



LO SCREENING COLO-RETTALE:  
DALLE LINEE-GUIDA EUROPEE AL PROTOCOLLO  
DELLA REGIONE EMILIA-ROMAGNA

Ferrara, 17 novembre 2012

Tavola rotonda:  
Trattamento dell'adenocarcinoma T1 (adenoma cancerizzato)

Prof. Giovanni Lanza  
Anatomia Patologica - Ferrara

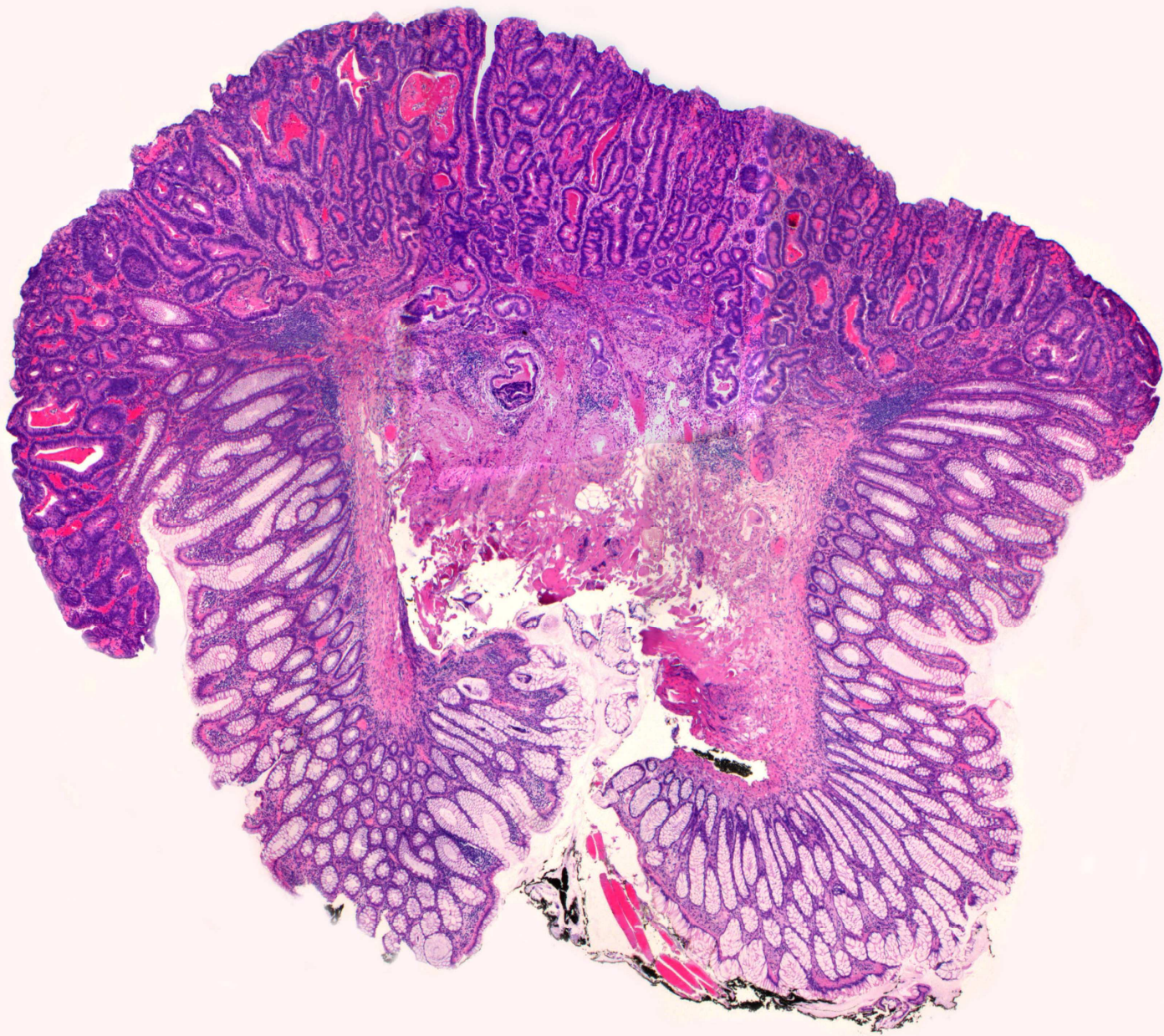
Cosa si intende per  
adenocarcinoma pT1  
(adenoma cancerizzato)?

# Adenocarcinoma pT1

- Definizione: “pT1 cancers are those showing invasion through the muscularis mucosae into the submucosa but not into the muscularis propria”
- E' la forma più precoce di CCR con potenziale metastatico
- L'adenocarcinoma in situ e intramucoso non rientrano in questa definizione e non avendo potenziale metastatico sono equiparati alla displasia grave (alto grado)
- Altri termini spesso utilizzati sono adenoma (polipo) cancerizzato e early colorectal cancer

# Adenocarcinoma pT1

- Frequente configurazione polipoide
- Frequente associazione con una componente adenomatosa da cui trae origine (adenoma cancerizzato)
- Spesso il trattamento iniziale è la rimozione endoscopica
- Incidenza in aumento
- Basso potenziale metastatico:
  - Metastasi linfonodali (10-15% dei casi)
  - Metastasi a distanza (rare)



# CCR pT1 – casistica operatoria

Residui adenomatosi presenti	67	56,3%
Residui adenomatosi assenti	52	<b>43,7%</b>
Totale	119	100%

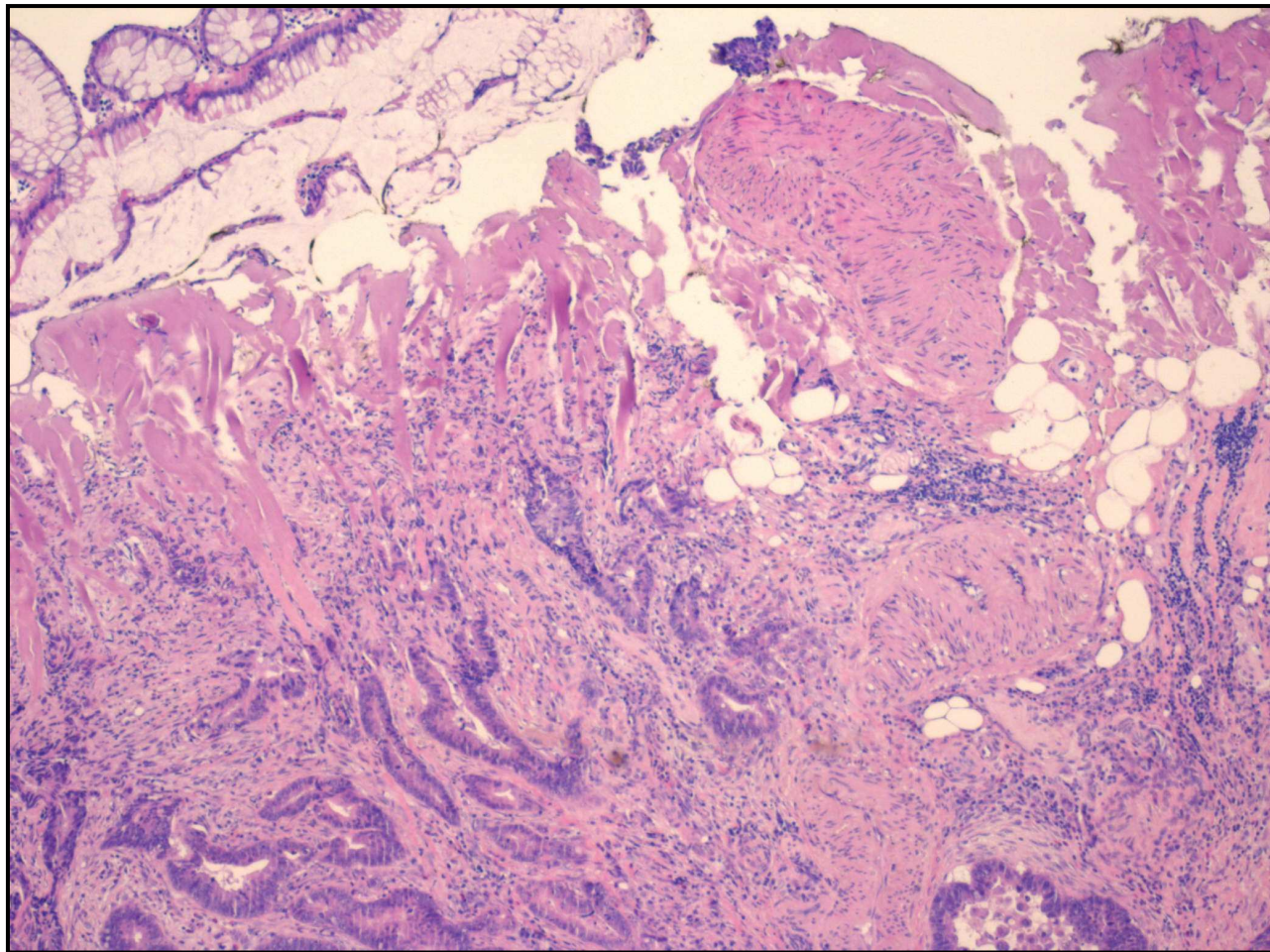
Quali sono i principali problemi diagnostici che pone al patologo?

