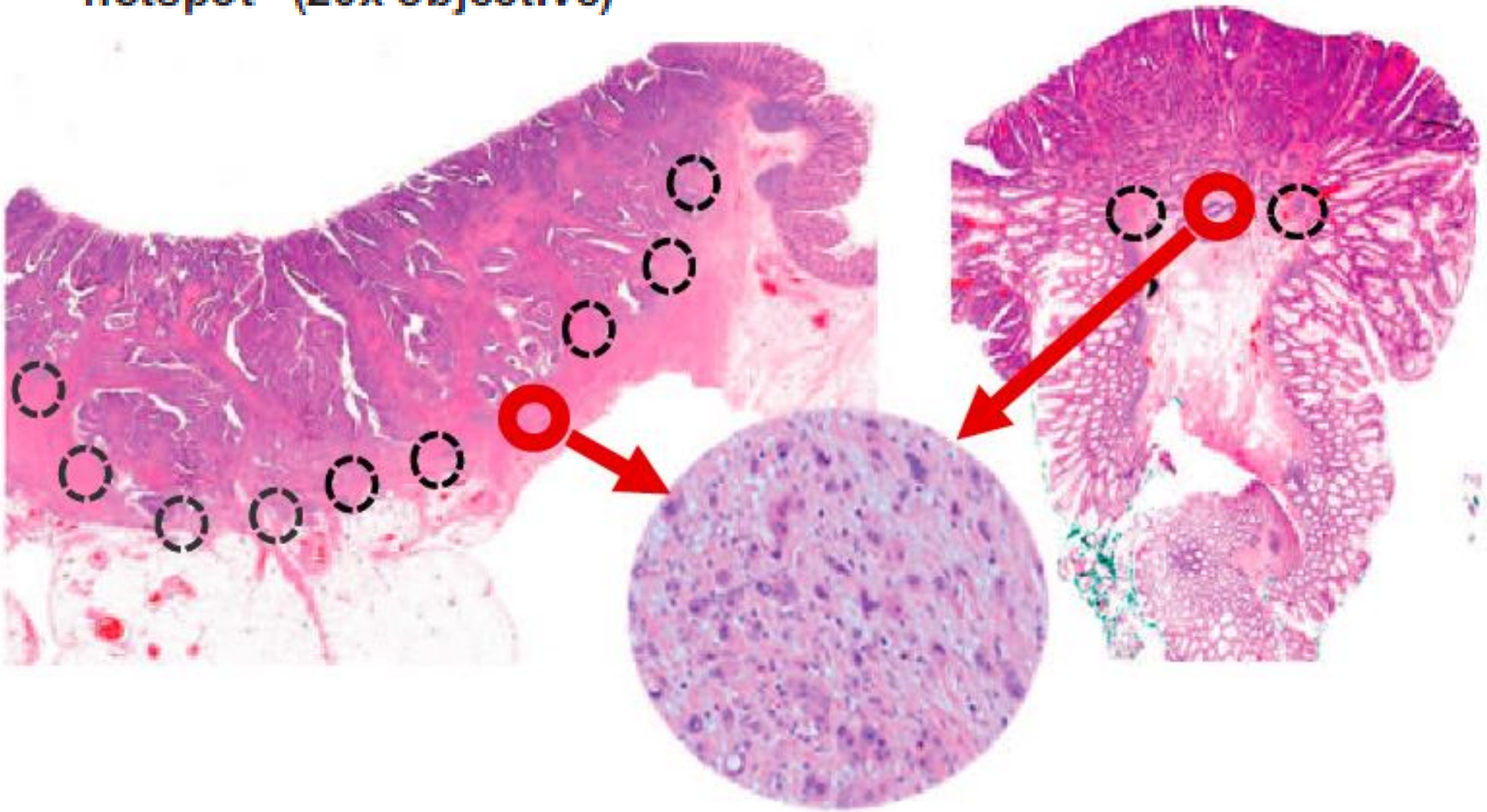
Count tumor buds in the selected "hotspot" (20x objective)



Selected hotspot indicated in red

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5 **Divide the bud count by the normalization factor (figure 2) to determine the tumor bud count per 0.785mm²**

Select the budding [Bd] category based on bud count and indicate the absolute count per 0.785mm² (see reporting example)

$$\text{Tumor bud count per 0.785 mm}^2 = \frac{\text{Bud count (20x objective)}}{\text{Normalization factor*}}$$

Bd1 (low):	0-4 buds	per 0.785 mm²
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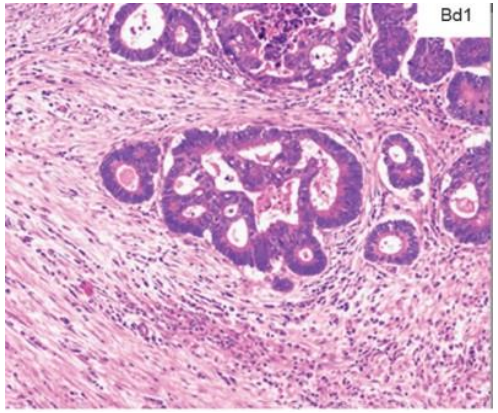
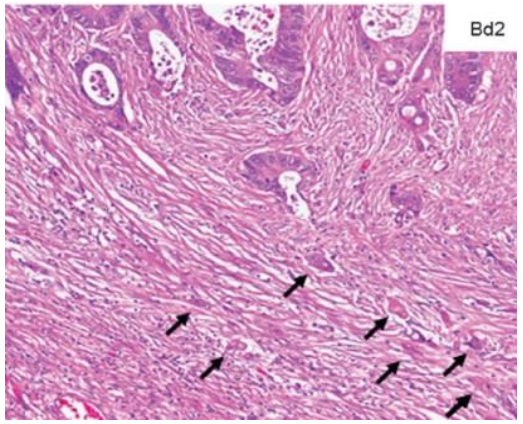
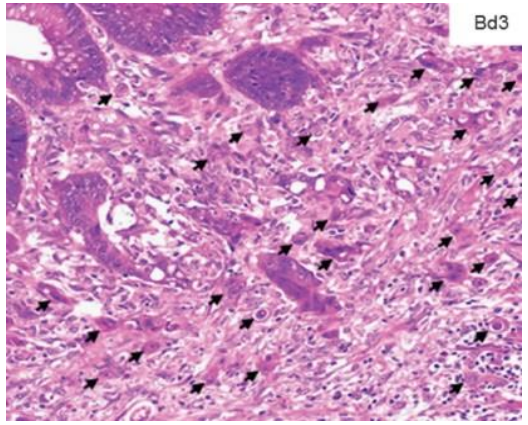
Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016

Alessandro Lugli[1,22], Richard Kirsch[2,22], Yoichi Ajioka[3], Fred Bosman[4], Gieri Cathomas[5], Heather Dawson[1], Hala El Zimaity[6], Jean-François Fléjou[7], Tine Plato Hansen[8], Arndt Hartmann[9], Sanjay Kakar[10], Cord Langner[11], Iris Nagtegaal[12], Giacomo Puppa[13], Robert Riddell[2], Ari Ristimäki[14], Kieran Sheahan[15], Thomas Smyrk[16], Kenichi Sugihara[17], Benoît Terris[18], Hideki Ueno[19], Michael Vieth[20], Inti Zlobec[1] and Phil Quirke[21]







- pT1
- CCR estadio II
- Biopsias rectales ITB

20x objective

Tumor bud count per 0.785 mm² = Bud count (20x objective) / Normalization factor*

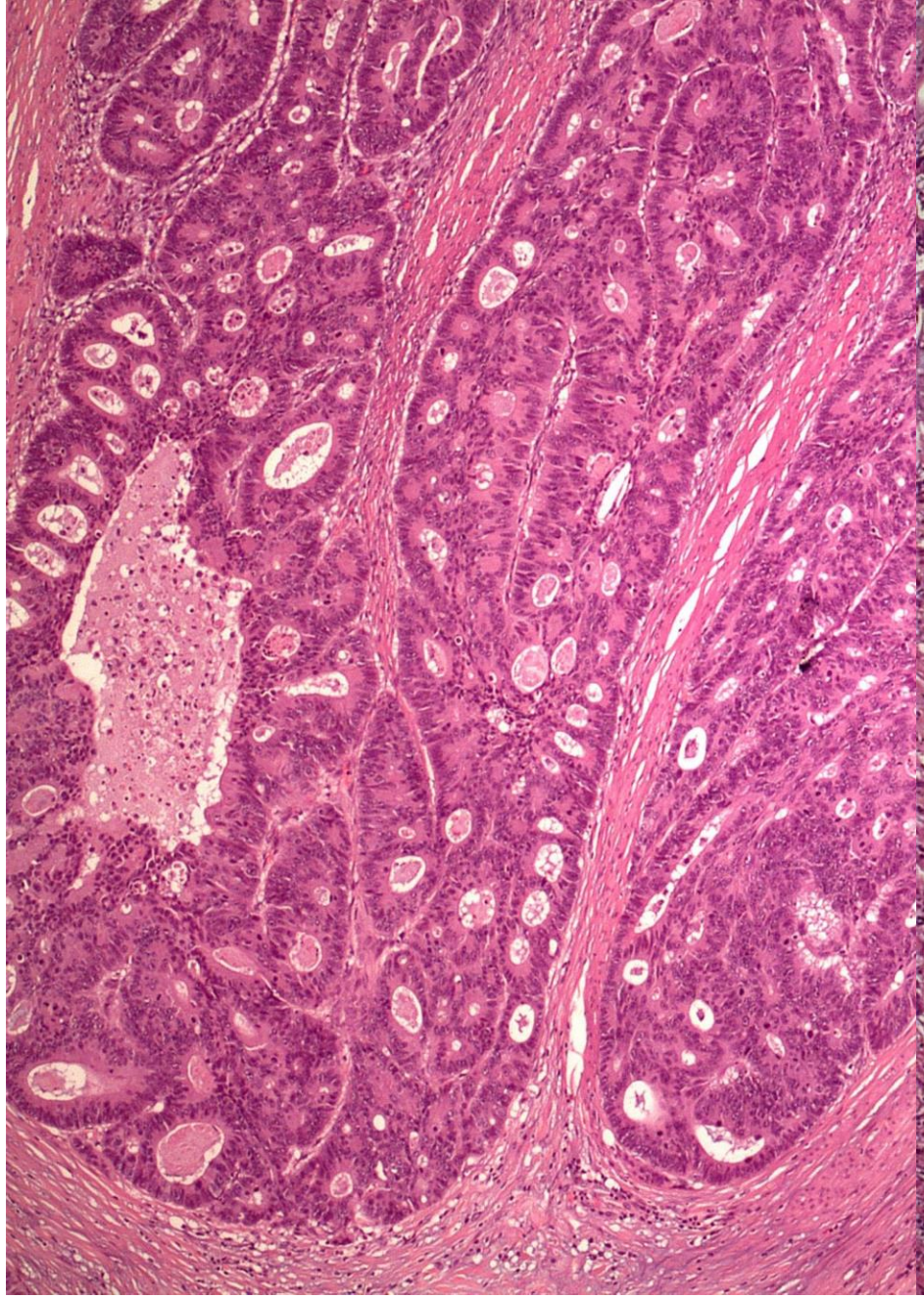
Bd1 (low):	0-4 buds	per 0.785 mm²
Bd2 (intermediate):	5-9 buds	
Bd3 (high):	≥10 buds	

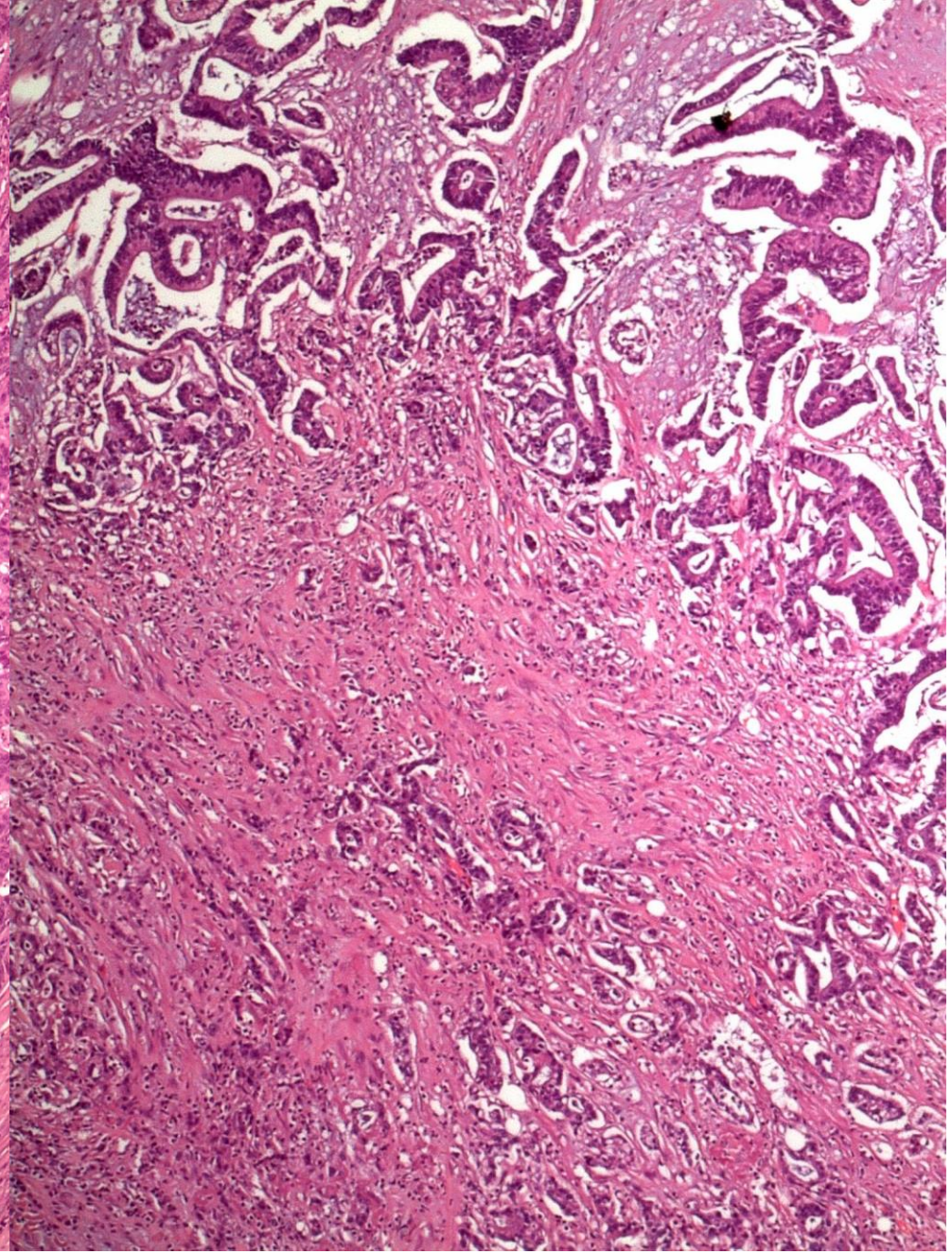
Reporting example:
Tumor budding: Bd3 (high), count 14 (per 0.785 mm²)

MODERN PATHOLOGY (2017), 1–13

	Statement	Grade	
		Recommendation	Evidence
1	Tumor budding is defined as a single tumor cell or a cell cluster consisting of four tumor cells or less	Strong Vote: 22/22 (100%)	High
2	Tumor budding is an independent predictor of lymph node metastasis in pT1 colorectal cancer	Strong Vote: 23/23 (100%)	High
3	Tumor budding is an independent predictor of survival in stage II colorectal cancer	Strong Vote: 23/23 (100%)	High
4	Tumor budding should be taken into account along with other clinicopathological features in a multidisciplinary setting	Strong Vote: 23/23 (100%)	High
5	Tumor budding is counted on H&E	Strong Vote: 19/22 (86%)	Moderate

