La Patologia Neoplastica Borderline
Casale Monferrato, 2012

Patologia Neoplastica *Borderline* del Colon

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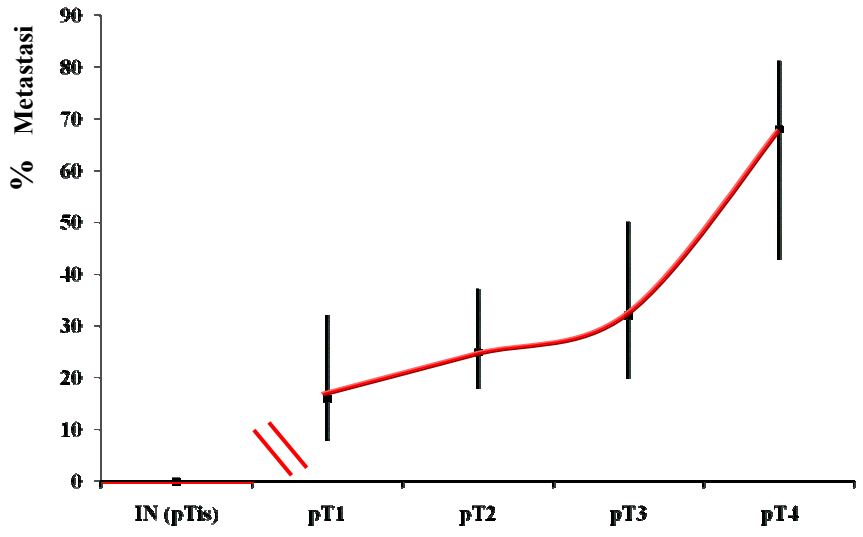
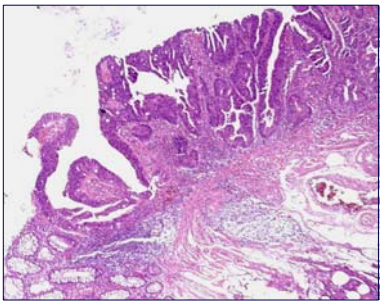
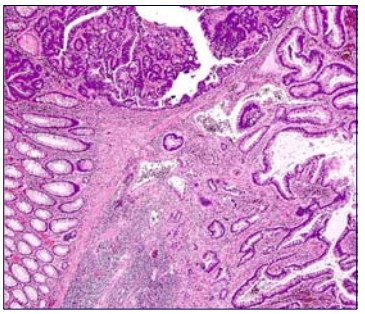
La Progressione Tumorale del Colon: Il Modello Lineare



The Malignant Transformation of the Colonic Epithelium: An Anatomic Paradox



"…Neoplastic lesions confined to mucosa have virtually no risk of metastasis…"

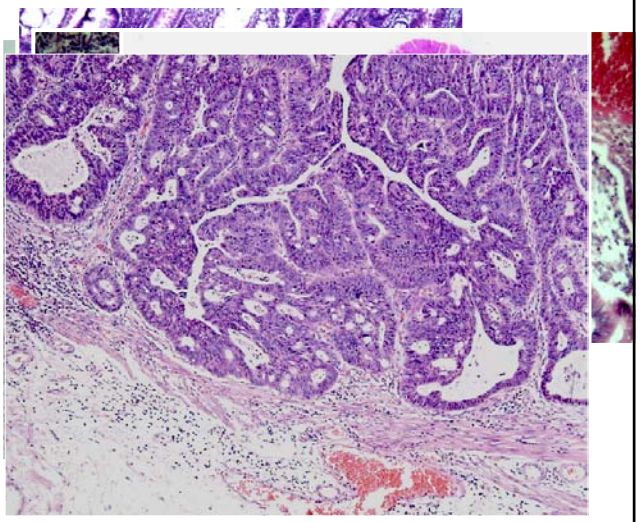


"…The defining feature of colorectal adenocarcinoma is invasion through the muscularis mucosae..

[S.R. Hamilton, 2000]

Morfogenesi della cancerizzazione colonica: La Barriera Muscolare e la Rete Linfatica

"Adenoma comprendente aree di carcinoma invasivo che dissocia e supera la muscolaris mucosae e si estende alla sottomucosa"



EPITHELIAL TUMORS OF THE COLON AND RECTUM

G. Lanza, L. Messerini, R. Gafà, M. Risio

WHO 1989	WHO 2000 / 2010	REVISED VIENNA CLASSIFICATION
		Category 1: Negative for Neoplasia
		Category 2: Indefinite for Neoplasia
Low Grade Dysplasia (Mild and Moderate Dysplasia)	Low Grade Intraepithelial Neoplasia (Mild and Moderate Displasia)	Category 3: Mucosal Low Grade Neoplasia Low Grade Adenoma Low Grade Dysplasia
High Grade Dysplasia (Severe Dysplasia) Carcinoma InSitu (Carcinoma In Situ, Intramucosal Carcinoma)	High Grade Intraepithelial Neoplasia (Severe displasia, Adenocarcinoma In-Situ) Intramucosal Neoplasia (Intramucosal Adenocarcinoma)	Category 4: Mucosal High Grade Neoplasia 4.1 High Grade Adenoma / Dysplasia 4.2 Non-invasive Carcinoma (Carcinoma in situ) 4.3 Suspicious for Invasive Carcinoma 4.4 Intramucosal Carcinoma
Invasive Carcinoma (Spreading into the Submucosa)	Invasive Carcinoma Invasion into the Submucosa)	Category 5: Submucosal Invasion by Carcinoma

European Guidelines for Quality Assurance in Colorectal Cancer Screening

European Commission

Authors: Phil Quirke, Mauro Risio, Renè Lambert, Michael Vieth

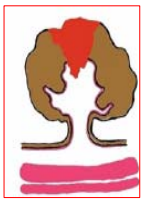
Table 7.1: Modification for colorectal cancer screening of the revised Vienna classification, and the categories encompassed by the terms

NO NEOPLASIA = Category 1 of the original Vienna Classification

MUCOSAL LOW GRADE NEOPLASIA = Category 3; mild and moderate dysplasia; low grade dysplasia; low grade intraepithelial neoplasia – (WHO 2000).

