Riunione annuale screening colorettale

Il tumore eredo familiare: il protocollo di sorveglianza e trattamento

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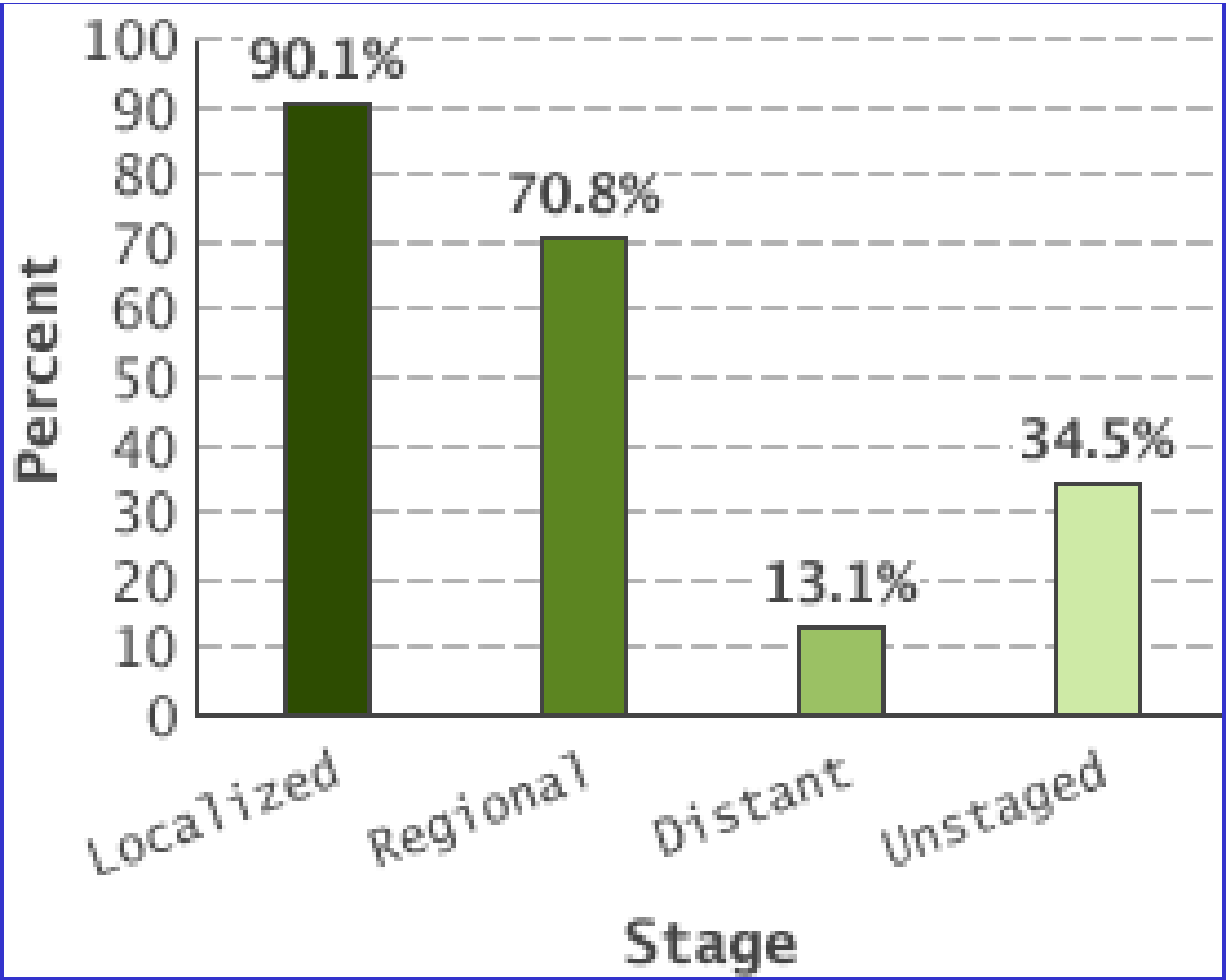
Padova, 21-11-2017

5 years survival for colorectal cancer



cancer.gov

Le sindromi ereditarie gastrointestinali

Poliposiche

1% di tutti i CRC

- **Poliposi adenomatosa familiare (FAP) e la sua forma attenuata (a-FAP)**
- **MutYH associated polyposys (MAP)**
- **Multiple colorectal adenomas**