6	Intratumoral budding exists in colorectal cancer and has been shown to be related to lymph node metastasis	Strong Vote: 22/22 (100%)	Low
7	Tumor budding is assessed in one hotspot (in a field measuring 0.785 mm^2) at the invasive front	Strong Vote: 22/22 (100%)	Moderate
8	For tumor budding assessment in colorectal cancer, the hotspot method is recommended	Strong Vote: 22/22 (100%)	Moderate
9	A three-tier system should be used along with the budding count in order to facilitate risk stratification in colorectal cancer	Strong Vote: 23/23 (100%)	Moderate
10	Tumor budding should be included in guidelines/ protocols for colorectal cancer reporting	Strong Vote: 23/23 (100%)	High
11	Tumor budding and tumor grade are not the same	Strong Vote: 23/23 (100%)	High





Bd 1 - Budding bajo

Bd3 – Budding alto

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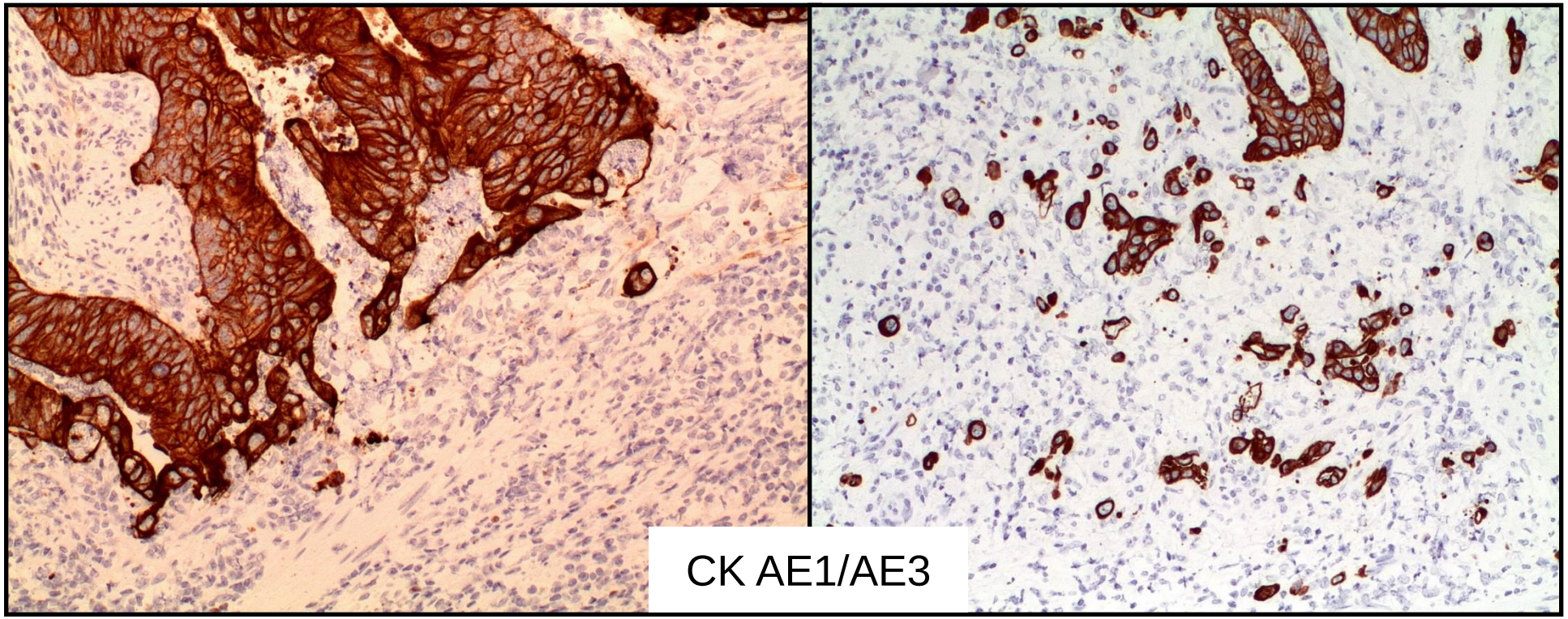
Tumor budding en CCR

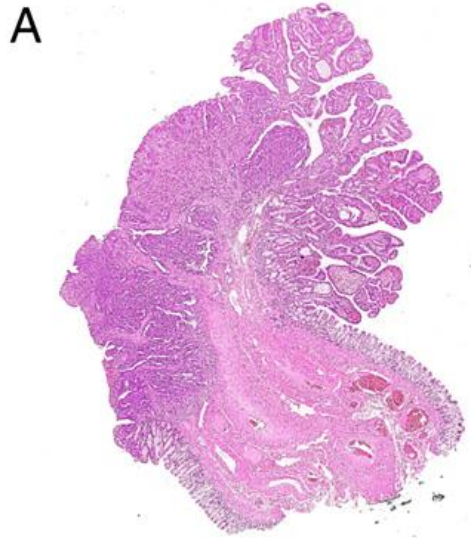


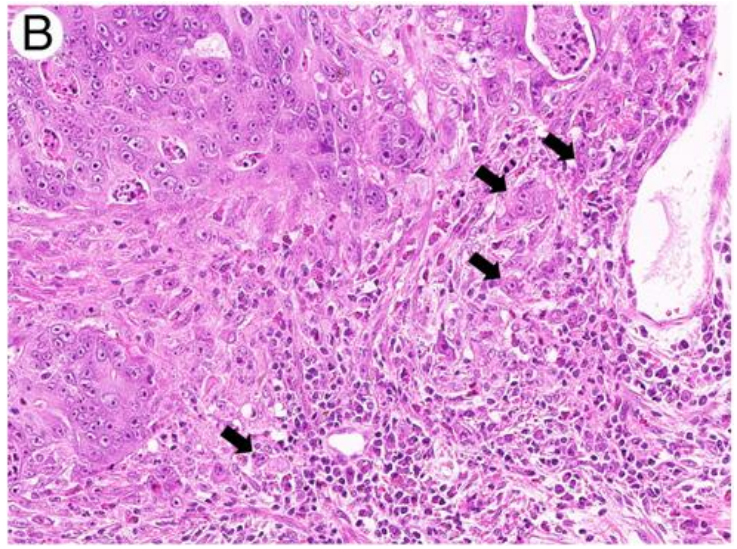
Bajo grado 4 buds (Bd1)

Alto grado ≥10 buds (Bd3)

Tumor budding as a risk factor for nodal metastasis in pT1 colorectal cancers: a meta-analysis☆,☆☆,★

- TB refleja el comportamiento biológico del tumor en el frente invasivo antes de infiltrar vasos linfáticos
- Refleja la agresividad tumoral, es predictor de metástasis ganglionar, se asocia a alto grado histológico, invasión vascular, supervivencia, progresión y muerte por enfermedad
- Parámetro histológico independiente. Se asocia a peor pronóstico. Asociado al riesgo de metástasis ganglionares en CCR precoz (estadios I-II)
- Es OBLIGATORIO informar el Tumor Budding en CCR pT1 resecados por endoscopia, para identificar pacientes que requieren tratamiento quirúrgico. Prevalencia de metastasis ganglionares 15% si TB alto



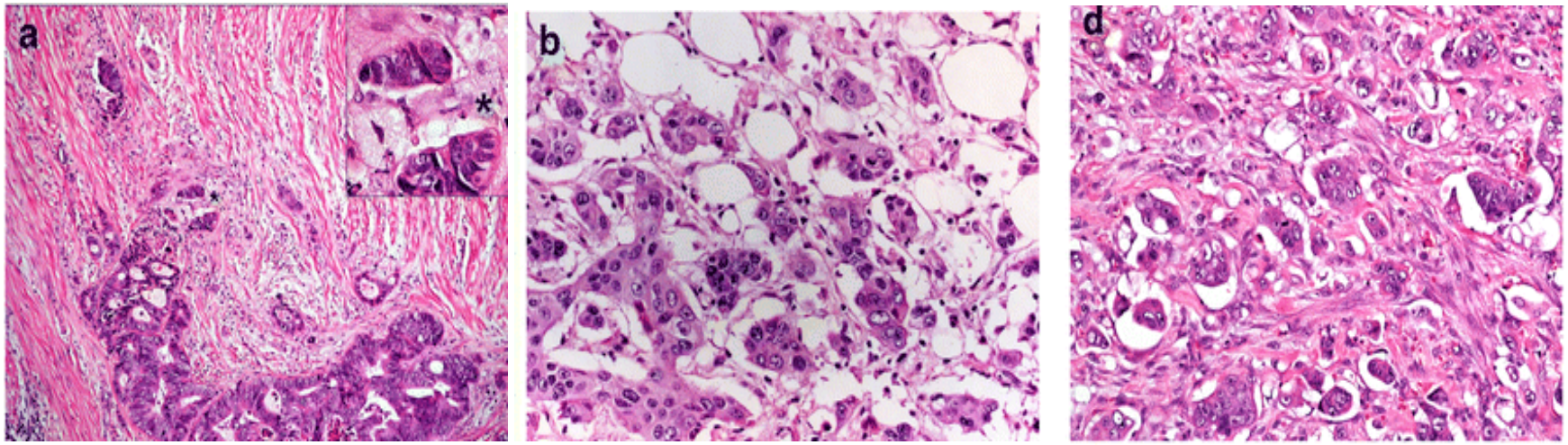


Capellesso R, et al. Human Pathology (2017) 65, 62

Poorly differentiated clusters (PDC) in colorectal cancer: what is and ought to be known

Reggiani Bonetti *et al. Diagnostic Pathology* (2016) 11:31

Grupos de células tumorales en el estroma compuestos por ≥5 células que NO formen una estructura glandular



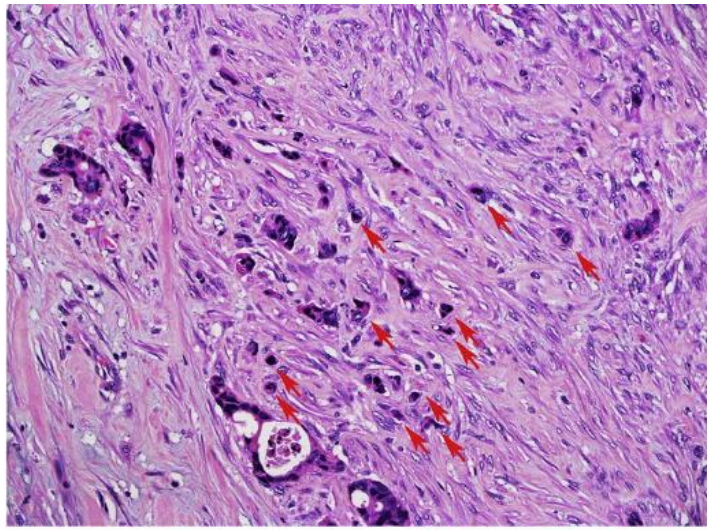
PDC G1: <5 clusters
PDC G2: 5-9 clusters
PDC G3: ≥10 clusters

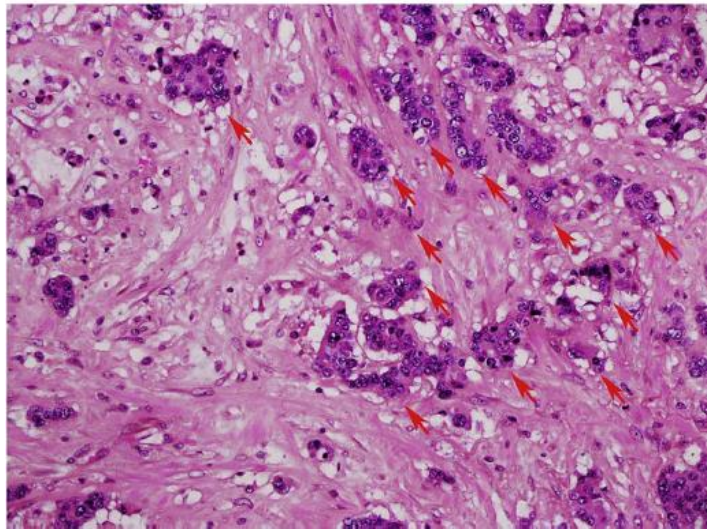
× 20 objective lens (1 mm)

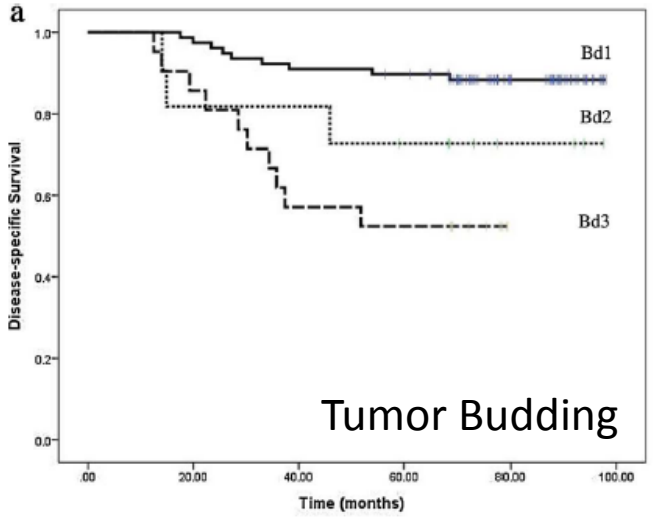
Tumor budding and poorly-differentiated cluster in prognostication in Stage II colon cancer

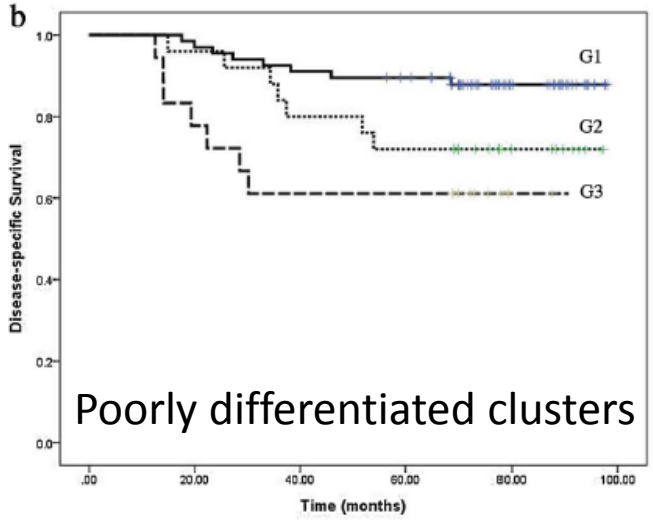
Victor Wai Kwan Lee*, Kui Fat Chan

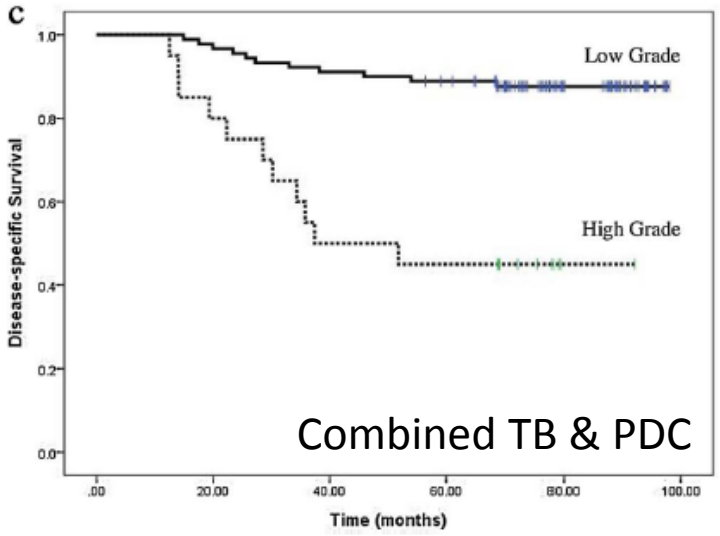
Pathology - Research and Practice 214 (2018) 402–407







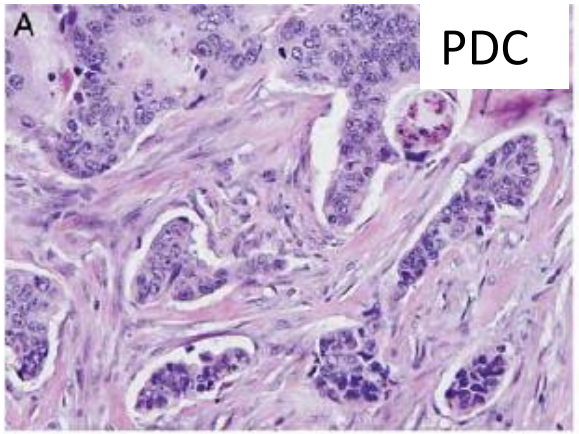


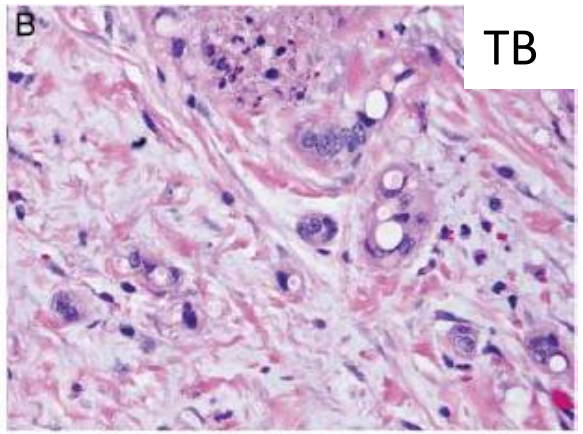


This is, to the best of our knowledge, the largest study which assessed both TB (according to the consensus statement in 2016) and PDC in Stage II colon adenocarcinoma. In summary, our study has demonstrated TB and PDC as independent prognostic factors in Stage II colon cancer patients, according to the recent consensus definition for tumor budding. Survival curves of Stage II patients could be further stratified by TB and PDC grades, which might help selecting high-risk patients with poorer prognosis for adjuvant chemotherapy. Majority of the cases showed concordance between TB and PDC grades. As recent studies had suggested pathogenetic overlap between TB and PDC, combining TB and PDC counts into a single grading system worth further investigation. A preliminary method for combining TB/PDC grades (high-grade: Bd3 + G2, Bd2 + G3 and Bd3 + G3; low-grade: other combinations) was found to have strong correlation with survival.