MUCOSAL HIGH GRADE NEOPLASIA = Category 4.1 – 4.4; severe dysplasia; high grade dysplasia; high grade intraepithelial neoplasia; carcinoma in situ; intramucosal carcinoma.

INVASIVE SUBMUCOSAL NEOPLASIA = Category 5; Carcinoma invading the submucosa or beyond.

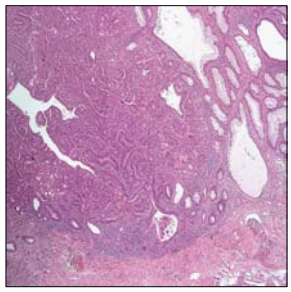


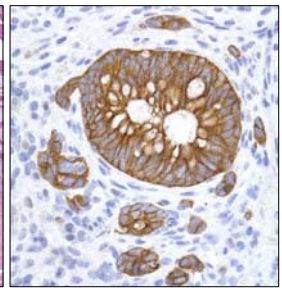
"Metastatic" Intramucosal Neoplasia ?

Pro
Urabe et al, Stomach Intestine, 1998

&

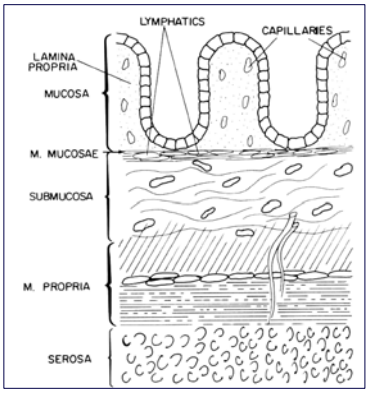
Con
Lewin et al, AJSP 2007

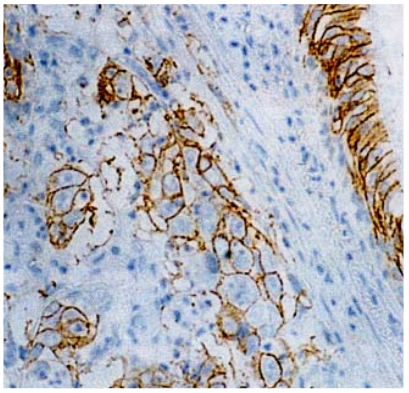




Case No.	Age (y)	Sex	F/U Procedure	F/U	F/U Interval (mo)
1	62	M	Colonoscopy	Negative	2
2	58	F	Partial Colectomy	Second mass; T3 disease	25
3	74	M	Colonoscopy	NRD	8
4	54	M	Colectomy	NRD	32
5	68	M	Colonoscopy	NRD	96
6	38	F	Partial colectomy	NRD	1
7	69	F	Partial colectomy	NRD	46
8	65	M	Colonoscopy	NRD	18
9	65	M	NA	NRD	10
10	48	M	Colonoscopy	NRD	23
11	79	M	Colonoscopy	NRD	13
12	62	M	Resection	NRD	12
13	70	M	Colonoscopy	NRD	7
14	62	M	LAR	Anal Paget's	20
15	36	M	Colonoscopy	NRD	6

The Malignant Transformation of the Colonic Epithelium: An Anatomic Paradox





- **Histologic Examination**
- **Carcinomatous Autoinjection**
- **Ultrastructural Observations**
- **Immunological Studies**
- **Injection Studies**

Fenoglio et al, Gastroenterology 1973

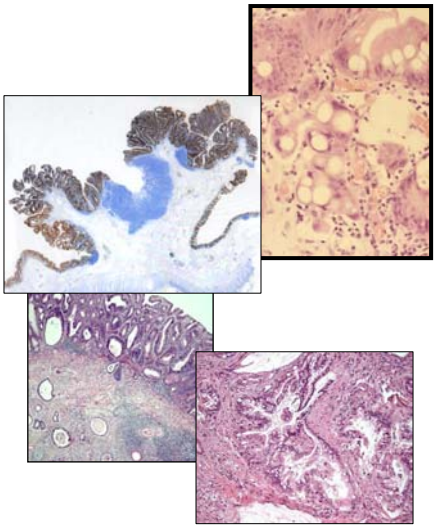
E-cadherin → **Alpha-catenin** ↕ **Beta-catenin**

APC → **Beta-catenin**

Tamura et al, Cancer Res, 1996

Forme Inusuali di Carcinoma Colorettale pT1

- **Carcinoma Minimale De Novo**
- **Carcinoma Piatto**
- **Carcinoma Polipoide Minimale**
- **Carcinoma Endocrino**
- **Carcinoma a Cellule ad Anello con Castone in Adenoma**

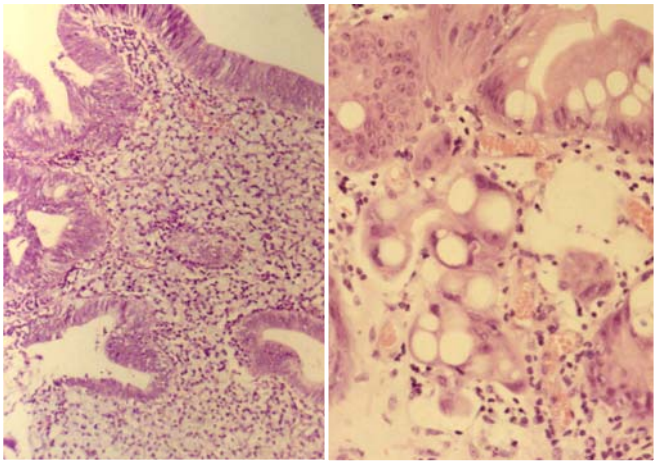


".....potranno essere singolarmente valutate da un panel di patologi in ambito GISCoR..."

