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GISCoR

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Mantova

8-9 Novembre 2012

Adenomi Cancerizzati

ovvero

“Ci sono novità morfologiche o molecolari nella definizione dei polipi cancerizzati ?”

Mauro Risio
Department of Pathology
Institute for Cancer Research and Treatment
Candiolo – Torino, Italy

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CANCERISED ADENOMA: Carcinoma Microstaging

European Guidelines for Quality Assurance in Colorectal Cancer Screening

European Commission

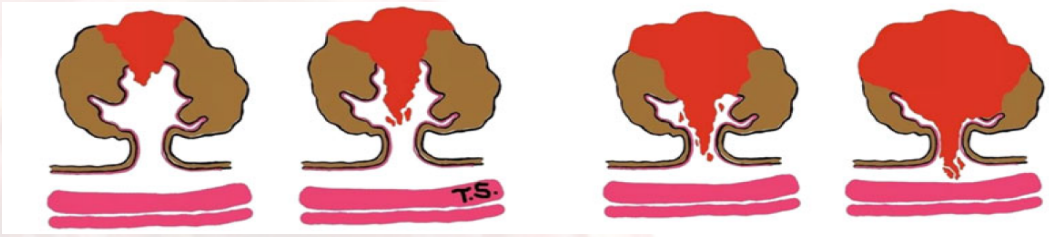
pT1 Cancer Substaging

Neither the Kikuchi (for sessile lesions) nor Haggitt (for polypoid tumors are easy to use in practice. The depth and the width of invasion provides a more objective measure.

Each classification has advantages and disadvantages.

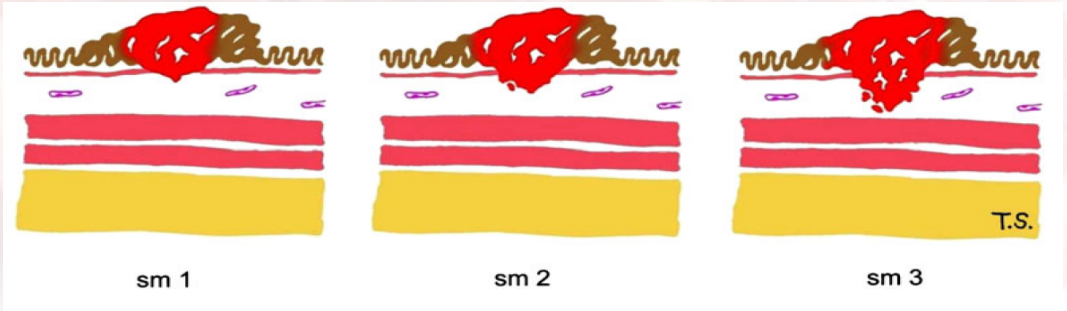
All three approaches need to be evaluated on large series from screening programmes to derive evidence-based recommendations.

[Quirke, Risio , Lambet, Vieth 2010]



1 2 3 4

Haggitt Levels



Kikuchi Levels

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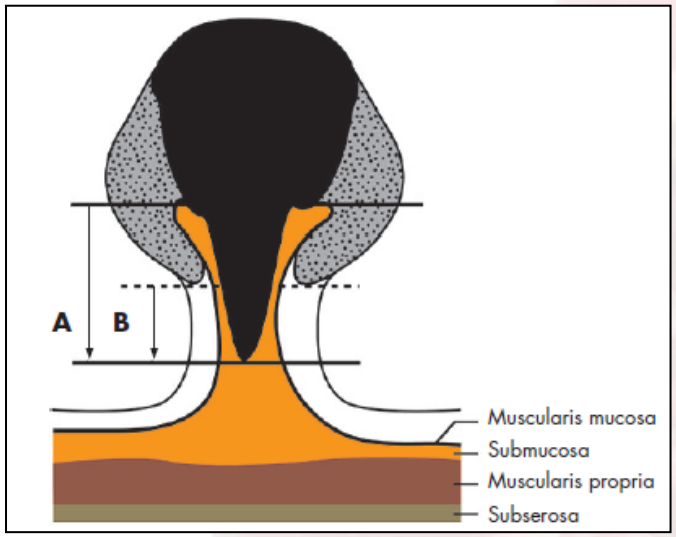
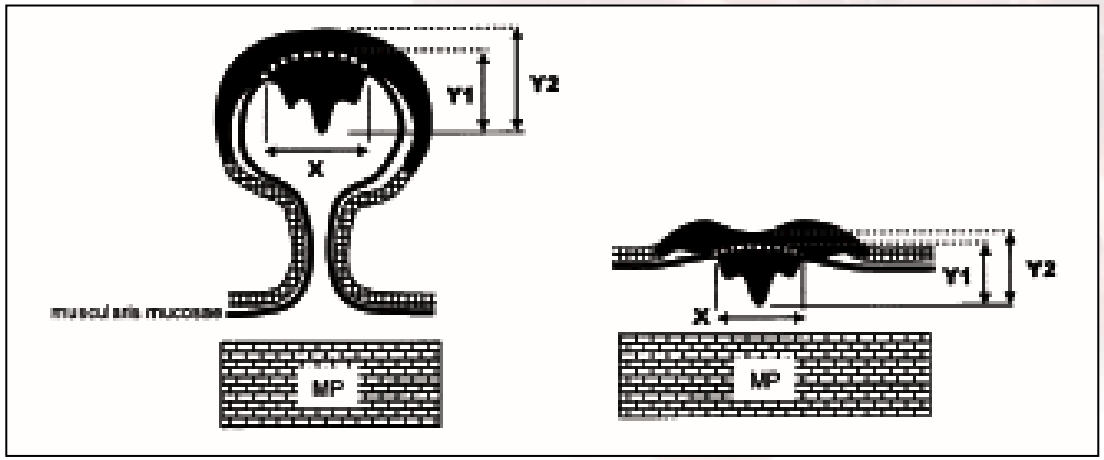
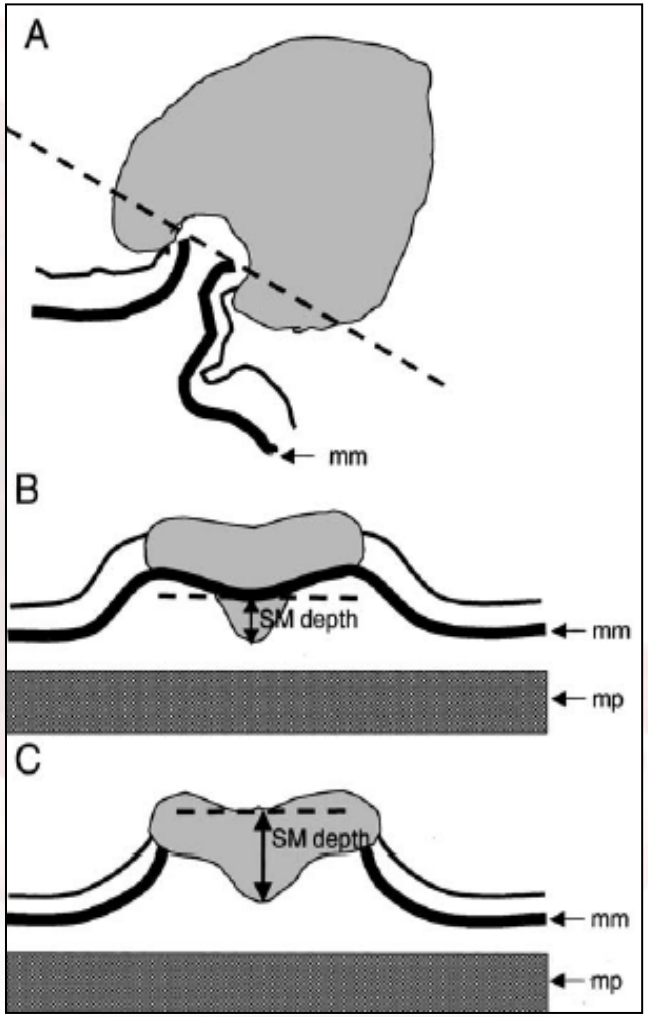
CANCERISED ADENOMA:
Carcinoma Microstaging



[Sohn et al, 2007]



[Ueno et al, 2004]



[Kitajma et al, 2004]

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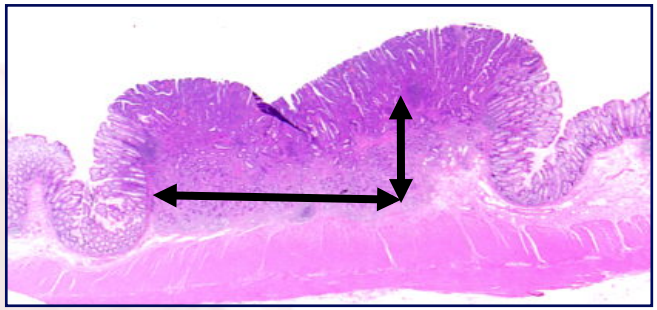
Cancerised Adenomas (pT1): Microstage as a Prognosticator

Lymph Node Metastasis
PEDUNCOLATED AND NON PEDUNCOLATED LESIONS

Width sm < 4000 µm:	**2.5%**
Width sm > 4000 µm:	**18.2%**
Depth sm < 2000 µm:	**3.9%**
Depth sm > 2000 µm:	**17.1%**

Ueno et al, 2004



	With Lymph Node Metastasis	Without Lymph Node Metastasis	P value
NON PEDUNCOLATED LESIONS			
SM Depth (µm):	**3343.2 ±1539.7**	**2743.3 ±2468.6**	**0.0038**
PEDUNCOLATED LESIONS			
SM Depth (µm):	**3455.4 ±1634.1**	**2500.3 ±1111.1**	**0.5022**

Kitajima et al, 2004

	With Lymph Node Metastasis	Without Lymph Node Metastasis	P value
PEDUNCOLATED LESIONS			
Objective SM Depth (Mean, mm):	**2.9**	**2.8**	**NS**
Depth of Stalk Invasion (Mean, mm):	**1.5**	**1.6**	**NS**