# Adenocarcinoma pT1

Principali problemi di diagnostica istologica

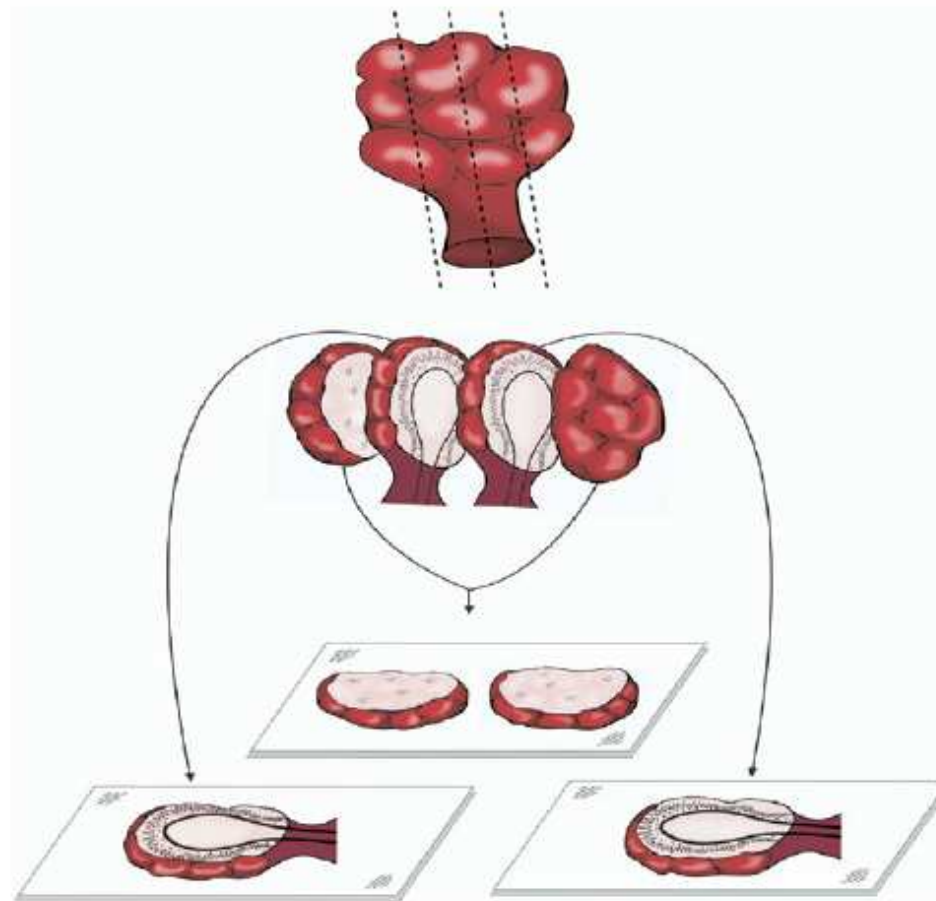
- **Misclassificazione**
  - “Epithelial misplacement” (sovradiagnosi)
  - Difficoltà di stabilire la reale presenza di invasione della sottomucosa (sovradiagnosi o sottodiagnosi)
- **Definizione dello stato del margine di resezione**
- **Determinazione del potenziale metastatico della lesione** (identificazione delle lesioni ad alto rischio)

# Margine di resezione



LG europee: interessato se la distanza è  $< 0 = 1$  mm

# Margine di resezione



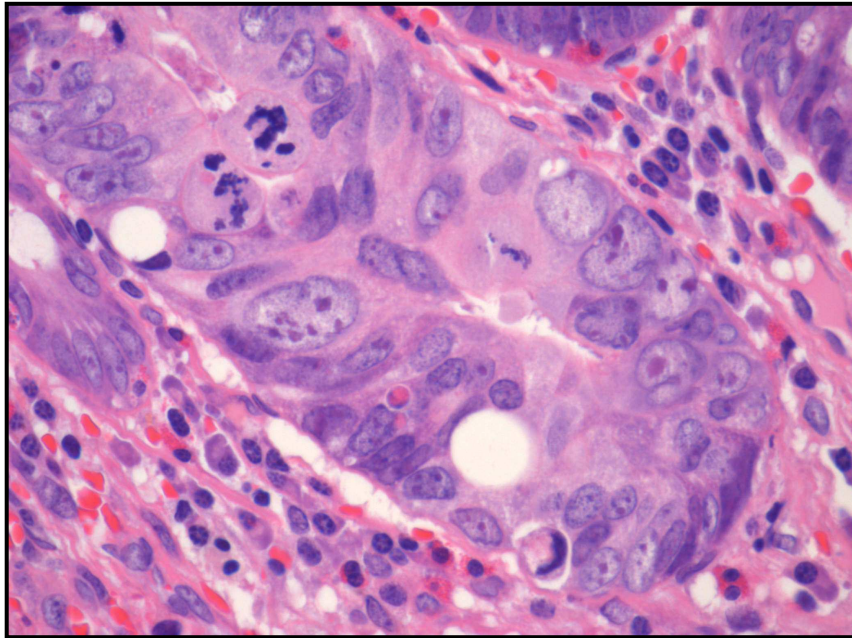
Quali sono i parametri patologici correlati al potenziale metastatico della lesione, che concorrono alla scelta del trattamento nei pazienti con carcinoma pT1 asportato endoscopicamente?

# LG europee – adenocarcinoma pT1

Definizione di lesione ad alto rischio

- Interessamento margine di resezione
- Scarsa differenziazione (alto grado)
- Invasione linfatica o venosa
- Sub-staging
- Tumor budding

# *LG europee: grado di differenziazione*



- Ogni area di scarsa differenziazione concorre a definire una lesione come ALTO GRADO (grading sull'area peggiore)
- La categoria alto grado comprende i tumori classificati come poco differenziati o indifferenziati
- La frequenza dell'alto grado non deve superare il 20%
- Il tumor budding non va considerato nella valutazione del grado di differenziazione

## CCR pT1 – casistica operatoria

Grado/pN	N0	N1-2	Totale
Basso grado	92 (88,5%)	12 (11,5%)	104
Alto grado	5 (45,5%)	6 (54,5%)	11 ( <b>9,6%</b> )
Totale	97	18 ( <b>15,7%</b> )	115

**Incidence of Grade 3 (Poorly Differentiated) in T1 CRC Cases Reported in the Literature**

Study	No. of T1 CRC Cases Analyzed*	Incidence of Grade 3, Poorly Differentiated, % (No. of Cases)	Incidence of Nodal Involvement in Grade 3 T1 CRC, % (No. of Cases)
Yamamoto et al, <sup>41</sup> 2004	301	0.1 (4)	—
Tominaga et al, <sup>42</sup> 2005	155	1.3 (2)	50.0 (1)
Kurokawa et al, <sup>43</sup> 2005	180	1.1 (2)	50.0 (1)
Whitlow et al, <sup>44</sup> 1997	59	1.7 (1)	0 (0)
Haggitt et al, <sup>4</sup> 1985	64	3.1 (2)	0 (0)
Geraghty et al, <sup>9</sup> 1991	81	2.5 (2)	—
Suzuki et al, <sup>45</sup> 2003	65	3.1 (2)	100 (2)
Sakuragi et al, <sup>30</sup> 2003	278	2.5 (7)	57.1 (4)
Seitz et al, <sup>46</sup> 2004	116	3.4 (4)	—
Wang et al, <sup>28</sup> 2005	159	4.4 (7)	85.7 (6)
Morson et al, <sup>47</sup> 1984	61	5 (3)	—
Cooper et al, <sup>11</sup> 1995	140	5.7 (8)	—
Netzer et al, <sup>12</sup> 1998	62	8.1 (5)	40.0 (2)
Hackelsberger et al, <sup>48</sup> 1995	87	11.5 (10)	—
Hassan et al, <sup>27</sup> 2005	380	14.7 (56)	23.2 (13)
Nascimbeni et al, <sup>29</sup> 2002	344	34.0 (117)	—
Nascimbeni et al, <sup>49</sup> 2004	144	39.6 (57)	—