- **Peutz-Jeghers**
- **Poliposi giovanile**
- **Forme rarissime**

Non poliposiche

1-5 % di tutti i CRC

- **Hereditary non-polyposis colorectal cancer (HNPCC) o Sindrome di Lynch**

POle/POld1 mut syndromes

- **Familial colorectal cancer type X**

HNPCC
Fenotipo

1. Età di insorgenza precoce (età media 44 aa)

1. Localizzazione al colon destro (60-70%)

1. Aumentata chance di CRC sincroni e metacroni (25%)

1. 70% chance di sviluppare CRC entro i 65 anni

1. Aumentata chance di altri tumori

HNPCC
Rischio di ca associati (entro i 70 aa.)

Cancro associato con HNPCC	Rischio (%)	Rischio nella popolazione generale (%)
Colonretto	82	2
Endometrio	60	1.5
Ovaio	12	1
Stomaco	13	< 1
Altri cancri	1-4	< 1

HNPCC
Genotipo

Sdr di Lynch

Amsterdam +/-

- H-MSI (90% dei casi)
- Mutazione MMR (MLH1, MSH2, PMS2, MSH6, EPCAM)
- Autosomica dominante
- Penetranza 70-80%
- Mutazione nel 50-60% delle famiglie

Familial Colorectal Cancer Type X

Amsterdam criteria +

- S-MSI
- NO Mutazione MMR
- trasmissione?
- penetranza ?

Lindor NM et al, JAMA 2005

HNPCC

COME GESTIRE IL PAZIENTE con Mutazione nei geni del MMR

Ricerca del gene: prima dei 18 anni

↓

Scoperta della mutazione

↙ ↘

Test genetico nei familiari di I° grado

Sorveglianza clinica e terapia quando diagnosi di Carcinoma o adenoma non asportabile endoscopicamente

HNPCC

Sorveglianza della sdr di Lynch: mutation carriers

- Colonscopia annuale da 20-25 anni *
- Ecografia transvaginale + Ca 125 per le donne, annuale **

Sorveglianza delle altre neoplasie presenti nella sindrome di Lynch solo se presenti nella famiglia

*: provata l'efficacia nel diagnosticare casi precoci e diminuire le morti per CRC

** non provata l'efficacia della sorveglianza dei tumori genitali femminili

Sorveglianza ed HNPCC

151 pts asintomatici/22 famiglie HNPCC

a) 133 colonscopia 1-3 aa **b) 118 non sorveglianza**

OSSERVAZIONE per 10 anni

	GRUPPO A	GRUPPO B	
Nuovi casi di CRC	6(4,5%)	14 (12%)	p.03
Cancer specific mortality	0	5	

Jarvinen et al, 1995

SORVEGLIANZA in HNPCC

150 CRC/ 57 FAMIGLIE HNPCC

Dukes	sorveglianza	non sorveglianza	
A	50%	17%	
B	35%	50%	p< .001
C	15%	16%	
D	0	17%	
5 yrs cancer survival	93%	68%	p< .02

Renkonen- Sinisalo et al, 2000

s-HNPCC

Familial Colorectal cancer type X
Sorveglianza

- **MSI test su uno degli affetti da CRC**

MSI-H

Test genetico

Positivo

sorveglianza come HNPCC

Non informativo

MSI-S

Colonscopia ogni 3 anni, iniziando 10 anni prima dell'età del più giovane CRC della famiglia o a 40 aa

Chirurgia della HNPCC

Quando diagnosi di adenoma non asportabile endoscopicamente o carcinoma

Quando adeguata sorveglianza endoscopica è impossibile

Perche':

- **penetranza incompleta: 80%**
- **coloscopia annuale è in grado di effettuare diagnosi precoce**
- **non c'è consenso internazionale alla colectomia profilattica**

colectomia estesa

HNPCC: chemoprevention

"although data suggest that daily aspirin may decrease the risk of CRC and extracolonic cancer in Lynch Syndrome, currently the evidence is not sufficient robuste or mature to make a reccomendation for its standard use" .

(conditional recommendation moderate quality of evidence)

Syngal S et al ACG Clinical Guideline: genetic testing and management of hereditary Gastrointestinal cancer syndromes.