Sohn et al, 2007

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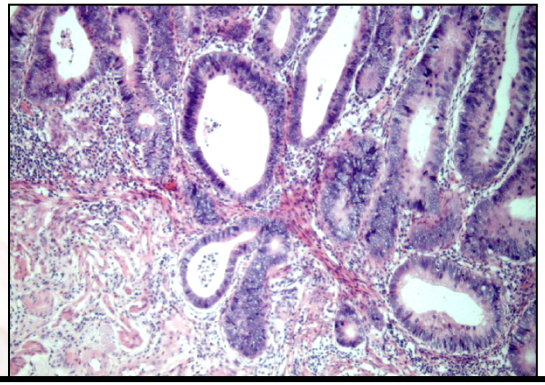
The Early Submucosal Invasion: Searching for the *"N0 Threshold"*

Depth of Submucosal Invasion: Y (μm)		
< 500	23	0
500<Y<1000	15	1(6.7%)
1000<Y<2000	38	2(5.3%)
2000<Y<3000	61	11(18%)



Minute depressed-type submucosal invasive cancer-5mm in diameter with intermediate lymph-node metastasis: a report of a case

Nakajima T, Saito Y, Hoshino T, Yamamoto S, Tamura T, Morriya Y, Saito D
Dis Colon Rectum 2007

«… Although this depressed-type cancer invaded the submucosal layer only 900 μm and there was no lymphovascular invasion, intermediate lymph node metastasis was detected…»

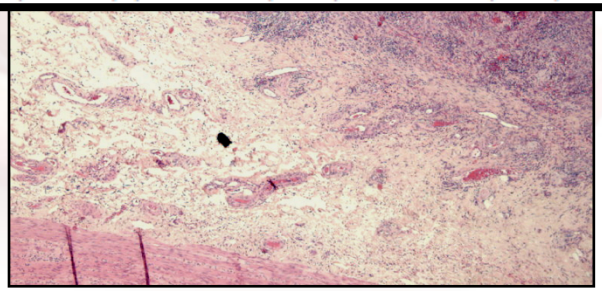
500 ≤ X < 1000 (*n* = 58)	0 (0)	12 (20.7)	7 (12.1)	7 (12.1)	58 (100)	0 (0)	51 (87.9)	7 (12.1)

< 1,500 μm	79	0 (0%)

Oh-e et al, 2001

Width of Submucosal Invasion: X (μm)		
< 2000	35	0
2000<X<3000	22	1(4.5%)
3000<X43000	24	1(4.2%)

Ueno et al, 2004



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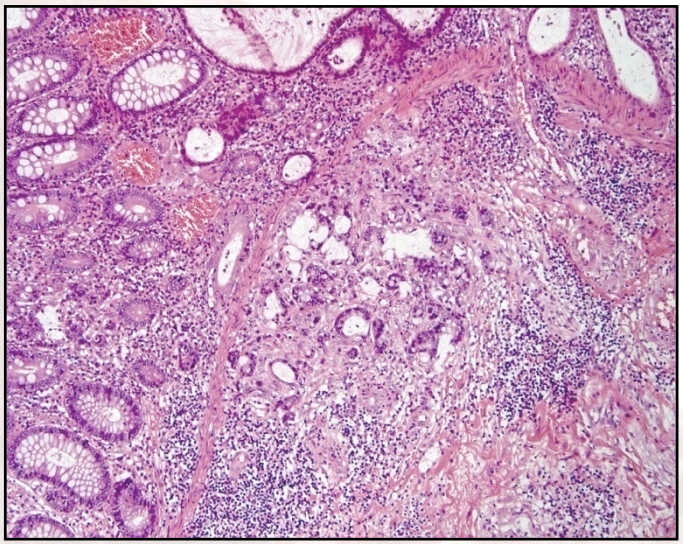
Cancerised Adenomas (pT1): Tumor Budding as Risk Factor

Tumor Budding as an Independent Prognosticator

• Hase et al, 1995	pT1 CRC
• Goldstein et al, 1999	pT1-2 CRC
• Masaki et al, 2001	pT1 CRC
• Ueno et al, 2002	pT2-4 CRC
• Okuyama et al, 2002	pT1-2 CRC
• Okuyama et al, 2003	pT3 CRC
• Ueno et al, 2004	pT1 CRC
• Wang et al, 2005	pT1 CRC
• Kazama et al, 2006	pT1 CRC
• Shinto et al, 2006	pT3 CRC
• Nakamura et al, 2008	Stage II CRC



- Unfavorable Tumor Grade
- Definite Vascular Invasion
- Tumor Budding

No-risk Group:
0.7%

Single-risk Group:
20.7%

Multiple-risk Group:
36.4

[Ueno et al, 2004]

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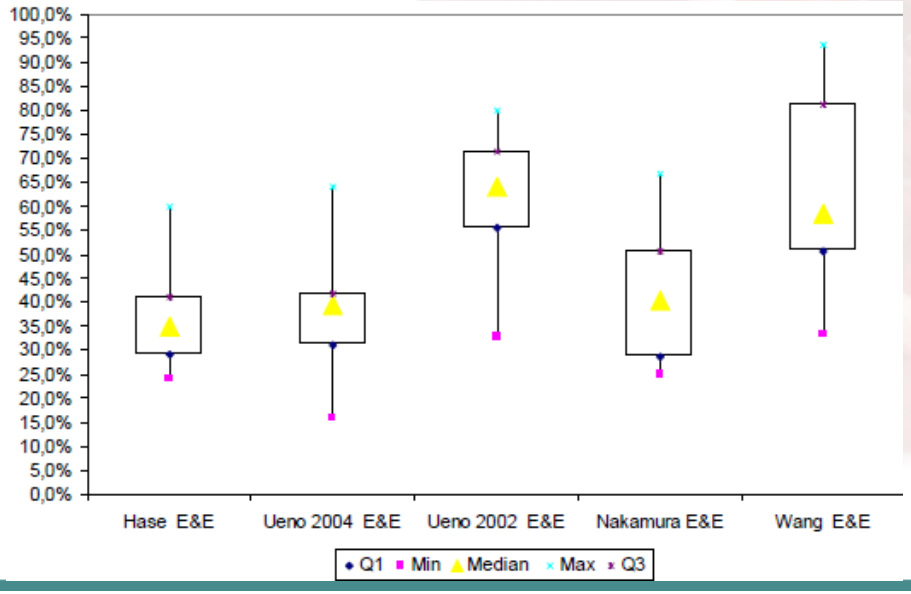
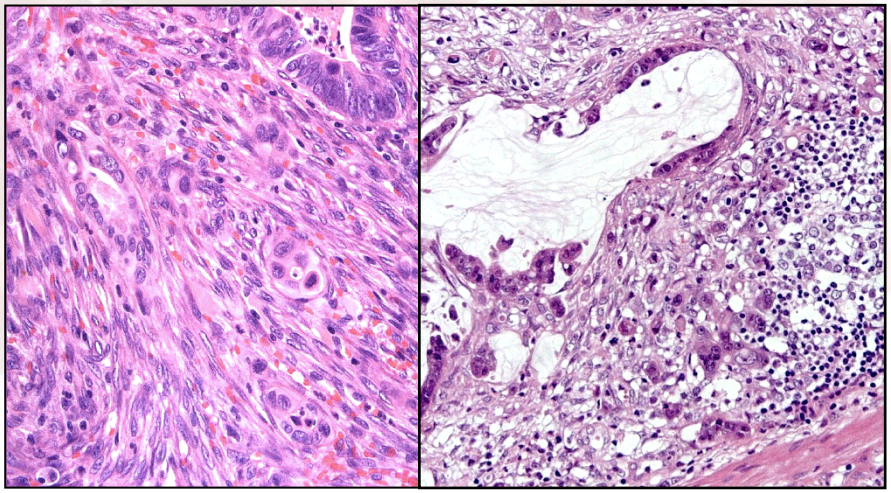
Diagnostic Reproducibility of Tumor Budding in Colorectal Cancer: a Multicentre, Multinational Study using Virtual Microscopy

Giacomo Puppa,1 Carlo Senore,2 Kieran Sheahan,3 Michael Vieth,4 Alessandro Lugli,5 Inti Zlobec,5 Sara Pecori,6 Lai Mun Wang,7 Cord Langner,8 Hiroyuki Mitomi,9 Takatoshi Nakamura,10 Masahiko Watanabe,10 Hideki Ueno,11 Jacques Chasle,12, Stephen A. Conley,13 Paulette Herlin,14 and MauroRisio15

Histopathology 2012

	H&E median range		IHC median range		H&E Kappa overall 95% CI	IHC Kappa overall 95% CI
pT1						
Hase	0.59		0.53		0.61	0.51
	1.00	−0.17	1.00	−0.08	0.53–0.69	0.43–0.58
Ueno (2004)	0.44		0.52		0.45	0.49
	1.00	−0.13	0.86	0.11	0.38–0.53	0.42–0.57
Ueno (2002)	0.46		0.32		0.42	0.28
	0.86	−0.29	1.00	−0.09	0.34–0.50	0.21–0.36





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CANCERISED ADENOMA :
Assessment of the Metastatic Risk

MICROSTAGING
Submucosal Invasion Depth

< 500 µm

MINIMAL RISK
(0-0,7%)

- **Carcinoma Grading:**
  1 – 2
- **Tumor Budding:**
  Absent / Low Grade
- **Vascular Invasion:**
  Absent

> 500 µm

LOW RISK
(8-10%)

INTERMEDIATE RISK
(10-20%)

>2000µm

HIGH RISK
(20-40%)

- **Carcinoma Grading:**
  3 – 4
  or
- **Tumor Budding:**
  Present / High Grade
  or
- **Vascular Invasion:**
  Present

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Adenomi Cancerizzati: Invasione Linfo-Vascolare

« Esiste un razionale biologico nel distinguere tra i parametri di rischio degli adenomi cancerizzati l'invasione vascolare linfatica da quella ematica ? «