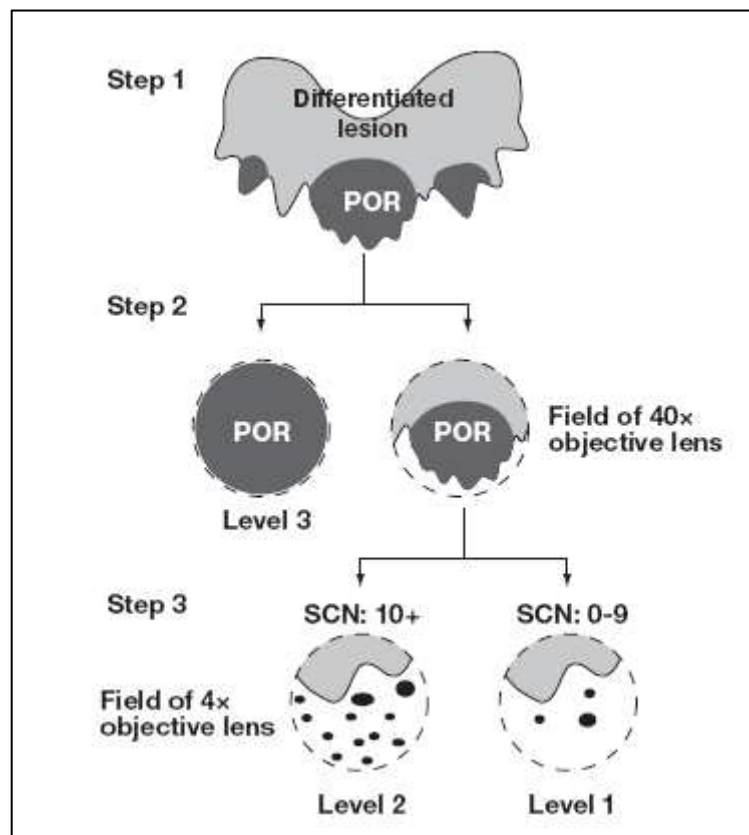
CRC, colorectal cancer.

\* Reports of 50 or more T1 CRC cases are included.

***Ueno et al. 2010***

## Proposed Objective Criteria for "Grade 3" in Early Invasive Colorectal Cancer

Hideki Ueno, MD,<sup>1</sup> Yojiro Hashiguchi, MD,<sup>1</sup> Yoshiki Kajiwara, MD,<sup>1</sup> Eiji Shinto, MD,<sup>1</sup> Hideyuki Shimazaki, MD,<sup>2</sup> Hiroyuki Kurihara,<sup>3</sup> Hidetaka Mochizuki, MD,<sup>1</sup> and Kazuo Hase, MD<sup>1</sup>



**Table 2**  
Impact of Factors Related to Tumor Morphologic Features on the Nodal Status in T1 Colorectal Cancer Treated by Laparotomy With Lymphadenectomy

Parameter	Nodal Involvement		P
	Negative	No. (%) Positive	
Tumor diameter (cm)			NS
<2 (n = 139)	125	14 (10.1)	
≥2 (n = 100)	87	13 (13.0)	
Configuration			NS
Sessile (n = 132)	114	18 (13.6)	
Pseudosessile (n = 66)	59	7 (11)	
Pedunculated (n = 41)	39	2 (5)	
Growth pattern			NS
Polypoid (n = 137)	125	12 (8.8)	
Nonpolypoid (n = 102)	87	15 (14.7)	
Adenoma component			NS
Absent (n = 155)	135	20 (12.9)	
Present (n = 84)	77	7 (8)	
Width of submucosal invasion (μm)			.005
<4,000 (n = 74)	72	2 (3)	
≥4,000 (n = 165)	140	25 (15.2)	
Depth of submucosal invasion (μm)			.01
<2,000 (n = 66)	64	2 (3)	
≥2,000 (n = 172)	147	25 (14.5)	

NS, not significant.

**Table 3**  
Impact of Histologic Features of Tumors on Nodal Status in T1 Colorectal Cancer Treated by Laparotomy With Lymphadenectomy

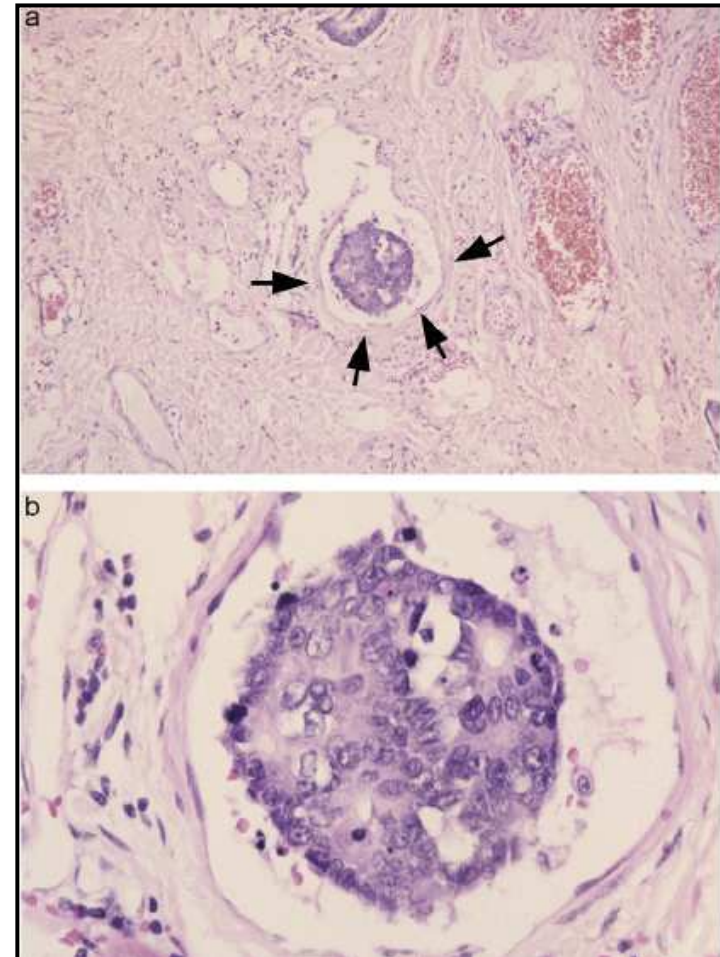
Parameter	Nodal Involvement		P
	Negative	No. (%) Positive	
Vascular invasion			<.0001
Absent (n = 167)	157	10 (6.0)	
Present (n = 72)	55	17 (24)	
Cribriform pattern			.03
Absent (n = 182)	166	16 (8.8)	
Present (n = 57)	46	11 (19)	
Tumor budding			<.0001
Negative (n = 206)	192	14 (6.8)	
Positive (n = 33)	20	13 (39)	
Extent of POR (level)			<.0001 (1 vs 2/3)
1 (n = 176)	166	10 (5.7)	
2 (n = 32)	26	6 (19)	
3 (n = 31)	20	11 (35)	
Extent of MUC (level)			.01 (1/2 vs 3)
1 (n = 213)	192	21 (9.9)	
2 (n = 7)	7	0 (0)	
3 (n = 19)	13	6 (32)	
Grade of the least differentiated component*			<.0001
High (n = 77)	56	21 (27)	
Low (n = 162)	156	6 (3.7)	

MUC, mucin-producing component; POR, poorly differentiated component.