Risio et al, GISCoR, 2006

Adenomi Cancerizzati: Istotipi Inusuali

CARCINOMA DI CELLULE AD ANELLO CON CASTONE



Morfogenesi della cancerizzazione colonica: La Distopia Sottomucosa

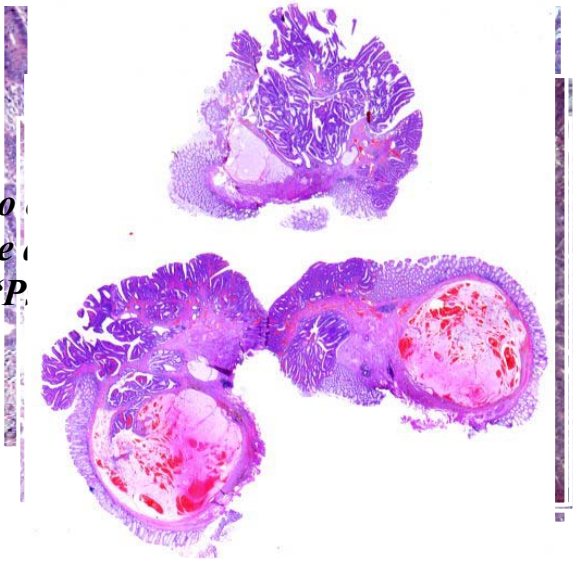
"Pseudoinvasione:

- Assenza di reazione desmoplastica

- Mantello connettivale attorno alle ghiandole displastiche

- Depositi emosiderinici

Dislocazione o
di isole
"P

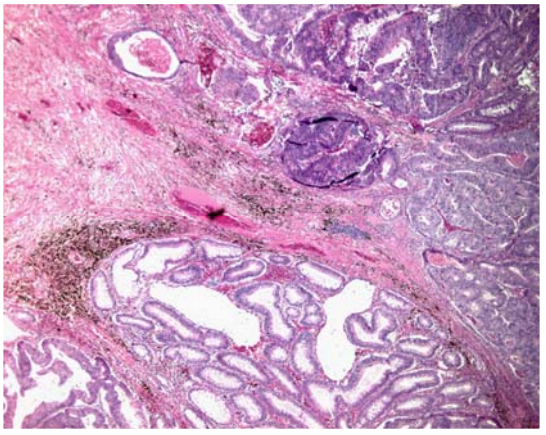


Colonic Cancerization: Bimarkers of Tumor Invasion

Immunohistochemical Stains In the Differential Diagnosis of Adernomas with Misplaced Epithelium Vs. Cancerized Adenomas

- **MMP-1**
- **E-Cadherin**
- **P53**
- **Collagen IV**

Yantiss et al, 2002

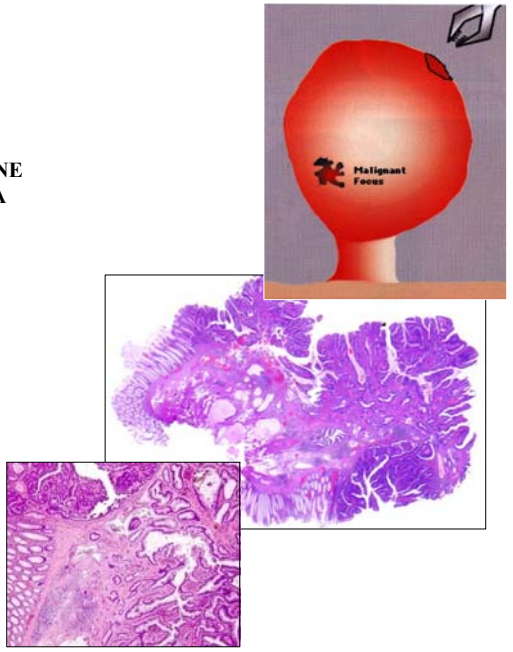


Le Condizioni della Diagnosi: Biopsia Endoscopica

PER LA DIAGNOSI DI CANCERIZZAZIONE E' IRRINUNCIABILE LA POLIPECTOMIA ENDOSCOPICA COMPLETA:

PRELIEVI BIOPTICI MULTIPLI O LA FRAMMENTAZIONE DELLA LESIONE NON CONSENTONO LA SICURA ESCLUSIONE DI UNA COMPONENTE NEOPLASTICA INFILTRANTE LA SOTTOMUCOSA

IN TALI CASI IL GIUDIZIO DIAGNOSTICO DOVRA' FORZATAMENTE ESSERE LIMITATO AD ELEMENTI DESCRITTIVI DEL CAMPIONE IN ESAME

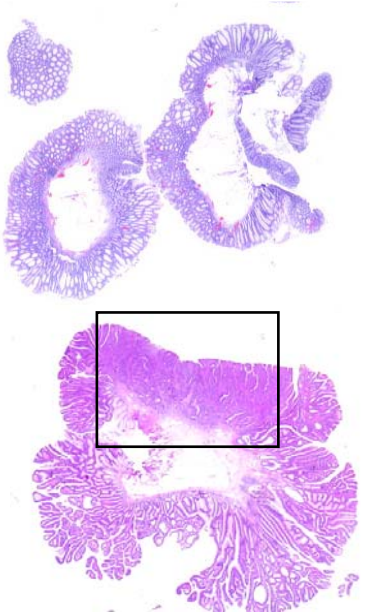


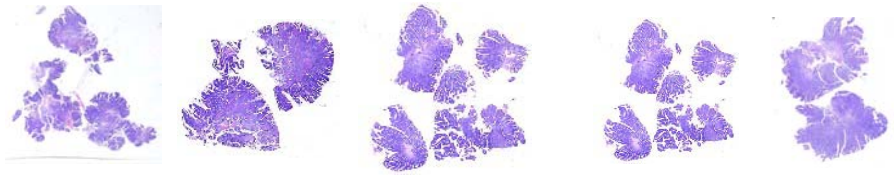
Le Condizioni della Diagnosi: Rimozione *Piecemeal*