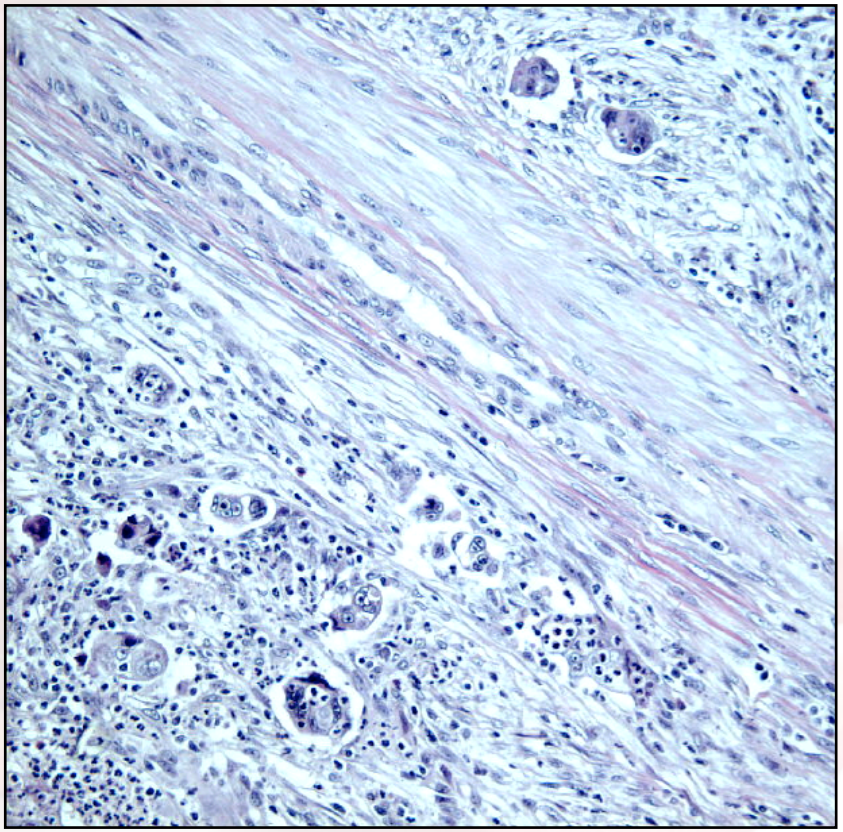
Mauro Risio
Department of Pathology
Institute for Cancer Research and Treatment
Candiolo – Torino, Italy

Cancerised Adenoma: Lymphovascular Invasion

It is NOT an independent risk factor at multivariate analysis
(Netzer et al., 1998; Masaki and Muto, 2000)

NO differences in clinical outcomes were found pooling low-risk pT1 carcinomas with those with only vascular invasion
(Hassan et al., 2005)

It has been demonstrated that definite vascular invasion without other unfavorable pathologic features is associated with an adverse outcome
(Ueno et al, 2004)



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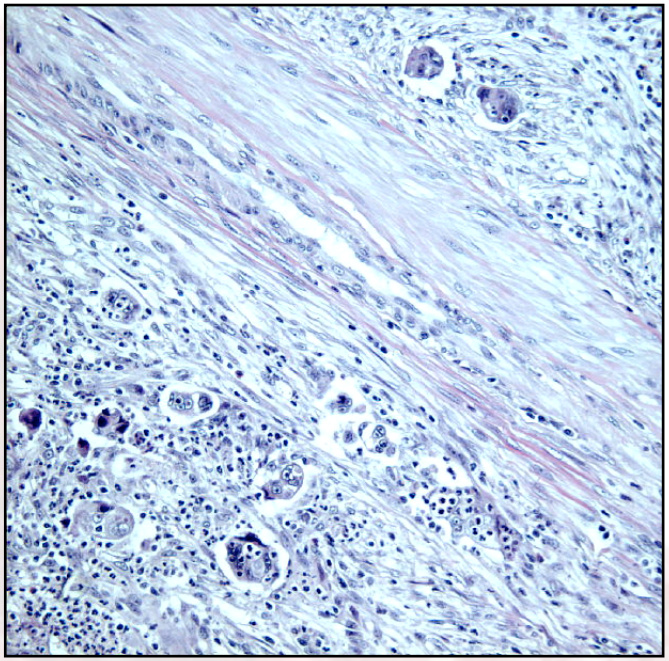
Cancerised Adenoma: Lymphovascular Invasion

Distinguishing true invasion of endothelium-lined vascular spaces in the submucosa from retraction artifact around cancer cell aggregates is difficult, could require the additional use of immunohistochemistry

(Cooper et al, 2007; Ishikawa et al., 2008; Suzuki et al., 2009)



Sometimes retraction artefact around tumour aggregates can make assessment uncertain, in which case this uncertainty should be recorded and the observation interpreted by the MDT in the light of any other adverse histological features. At the moment there are no consistent data available on the additional use of immunohistochemistry.

Quirke P, Risio M, Lambert R, von Karsa L, Vieth M.
EU Guidelines for Quality Assurance in Colorectal Cancer Screening, 2010

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Cancerised Adenomas: Histological Risk Factors and Clinical Outcomes

	RESIDUAL DISEASE	RECURRENT DISEASE	LYMPH NODE METASTASIS	HAEMATIC METASTASIS	MORTALITY
HIGH GRADE INVASIVE CARCINOMA	10 / 56 (18.7%) OR: 2.2 (1-4.8)	----	13 / 56 (23.2%) OR: 3.9 (1.9-8.4)	11 / 114 * (9.6%) OR: 3.9 (2-7.9)	14 / 96 * (14.6%) OR: 9.2 (4-18.3)
VASCULAR INVASION	6 / 34 (17.6%) OR: 1.2 (.4-3.3)	---	12 / 34 * (35.3%) OR: 7 (2.6-19.2)	13 / 250 (5.2%) OR: 1.8 (0.9-3.4)	7 / 210 (3.3%) OR: 1.4 (0.6-3.3)
RESECTION MARGIN	55 / 181 * (30.4%) OR: 15 (5.3-42.7)	13 / 77 * (16.8%) OR: 17.9 (5.7-56.7)	13 / 181 (72%) OR: 0.8 (0.3-1.7)	30 / 325 (9.2%) OR: 8.2 (3.7-18.2)	26 / 325 (8%) OR: 6.2 (5.2-13.5)

* $p < 0.05$

[Hassan, Risio, Morini, Dis Colon Rectum 2005]

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Cancerised Adenoma: Lymphatic and Vascular Invasion

Lymphatic invasion
(LYVE-1 immunohistochemistry)

<.0001*

Yes	**18**	**vs**	**4**
No	**10**	**vs**	**39**

Lymphatic invasion
(double staining with Victoria blue and H&E dyes)

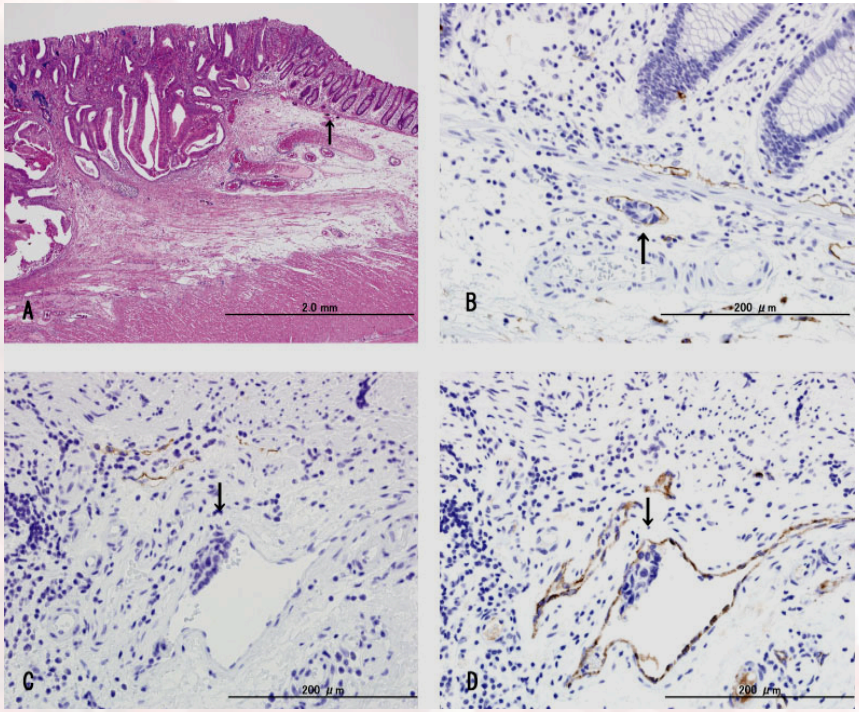
.0004*

Yes	**14**	**vs**	**5**
No	**14**	**vs**	**38**

Venous invasion

.1303

Yes	**8**	**vs**	**6**
No	**20**	**vs**	**37**



Lymphatic invasion corroborated by LYVE-1 immunohistochemistry was an independent predictor of LN metastasis in ECC, but venous invasion confirmed by vWF immunohistochemistry was not related to LN status

[Ishikawa et al, 2008]

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Gestione Clinica dei Polipi Serrati

ovvero:

"Cosa sono le lesioni serrate?"

"Ci sono anche i cancri serrati?"