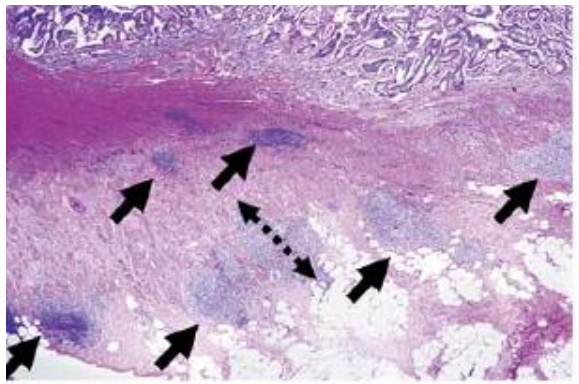
Poorly Differentiated Clusters Predict Colon Cancer Recurrence

An In-Depth Comparative Analysis of Invasive-Front Prognostic Markers

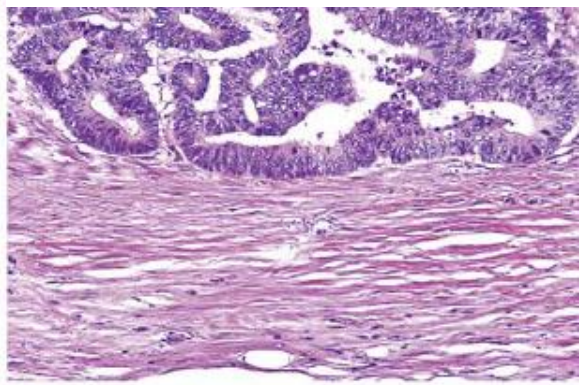


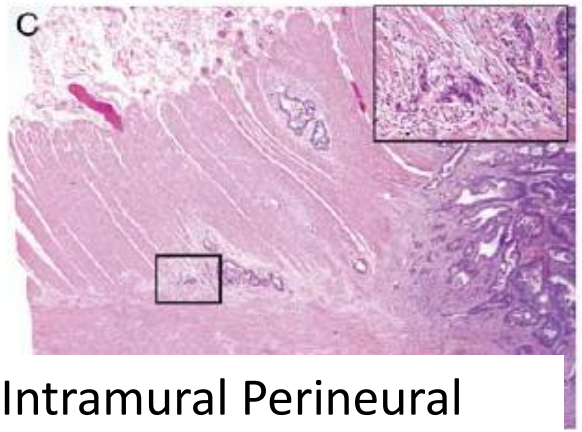


Crohn-like lymph reac

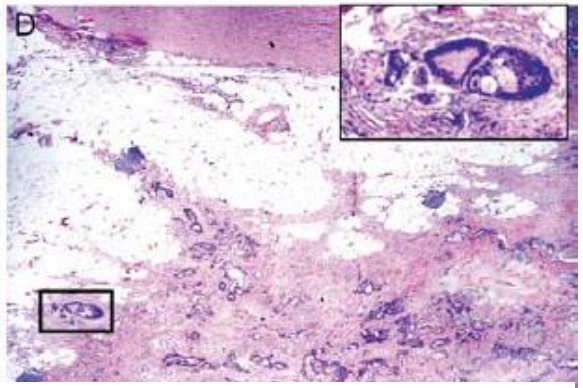


Mature Desmopl React

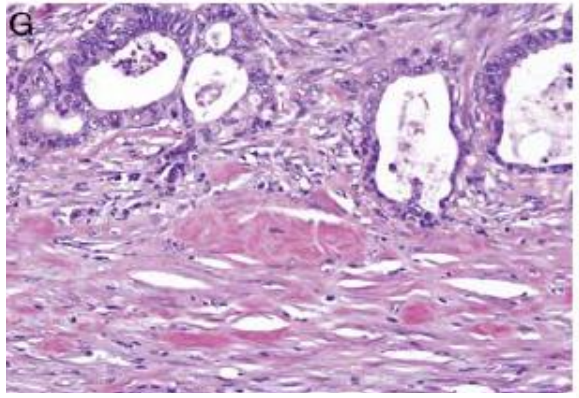




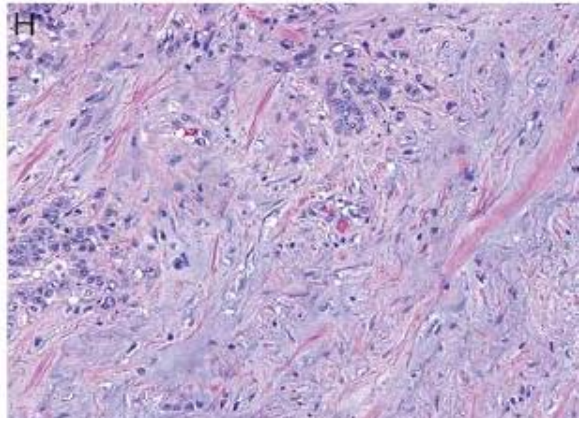
Intramural Perineural spreading



Extramural Perineural spreading



Intermed Desmopl React

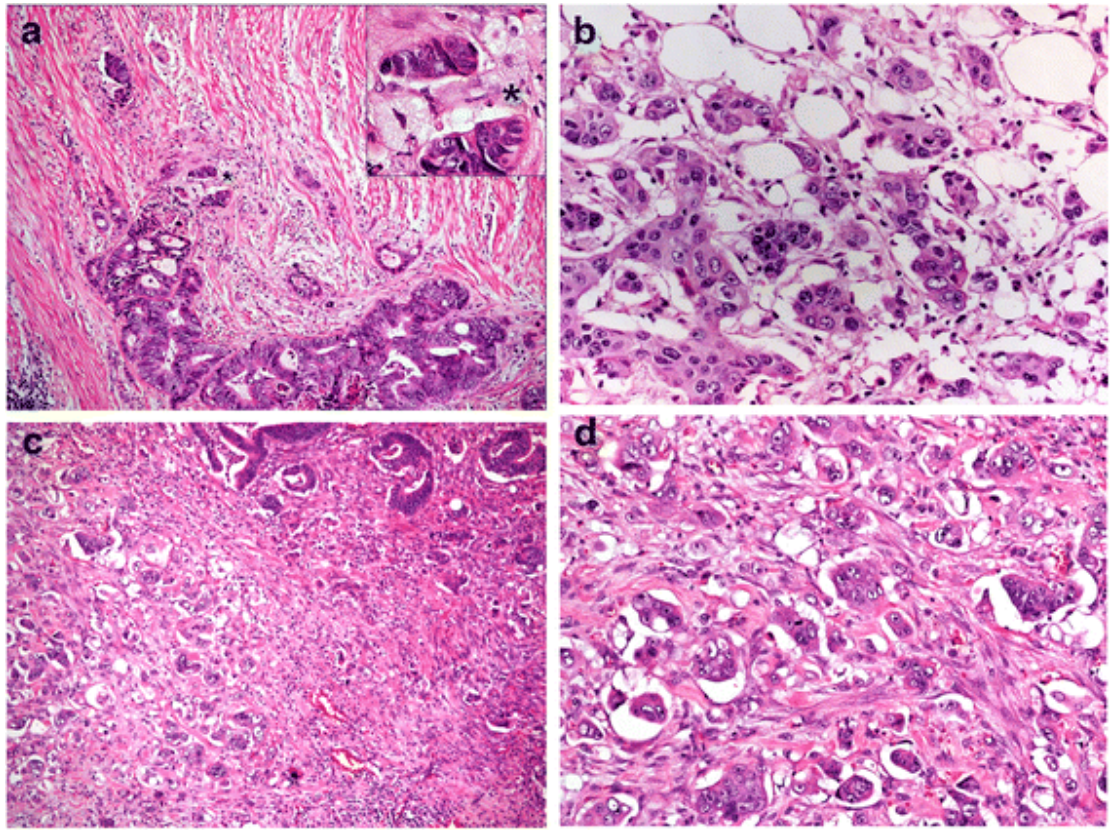


Inmature Desmopl React

Am J Surg Pathol • Volume 42, Number 6, June 2018

Poorly Differentiated Clusters Predict Colon Cancer Recurrence

An In-Depth Comparative Analysis of Invasive-Front Prognostic Markers



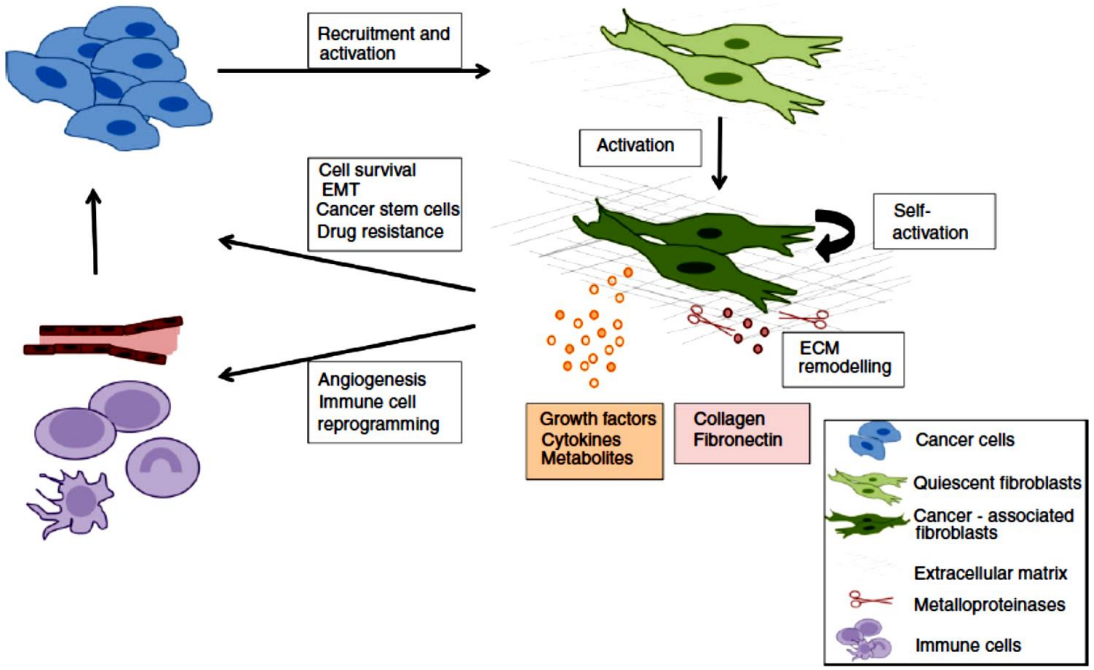
All invasive-front markers examined were associated with tumor recurrence and had better prognostic accuracy for recurrence than WHO grade (which is a broad measure

among pathologists. Our findings indicate that PDCs are clinically more useful in predicting recurrence than the other invasive-front histologic markers. In contrast, WHO grade performed poorly as a prognostic marker and had poor interobserver agreement between pathologists. The results of our study suggest that using the grade of PDCs at the invasive front instead of WHO grade of the entire tumor can help identify patients with a high risk of recurrence more accurately. Furthermore, the excellent in-

The tumour–stroma ratio in colon cancer: the biological role and its prognostic impact

GW van Pelt, et al. Histopathology 2018

Tumour compartment		Tumour microenvironment	
Tumour cell extension and invasion	Tumour cell characteristics	Tumour stroma characteristics	Immune response
TNM stage	Morphology	Tumour - stroma ratio	Immunoscore
	Gene expression		
	MSI status		
	Mutation status		
	Cell of origin		



JMIR Res Protoc. 2019 Jun; 8(6): e13464.
Published online 2019 Jun 14. doi: 10.2196/13464

PMCID: PMC6595942
PMID: 31199317

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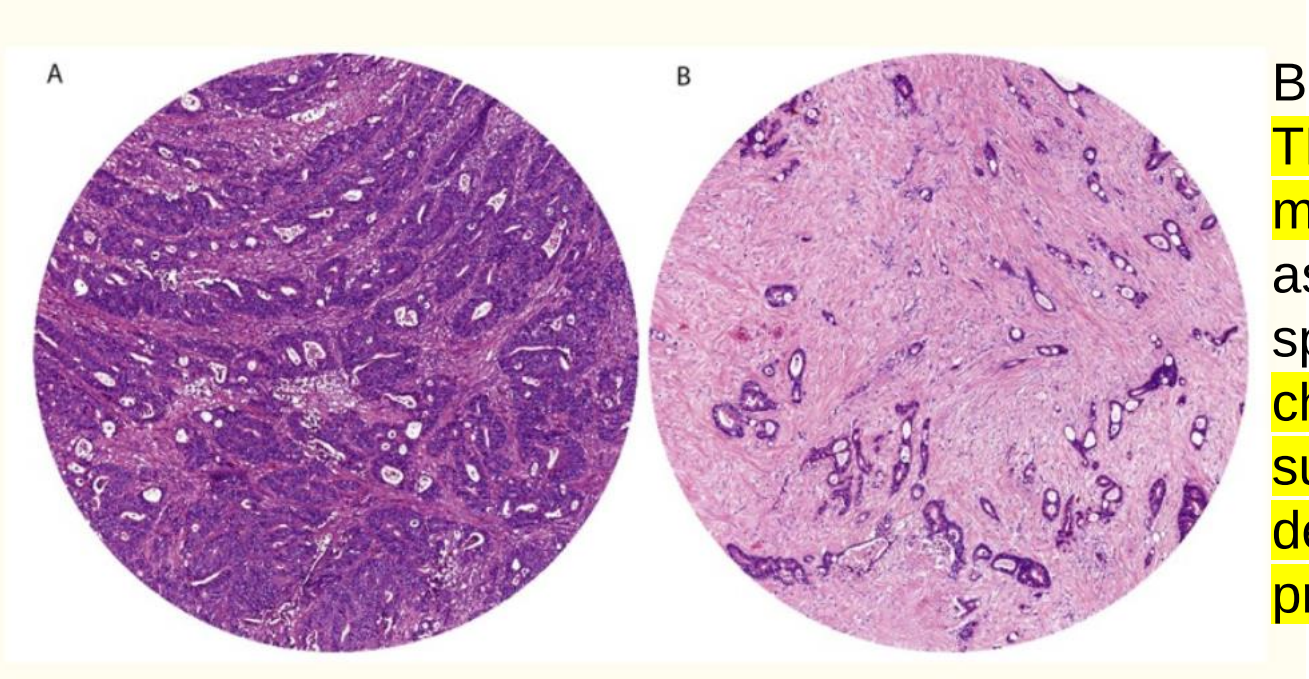
Uniform Noting for International Application of the Tumor-Stroma Ratio as an Easy Diagnostic Tool: Protocol for a Multicenter Prospective Cohort Study

Monitoring Editor: Gunther Eysenbach

Reviewed by Muhammad Shahzad Aslam and Prakash Muddegowda

Marloes Smit, MD,[1] Gabi van Pelt, BSc,[1] Annet Roodvoets, MSc,[2] Elma Meershoek-Klein Kranenbarg, MSc,[2] Hein Putter, MSc, PhD,[3] Rob Tollenaar, MD, PhD,[1] J Han van Krieken, MD, PhD,[4] and Wilma Mesker, PhD[1]



Beside tumor characteristics, as described in the TNM classification, to determine the p-stage, the microenvironment of the tumor is an important factor as well. The microenvironment of a tumor is a wide spread of different cell types. More tumor characteristics in the microenvironment are studied, such as tumor budding, Immunoscore, and desmoplastic reaction. They are all independent prognostic biomarkers for survival.