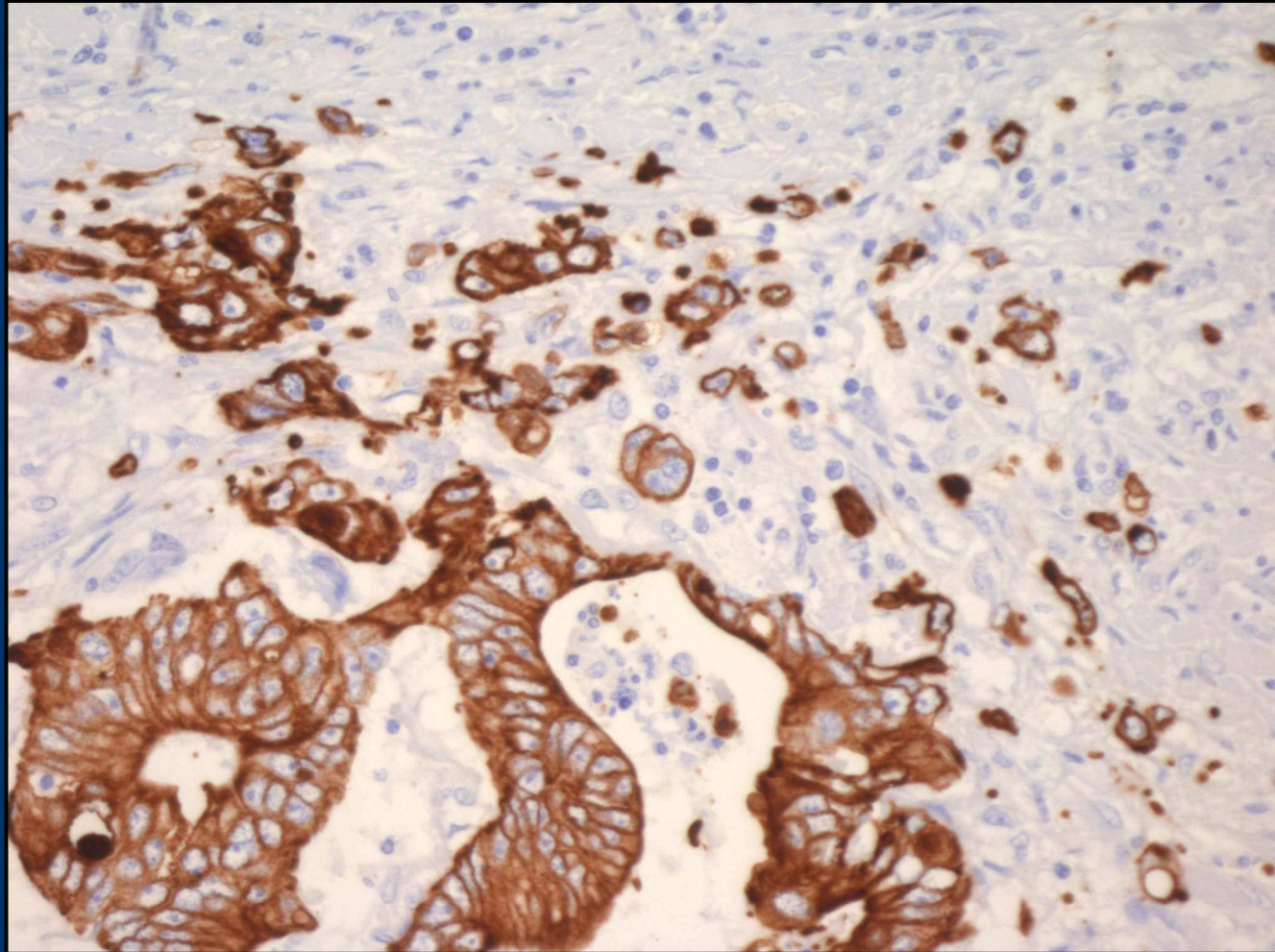
\* High-grade, level 2 + 3 of POR and level 3 of MUC.

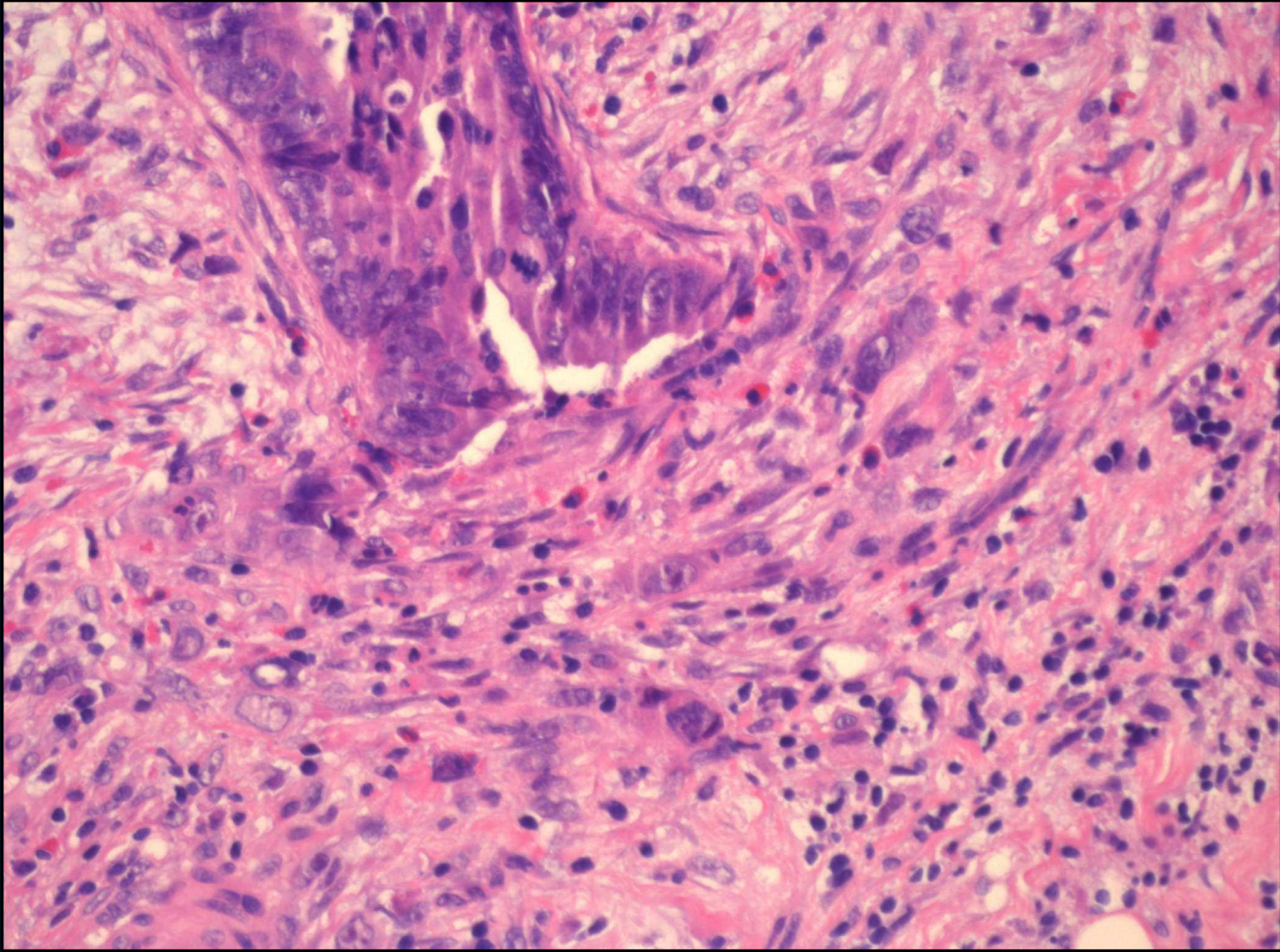
# *LG europee: invasione linfo-vascolare*

- E' un significativo fattore di rischio per metastasi linfonodali o a distanza
- Artefatti da retrazione (da non confondere con aspetti micropapillari) possono creare dubbi interpretativi, che devono essere riportati nel referto
- Il ruolo della IHC è oggetto di valutazione