Mauro Risio
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Polipi Serrati:
La Displasia Cito-Cariologica

Adenoma Serrato Polipoide

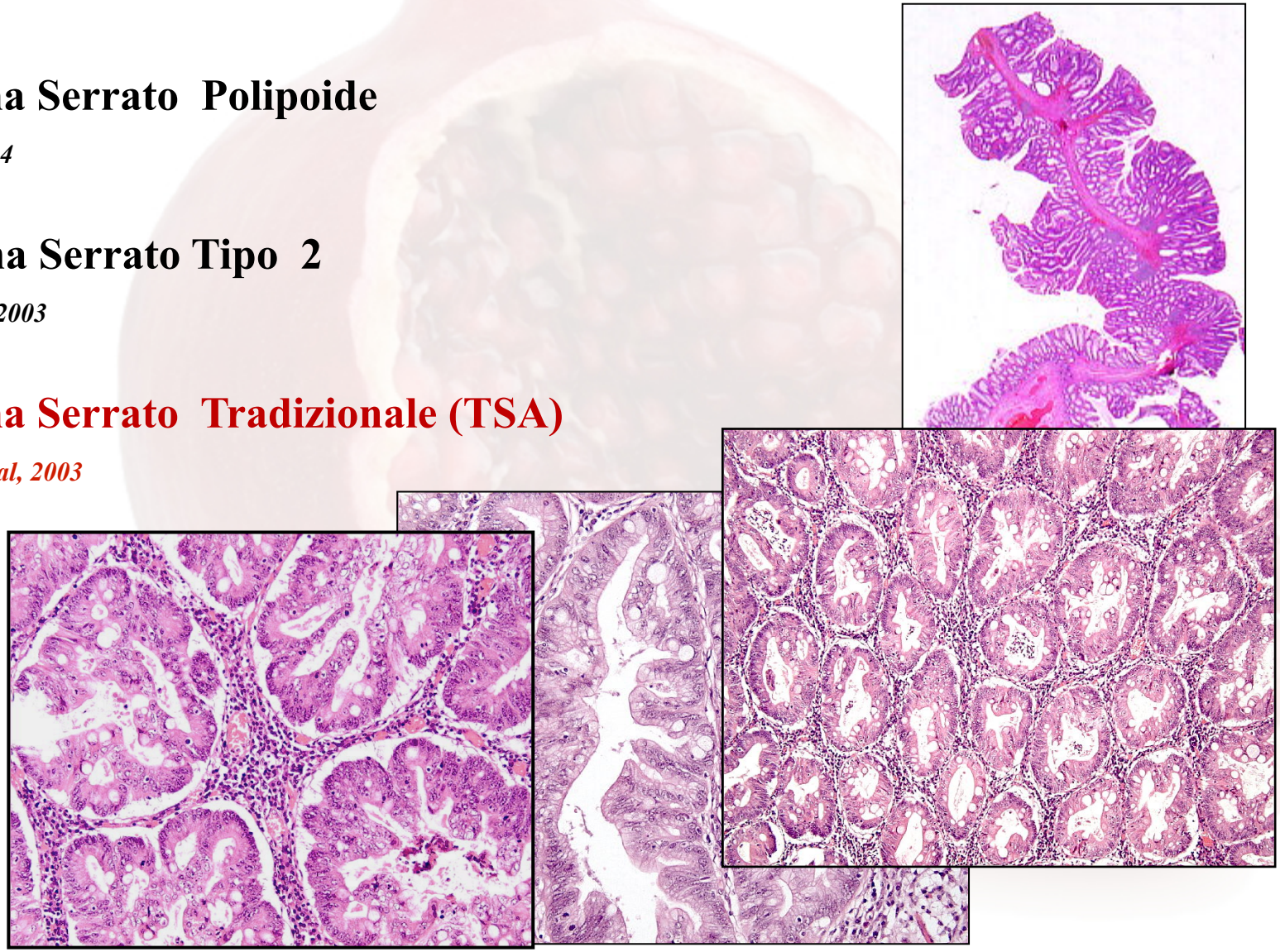
Oka et al, 2004

Adenoma Serrato Tipo 2

Mitomi et al, 2003

Adenoma Serrato Tradizionale (TSA)

Torlakovic et al, 2003



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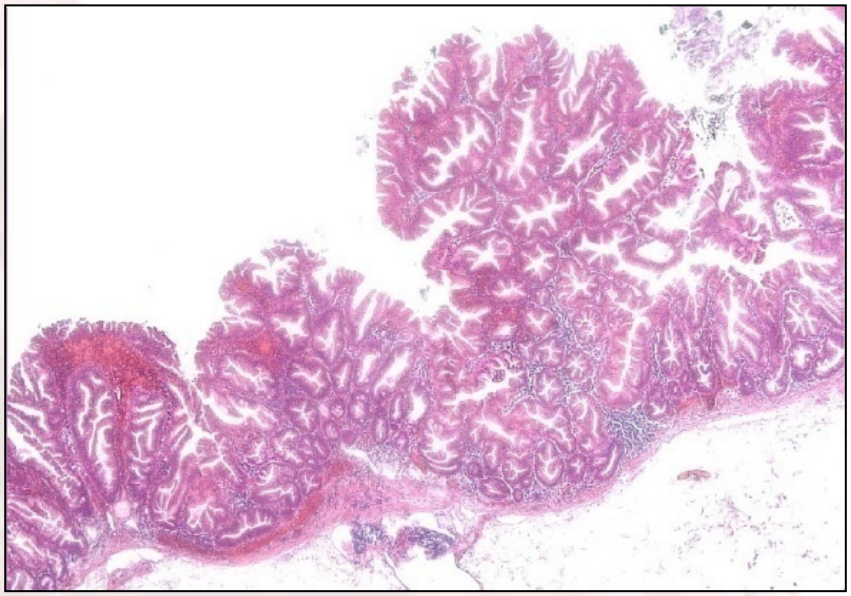
Polipi Serrati:
Le Alterazioni Architetturali

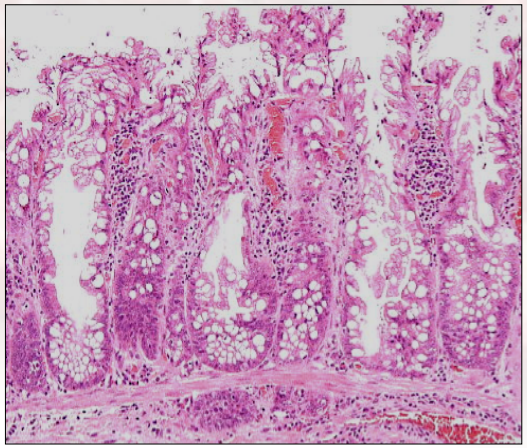
Polipi Serrati Sessili

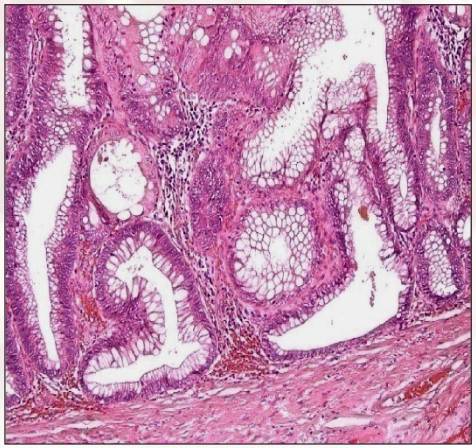


Polipo Serrato Sessile (SSP)
Quirke, Risio, Lambert, Vieth, 2011

Adenoma Serrato Sessile (SSA)
Torlakovic, Snover 1996

(SSA / SSP)





Adenoma Serrato Superficiale
Oka et al, 2004

Adenoma Serrato Tipo 1
Mitomi et al, 2003

Polipo Serrato con Anomalie Proliferative
Torlakovic et al, 2003

Diagnostic Reproducibility

	TSA	SSA	HP	Overall
First Round	0.809	0.455	0.519	0.556
Second Round	0.784	0.323	0.422	0.469
Third Round	0.831	0.478	0.527	0.581

[Farris et al, AJSP 2008]

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Diagnostic Reproducibility

Table 3 Intraobserver agreement (first diagnosis using optical microscopy, second using virtual microscopy) in 457 screen-detected polyps

A unit	Advanced	High-grade dysplasia	Villous component	Hyperplastic/sessile serrated lesion
Optical	105	40	95	167
Virtual	108	54	81	151
κ statistics (95% CI)	0.76 (0.69 to 0.83)	0.70 (0.59 to 0.81)	0.78 (0.70 to 0.85)	0.87 (0.82 to 0.6491)
B unit	**Advanced**	**High-grade dysplasia**	**Villous component**	**Hyperplastic/sessile serrated lesion**
Optical	112	99	57	153
Virtual	117	101	62	147
κ statistics (95% CI)	0.81 (0.74 to 0.87)	0.78 (0.71 to 0.85)	0.89 (0.83 to 0.96)	0.88 (0.83 to 0.92)

Table 4 Interobserver agreement using either optical or virtual microscopy in 457 screen-detected polyps

Optical	Advanced	High-grade dysplasia	Villous component	Hyperplastic/sessile serrated lesion
A unit	105	40	95	167
B unit	112	99	57	153
κ statistics (95% CI)	0.63 (0.55 to 0.70)	0.42 (0.32 to 0.53)	0.52 (0.41 to 0.62)	0.77 (0.71 to 0.83)
Virtual	**Advanced**	**High-grade dysplasia**	**Villous component**	**Hyperplastic/sessile serrated lesion**
A unit	108	54	81	151
B unit	117	101	62	147
κ statistics (95% CI)	0.65 (0.57 to 0.73)	0.39 (0.28 to 0.49)	0.66 (0.57 to 0.76)	0.79 (0.73 to 0.85)

[Risio et al, AJCP 2010]

Polipi Serrati Sessili e Neoplasia Colorettale Sincrona

Baseline	Advanced adenoma	≥3 Tubular adenomas[a]
Proximal ND-SP (n = 248), %	17.3	10.7
No Proximal ND-SP (n = 2873), %	10.0	5.3
OR (95% CI)	1.90 (1.33–2.70)	2.19 (1.36–3.52)
Large ND-SP (n = 44), %	27.3	9.4
No Large ND-SP (n = 3077), %	10.3	5.6
OR (95% CI)	3.37 (1.71–6.65)	1.72 (0.52–5.73)

[Schreiner, Weiss and Liebermann, 2010]

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Polipi Serrati Sessili e Neoplasia Colorettale Metacrona