PER LA DIAGNOSI DI CANCERIZZAZIONE E' IRRINUNCIABILE LA POLIPECTOMIA ENDOSCOPICA COMPLETA:

PRELIEVI BIOPTICI MULTIPLI O LA FRAMMENTAZIONE DELLA LESIONE NON CONSENTONO LA SICURA ESCLUSIONE DI UNA COMPONENTE NEOPLASTICA INFILTRANTE LA SOTTOMUCOSA

IN TALI CASI IL GIUDIZIO DIAGNOSTICO DOVRA' FORZATAMENTE ESSERE LIMITATO AD ELEMENTI DESCRITTIVI DEL CAMPIONE IN ESAME

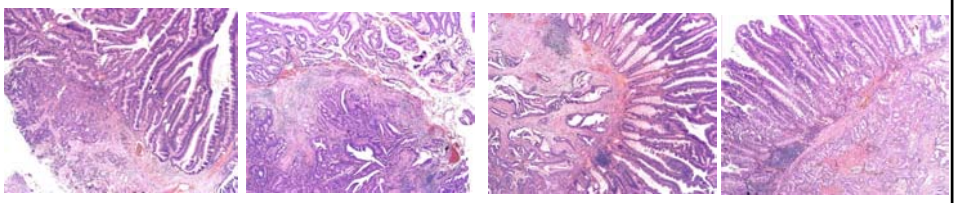




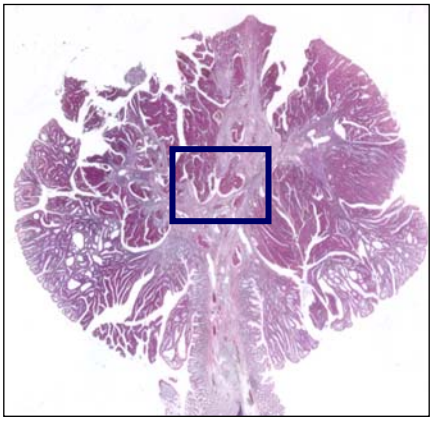
ORIENTAMENTO DEL PIANO DI MICROTOMIA

"…I frammenti derivanti da piecemeal saranno appoggiati su supporto rigido con la faccia corrispondente alla superficie di exeresi a cura dello Staff di Endoscopia…."

[Risio et al, 2007]



Cancerized Adenomas: The Metastatic Risk (8-16%)



Histologic Features Distinguishing

LOW (7 %)
and
HIGH (35 %)

Risk of Lymph Node Metastasis

- **GRADE OF DIFFERENTIATION OF INVASIVE CARCINOMA (G1-G2, Low Grade vs G3-G4, High Grade)**
- **VASCULAR INVASION**
- **RESECTION MARGIN**

[Coverlizza, Risio, Fenoglio-Preiser, Cancer 1989]

CANCERIZED ADENOMAS: "Low Risk" (55%) vs "High Risk" (45%)

	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)

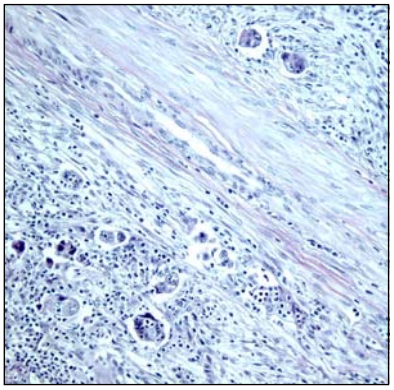
[Hassan, Risio, Dis Colon Rectum 2005]

Cancerized 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 and Risio, 2005)

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

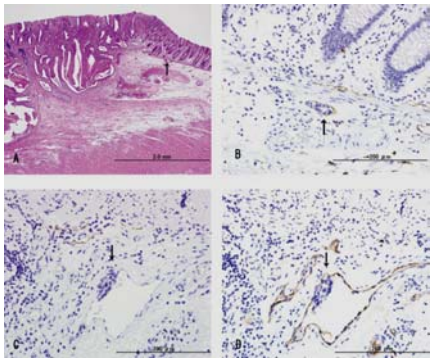


Cancerized Adenoma:
Lymphatic and Vascular Invasion

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

European Guidelines for Quality Assurance in Colorectal Cancer Screening

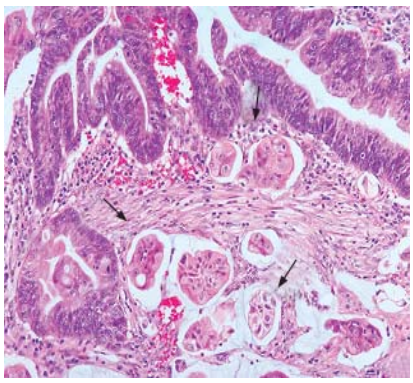
European Commission

pT1 Cancer
Cancerized Adenoma

8.5.3.2 TUMOR GRADE

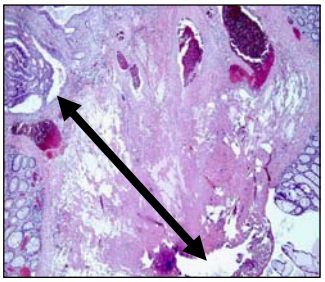
In the absence of good evidence we recommend that a grade of poor differentiation should be applied when ANY area of the lesion is considered to show poor differentiataion.

Budding of the tumor cells at the front of invasion should not influence grading of the tumour.