American Journal of Gastroenterology 2015; 110: 223-262

FAP
Fenotipo colico

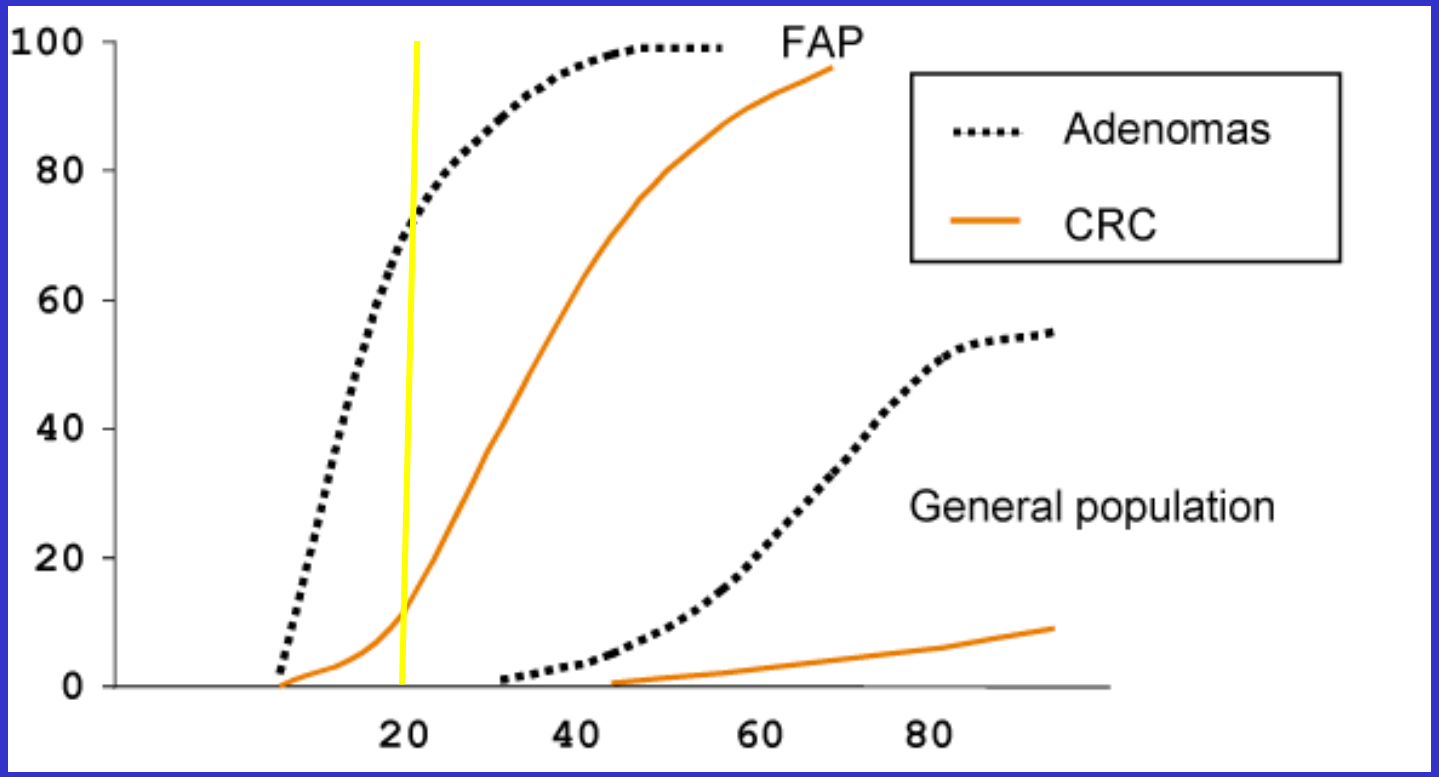
- Centinaia di polipi adenomatosi colici
- 50% dei pazienti FAP sviluppa adenomi entro i 15 anni, il 95% entro i 35 anni
- Proliferazione degli adenomi colici in senso distale → prossimale (retto → colon destro)
- rischio di carcinoma significativo dai 18-20 anni