Findings on baseline CSP	Baseline CSP (*n*)	Subjects with follow-up CSP, *n* (%)	Advanced neoplasia on follow-up CSP, *n* (%)	OR (95% CI)	Any neoplasia on follow-up CSP, *n* (%)	OR (95% CI)
No neoplasia	1950	454				
With proximal ND-SP	118	39 (33.1)	2 (5.1)	2.09 (0.44–9.87)	17 (43.6)	3.14 (1.59–6.20)
Without proximal ND-SP	1832	415 (22.6)	11 (2.7)		83 (20.0)	
Small tubular adenoma <10 mm	842	634				
With proximal ND-SP	87	63 (72.4)	5 (7.9)	1.23 (0.46–3.28)	26 (41.3)	0.96 (0.57–1.63)
Without proximal ND-SP	755	571 (75.6)	36 (6.3)		240 (41.8)	
Advanced neoplasia	329	283				
With proximal ND-SP	43	38 (88.4)	11 (28.9)	2.25 (1.02–4.96)	27 (71.1)	2.17 (1.03–4.59)
Without proximal ND-SP	286	245 (85.7)	36 (14.7)		127 (51.8)	

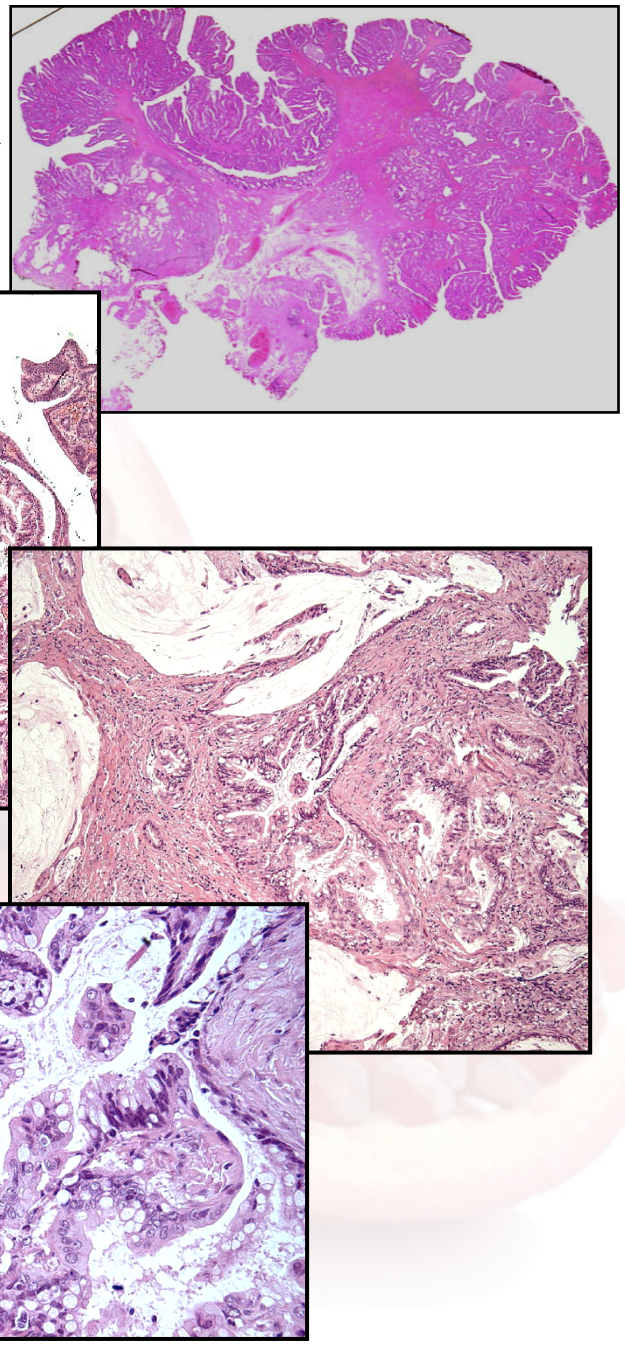
[Schreiner, Weiss and Liebermann, 2010]

Sequenza
Polipo Serrato – Adenocarcinoma

Polipi Serrati Sincroni con Adenocarcinoma
5.8% (27 / 466)
[Makinen et al, J Pathol 2001]

– **Polipi Serrati Sincroni con Adenocarcinoma MIN+**
55% (16 / 29)
[Hawkins et al, NCI 2001]

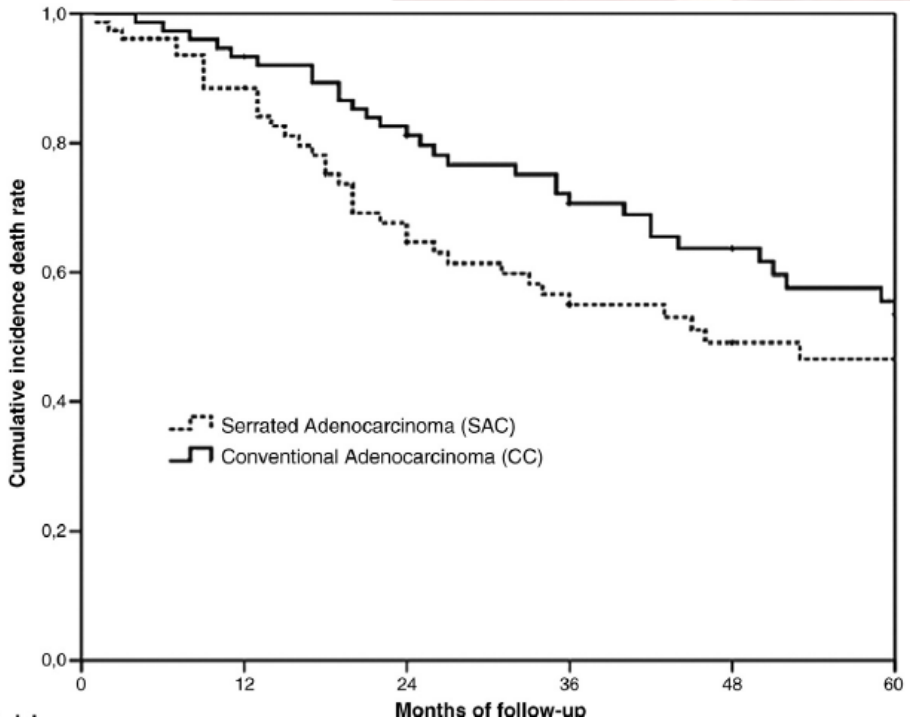
– **Poliposi Serrate con Adenocarcinoma**
58% (7 / 12)
[Leggett at al, AJSP 2001]