[Quirke, Risio , Lambet, Vieth 2010]

Histology of R0 pT1 Neoplasia



1 mm	COOPER, 1998
Healthy	ROSSINI, 1988
1 mm	SUGIHARA,1989
2 mm	CRANLEY, 1988
3 mm	WILLIAMS, 1987

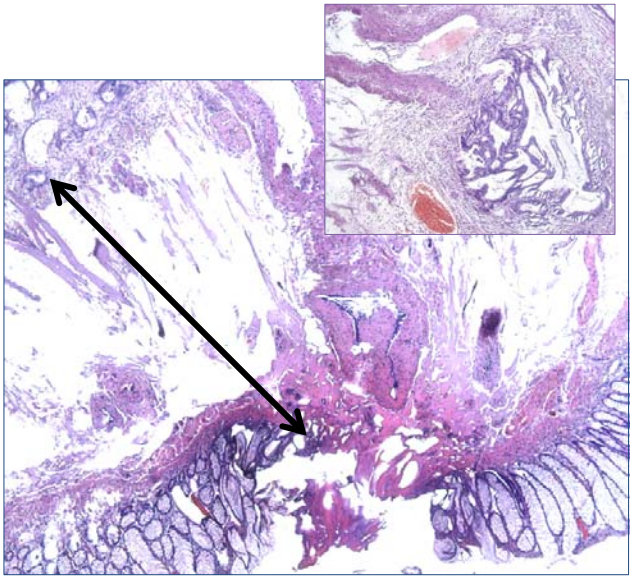
7.5.3.4. MARGIN INVOLVEMENT

There has been considerable discussion and controversy in the literature over what degree of clearance might be regarded as acceptable in tumours that extend close to the deep submucosal margin. It is important that clearance is measured and recorded in the report.

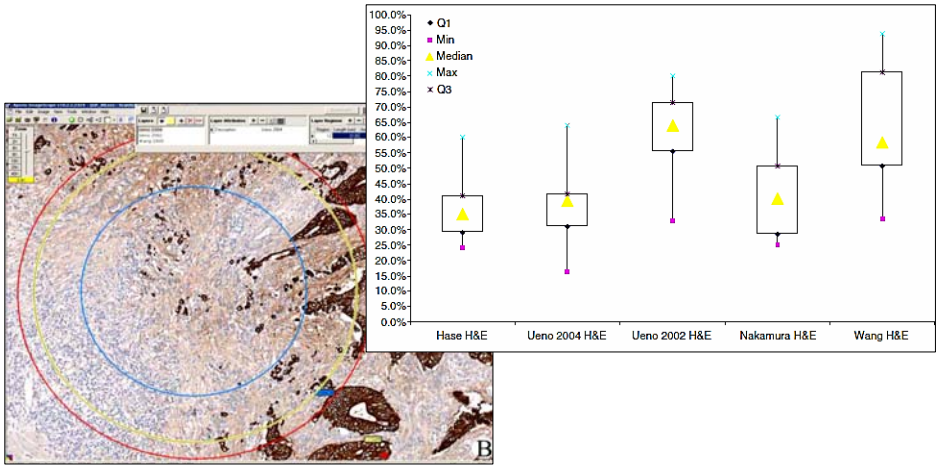
Currently we would recommend that clearance of 1 mm or less indicates margin involvement.

[Quirke, Risio,Lambert, Vieth, 2010]

Histology of R0 pT1 Neoplasia: Submucosal Injection and False Negative Cases



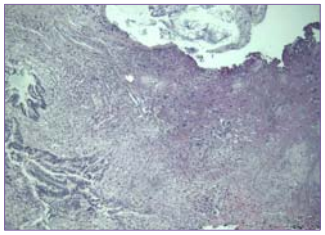
Histology of R0 pT1 Neoplasia: Skip Lesions and False Negative Cases



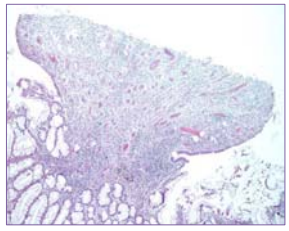
Diagnostic Reproducibility of Tumor Budding in Colorectal Cancer: a Multicentre, Multinational Study using Virtual Microscopy

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 Mauro Risio - Histopathology 2012

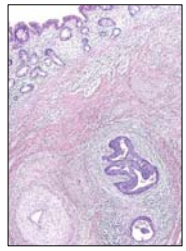
La Valutazione Istologica di Radicalità: Biologia e Storia Naturale della Neoplasia Residua



A): Diatermocoagulazione



B): Espulsione

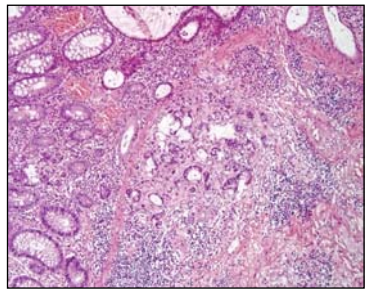


C):
- **Fibroplasia**
- **Deconnessione Vascolare**
- **Ipossia**

Cancerized 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
• Sohn et al, 2006	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]

CANCERIZED ADENOMA: Carcinoma Microstaging

European Guidelines for Quality Assurance in Colorectal Cancer Screening

European Commission

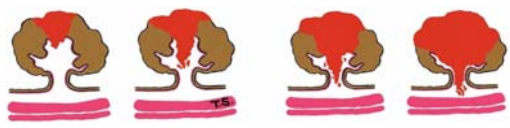
pT1 Cancer Substaging

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.