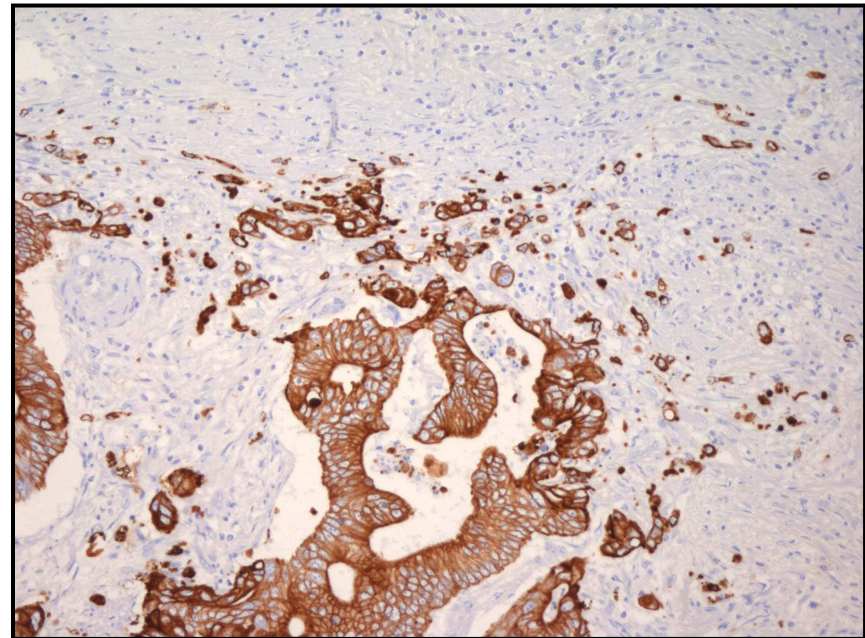
## *Tumor budding*



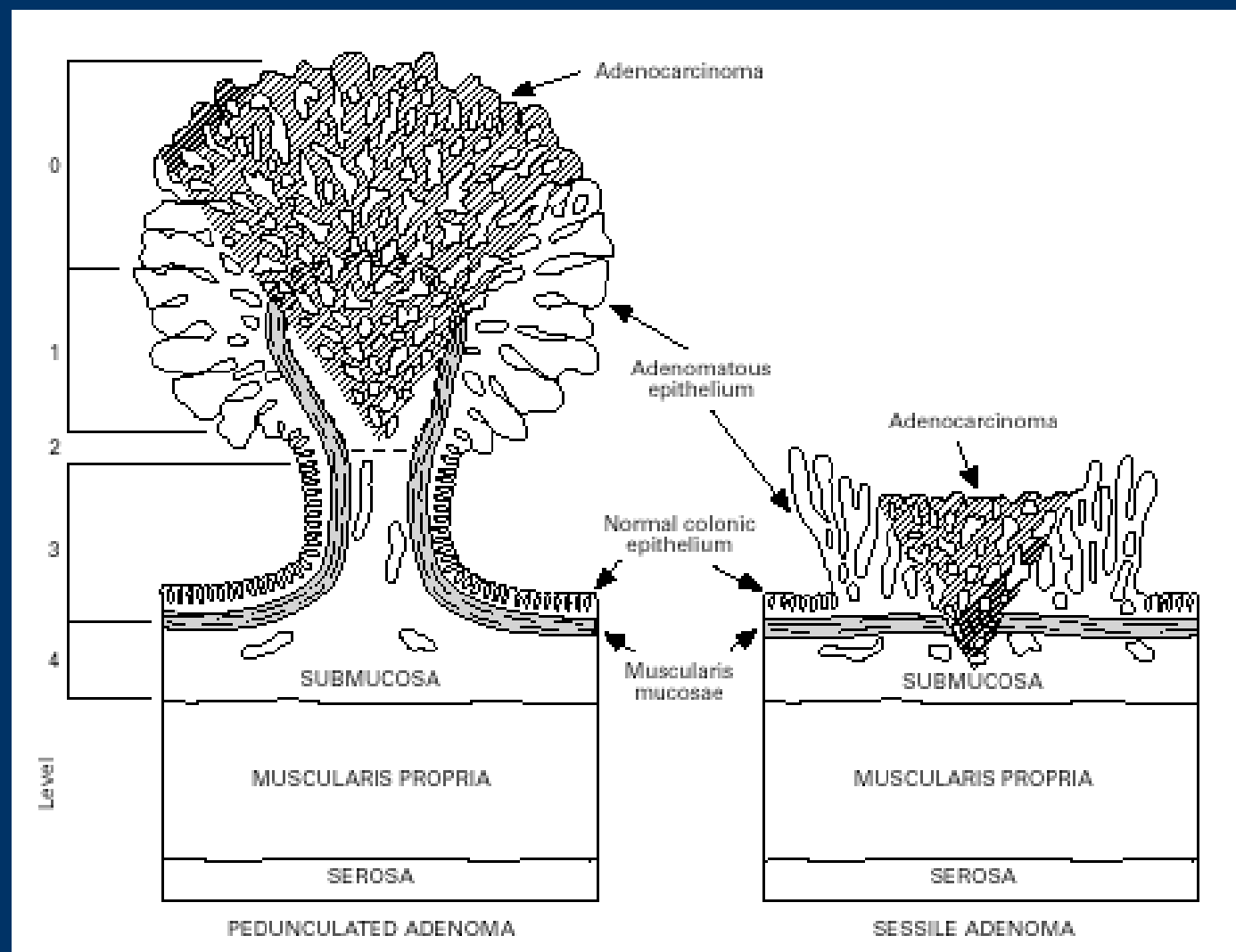


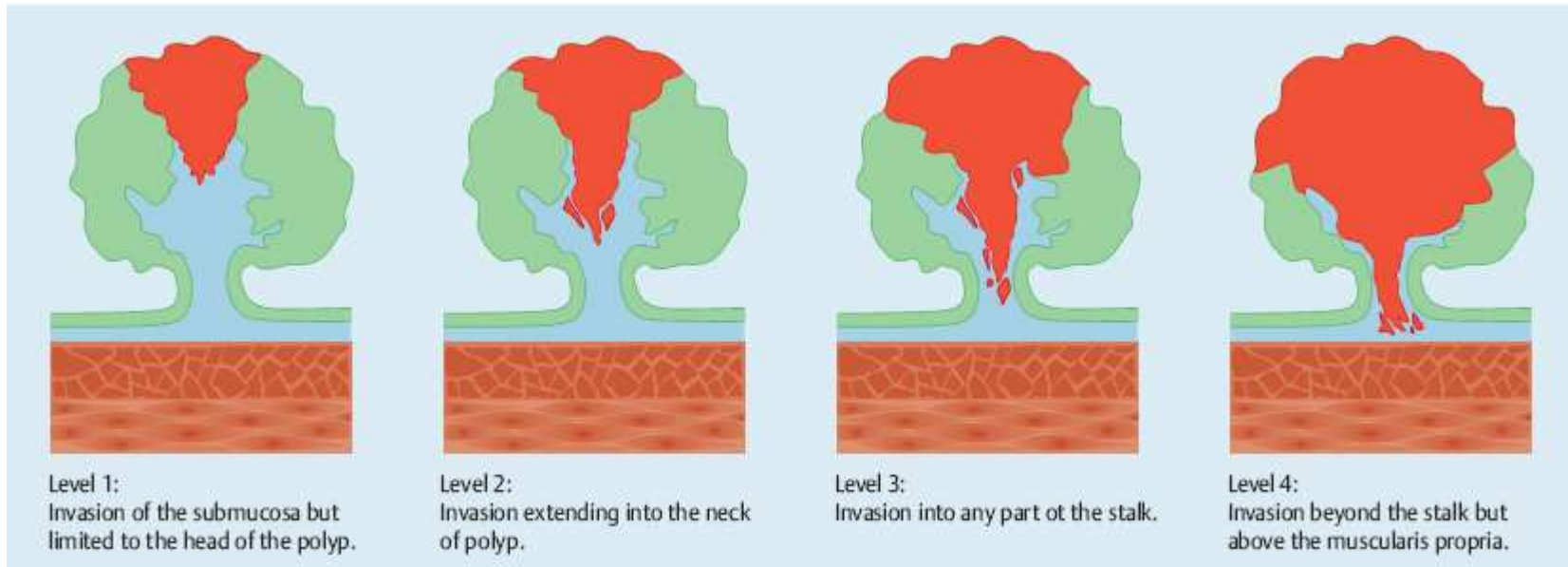
# ***Screening CCR: tumor budding***

- Presenza sul fronte di invasione del tumore di piccoli gruppi o singole cellule che si distaccano dalle strutture ghiandolari e dissociano lo stroma
- Proposto come fattore prognostico sfavorevole nel carcinoma avanzato e nel carcinoma in fase iniziale
- Variabilità dei criteri di valutazione proposti
- Scarsa riproducibilità
- Potere predittivo non comprovato