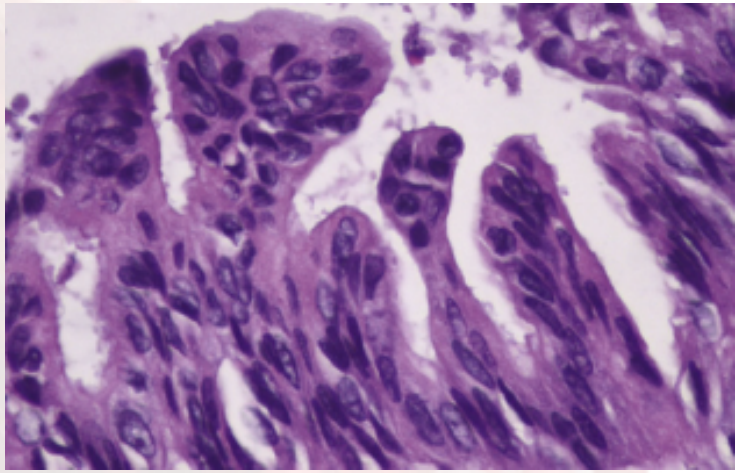


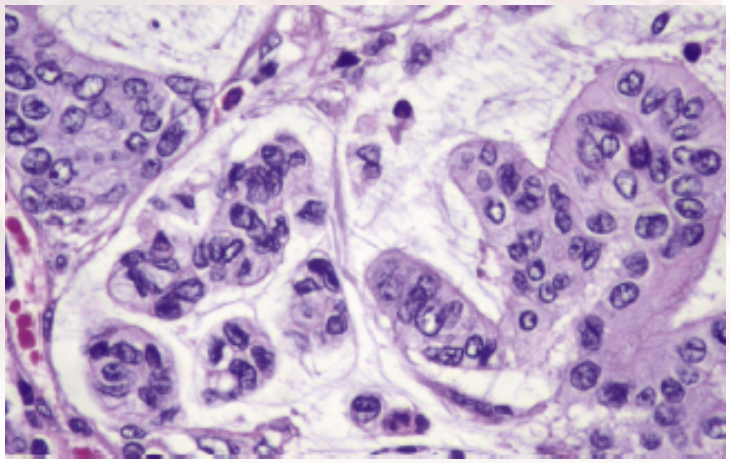
L'Adenocarcinoma Serrato

Serrated adenocarcinomas were encountered in 9.1%

More often accompanied by synchronous residual serrated adenomas

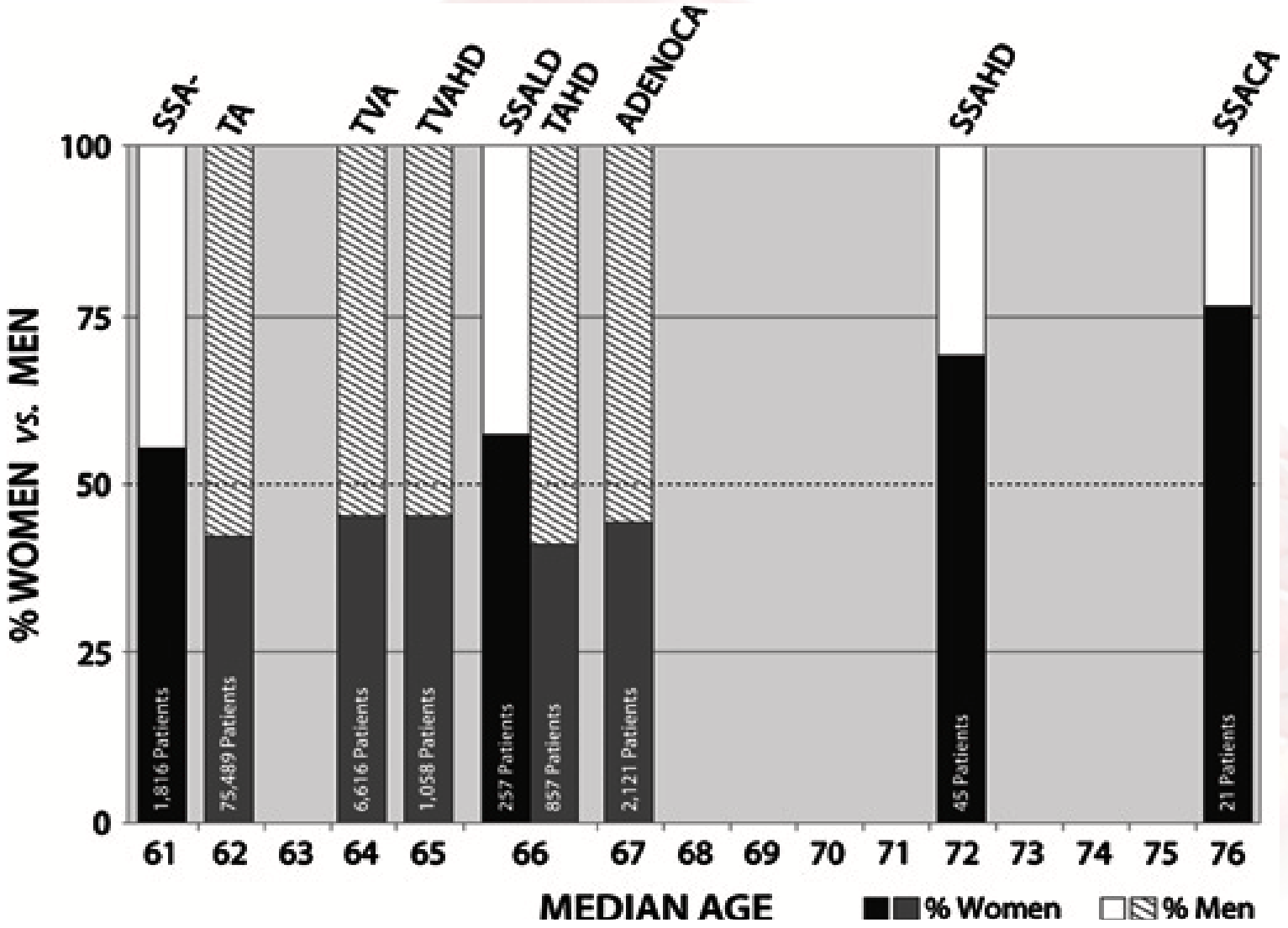






Garcia-Solano et al, 2010

Serrated Polyp – Carcinoma Sequence: Progression Times



Lash et al, JCP 2010

Serrated Polyp – Carcinoma Sequence: Progression Times

Case No./ Sex/Age (y)	Location	Size (cm)	Lesion	MLH1	PMS2	MSH2	MSH6
1/M/72	Mid-descending	1.0	HGD and focal invasion	SSA, +; HGD, –; invasive, –	SSA, +; HGD, –; invasive, –	+	+
2/M/56	Rectosigmoid	1.3	HGD	SSA, +; HGD, +	SSA, +; HGD, +	+	+
3/F/60	Ascending	0.3	HGD	SSA, +; HGD, –	SSA, +; HGD, –	+	+
4/M/54	Distal sigmoid	1.0	HGD and invasive	SSA, +; HGD, +; invasive, +	SSA, +; HGD, +; invasive, +	+	+
5/F/82	Ascending	0.5	HGD	SSA, +; HGD, –	SSA, +; HGD, –	+	+
6/F/87	Proximal ascending	0.6	HGD and focal invasion	SSA, +; HGD, –*	SSA, +; HGD, –*	+	+
7/F/81	Descending	1.4	HGD	SSA, +; HGD, —	SSA, +; HGD, –	+	+
8/M/71	Rectosigmoid	1.0	HGD	SSA, +; HGD, +	SSA, +; HGD, +	+	+
9/F/80	Transverse	0.3	HGD and invasive	SSA, unavailable; HGD, –; invasive, –	SSA, unavailable; HGD, –; invasive, –	+	+
10/F/67	Ascending	1.0	LGD	SSA, + (weak); LGD, –/weaker	SSA, +; LGD, –	+	+
11/F/72	Ascending	1.4	HGD and invasive	SSA, +; HGD, +; invasive, +	SSA, +; HGD, +; invasive, +	+	+

Sheridan et al, AJP 2006

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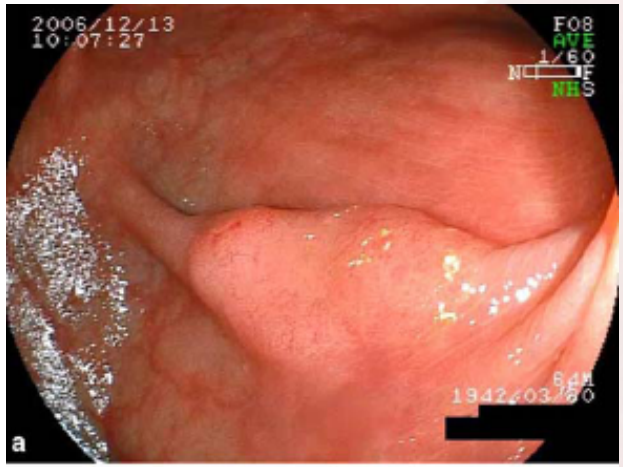
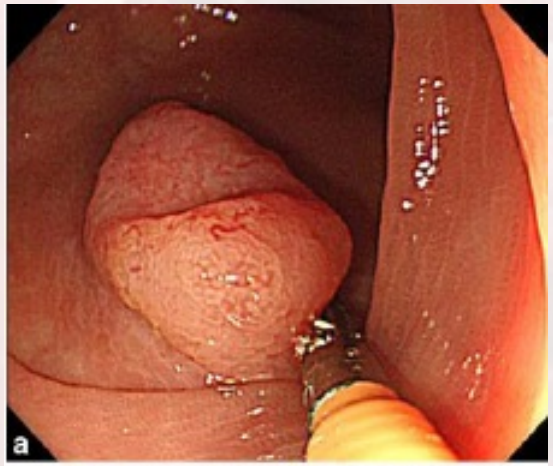
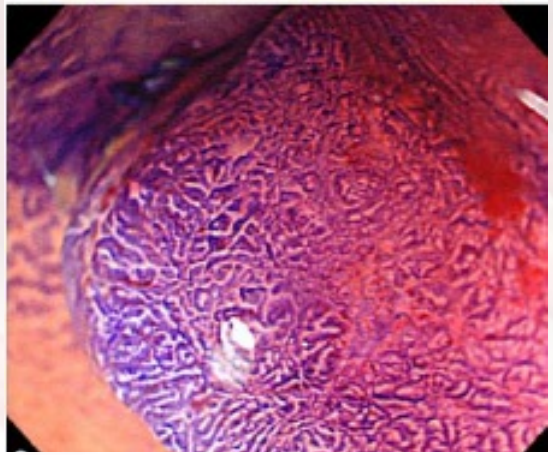
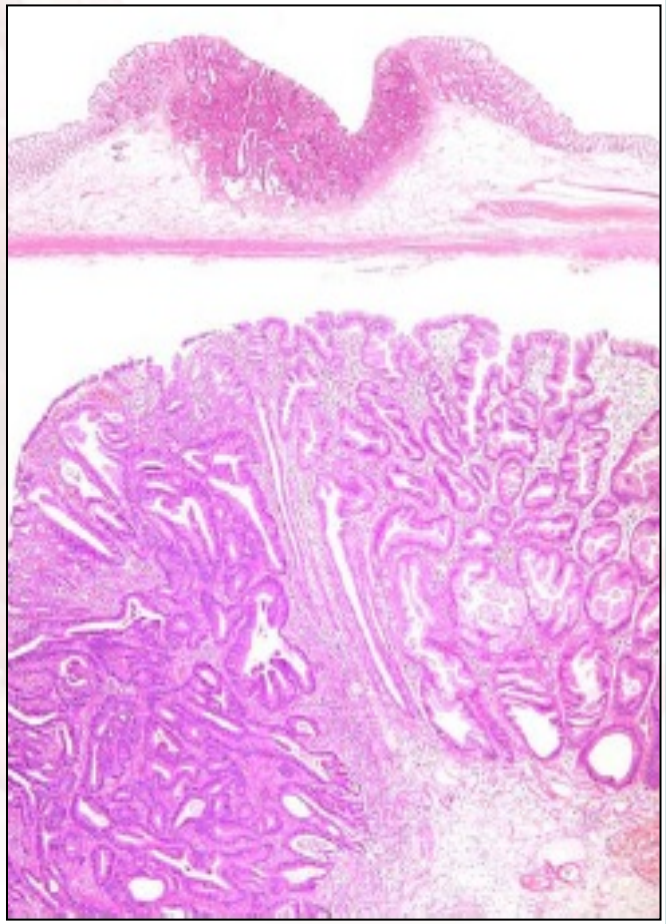
Progression of a Sessile Serrated Adenoma to an Early Invasive Cancer Within 8 Months

Yasuhiro Oono · Kuangi Fu · Hisashi Nakamura · Yosuke Iriguchi · Akihiko Yamamura · Yasuhiro Tomino · Johji Oda · Masaru Mizutani · Satoshi Takayanagi · Daisuke Kishi · Tomoaki Shinohara · Kozo Yamada · Jun Matumoto · Kazuhiro Imamura









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Serrated Polyp – Carcinoma Sequence: Interval Cancers

Variable	Interval (*n*=63)	Non-interval (*n*=131)	*P* value
Age (years)	75±8	73±8	NS
Follow-up (months)	46.4±5.4	47.1±3.8	NS
Proximal location	40 (63%)	51 (39%)	0.002
Size (cm)	3.6±2	4.5±2	0.001
Mucinous histology	20 (32%)	11 (9%)	0.001
Differentiation			
Poor	11 (17%)	19 (14%)	
Moderate/well	48 (76%)	107 (81%)	NS
Unknown	4 (6%)	5 (4%)	
TNM stage			
I	19 (31%)	33 (26%)	
II	25 (41%)	44 (34%)	
III	11 (17%)	31 (24%)	NS
IV	6 (9%)	21 (15%)	
Unknown	2 (2%)	2 (1%)	