FAP: adenomi del colon

Centro per i Tumori Ereditari del Colon
prevenzione diagnosi terapia

FAP: ETÀ E SVILUPPO DEGLI ADENOMI E DEL CRC

% di pazienti affetti da neoplasia



Età

Poliposi adenomatosa Familiare (FAP)
Manifestazioni extracoliche

- Epatoblastomi (in età infantile)
- Polipi gastrici, duodenali
- Adenomi e Ca duodenali
- Polipi del piccolo intestino
- Osteomi, spec. mandibolari
- Desmoidi
- cisti dermoidi
- medulloblastomi
- ipertrofia pigmentata dell'epitelio retinico

COME GESTIRE IL PAZIENTE APC POSITIVO

Ricerca del gene: a 10-12 anni

↓

Scoperta della mutazione

↙ ↘

Test genetico nei familiari di I° dai 10-12 anni d'età

Sorveglianza clinica e terapia quando compare la poliposi

Sorveglianza della FAP

- **Rettosigmoidoscopia dai 10-12 anni, poi colonscopia dalla comparsa dei polipi: annuale, fino all'intervento chirurgico**
- **EGDS: dalla comparsa dei polipi del colon: le scadenze dei controllo dipendono dal numero, dalle dimensioni e dal grado di displasia degli adenomi gastroduodenali**
- **Ecografia epatica: in età pediatrica**
- **Ecografia tiroidea: i controlli dipendono dal riscontro dell'ecografia precedente**
- **TAC/RM addome per i desmoidi: se traumi severi, chirurgia, gravidanza recente.**

- ***Endoscopia capsulare? per controllo morfologico gastroduodeno-digiuno-ileale***

Terapia chirurgica della FAP

- **Chi deve essere operato per FAP?**
- **i soggetti maggiorenni con > 100 adenomi del colon**
- **i soggetti maggiorenni con poliposi colica (anche <100 adenomi) e mutazione riscontrata**
- **i soggetti maggiorenni o minorenni con poliposi e neoplasia maligna**