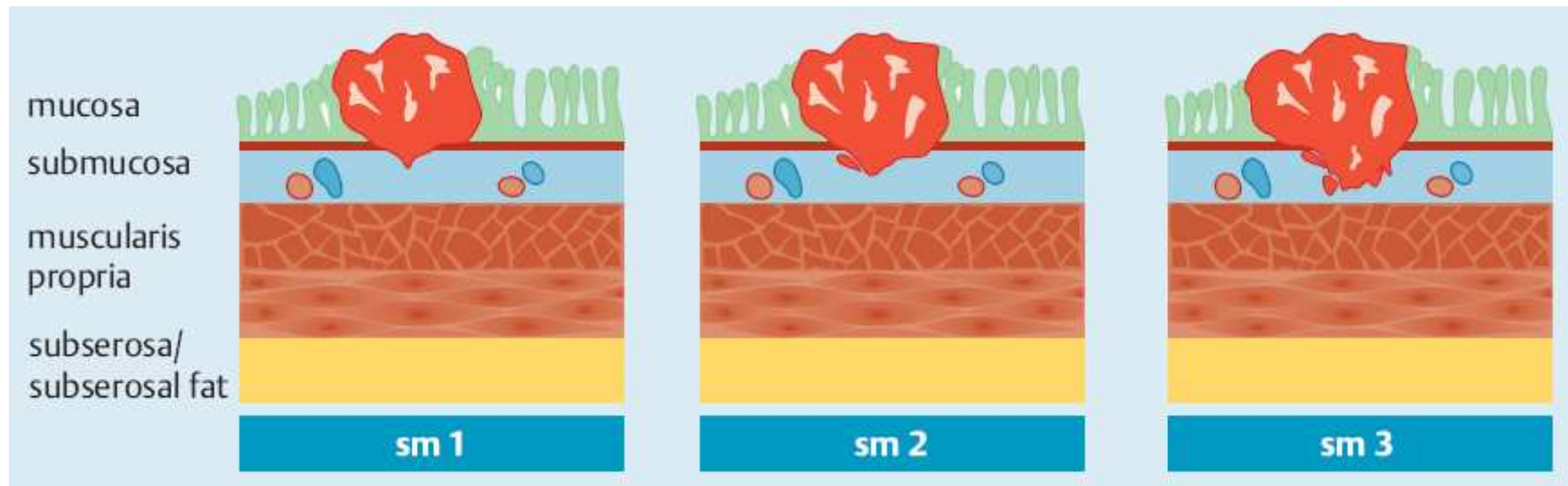


# *Livelli di infiltrazione secondo Haggitt*



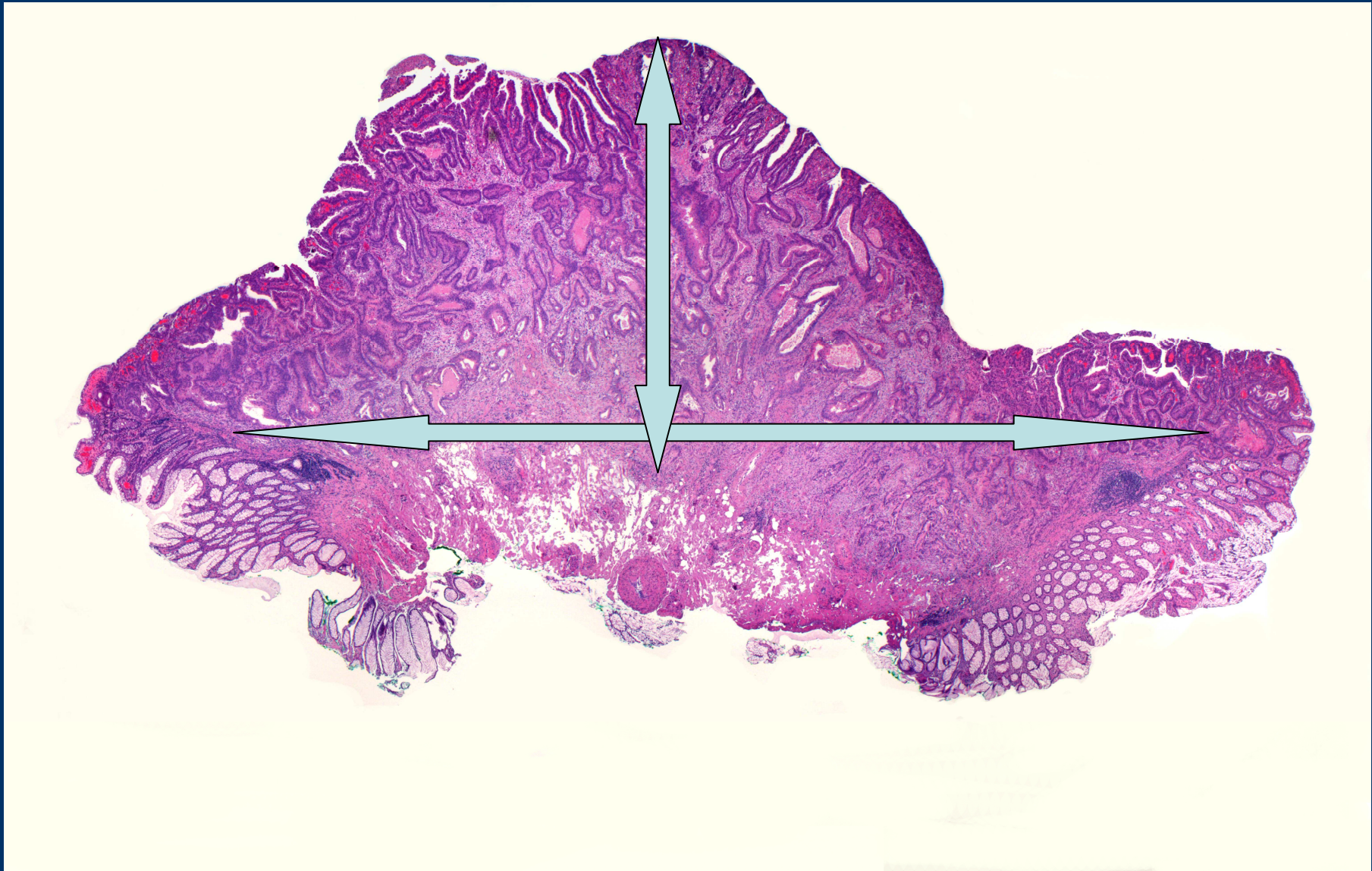


### Livelli di Haggitt



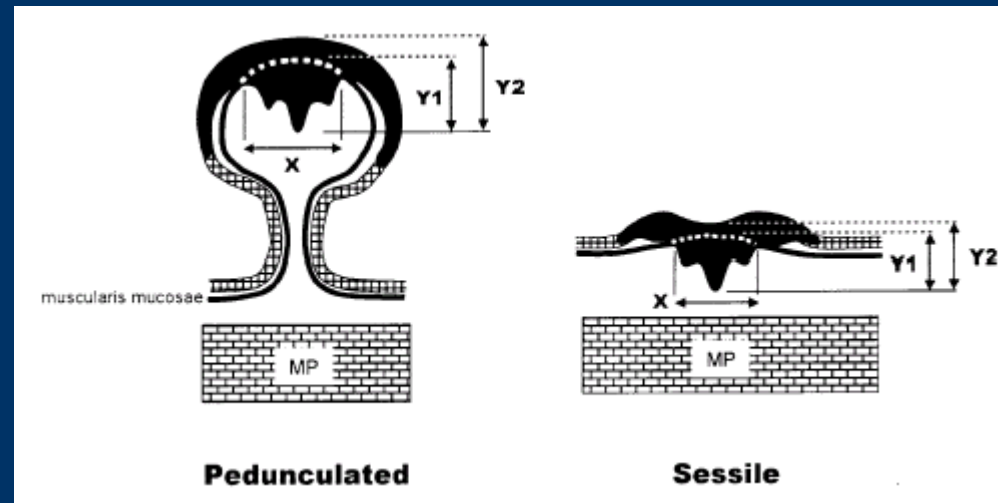
### Livelli di Kikuchi

## ***Adenoma cancerizzato – sub-staging***

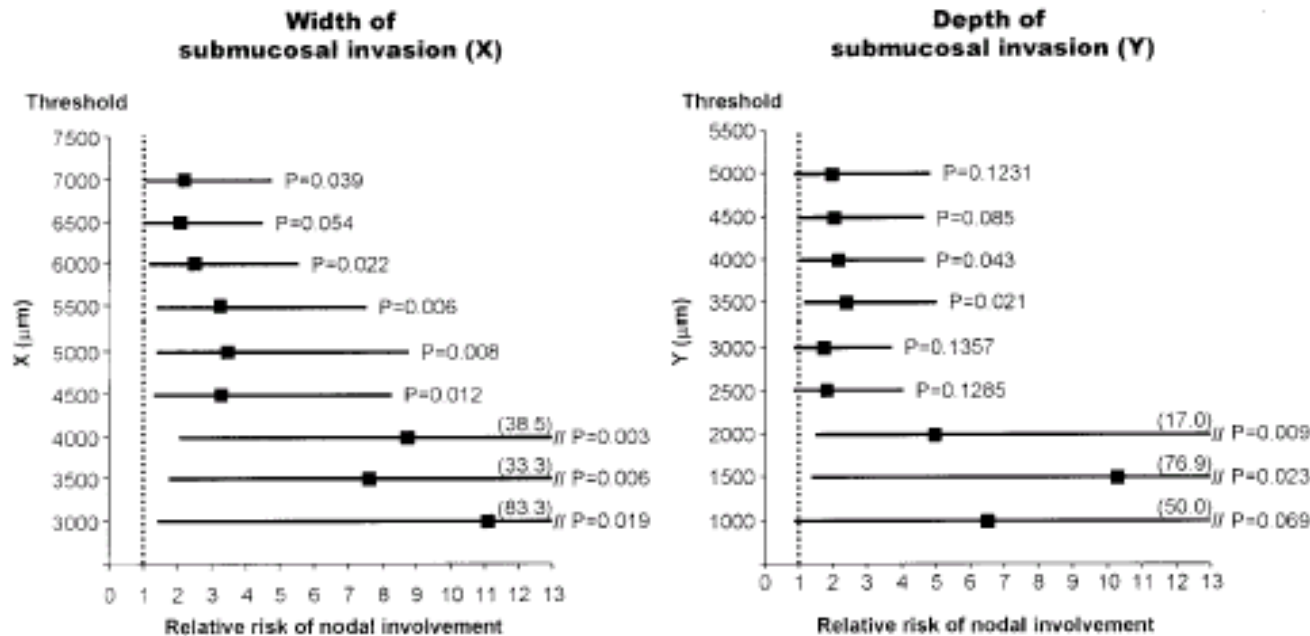


# Ampiezza e profondità di invasione della sottomucosa

Ampiezza  
> 4000  $\mu\text{m}$



Spessore  
> 2000  $\mu\text{m}$



Ueno et al.  
2004

**Table 5.** Combination of Qualitative and Quantitative Risk Factors and the Incidence of Nodal Involvement

Number of risk factors	Qualitative risk factors 1–3 <sup>a</sup>		Qualitative risk factors 1–3 <sup>a</sup> plus Haggitt's level 3–4		Qualitative risk factors 1–3 <sup>a</sup> plus width $\geq 4000 \mu\text{m}$		Qualitative risk factors 1–3 <sup>a</sup> plus depth $\geq 2000 \mu\text{m}$	
	Nodal involvement	Micrometastasis	Nodal involvement	Micrometastasis	Nodal involvement	Micrometastasis	Nodal involvement	Micrometastasis
None	0.7% (1/138) <sup>b</sup>	6.8% (4/59) <sup>c</sup>	0.0% (0/27) <sup>d</sup>	15.4% (2/13) <sup>c</sup>	0.0% (0/62) <sup>e</sup>	0.0% (0/26) <sup>f</sup>	0.0% (0/56) <sup>g</sup>	0.0% (0/19) <sup>c</sup>
1	20.7% (12/58)	14.3% (3/21)	0.8% (1/118)	4.3% (2/47)	2.3% (2/87)	10.8% (4/37)	3.3% (3/92)	8.9% (4/45)
2 or more	36.4% (20/55)	16.7% (3/18)	30.2% (32/106)	15.8% (6/38)	30.4% (31/102)	17.1% (6/35)	29.1% (30/103)	17.6% (6/34)

NOTE. Nodal involvement was based on the conventional examination.

<sup>a</sup>Risk factors: 1, unfavorable grade; 2, vascular invasion; 3, tumor budding. <sup>b</sup> $P < 0.0001$ ; <sup>c</sup> $P > 0.1$ ; <sup>d</sup> $P = 0.031$  (Fisher exact test); <sup>e</sup> $P = 0.0004$ ; <sup>f</sup> $P = 0.058$  (Fisher exact test); <sup>g</sup> $P = 0.0010$ .