	Interval	Non-interval	*P* value
CIMP[a]			
Positive	31 (57%)	33 (33%)	0.004
Negative	23 (43%)	75 (66%)	
MSI[b]			
MSI	16 (29%)	12 (11%)	0.004
MSS	39 (71%)	95 (89%)	

	CIMP+ *n*=69 (%)	CIMP– *n*=98 (%)	*P* value
Size (cm)	4.0±2.1	4.5±2.3	NS
Location			
Proximal	40 (58%)	40 (41%)	0.02
Distal	29 (42%)	58 (57%)	
Mucinous histology	13 (19%)	15 (15%)	NS

	MSI *n*=28 (%)	MSS *n*=134 (%)	*P* value
Size (cm)	4.9±2.5	4.2±2.2	NS
Location			
Proximal	21 (78%)	57 (42 %)	0.001
Distal	7 (25%)	77 (58%)	
Mucinous histology	13 (46%)	13 (9%)	0.001

[Arain et al, 2010]

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Adenomi Sanguinanti e non Sanguinanti: Due Categorie Istologiche?

ovvero:

“ Un adenoma di 4 mm lo troviamo per caso o perché sanguina? ”

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Candiolo – Torino, Italy

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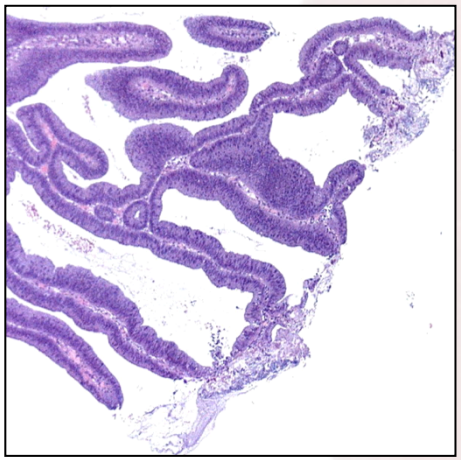
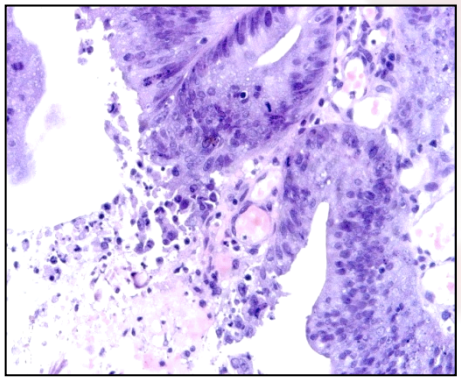
FASE 1





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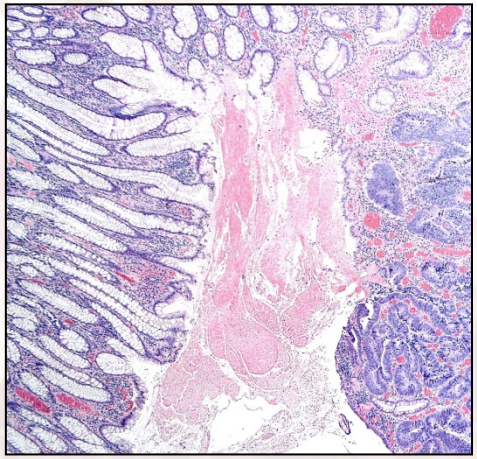

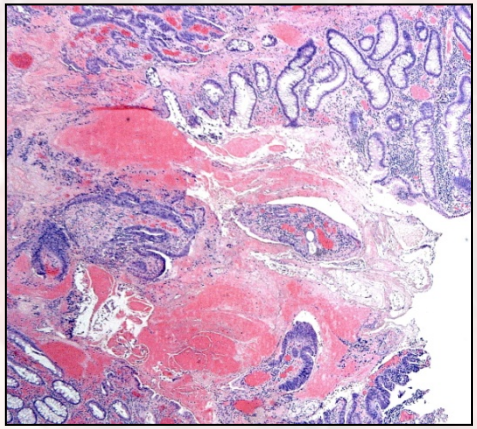

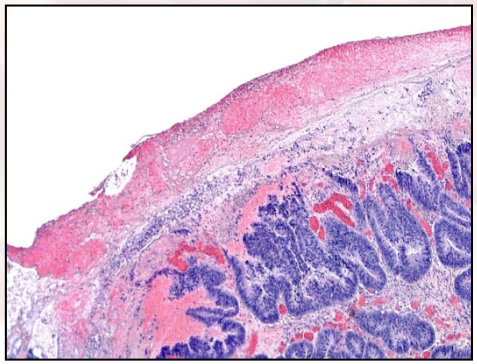

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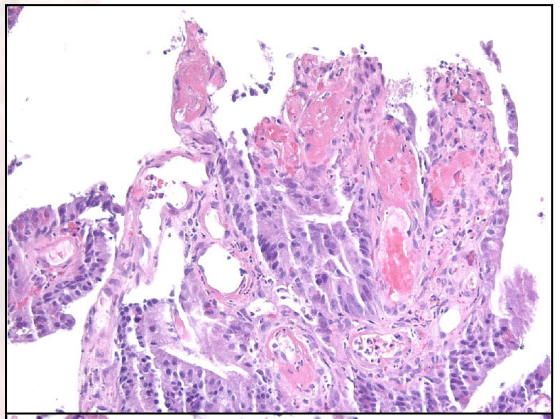

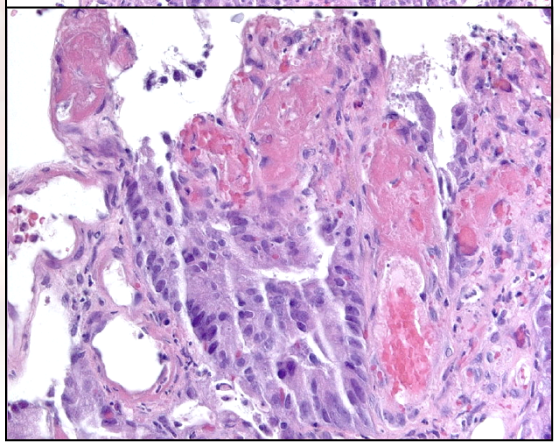

Istologia del Sanguinamento Endoluminale: Distribuzione per Modalità di Detezione

	Negativi	Fase 1	Fase 2	Fase 3	Totale
FOBT	7 / 33	8 / 33	12 / 33	6 / 33	26 / 33 (79%)
Endoscopia	84 / 90	10 / 90	4 / 90	2 / 90	16 / 90 (18%)

p = 0.0001

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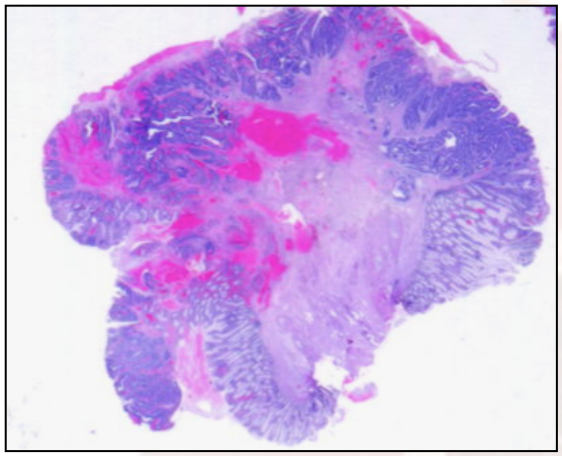

Polipi FOBT+
"Il Polipo "Sanguinante"

- **E' identificato casualmente *("Random Detection")* dal Test FOBT tra i Polipi Adenomatosi, prevalentemente di Tipo avanzato.**

OPPURE

- **E' un sottogruppo di Polipi Adenomatosi Avanzati, con Meiopragia al Sanguinamento, il cui Fenotipo è espressione di un percorso genetico-molecolare differenziato.**

Storia Naturale Diversificata ?