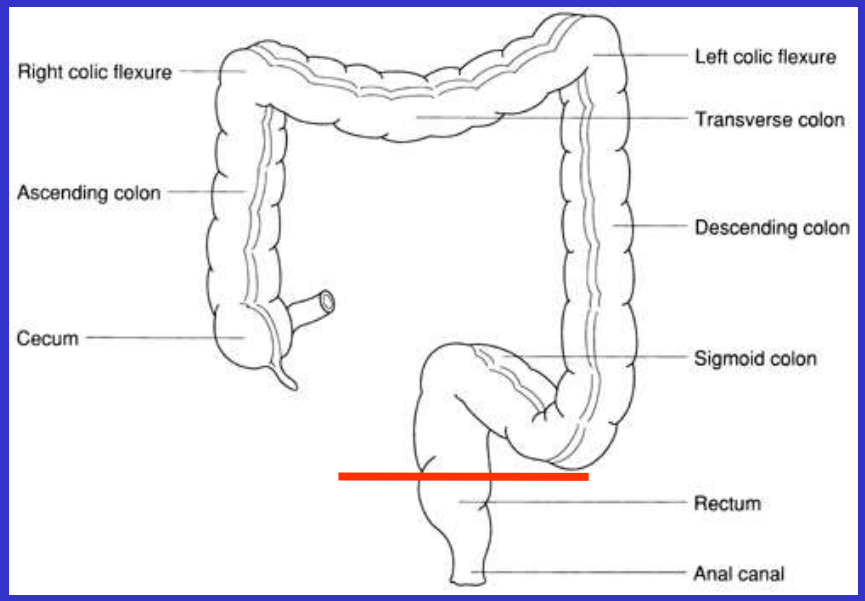
FAP

Chirurgia della poliposi colorettale

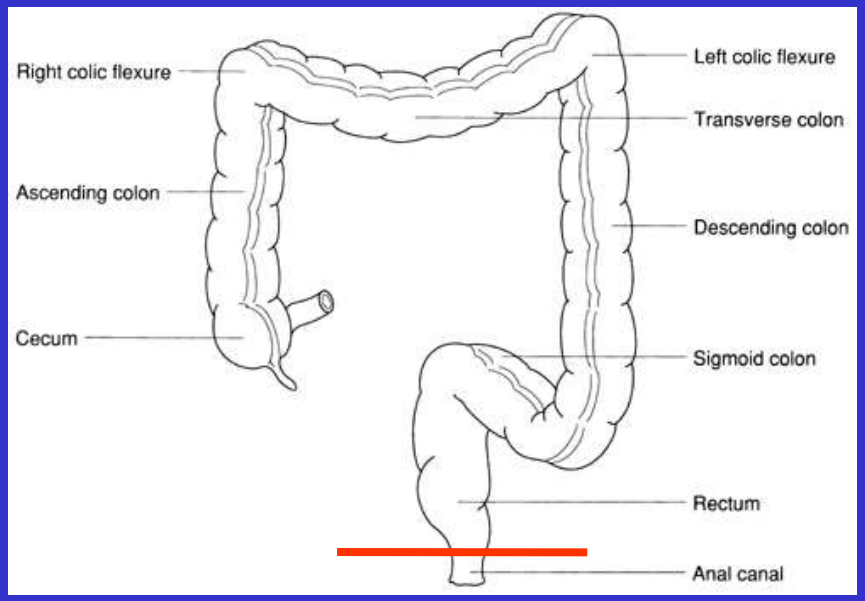
Quando operare?

Che intervento eseguire?

Colectomia totale con ileo-rettoanastomosi
(conservazione dell'ampolla rettale)



Coloproctectomia totale con ileo-anoanastomosi
(asportazione di tutto il retto)



Ishikawa H et al

Endoscopic management of familial adenomatous polyposis in patients refusing colectomy. Endoscopy. 2016 48(1):51-5.

PATIENTS AND METHODS:

A retrospective review of medical records was performed to identify adult patients with FAP who refused colectomy and were managed by repeated colonoscopies to remove numerous polyps between 2001 and 2012.

RESULTS:

90 patients (median age at first visit 29 years [range 16-68 years]; 46 males) were followed for a median of 5.1 years (interquartile range [IQR] 3.3-7.3 years). During this period, a total of 55701 polyps were resected without adverse events such as bleeding or perforation. The median numbers of endoscopic treatment sessions and polyps removed per patient were 8 (IQR 6-11) and 475 (IQR 211-945), respectively.

Five patients had noninvasive carcinoma, detected within 10 months from the start of the follow-up period. All of these patients were treated endoscopically, without signs of recurrence during a median follow-up of 4.3 years (IQR 2.0-7.1 years). No invasive colorectal cancer was recorded during the study period. Two patients (2.2%) underwent colectomy because the polyposis phenotype had changed to dense polyposis.

CONCLUSION:

Endoscopic management of FAP is feasible and safe in the medium term.

Duodenal adenomas and FAP

- Duodenal adenomas 15 years after the appearance of colonic adenomas
- 30%-92% of FAP patients, with a lifetime risk approaching 100%
- Duodenal cancer is one of the two leading causes of death (the other being desmoid tumors) in patients with FAP after they receive prophylactic colectomy
- The relative risks of developing duodenal ADK: 331 x (compared t general population)
- The absolute lifetime risk: 3%-5%
- Spigelman Stage IV patients have the greatest risk of developing duodenal cancer, with rates of 7%-36% having been described in 7.6- to 10-year follow-up periods
- Mortality rates from duodenal cancer vary from 1.7% to 8.2%

Spigelman classification for duodenal polyposis

Criterion	Points		
	1	2	3
Polyp number	1-4	5-20	> 20
Polyp size (mm)	1-4	5-10	> 10
Histology	Tubular	Tubulo-villous	Villous
Dysplasia	Mild	Moderate	Severe

Stage 0: 0 points; stage I: 1-4 points; Stage II: 5-6 points; Stage III: 7-8 points; Stage IV: 9-12 points

WHO criteria for Serrated polyposis syndrome definition

At least one of the follow:

- **at least 5 serrated polyps (SPs) proximal to the sigmoid colon with ≥2 of these being >10 mm**
- **any number of SPs proximal to the sigmoid colon in an individual who has a fi rst-degree relative with serrated polyposis**
- **>20 SPs polyps of any size, distributed throughout the large intestine.**

Rischio di CRC ~>50%; età media 48 anni

Increased Risk of Colorectal Cancer Development Among Patients With Serrated Polyps