UNITED

http://watchstroma.com/the-stroma-research/

Home UNITED E-learning Prospective study

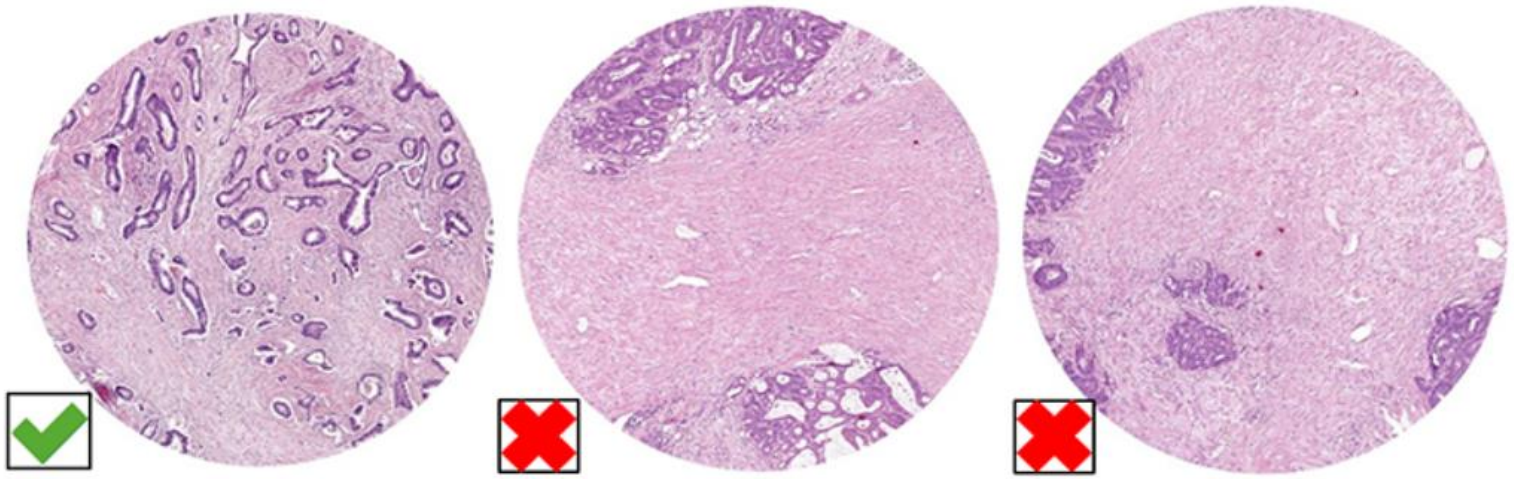
Exceptions

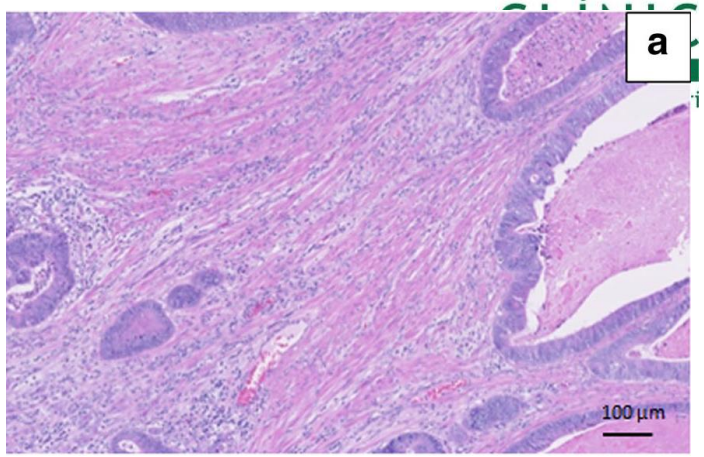
When determining the TSR a number of aspects must be taken into account:

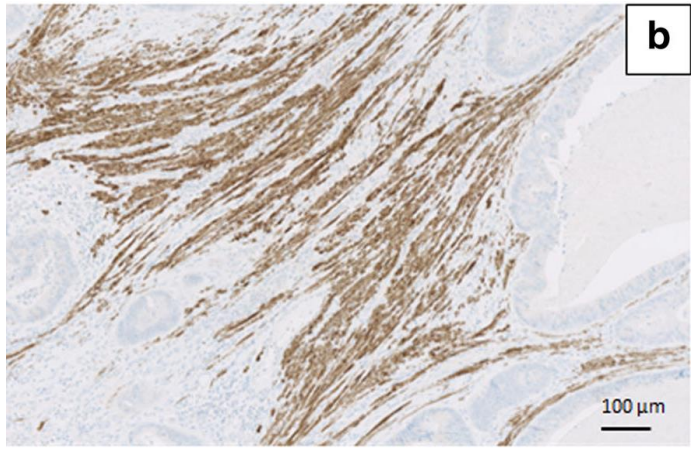
Mucinous tumours can be difficult. An area containing mucus may be used. However, mucus should be excluded when determining the tumour-stroma ratio.

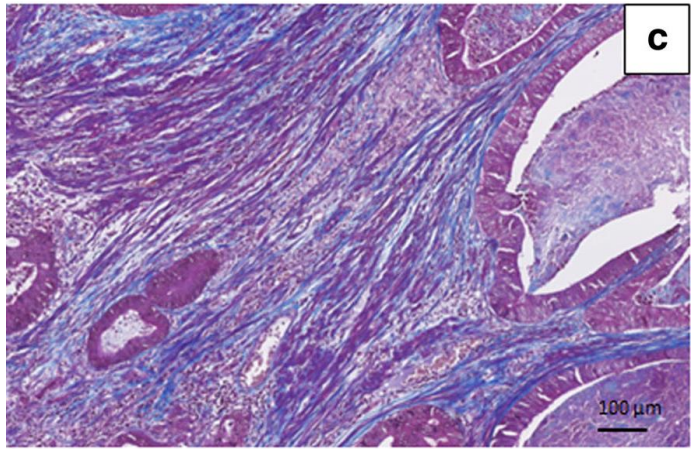
Score an area with as little necrosis or muscle tissue as possible, or preferably even none at all.

Tumour cells should be present on all sides of the view.





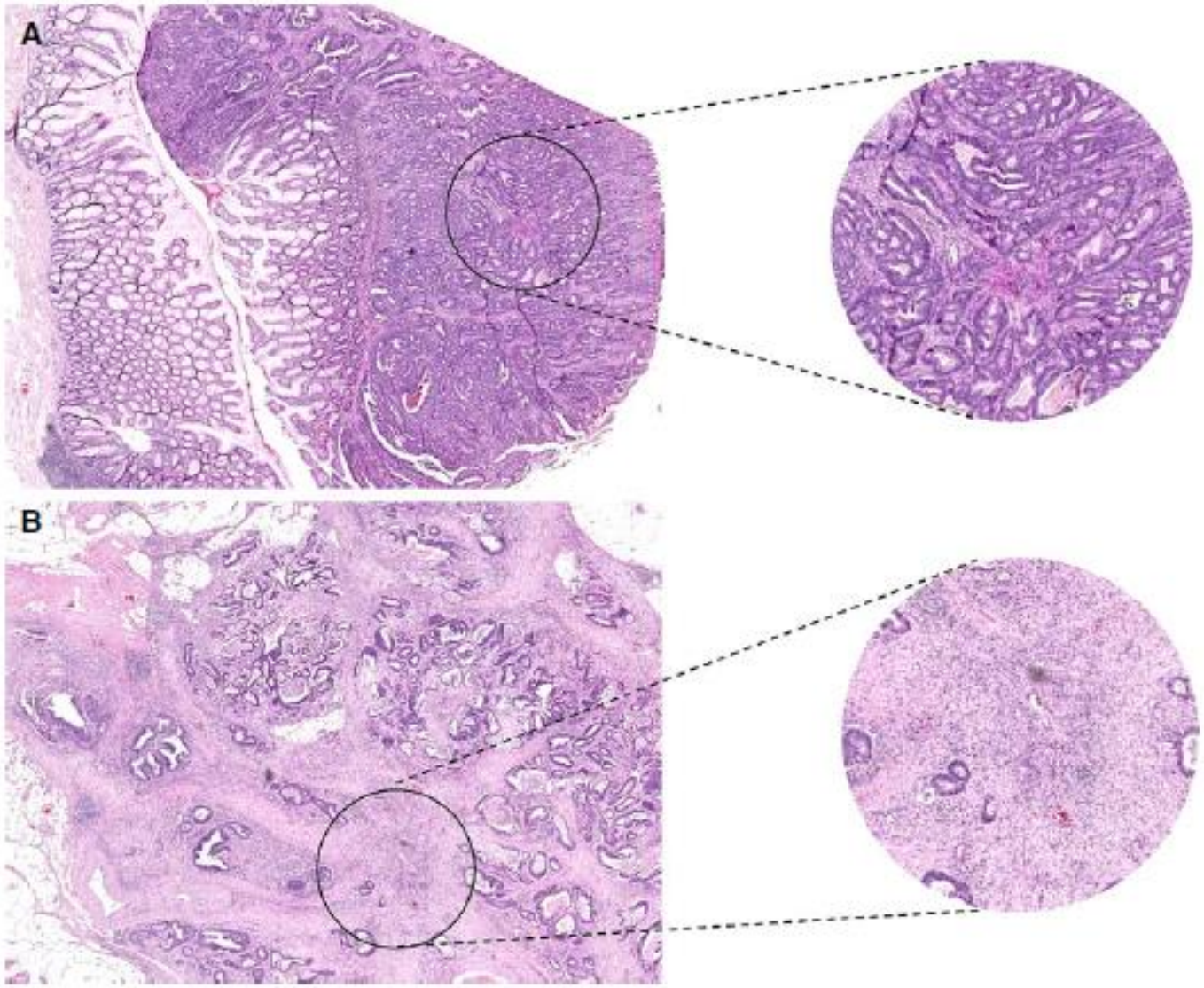




Eriksen *et al. Diagnostic Pathology* (2018) 13:20

The tumour–stroma ratio in colon cancer: the biological role and its prognostic impact

GW van Pelt, et al. Histopathology 2018



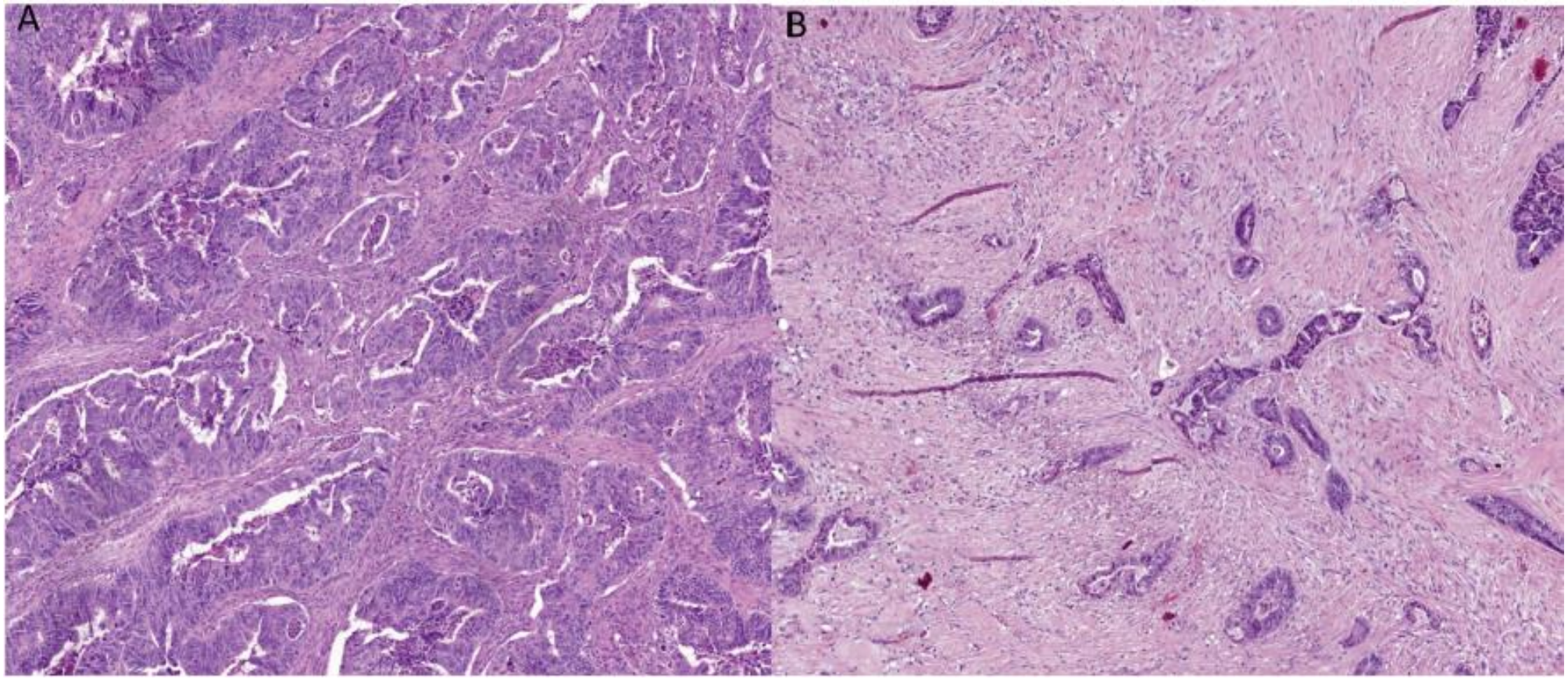
Given the current understanding of the tumour stroma, colon cancer should not be categorized based solely on tumour cell characteristics, but also according to the tumour microenvironment. The TSR has been proved to have prognostic relevance in colon cancer patients. Combining this knowledge, it would suggest that the TSR should be added to the current TNM classification. Owing to its simplicity, reliability and low costs, the TSR score can be implemented with little effort in current routine diagnostics of the pathologist.