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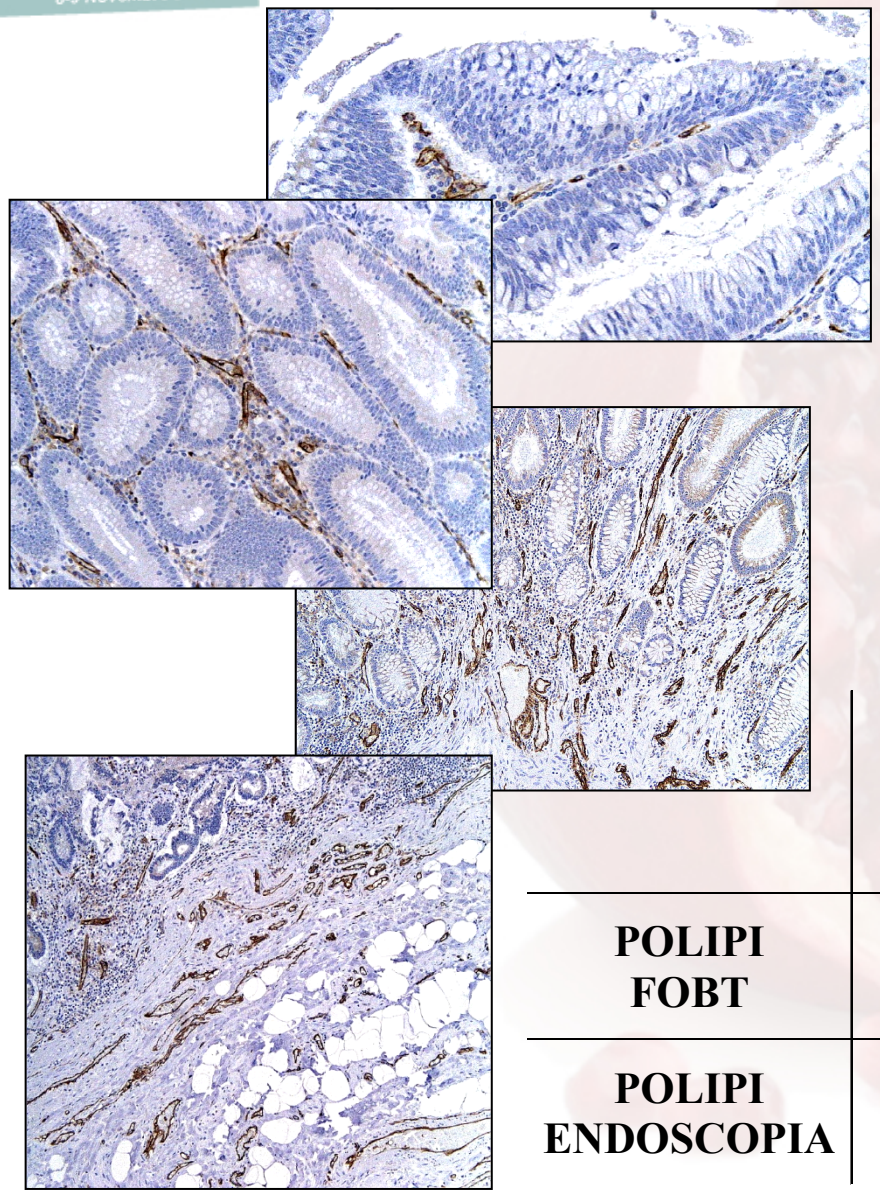
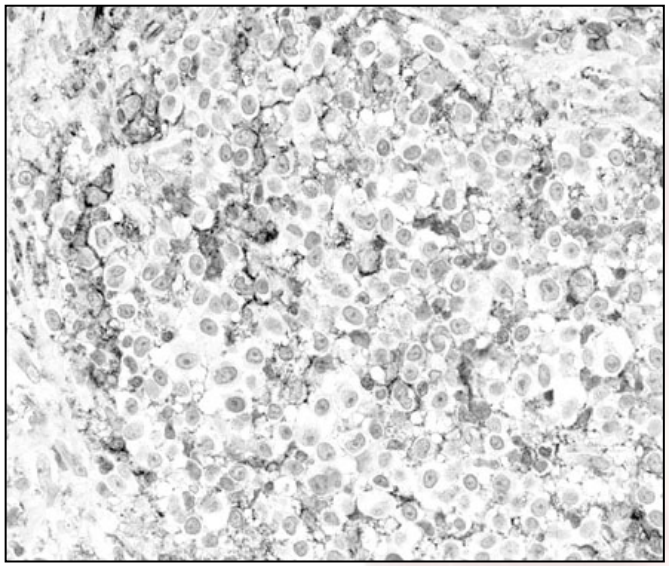
Polipi FOBT+: L'Impalcatura Microvascolare



DENSITÀ MICROVASCOLARE (MVD)
Numero di Microvasi CD31+ / mm²

	Asse dei Villi	Aree Tubulari (1/2 Profonda)	Aree Tubulari (1/2 Superficiale)	Sottomucosa
POLIPI FOBT	**3,5**	**8,6**	**5,9**	**4,2**
POLIPI ENDOSCOPIA	**4,1**	**7,7**	**11,9**	**4,8**

IMITAZIONE VASCULOGENICA TUMORALE
"Vasculogenic Mimicry"



Rete canalicolare extracellulare delimitata da matrice extracellulare generata dalle cellule tumorali, che Simula un evento vasculogenico microcircolatorio

- **Descritta in vivo in molti tumori maligni umani, in associazione con aggressività tumorale, stadi avanzati di progressione, prognosi sfavorevole**
- **Abbozzo di paracircolazione intratumorale per lo scambio fluidico extravascolare *("Fluid-Conducting Meshwork")***
- **Associata alla deregolazione di geni coinvolti nell'angiogenesi: CDH5, EPHA2, LAMC2**

[Pisacane AM, Risio M. Cell Oncol 2006]

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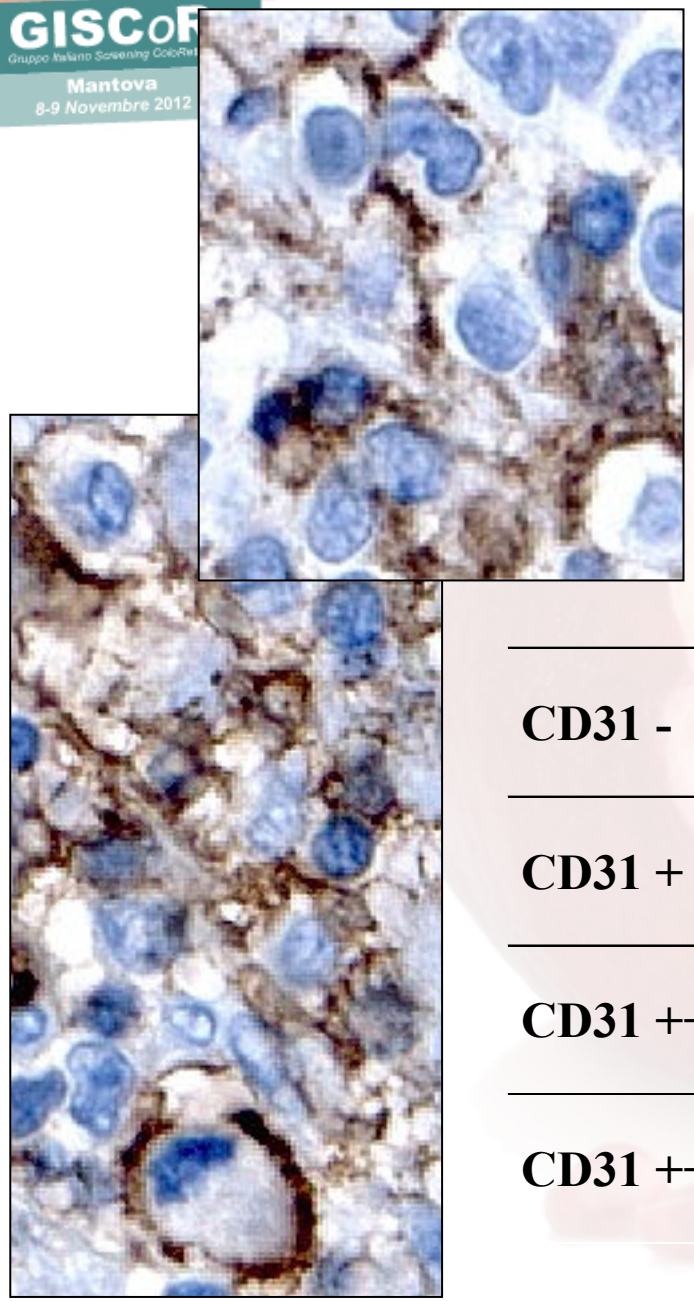
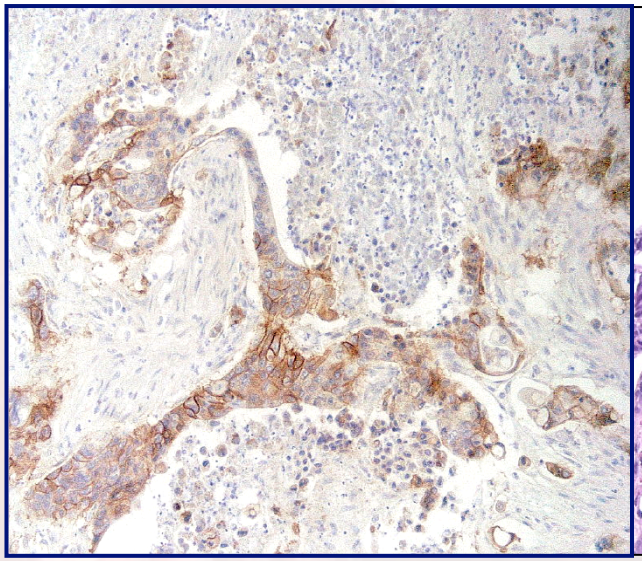


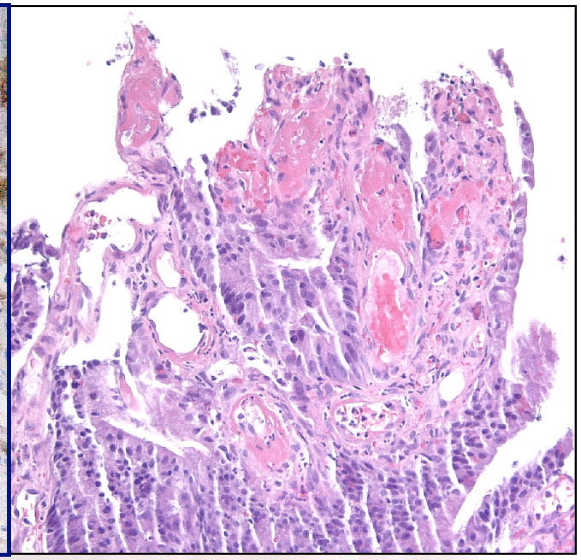
	CD31 Negativi	CD31 Positivi (+, ++, +++)
POLIPI FOBT	13 (40%)	20 (60%)
POLIPI ENDOSCOPIA	59 (65%)	31 (35%)

	Negativi	Fase 1	Fase 2	Fase 3
CD31 -	61 / 81 (75%) *	2 / 18 (11%)	2 / 16 (13%)	0 / 8
CD31 +	7 / 81 (9%)	5 / 18 (28%)	5 / 16 (31%)	1 / 8 (12%)
CD31 ++	7 / 81 (9%)	5 / 18 (28%)	5 / 16 (31%)	4 / 8 (50%)
CD31 +++	6 / 81 (7%)	6 / 18 (33%)	4 / 16 (25%)	3 / 8 (38%)

p = 0.000 vs CD31 positivo (+, ++, +++)

Polipi FOBT+:
Vascular Endothelial Growth Factor (VEGF)





Tumor Cell Proliferation

⇩

Local Tissue Hypoxia

⇩

VEGF Upregulation

⇨ **Tumor Growth**
"VEGF / VEGFR Autocrine Loop"

⇨ **Compensatory Angiogenic Sprouting**
"Tumoral Neovascularization"

[Pisacane AM, Risio M. Mel Res, 2005]

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Profiling the *"Hypoxic Tumor Phenotype"* in Adenoma Cancerization