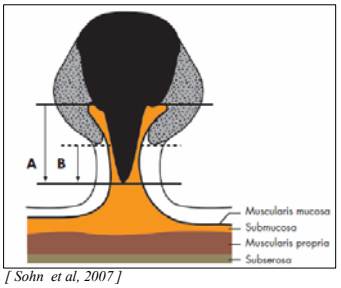
[Quirke, Risio , Lambet, Vieth 2010]



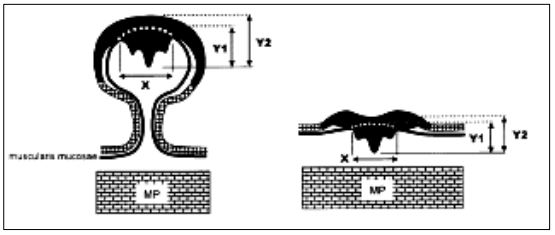
Haggitt Levels

Kikuchi Levels

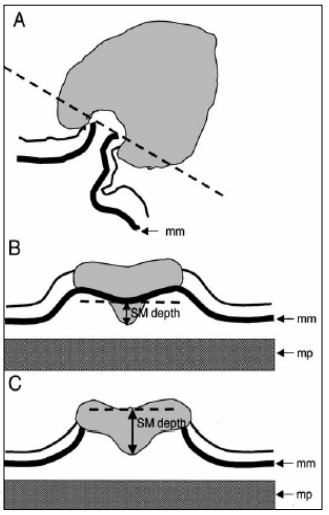
CANCERIZED ADENOMA:
Carcinoma Microstaging



[Sohn et al, 2007]



[Ueno et al, 2004]

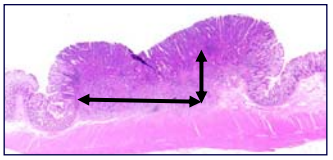


[Kitajma et al, 2004]

Cancerized 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
NONPEDUNCOLATED 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**

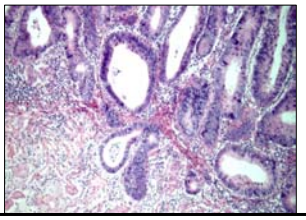
Kitajima et al, 2004

	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,

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%)



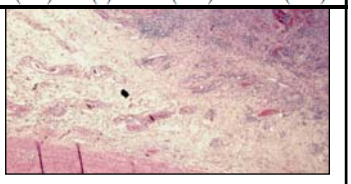
Minute depressed-type submucosal invasive cancer-5mm in diameter

SM depth (μm)	LNM (+) (%)	Ly (+) (%)	V (+) (%)	Sp (+) (%)	Histological type at the deepest portion: wel, mod (%)	Histological type at the deepest portion: por (%)	Status of muscularis mucosae: Identified (%)	Status of muscularis mucosae: Not identified (%)
0 < X < 500 (*n* = 65)	0 (0)	5 (7.7)	3 (4.6)	9 (13.8)	64 (98.5)	1 (1.5)	64 (98.5)	1 (1.5)
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



CANCERIZED 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*

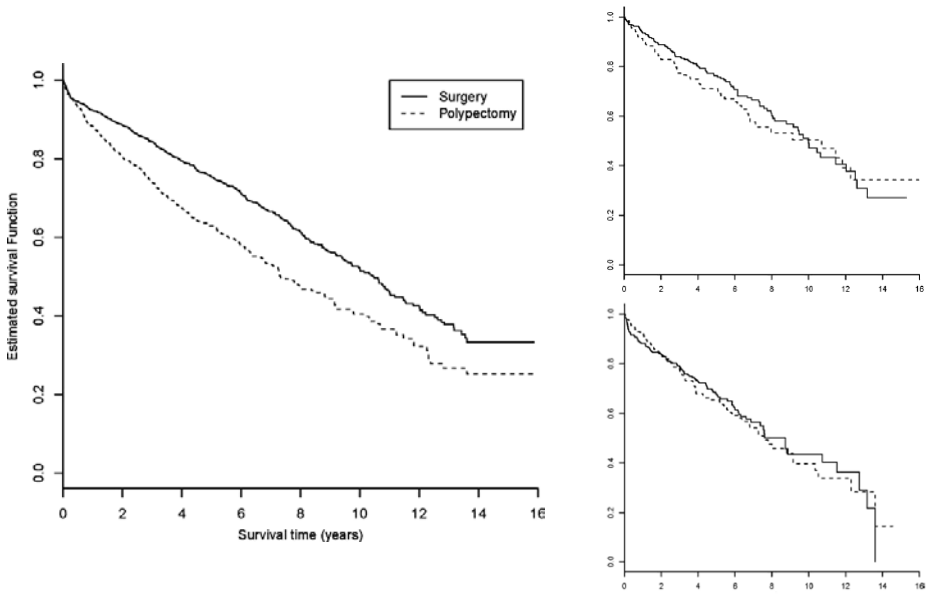
> 500 μm → **LOW RISK (8-10%)**

>2000 μm → **INTERMEDIATE RISK (10-20%)**

HIGH RISK (20-40%)

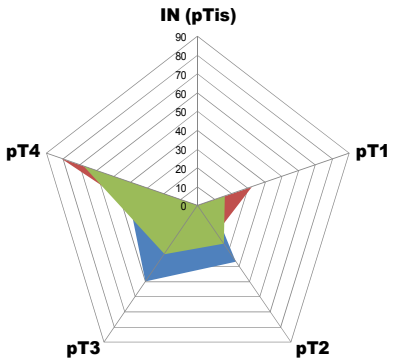
- Carcinoma Grading: *3 – 4*
- *or*
- Tumor Budding: *Present / High Grade*
- *or*
- Vascular Invasion: *Present*

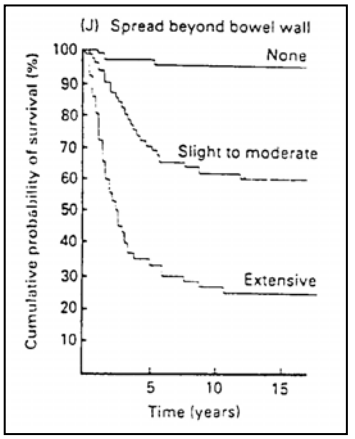
Management of Malignant Colonic Polyps:
A Population-Based Analysis of Colonoscopic Polypectomy vs Surgery
Cooper et al, Cancer 2012