Tumor-stroma ratio

- La relación tumor-estroma (TSR) se basa en la cantidad de estroma dentro del tumor primario
- Predice la supervivencia libre de enfermedad y global de pacientes con carcinoma de colon en estadios II y III
- El TSR, combinado con los datos histológicos de rutina, puede mejorar el tratamiento personalizado
- El estroma tumoral es un biomarcador
- Se puede determinar fácilmente en la rutina diaria en 1-2 minutos, en secciones teñidas con hematoxilina y eosina
- No hay costos adicionales
- Divide los tumores en dos categorías: con estroma bajo o alto (bajo % de estroma < 50% y alto % de estroma > 50%)
- Los pacientes con un CCR con estroma alto tienen peor supervivencia global y libre de enfermedad

http://watchstroma.com/the-stroma-research/

Tumor-Stroma Ratio (TSR)



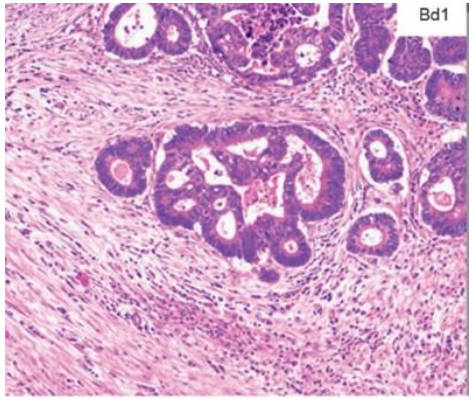
Bajo – 20%

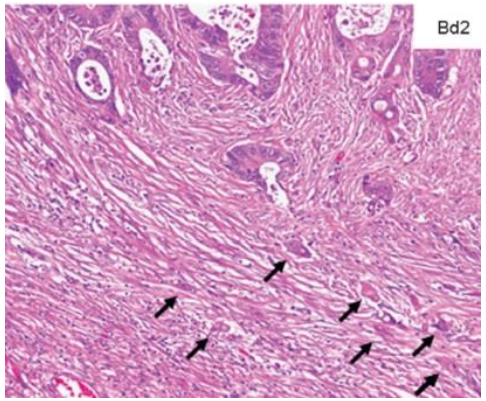
Alto – 90%

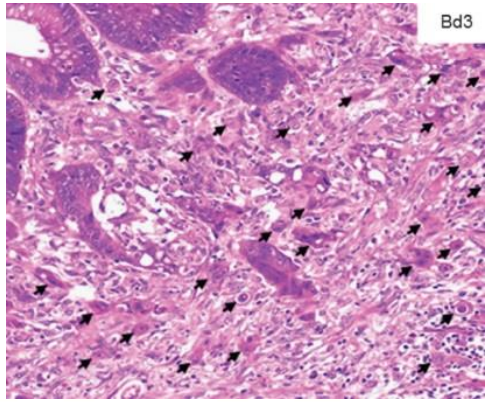
Molecular profiling of colorectal tumors stratified by the histological tumor-stroma ratio - Increased expression of galectin-1 in tumors with high stromal content.

Tessa P. Sandberg1,2, Jan Oosting1, Gabi W. van Pelt2, Wilma E. Mesker2, Rob A. E. M. Tollenaar2 and Hans Morreau1 Oncotarget, 2018, Vol. 9, (No. 59), pp: 31502-31515

Tumor Budding - Poorly Differentiated Clusters - Tumor Stroma Ratio



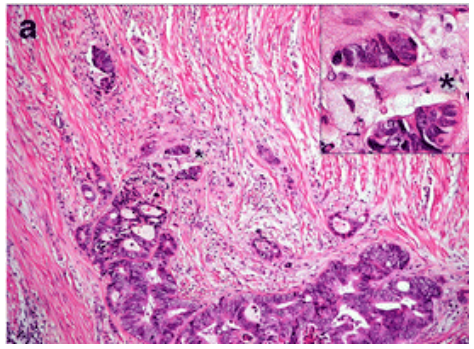


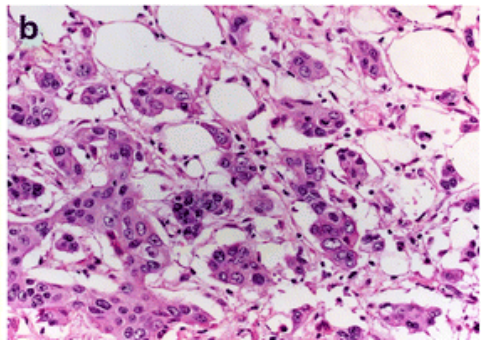


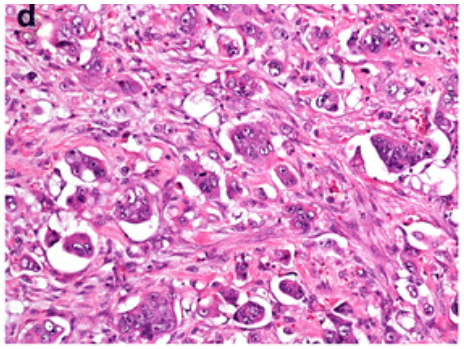
Bd1 (low): 0-4 buds
Bd2 (intermediate): 5-9 buds
Bd3 (high): ≥10 buds

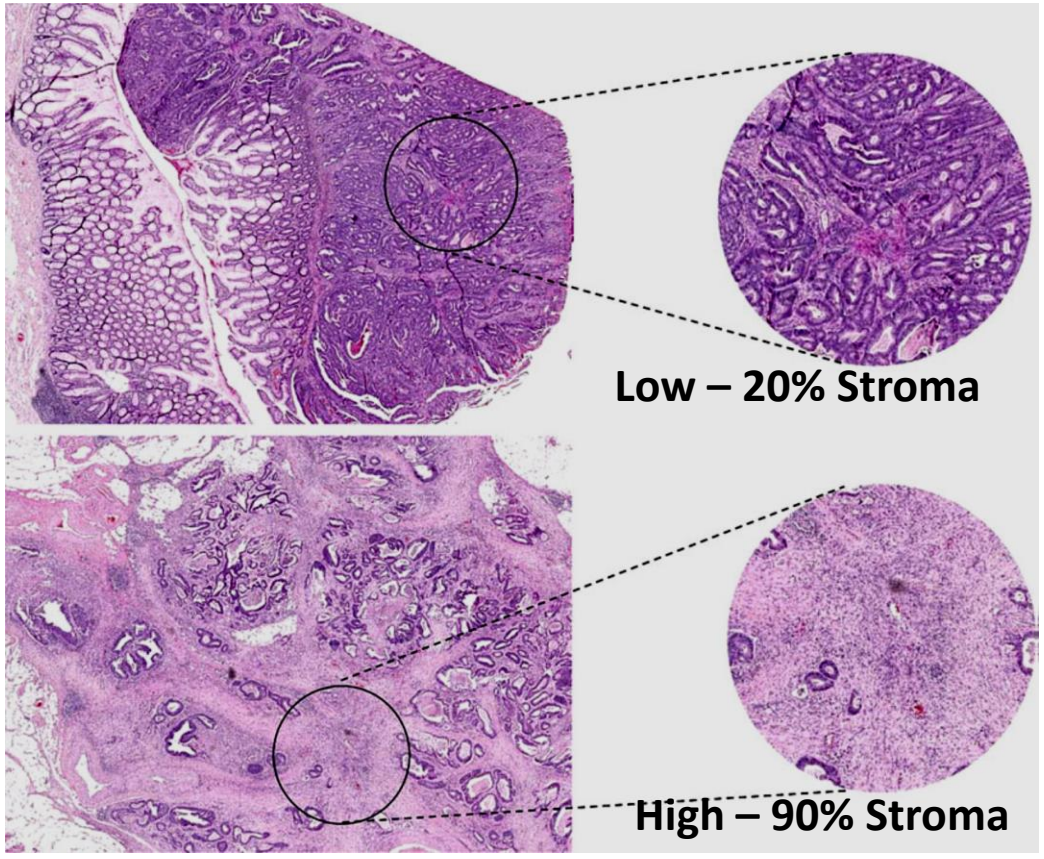
per 0.785 mm²

Bud count (20x objective) / Normalization factor*









PDC G1: <5 clusters
PDC G2: 5-9 clusters
PDC G3: ≥10 clusters
× 20 objective lens (1 mm)

Lugli A, et al. Modern Pathology 2017
van Pelt GW. Histopathology 2018
Reggiani Bonetti L, et al. DiagnPathol 2016

Adenocarcinoma infiltrante sobre polipectomía (pT1)

- Diagnóstico frecuente en pacientes asintomáticos, colonoscopia por test de sangre oculta en heces positivo en programas de cribado de carcinoma colorectal

- Tratamiento tras polipectomía endoscópica:
  - **Seguimiento** si el riesgo de enfermedad residual es bajo
  - **Resección quirúrgica** en pacientes con riesgo de recidiva o resección incompleta del tumor

- El nivel de **riesgo de metastasis ganglionares** es difícil de calcular → factores histológicos de alto riesgo en el pólipo

RECOMENDACIONES SOBRE LOS INFORMES ANATOMOPATOLÓGICOS DE LOS PÓLIPOS DE COLON EXTIRPADOS MEDIANTE POLIPECTOMÍA ENDOSCÓPICA

DOCUMENTO DE POSICIONAMIENTO

SOCIEDAD CATALANA DE ANATOMÍA PATOLÓGIC

Y

SOCIEDAD CATALANA DE DIGESTOLOGÍA

PLA ESTRATÈGIC DE NEOPLÀSIA COLORECTAL

Societat Catalana d'Anatomia Patològica i Societat Catalana de Digestologia

Informes Anatomopatològics dels Pòlips de Còlon Extirpats Mitjançant Polipectomia Endoscòpica

Grup de Treball

Míriam Cuatrecasas Freixas[1], Mar Iglesias Coma[2], Eva Musulén Palet[3], Maria Pellisé Urquiza[2] i Montserrat Andreu Garcia[4]

(1) Servei d'Anatomia Patològica, Hospital Universitari Clínic, Barcelona.
(2) Servei de Gastroenterologia, Hospital Universitari Clínic, Barcelona.
(3) Servei d'Anatomia Patològica, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona.
(4) Servei de Digestologia, Hospital del Mar-Parc de Salut Mar, Barcelona.

SOCIETAT CATALANA D'ANATOMIA PATOLÒGICA

Societat Catalana de Digestologia A·C·M·S·C·B

L'Acadèmia

CLÍNIC
BARCELONA
Hospital Universitari

Libro Blanco de la Anatomía Patológica en España 2017

Diagnóstico estructurado de los pólipos de colon resecados mediante polipectomía endoscópica y actitud terapéutica

Documento de recomendaciones

Josep Antoni Bombí[1], Miriam Cuatrecasas[1], Mar Iglesias[2], Stefania Landolfi[3], Eva Musulén[4], María Eugenia Semidey[3]. Justyna Szafranska[5]. Grupos de trabajo de las Sociedades Catalanas de Anatomía Patológica, Gastroenterología y Cirugía Gastrointestinal. (Por orden alfabético)

1 *Hospital Clínic. Universitat de Barcelona. Barcelona*
2 *Hospital del Mar. Universitat Autònoma de Barcelona. Barcelona.*
3 *Hospital Universitari Vall d'Hebron. Universitat Autònoma de Barcelona. Barcelona.*
4 *Hospital Universitari General de Catalunya. Sant Cugat del Vallès. Universitat Internacional de Catalunya. Barcelona.*
5 *Hospital de Sant Pau. Universitat Autònoma de Barcelona. Barcelona.*

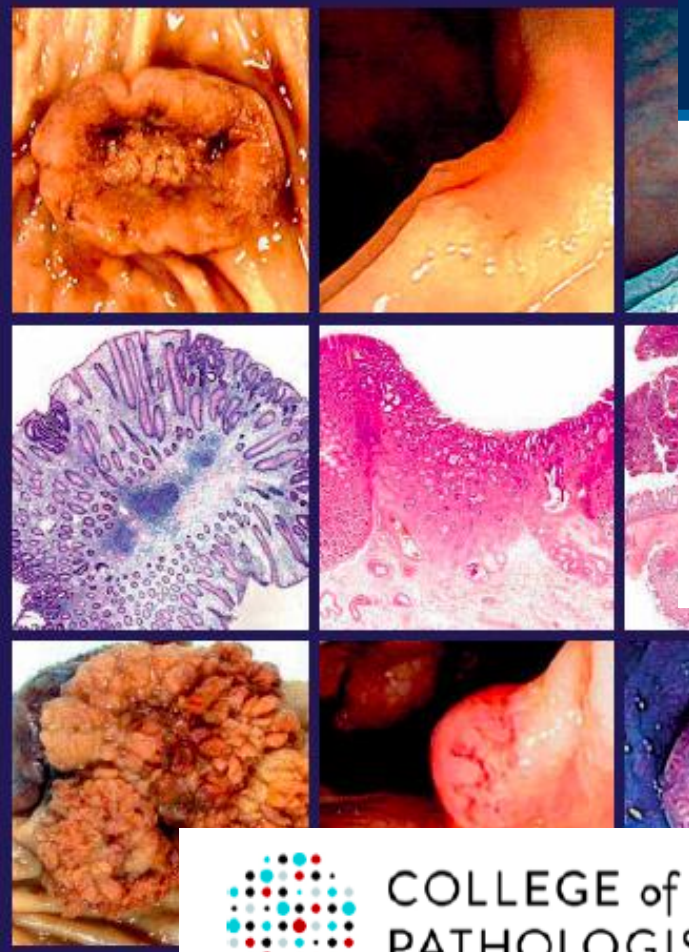
AJCC
American Joint Committee on Cancer

AJCC Cancer Staging Manual

Eighth Edition

Springer

Segnan N, Patnick J, von Kars



European

cancer scr

NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Colon Cancer

NCCN Evidence Blocks™

Version 1.2019 — April 25, 2019

NCCN.org

COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Specimens From Patients With Primary Carcinoma of the Colon and Rectum

Version: Colon Rectum 4.0.0.1 **Protocol Posting Date:** June 2017

Includes pTNM requirements from the 8th Edition, AJCC Staging Manual

PRINCIPLES OF PATHOLOGIC REVIEW

Endoscopically Removed Malignant Polyps

- A malignant polyp is defined as one with cancer invading through the muscularis mucosa and into the submucosa (pT1). pTis is not considered a "malignant polyp."
- Favorable histologic features: grade 1 or 2, no angiolymphatic invasion, and negative margin of resection. There is no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as: 1) tumor <1 mm from the transected margin; 2) tumor <2 mm from the transected margin; and 3) tumor cells present within the diathermy of the transected margin.[1-4]
- Unfavorable histologic features: grade 3 or 4, angiolymphatic invasion, or a "positive margin." See the positive margin definition above. In several studies, tumor budding has been shown to be an adverse histologic feature associated with adverse outcome and may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps.
- There is controversy as to whether malignant colorectal polyps with a sessile configuration can be successfully treated by endoscopic removal. The literature seems to indicate that endoscopically removed sessile malignant polyps have a significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, and hematogenous metastasis, but not lymph node metastasis) than do pedunculated malignant polyps. However, when one closely looks at the data, configuration by itself is not a significant variable for adverse outcome, and endoscopically removed malignant sessile polyps with grade I or II histology, negative margins, and no lymphovascular invasion can be successfully treated with endoscopic polypectomy.[3-7]

Colon Cancer Appropriate for Resection

- Histologic confirmation of primary colonic malignant neoplasm.