**Ueno et al. 2004**

# *Fattori di rischio e metastasi linfonodali*

Fattori di rischio	Grado, invasione vasi, budding	Grado, invasione vasi, budding, depth > 2 $\mu$
0	<b>0,7%</b> (1/138)	<b>0,0%</b> (0/56)
1	<b>20,7%</b> (12/58)	<b>3,3%</b> (3/92)
$\geq 2$	<b>36,4%</b> (20/55)	<b>29,1%</b> (30/103)

**Table 1** Univariate analysis of relationship between histopathological predictive factors for lymph node metastasis

	<i>No. of patients with LNM (n = 46)</i>	<i>No. of patients without LNM (n = 276)</i>	<i>Univariate P-value</i>
<i>Status of the muscularis mucosa</i>			
Type A <sup>a</sup>	1 (2%)	40 (98%)	0.02
Type B <sup>b</sup>	45 (16%)	236 (84%)	
<i>Submucosal invasion depth (µm)</i>			
< 1000	1 (3%)	33 (97%)	0.05
> 1000	45 (16%)	243 (84%)	
<i>Tumor budding</i>			
Positive	28 (26%)	78 (74%)	< 0.01
Negative	18 (8%)	198 (92%)	
<i>Tumor differentiation</i>			
Well	23 (9%)	225 (91%)	< 0.01
Moderate/poor	23 (31%)	51 (69%)	
<i>Lymphatic invasion</i>			
Positive	25 (33%)	51 (67%)	< 0.01
Negative	21 (9%)	225 (91%)	
<i>Venous invasion</i>			
Positive	13 (29%)	32 (71%)	< 0.01
Negative	33 (12%)	244 (88%)	

<sup>a</sup>Preserved or incompletely disrupted muscularis mucosa.

<sup>b</sup>Completely disrupted muscularis mucosa.

**Table 2** Multivariate analysis of risk factors for lymph node metastasis

<i>Factors</i>	<i>Odds ratio</i>	<i>95% CI</i>	<i>P-value</i>
Lymphatic invasion (+) vs lymphatic invasion (-)	3.19	0.22–0.94	< 0.01
Well differentiation vs moderate/poor differentiation	3.02	0.20–0.90	< 0.01
Tumor budding (+) vs tumor budding (-)	2.59	0.12–0.83	< 0.01