La Progressione Tumorale del Colon: Modelli Complessi e Teorie del Caos

$$d(t) = d(t_0)e\lambda^{(t-t0)}$$





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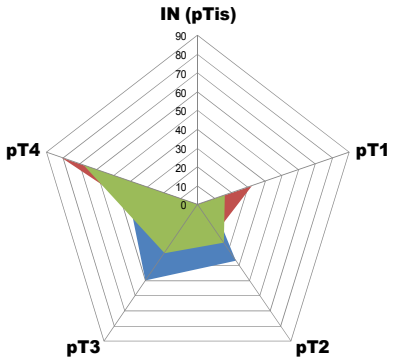
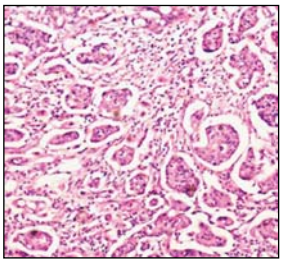
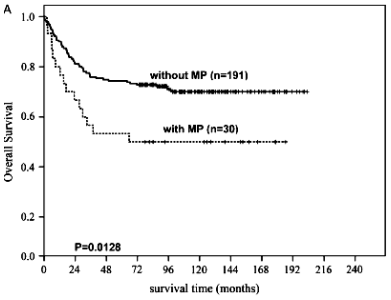
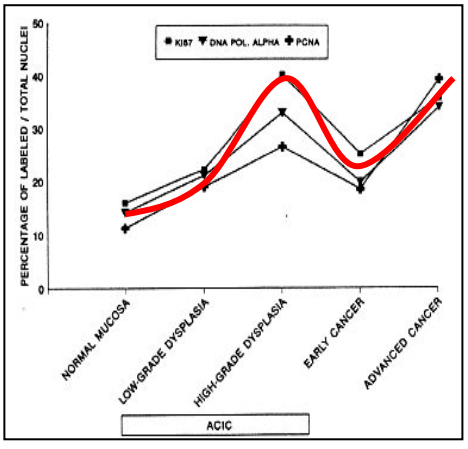




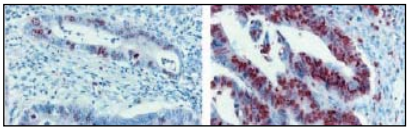


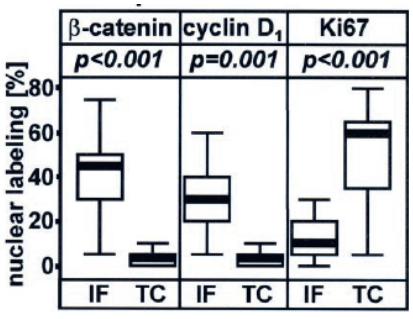
AJSP 2009

Early Colorectal Cancer: Cell Proliferation



[Risio et al, 1997]





[Jung et al, 2001]