Pathologic Stage

- The following parameters should be reported:
  - Grade of the cancer
  - Depth of penetration (T)
  - Number of lymph nodes evaluated and number positive (N)
  - Status of proximal, distal, radial, and mesenteric margins[8-9] See Staging (ST-1)
  - Lymphovascular invasion[10,11]
  - Perineural invasion (PNI)[12-14]
  - Tumor deposits[15-18]

LISTADO DE VERIFICACIÓN PÓLIPOS MALIGNOS RESECADOS POR ENDOSCOPIA

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ENDOSCOPISTA

- Remitir cada pólipo por separado en un frasco con formol
- Tipo de pólipo (plano, semipediculado, pediculado)
- Localización anatómica del pólipo
- Diámetro del pólipo en mm
- Resección en bloque/fragmentada
- Recuperación parcial/total
- Marcar margen de resección (tinta o aguja)

Datos facilitados por el endoscopista

Deben constar en el macro / Título del diagnóstico del informe de anatomía patológica

Colorectal carcinomas with submucosal invasion (pT1): analysis of histopathological and molecular factors predicting lymph node metastasis

Reetesh K Pai[1,4], Yuwei Chen[2,4], Maureen A Jakubowski[2], Bonnie L Shadrach[2], Thomas P Plesec[2] and Rish K Pai[3]

MODERN PATHOLOGY (2016), 1–10

Checklist Pólipos malignos (pT1) - AP

PATÓLOGO

- Adenocarcinoma sobre _ AT/ ATV/ASS/AST, etc
- Tamaño del carcinoma (mm)
- Tamaño del pólipo (mm)
- Grado histológico_bajo grado/alto grado
- Tumor budding_bajo Bd1/intermedio Bd2/alto Bd3
- Poorly Differentiated Clursters (PDC) G1, G2, G3
- Invasión de la submucosa por el carcinoma (mm) / Haggitt, otros
- Invasión vascular angiolinfática_presente/ausente
- Invasión perineural_presente/ausente
- Márgenes laterales (mucosos)_positivos/negativos/no valorables
- Margen profundo_positivo/negativo/no valorable
- Distancia al margen_lateral/profundo (mm)
- Estadio pT1/pT…

Checklist Pólipos malignos (pT1) - AP

PATÓLOGO

- Adenocarcinoma sobre _ AT/ ATV/ASS/AST, etc
- Tamaño del carcinoma (mm)
- Tamaño del pólipo (mm)
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- Tumor budding_bajo Bd1/intermedio Bd2/alto Bd3
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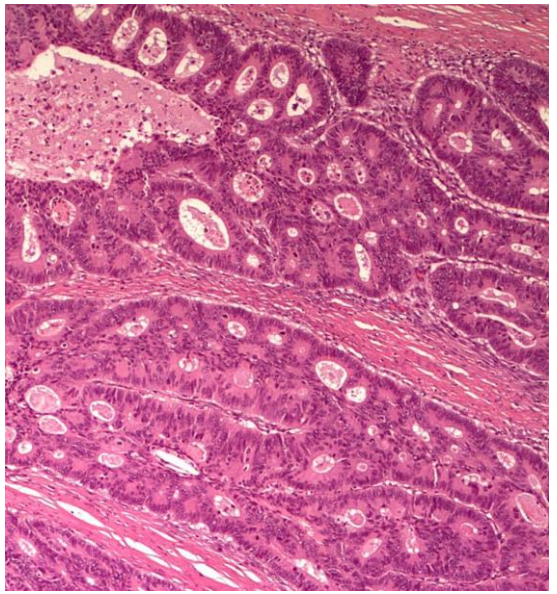
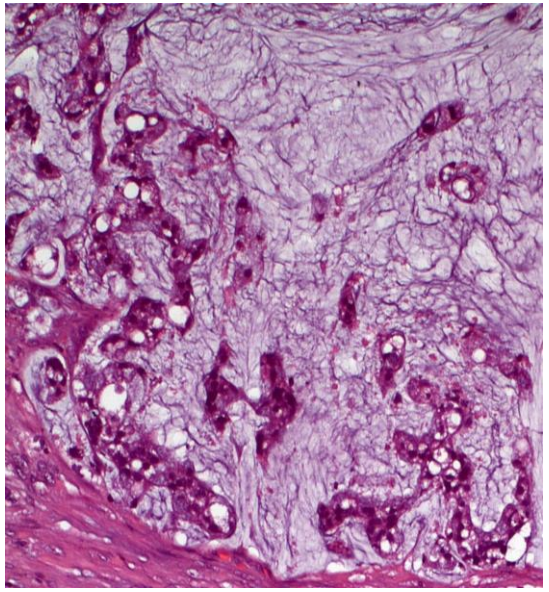
- Invasión vascular angiolinfática_presente/ausente
- Invasión perineural_presente/ausente
- Márgenes laterales (mucosos)_positivos/negativos/no valorables
- Margen profundo_positivo/negativo/no valorable
- Distancia al margen_lateral/profundo (mm)
- Estadio pT1/pT…

Grado de diferenciación

- Alto grado es infrecuente en ADK sobre pólipos
  - Riesgo metástasis ganglionares (+) 23%
  - Riesgo Metástasis a distancia 10%
- ¿Dónde se evalua?
  - ¿En el frente de invasión?
  - ¿En cualquier parte del carcinoma?
- Siempre informar el área de mayor grado (%)
- Variabilidad interobservador entre patólogos expertos k=0.725

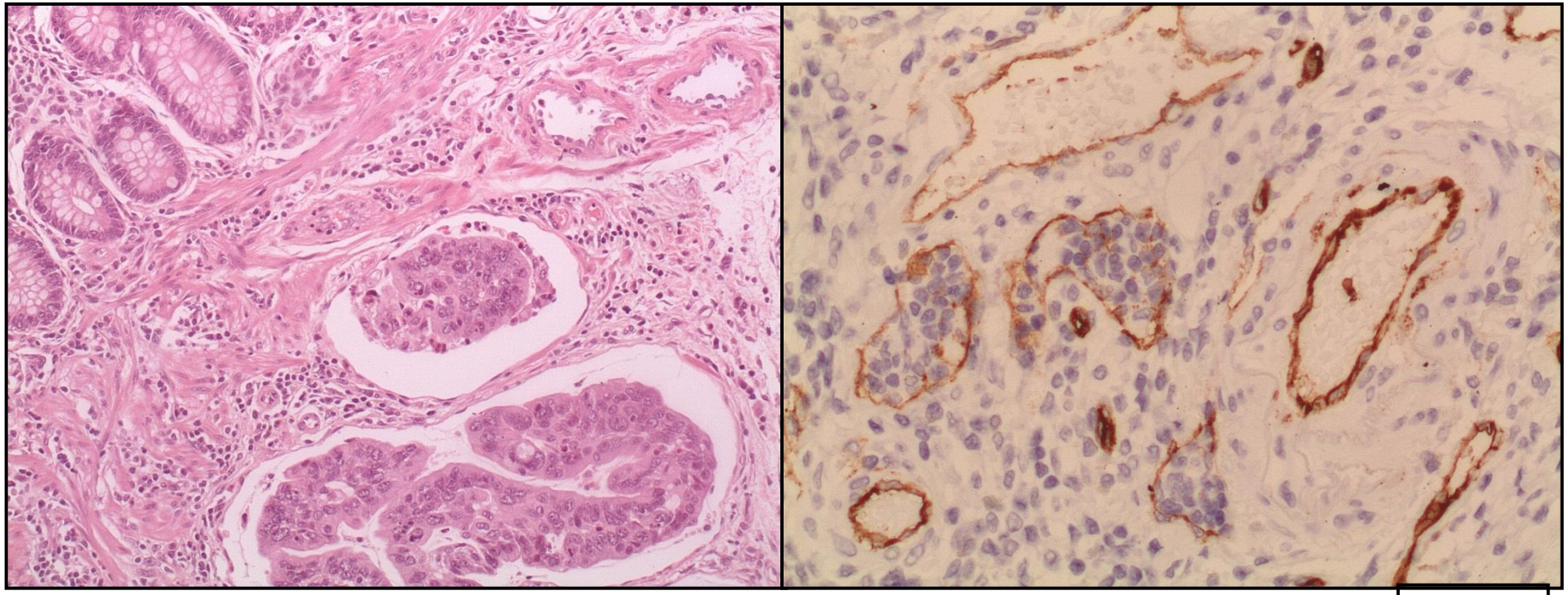


Bajo grado



Alto grado

Invasión linfovascular



CD 31

Resección curativa
= márgenes de resección negativos

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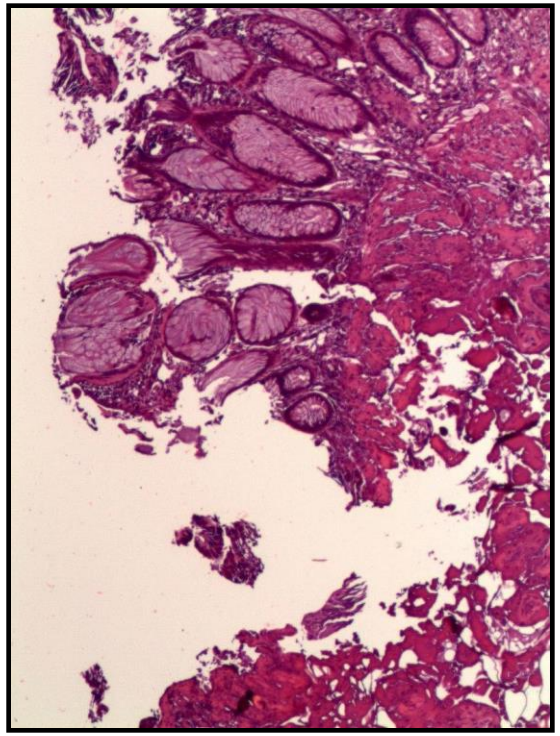
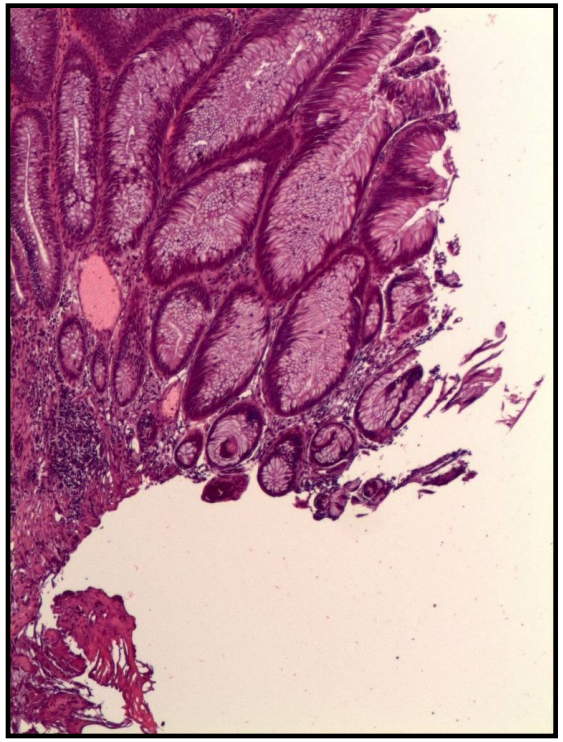
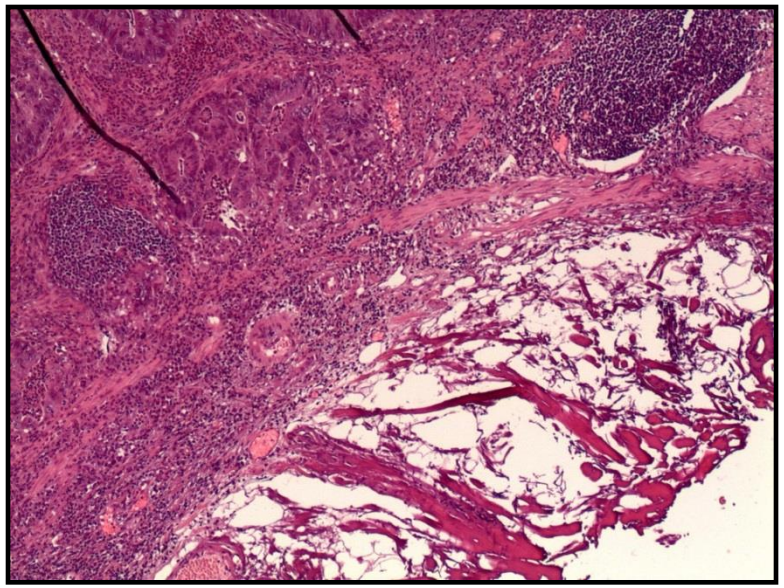
Laterales (mucosos)

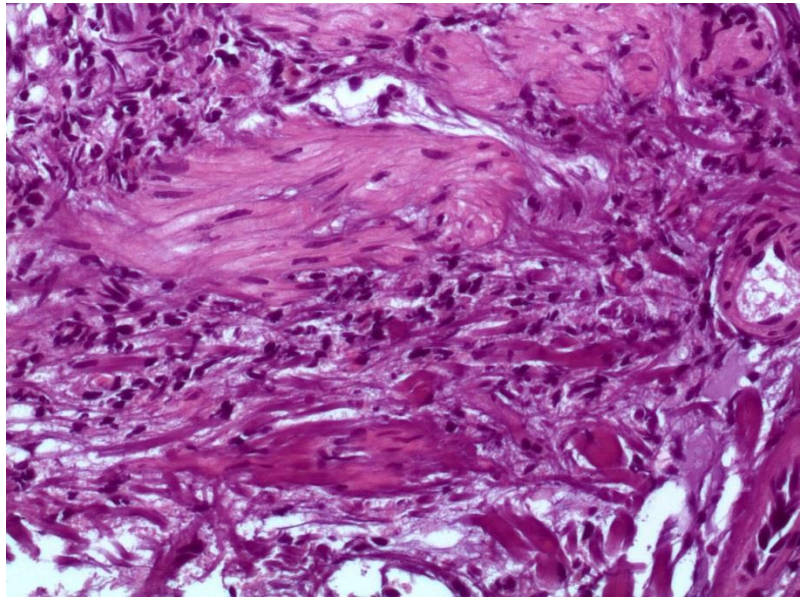


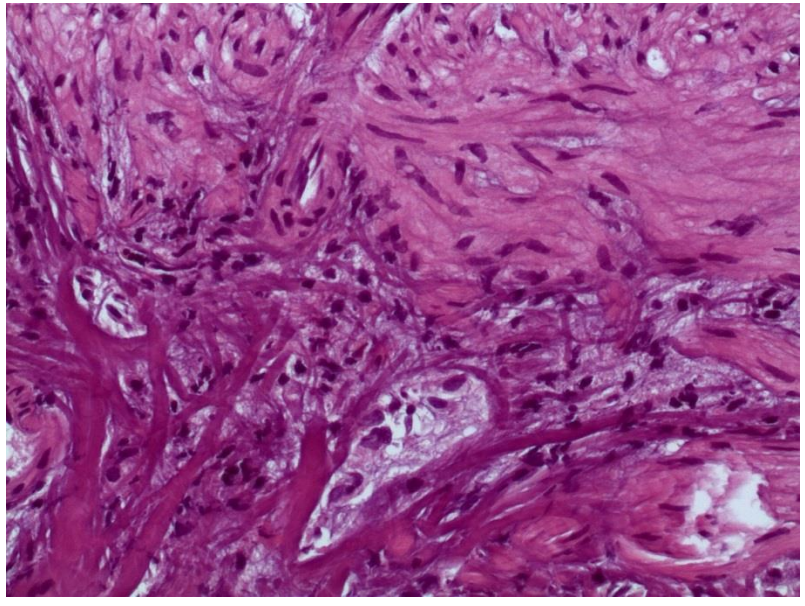


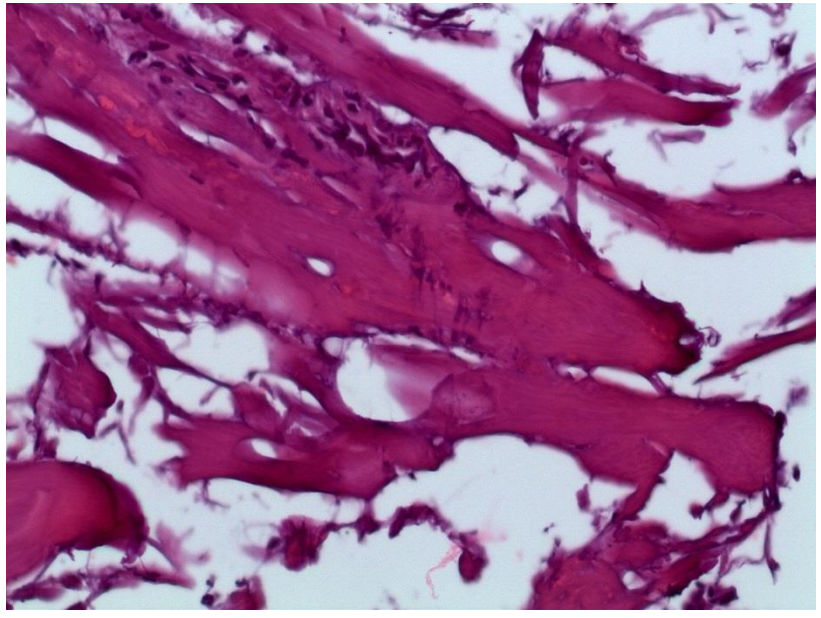
Profundo



Artefacto de cauterio-cauterización







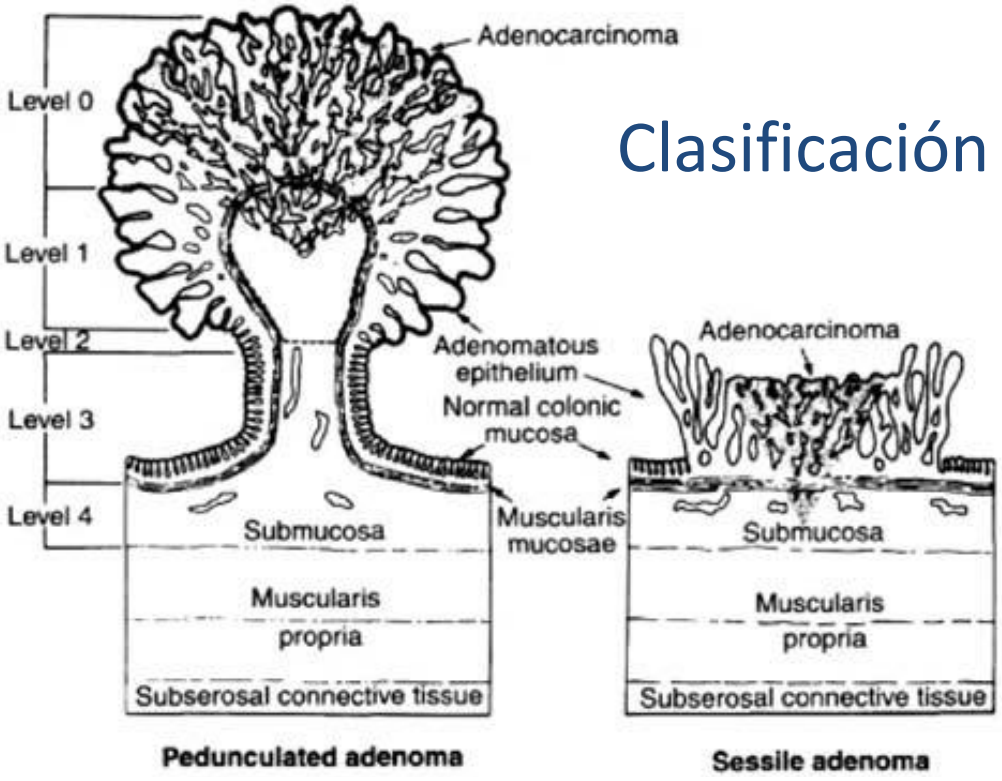
Profundidad de invasión

El modo de medir la profundidad de invasion submucosa depende de:

- Tipo de pólipo: sésil, pediculado o semipediculado
- Orientación
- Estado de la muscularis mucosae: intacta o alterada

Infiltración submucosa

Clasificación Microscópica - Haggitt



Level 0	Mucosal invasion superficial to *muscularis mucosae* (carcinoma *in situ*)	pTis	
Level 1	Submucosal invasion, limited to the head of the polyp	Low-risk of LN metastases	pT1
Level 2	Submucosal invasion of the neck		
Level 3	Submucosal invasion anywhere in the stem		
Level 4	Submucosal invasion below the stem without reaching *muscularis propria* or submucosal invasión in sessile adenomas		

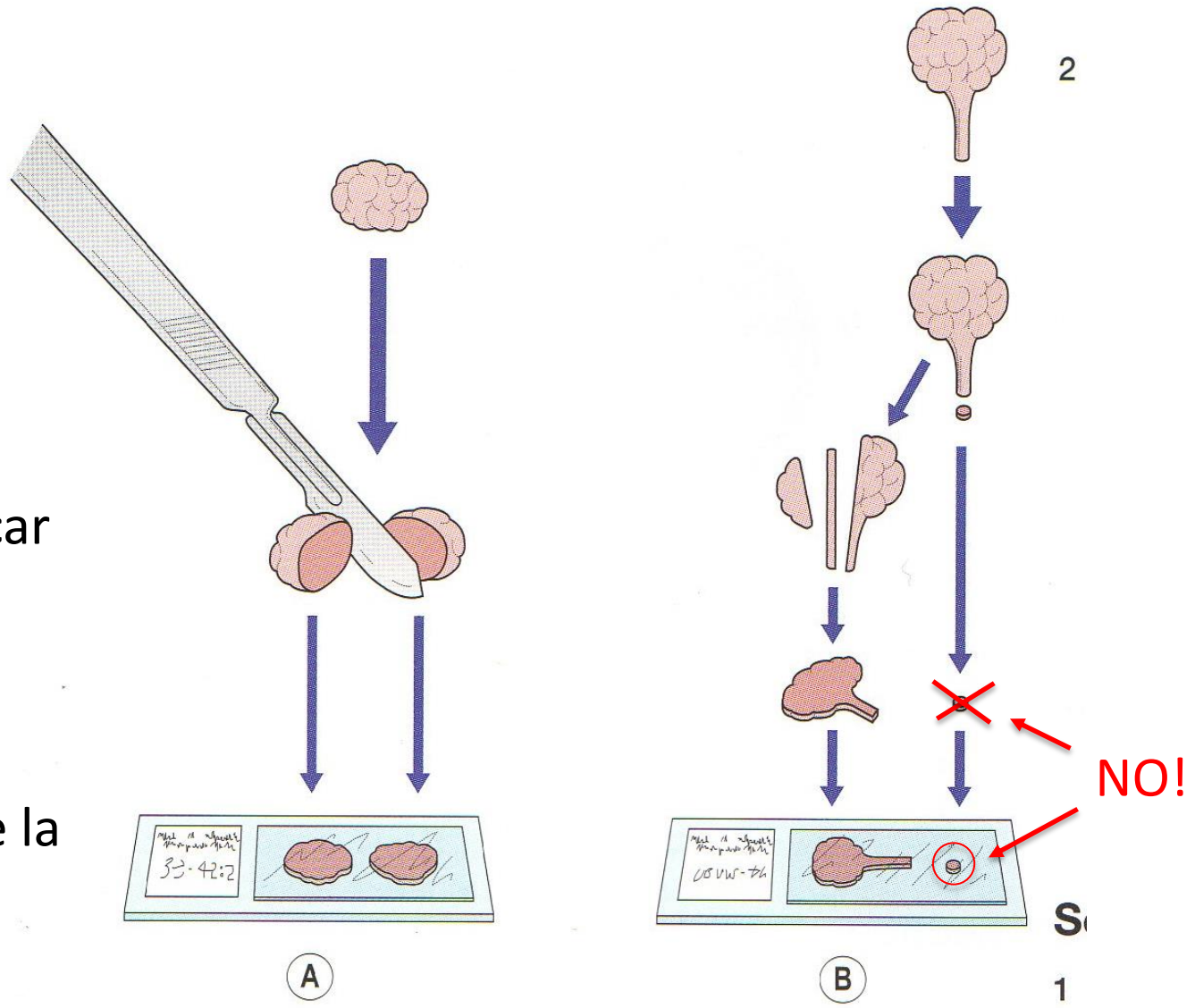
Haggitt RC, et al. Gastroenterology 1985; 89: 328-36

Atención - Haggitt

- La valoración correcta depende de:
  - Una buena orientación del pólipo
  - Longitud del tallo
  - Reconocimiento de la submucosa

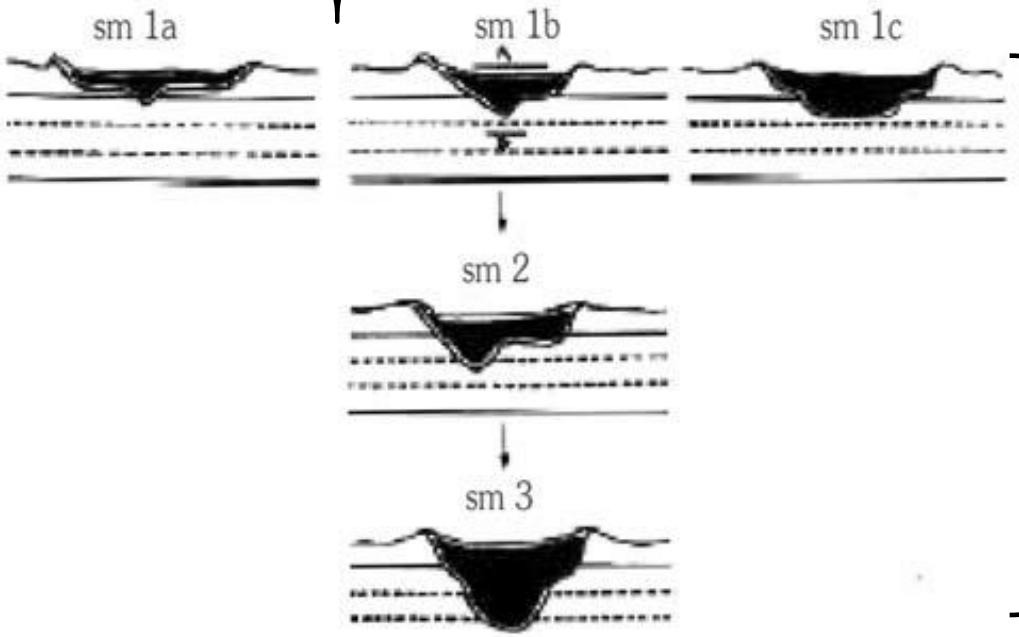
- Siempre que sea posible, el endoscopista debería remitir el pólipo entero e identificar el margen de resección

- El manejo, procesamiento e inclusión macroscópica es muy importante, se mide la distancia al margen de resección!



Infiltración submucosa

without invasion = no LN metastases



Clasificación Microscópica Kikuchi

= Haggitt 4

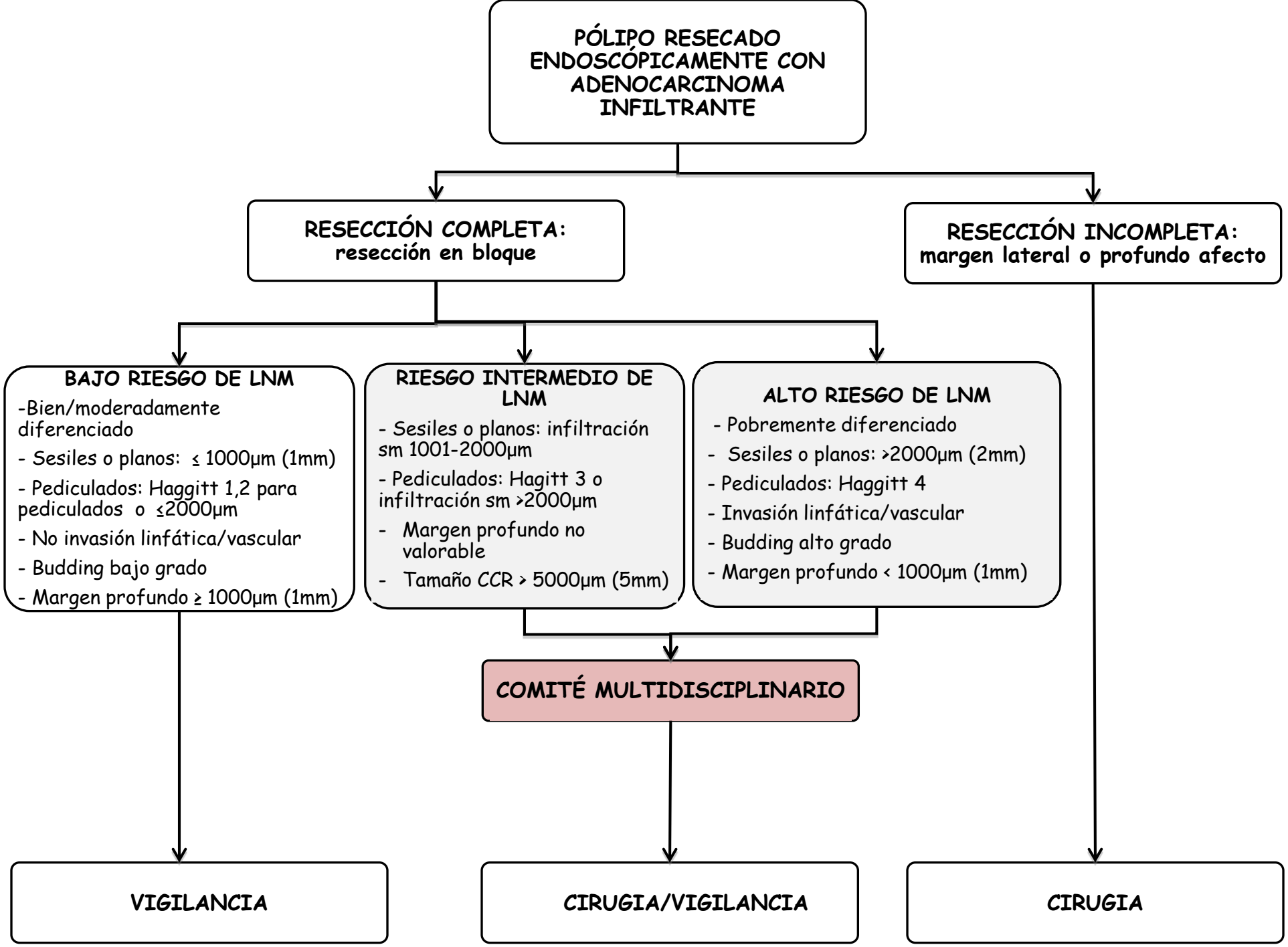
Se necesita la referencia de la capa muscular propia

Table IV. Submucosal invasion classification in early colorectal cancer by Kikuchi (19)

Sm1	Superior third of the submucosa	Risk of lymph node metastases 1-3%
Sm1a	Submucosal invasion under ¼ of the tumoral width	
Sm1b	Submucosal invasion between ¼ and ½ of the tumoral width	
Sm1c	Horizontal affection of the superior third of the submucosa over ½ of the tumoral width	
Sm2	Medium third of the submucosa	Risk of lymph node metastases 8%
Sm3	Inferior third of the submucosa	Risk of lymph node metastases 23%

pT1

Kikuchi R, et al. Dis Colon Rectum 1995; 38: 1286-95


PÓLIPO RESECADO ENDOSCÓPICAMENTE CON ADENOCARCINOMA INFILTRANTE
RESECCIÓN COMPLETA: resección en bloque
RESECCIÓN INCOMPLETA: margen lateral o profundo afecto
BAJO RIESGO DE LNM
-Bien/moderadamente diferenciado
- Sesiles o planos: ≤ 1000µm (1mm)
- Pediculados: Haggitt 1,2 para pediculados o ≤2000µm
- No invasión linfática/vascular
- Budding bajo grado
- Margen profundo ≥ 1000µm (1mm)
RIESGO INTERMEDIO DE LNM
- Sesiles o planos: infiltración sm 1001-2000µm
- Pediculados: Hagitt 3 o infiltración sm >2000µm
- Margen profundo no valorable
- Tamaño CCR > 5000µm (5mm)
ALTO RIESGO DE LNM
- Pobremente diferenciado
- Sesiles o planos: >2000µm (2mm)
- Pediculados: Haggitt 4
- Invasión linfática/vascular
- Budding alto grado
- Margen profundo < 1000µm (1mm)
COMITÉ MULTIDISCIPLINARIO
VIGILANCIA
CIRUGIA/VIGILANCIA
CIRUGIA

European guidelines for quality assurance in CRC screening and diagnosis

- After excision of a pT1 cancer, a standardised follow-up regime should be instituted (VI - A).Rec 8.18
- After removal of a low-risk pT1 cancer, many endoscopists consider the surveillance policy employed for high-risk adenomas to be appropriate follow-up (see Ch. 9, Sect. 9.5.1, Rec. 9.16) (III - B).Rec8.18
- In the case of removal of a high-risk pT1 cancer without additional completion surgery for whatever reason, a more intensive programme of follow-up would be appropriate because of the increased risk of cancer recurrence. ***It is suggested that such patients benefit from quarterly endoscopic inspection of the polypectomy site for 1 year and then bi-annual inspection for a further 2 years.*** After this, the surveillance protocol for high-risk adenomas can be adopted. Given the increased risk of extramural recurrence in patients with high-risk pT1 cancers without completion surgery, it is also appropriate to use cross-sectional imaging of the abdomen on a bi-annual basis for a period of 3 years

Summary of evidence

• When invasive cancer is present in a polypectomy specimen, the risk of residual disease is associated with distance from the resection margin, degree of differentiation and degree of lymphovascular invasion (III).