**322 CCR consecutivi  
Terapia chirurgica  
Metastasi linfonodali in 46 (14,3%)**

***Tateishi et al. 2010***

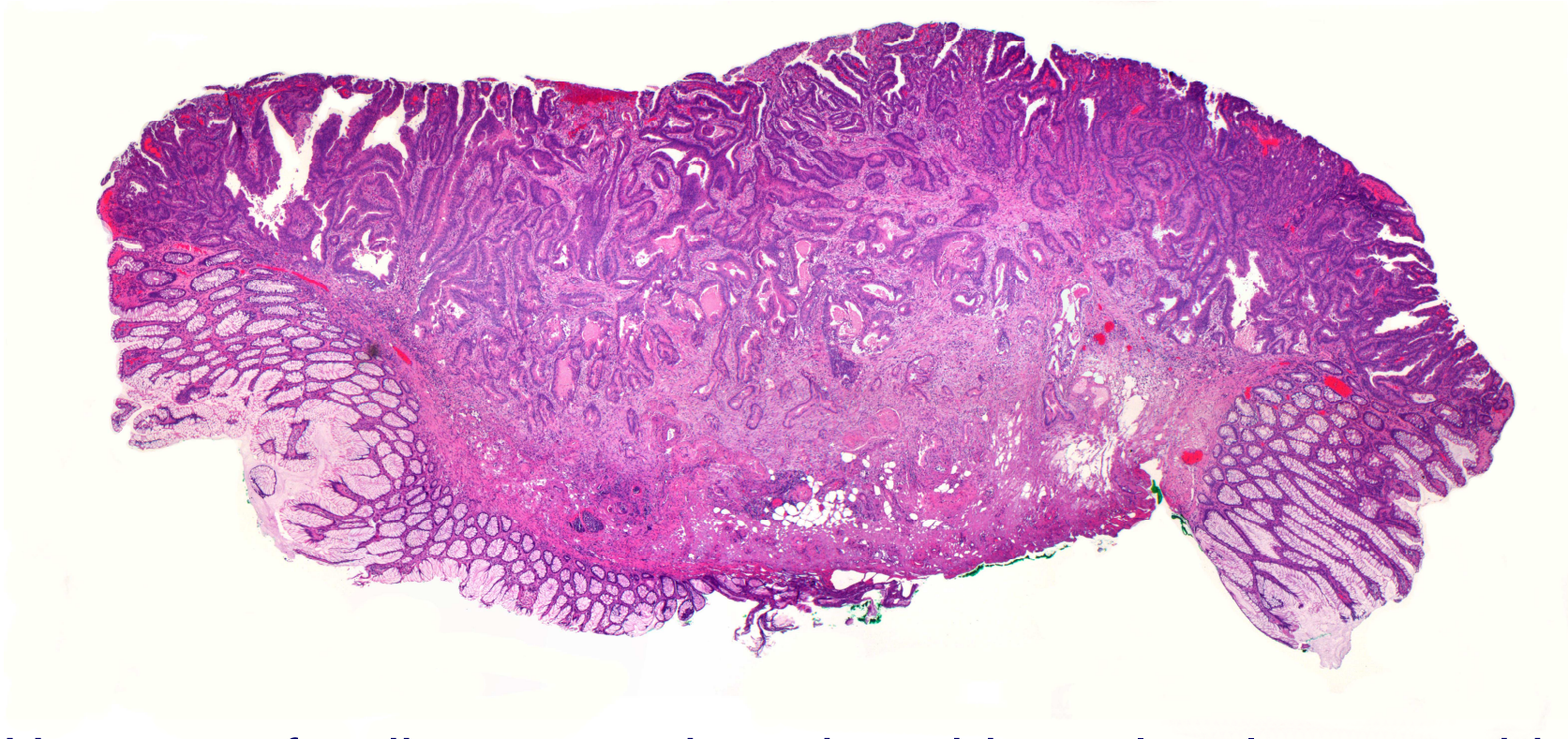
# *LG europeee - recommendations*

7.7 Sub-staging of T1 cancers should be performed to determine the risk of residual disease. Consideration should be given to the appropriate method, which may vary depending on the morphology of the lesion (Kikuchi/Haggitt or measurement). For non-polypoid lesions the Kikuchi stage and for pedunculated lesions Haggitt are currently recommended **(VI - C)**. High-risk features for residual disease such as lack of margin clearance ( $\leq 1$  mm), poor differentiation and lymphatic and vascular invasion should be reported **(V - B)**. The multidisciplinary team should be consulted on whether or not surgical resection of pT1 adenocarcinoma is recommended; 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 **(VI - A)**.<sup>Sect 7.5.3</sup>



Esistono markers da utilizzare  
nella pratica clinica per  
identificare i pazienti con lesioni  
ad alto rischio?

I CCR pT1 sono lesioni eterogenee come storia naturale e come caratteristiche biologiche



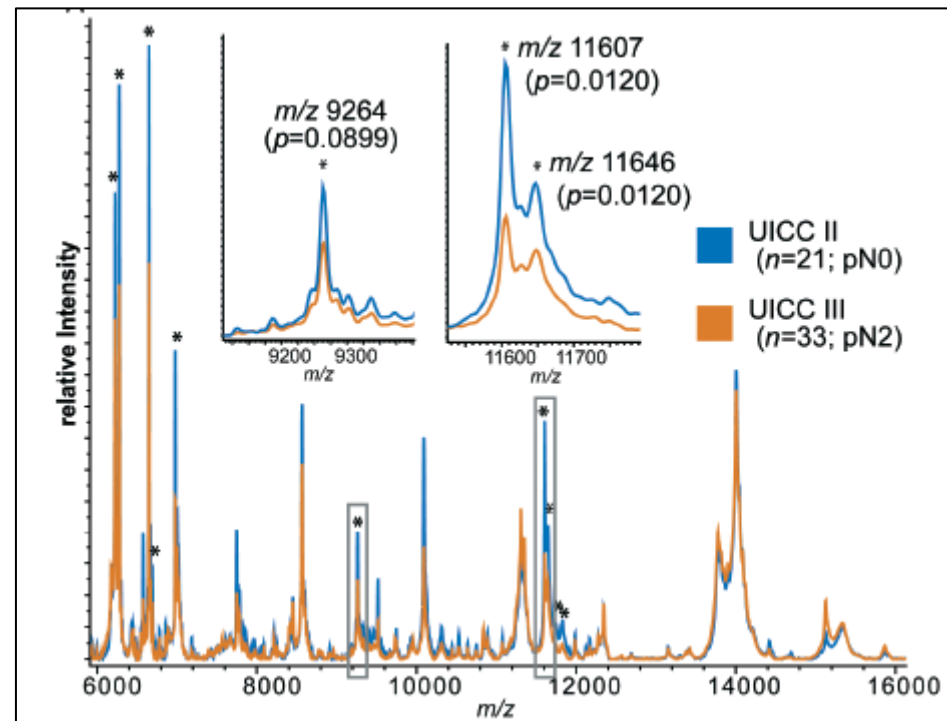
Una approfondita caratterizzazione bio-molecolare potrebbe consentire un approccio terapeutico mirato più appropriato



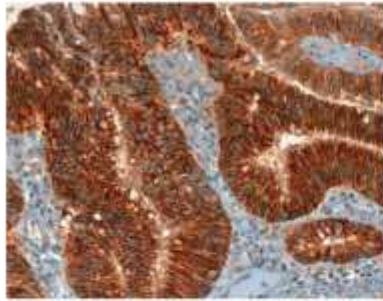
[giovanni.lanza@unife.it](mailto:giovanni.lanza@unife.it)

## Tissue-based proteomics reveals FXD3, S100A11 and GSTM3 as novel markers for regional lymph node metastasis in colon cancer

Stephan Meding,<sup>1</sup> Benjamin Balluff,<sup>1</sup> Mareike Elsner,<sup>1</sup> Cédrik Schöne,<sup>1</sup> Sandra Rauser,<sup>1</sup> Ulrich Nitsche,<sup>2</sup> Matthias Maak,<sup>2</sup> Alexander Schäfer,<sup>3</sup> Stefanie M Hauck,<sup>3</sup> Marius Ueffing,<sup>3,4</sup> Rupert Langer,<sup>5</sup> Heinz Höfler,<sup>1,5</sup> Helmut Friess,<sup>2</sup> Robert Rosenberg<sup>2,6</sup> and Axel Walch<sup>1\*</sup>

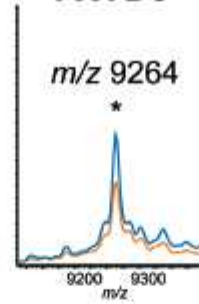


**UICC II (pN0)** ■

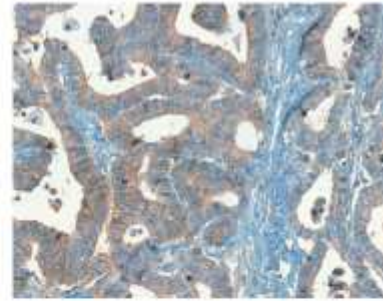


100  $\mu$ m

**FXYD3**

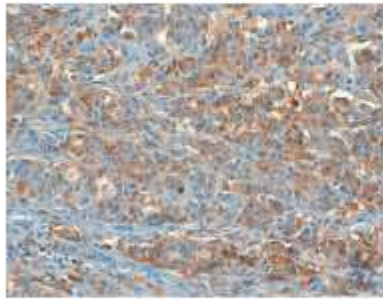
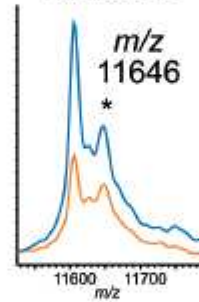


**UICC III (pN2)** ■

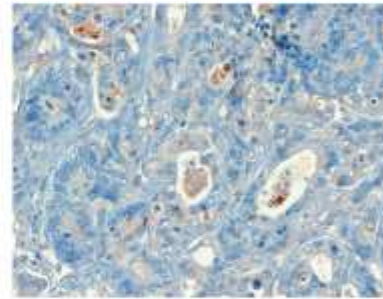


100  $\mu$ m

**S100A11**

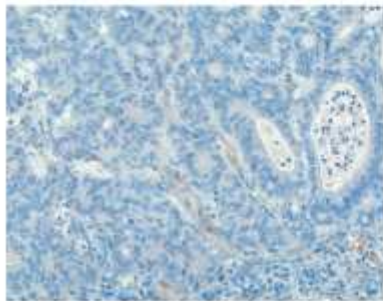
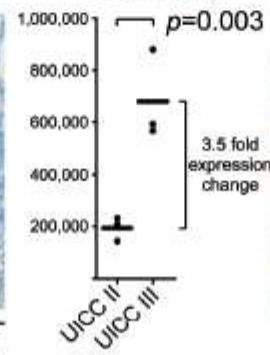


100  $\mu$ m

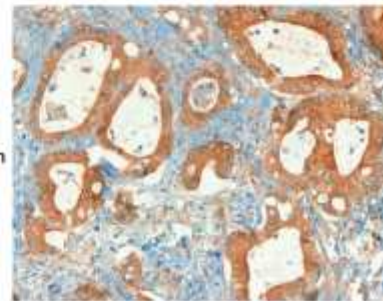


100  $\mu$ m

**GSTM3**



100  $\mu$ m



100  $\mu$ m