Early Colorectal Cancer: The Avascular Growth

NORMAL

⇩

LG INTRAEPITHELIAL NEOPLASIA

⇩

HG INTRAEPITHELIAL NEOPLASIA

⇩

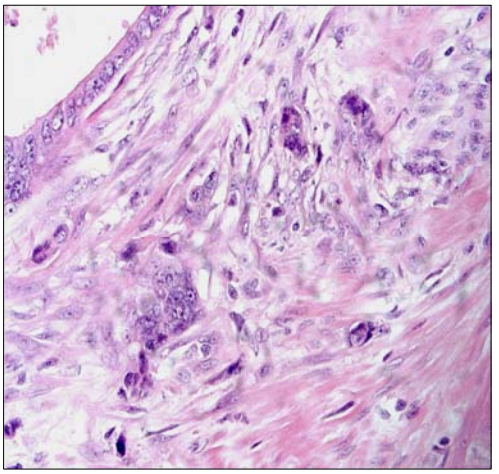
MICROINVASION

⇩

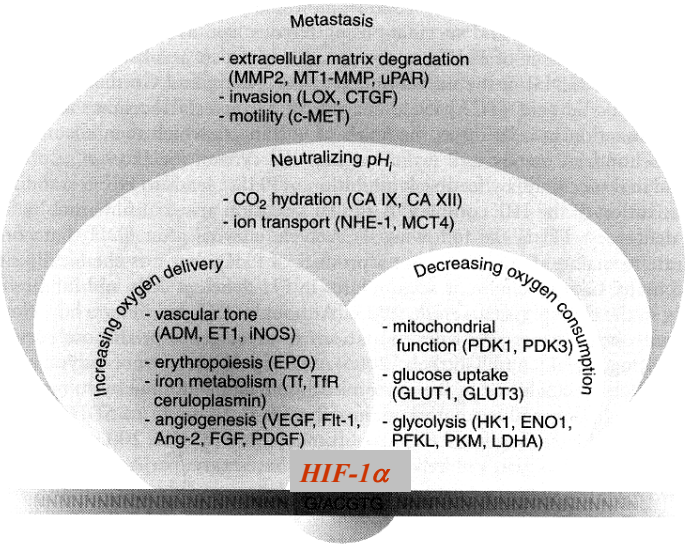
ADVANCED INVASION

Avascular Growth Phase

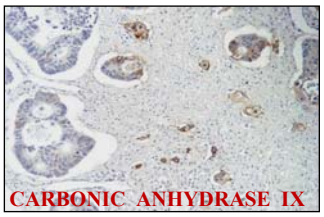
Angiogenic Switch

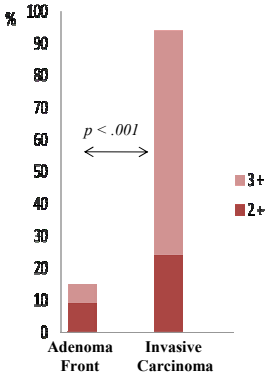


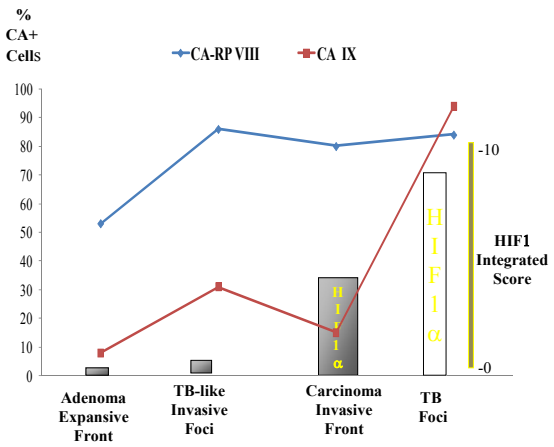
Profiling the *"Hypoxic Tumor Phenotype"* in pT1 Adenoma Cancerization



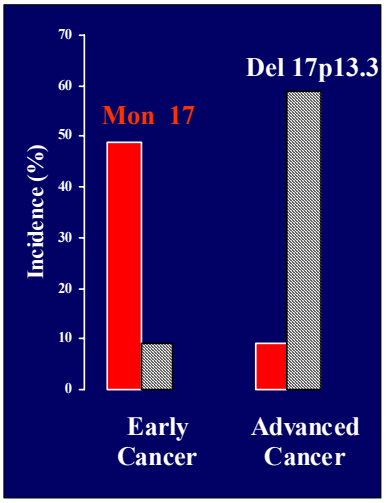
Profiling the *"Hypoxic Tumor Phenotype"* in Adenoma Cancerization

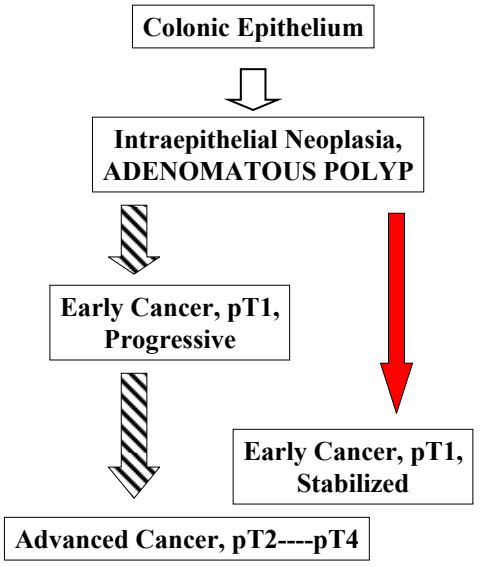






Advanced Colorectal Carcinogenesis: *Progressive* vs *Stabilized* pT1 Cancer

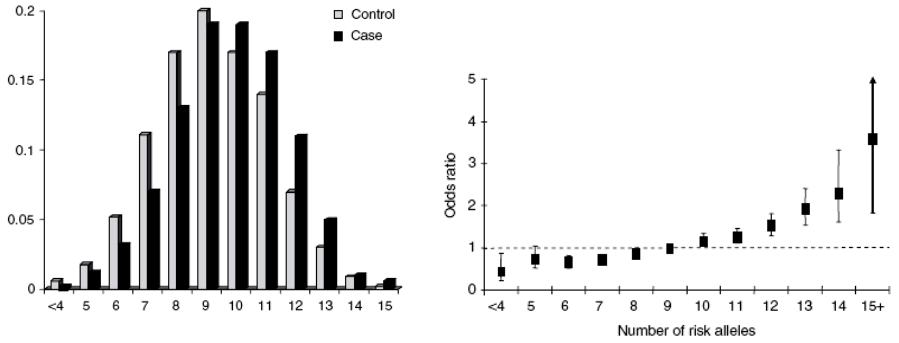




[Risio et al, 2003]

NONSYNDROMIC FAMILIAL COLORECTAL CANCER

Susceptibility Low-Penetrance Genes and CRC Risk



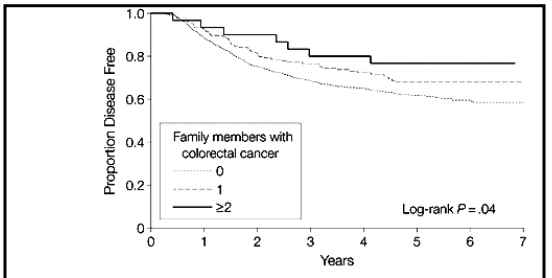
COGENT (COlorectal cancer GENeTics): ***an international consortium to study the role of polymorphic variation on the risk of colorectal cancer [2010]***

NONSYNDROMIC FAMILIAL COLORECTAL CANCER

Natural History and Clinical Outcomes

Familial Stage III Colon Cancer:

- **DFS: Hazard Ratio 0.72**
  (CI 95% 0.54-0.96)
- **RFS: Hazard Ratio 0.74**
  (CI 95% 0.55-0.99)
- **OS: Hazard Ratio 0.75**
  (CI 95% 0.54-1.05)



No. at risk							
Family members with colorectal cancer							
0	892	786	650	572	513	405	124
1	165	151	128	113	99	83	22
≥2	30	28	27	24	24	21	8

No. of events						
Family members with colorectal cancer						
0	102	118	57	28	25	12
1	13	18	7	6	6	0
≥2	2	1	3	0	1	0

Chan et al, JAMA 2008

Neoplasie *Borderline* del Colon

1):
Sono rappresentate dalle forme più iniziali di invasione neoplastica della sottomucosa.
I valori dimensionali soglia predittivi dello stato N0 sono in corso di definizione :
- **< 500μm di profondità**
- **< 2000μm di ampiezza**

2):
Eventi genetici ed epigenetici non correlati alla morfologia possono azzerare il potenziale metastatico di alcuni carcinomi colorettali pT1 e bloccarne la progressione