• The precise site of a polyp within the colon is difficult to define at colonoscopy (VI).

Recommendations for management of pT1 cancers

• If there is clinical suspicion of a pT1 cancer a site of excision should be marked with sub-mucosal India ink (VI - C).Rec 8.16

• Where a pT1 cancer is considered high-risk for residual disease, consideration should be given to completion colectomy along with radical lymphadenectomy, for both rectal cancer (II - A) and colon cancer (VI - A).Rec 8.17 If surgical resection is recommended, consideration should be given to obtaining an opinion from a second histopathologist as variation exists in evaluating high risk features (see also Ch. 7, Sect. 7.5.3 and Rec. 7.7) (III - A).Rec 8.17

• After excision of a pT1 cancer, a standardised follow-up regime should be instituted (VI - A). The surveillance policy employed for high-risk adenomas is appropriate for follow-up after removal of a low-risk pT1 cancer (see Ch. 9, Sect. 9.5.1, Rec. 9.16) (III - B).Rec 8.18

Japanese guidelines recommend **additional surgery** for endoscopically treated colorectal cancers if the lesion has **one** of the following factors:

1. **Positive vertical** resection **margin**
2. **Poorly differentiated, signet ring cell, or mucinous** adenocarcinoma component
3. **Depth of submucosal invasion ≥1000 μm**
4. **Lymphovascular invasion**
5. High budding/sprouting; Bd3

Histologic Factors Associated With Need for Surgery in Patients With Pedunculated T1 Colorectal Carcinomas

Gastroenterology 2018;154:1647–1659

Yara Backes,[1] Sjoerd G. Elias,[2] John N. Groen,[3] Matthijs P. Schwartz,[4] Frank H. J. Wolfhagen,[5]

- El riesgo de metàstasis ganglionares en CCR-pT1 sobre pólipos pediculados es del 3-7% (7-14% en no-pediculados)
- No hay criterios objetivos para calcular el riesgo de metàstasis ganglionares en CCR-pT1 originados en pólipos pediculados
- Se dividen los pacientes en alto y bajo riesgo según criterios histológicos
- Se realiza resección quirúrgica en 46-76% de pacientes

- Comparan tres modelos de riesgo de metàstasis ganglionares y diseñan un modelo de predicción de metàstasis ganglionares en pacientes con CCR-pT1

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Yara Backes,[1] Sjoerd G. Elias,[2] John N. Groen,[3] Matthijs P. Schwartz,[4] Frank H. J. Wolfhagen,[5] Joost M. J. Geesing,[6] Frank ter Borg,[7] Jeroen van Bergeijk,[8] Bernhard W. M. Spanier,[9] Wouter H. de Vos tot Nederveen Cappel,[10] Koen Kessels,[11] Cornelis A. Seldenrijk,[12] Mihaela G. Raicu,[12] Paul Drillenburg,[13] Anya N. Milne,[14] Marjon Kerkhof,[15] Tom C. J. Seerden,[16] Peter D. Siersema,[1,17] Frank P. Vleggaar,[1] G. Johan A. Offerhaus,[18] Miangela M. Lacle,[18,§] and Leon M. G. Moons;[1,§] on behalf of the Dutch T1 CRC Working Group

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budding). **RESULTS:** We identified 5 histologic factors that differentiated cases from controls: lymphovascular invasion, Haggitt level 4 invasion, muscularis mucosae type B (incompletely or completely disrupted), poorly differentiated clusters and tumor budding, which identified patients who required surgery with an area under the curve (AUC) value of 0.83 (95% confidence interval, 0.76–0.90). When we used a clinically plausible predicted probability threshold of ≥4.0%, 67.5% (478 of 708) of patients were predicted to not need surgery. This threshold identified patients who required surgery with 83.8% sensitivity (95% confidence interval, 68.0%–93.8%) and 70.3% specificity (95% confidence interval, 60.9%–78.6%). Conventional models 1 and 2 identified patients who required surgery with lower AUC values (AUC, 0.67; 95% CI, 0.60–0.74; $P = .002$ and AUC, 0.64; 95% CI, 0.58–0.70; $P < .001$, respectively) than our LASSO model.

In conclusion, current guidelines (European Society for Medical Oncology, American Society for Gastrointestinal Endoscopy, Japanese Society for Cancer of the Colon and Rectum) provide a weak recommendation to consider surgery in patients with pedunculated T1 CRC in the presence of one of the histologic high-risk factors, resulting in a high proportion of patients referred for surgery without any benefit. This multicenter study is not only

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Table 2. Histologic Risk Factors in Cases (With Metastasis) vs Matched Controls (Without Metastasis) With Pedunculated T1 CRC

Factor	Cases (n = 37)	Controls (n = 111)	*P* value	Univariate OR (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	AUC (95% CI)
Differentiation grade, n (%)			.07		37.8 (22.5–55.2)	77.5 (68.6–84.9)	0.58 (0.46–0.70)
Good or moderate	23 (62.2)	86 (77.5)		ref			
Poor	14 (37.8)	25 (22.5)		2.4 (1.0–5.7)			
Haggitt level, n (%)			.02		31.3 (16.1–50.1)	86.6 (78.2–92.7)	0.59 (0.47–0.71)
1–3	22 (68.8)	84 (86.6)		ref			
4	10 (31.3)	13 (13.4)		3.1 (1.0–9.8)			
Unable to determine	5	14					
Tumor budding, n (%)			.04		46.0 (29.5–63.1)	72.1 (62.8–80.2)	0.59 (0.48–0.70)
Negative	20 (54.1)	80 (72.1)		ref			
Positive	17 (45.9)	31 (27.9)		1.9 (1.0–3.9)			
Poorly differentiated clusters, n (%)			<.001		62.2 (44.8–77.5)	76.4 (67.3–83.9)	0.69 (0.59–0.80)
Negative	14 (37.8)	84 (76.4)		ref			
Positive	23 (62.2)	26 (23.6)		4.9 (2.0–9.5)			
Unable to determine	—	1					
Lymphovascular invasion, n (%)			<.001		73.0 (55.9–86.2)	66.7 (57.1–75.3)	0.70 (0.60–0.80)
Absent	10 (27.0)	74 (66.7)		ref			
Present	27 (73.0)	37 (33.3)		4.8 (2.1–11.0)			
MM, n (%)			.001		97.3 (85.8–99.9)	27.0 (19.0–36.3)	0.63 (0.53–0.72)
Type A	1 (2.7)	30 (27.8)		ref			
Type B	36 (97.3)	81 (72.2)		16.5 (2.1–129.7)			

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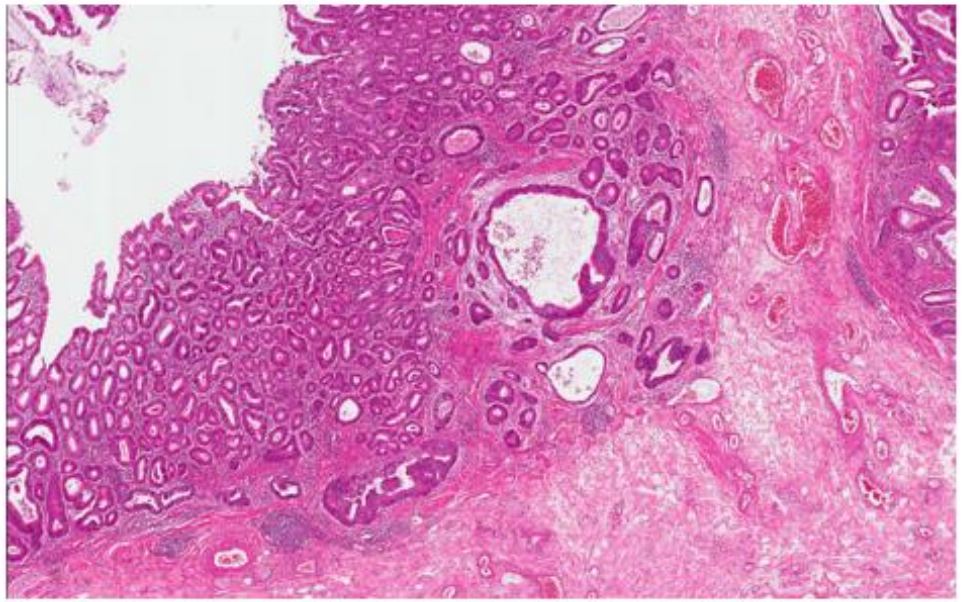
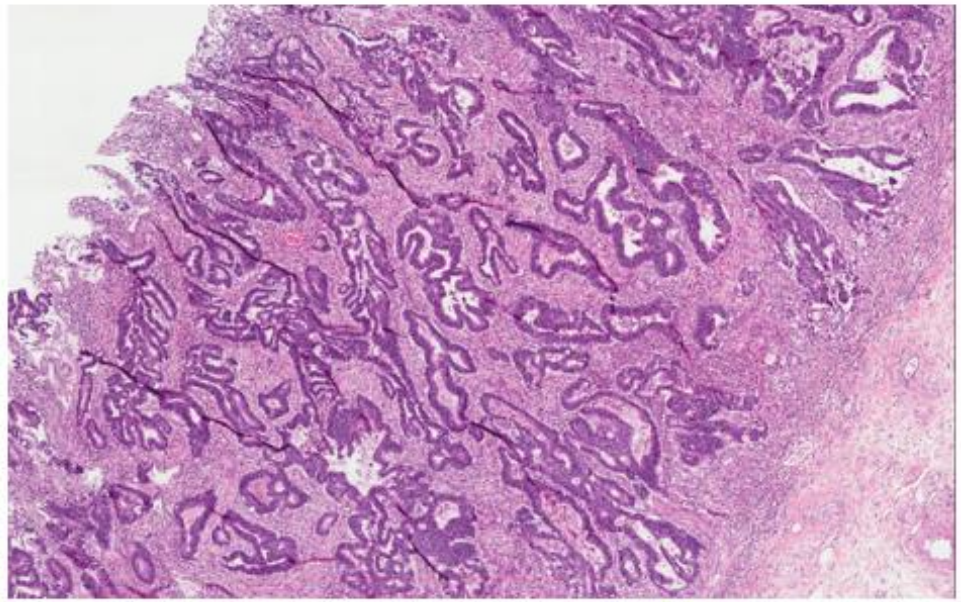
Histological factors

STATUS OF THE MUSCULARIS MUCOSA



Mucosae type A



Mucosae type B

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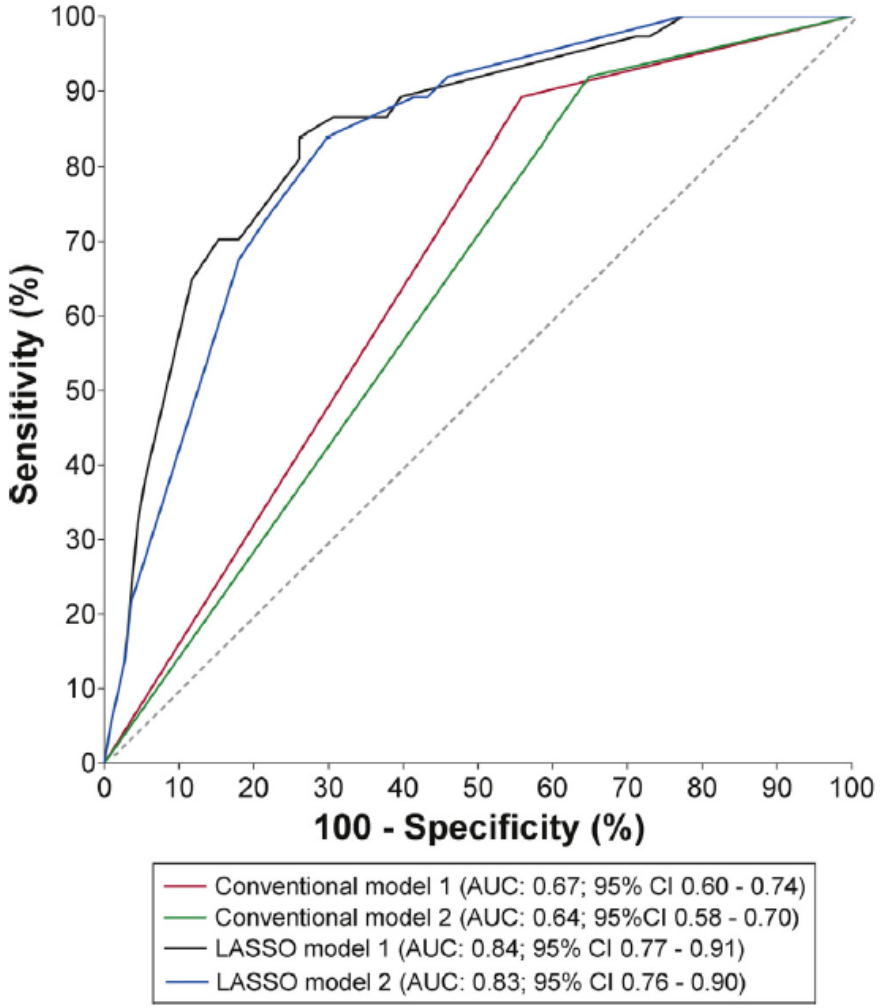

Figure 1. Receiver operating characteristic curves for metastasis in pedunculated T1 CRC for the 2 conventional models and the 2 LASSO-derived models. *Dashed line* is reference line.

- Calcula el riesgo individual de metàstasis ganglionar en CCR-pT1, ponderado con el riesgo quirúrgico del paciente (edad, condición, comorbilidad)
- Disminuye cirugías innecesarias, mayor especificidad
- La reproducibilidad intra-observador de PDC es mayor que para TB
- PDC se correlaciona con metàstasis en pT1, no con TB
- El riesgo de metàstasis es muy bajo con muscularis mucosae intacta
- Utilizan nivel de Haggitt en pediculados! No milímetros
- Parámetros útiles en pólipos fragmentados o mal seccionados

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https://t1crc.com/calculator/pedunculated/

Home | The working group | Research | T1 CRC Symposium | T1 CRC Protocol | Small Crowd Wisdom Panel | Calculator | Funding | Login | Contact

Calculator | Examples of the histological factors | Evidence | When to use | Pitfalls

Calculator for the risk of metastasis in pedunculated T1 CRC

Fill in the fields below to calculate the percentage of the risk of metastasis in pedunculated T1 CRC

Differentiation grade
More information

Good/moderate / Poor

Haggitt level
More information

Haggitt level 1-3 or unassessable / Haggitt level 4

Tumor budding
More information

Negative for tumor budding (budding grade 1) / Positive for TB (budding grade 2-3)

Poorly differentiated clusters (PDC)
More information

Negative for tumor PDC (PDC grade 1) / Positive for PDC (PDC grade 2-3)

Lymphovascular invasion
More information

Absent / Present

Status of the muscularis mucosa
More information

Type A / Type B

- **Type A:** shattered but aligned muscularis mucosa
- **Type B:** incompletely or completely disrupted muscularis mucosa

THE FIELD BELOW WILL SHOW THE CALCULATED SCORE.

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Predicted probability (%) of metastasis in penduculated T1 CRC

0.3 %

BELOW AN OVERVIEW OF ALL THE POSSIBLE OUTCOMES.

Example of the LASSO-derived predicted probability (%) of metastasis in pedunculated T1 CRC based on histological risk factors.

		Muscularis mucosa type A		Muscularis mucosa type B	
		Any kind of budding -	Any kind of budding +	Any kind of budding -	Any kind of budding +
Haggitt 1-3	LVI -	0.3	0.6	2.1	3.7
	LVI +	1.2	2.2	7.4	12.3
Haggitt 4	LVI -	1.4	2.4	8.2	13.6
	LVI +	5.0	8.5	24.8	36.8

Abbreviations: LASSO: least absolute shrinkage and selection operator; LVI: lymphovascular invasion. – indicates absence; + indicates presence.
For example, a pedunculated T1 CRC with muscularis mucosa type A, Haggitt level 4 invasion, no lymhovascular invasion and no budding (PDC or tumor budding) has a 1.4% risk of metastasis.

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Preguntas / propuestas?

Muchas gracias!