Gastroenterology 2016;150:895–902

Rune Erichsen,[1] John A. Baron,[1,2] Stephen J. Hamilton-Dutoit,[3] Dale C. Snover,[4] Emina Emilia Torlakovic,[5] Lars Pedersen,[1] Trine Frøslev,[1] Mogens Vyberg,[6] Stanley R. Hamilton,[7] and Henrik Toft Sørensen[1,2]

Table 4. Estimated 10-Year Risk of Colorectal Cancer for Each Polyp Type

	Cases/controls	Adjusted OR (95% CI)	Estimated 10-year risk[a]
SSA/P with synchronous conventional adenomas	30/61	2.66 (1.70–4.16)	2.47%
SSA/P without synchronous conventional adenomas	49/81	3.40 (2.35–4.91)	3.16%
SSA/P with cytologic dysplasia	20/25	4.76 (2.59–8.73)	4.43%
SSA/P without cytologic dysplasia	59/117	2.75 (1.99–3.80)	2.56%
Conventional adenomas without SSA/P	727/1631	2.50 (2.24–2.80)	2.33%
Traditional serrated adenomas overall	14/17	4.84 (2.36–9.93)	4.50%
Hyperplastic polyps only	55/235	1.30 (0.96–1.77)	1.21%

CONCLUSION: Patients with SSA/P or TSA are at increased risk for CRC; their level of risk is similar to or higher than that of patients with conventional adenomas.

Variation in the Detection of Serrated Polyps in an Average Risk Colorectal Cancer Screening Cohort

Jeremy T. Hetzel, BS, MPH[1], Christopher S. Huang, MD[1], Jennifer A. Coukos, BS[1], Kelsey Omstead, BS[2], Sandra R. Cerda, MD[2], Shi Yang, MD[2], Michael J. O'Brien, MD, MPH[2] and Francis A. Farraye, MD, MSc[1]

Am J Gastroenterol 2010; 105:2656–2664;

Pathologist (colonoscopies)	Adenoma (*n*=1,595*)	HP (*n*=844*)	SSA (*n*=46*)	DSP (*n*=15*)	Cancer (*n*=13*)	Other (*n*=593*)
A (332)	60.2 (51.9, 68.6)	34.6 (28.3, 41.0)	3.9 (1.8, 6.0)	0.3 (0.0, 0.9)	0.3 (0.0, 0.9)	21.7 (16.7, 26.7)
B (8)	75.0 (15.0, 100.0)	25.0 (0.0, 59.6)	—	—	—	—
C (289)	67.1 (57.7, 76.6)	35.3 (28.4, 42.1)	0.7 (0.0, 1.7)	0.3 (0.0, 1.0)	0.7 (0.0, 1.7)	20.1 (14.9, 25.2)
D (308)	59.4 (50.8, 68.0)	34.4 (27.9, 41.0)	—	0.3 (0.0, 1.0)	0.6 (0.0, 1.5)	24.0 (18.6, 29.5)
E (126)	55.6 (42.5, 68.6)	29.4 (19.9, 38.8)	0.8 (0.0, 2.3)	1.6 (0.0, 3.8)	—	29.4 (19.9, 38.8)
F (230)	60.0 (50.0, 70.0)	29.1 (22.2, 36.1)	1.7 (0.0, 3.4)	1.3 (0.0, 2.8)	2.2 (0.3, 4.1)	30.4 (23.3, 37.6)
G (498)	63.5 (56.5, 70.5)	29.7 (24.9, 34.5)	4.0 (2.3, 5.8)	1.2 (0.2, 2.2)	0.2 (0.0, 0.6)	24.9 (20.5, 29.3)
H (311)	62.1 (53.3, 70.8)	37.3 (30.5, 44.1)	0.3 (0.0, 1.0)	—	0.6 (0.0, 1.5)	20.6 (15.5, 25.6)
I (80)	66.2 (48.4, 84.1)	20.0 (10.2, 29.8)	1.2 (0.0, 3.7)	—	—	30.0 (18.0, 42.0)
J (352)	67.0 (58.5, 75.6)	36.9 (30.6, 43.3)	0.9 (0.0, 1.8)	0.3 (0.0, 0.8)	—	13.1 (9.3, 16.8)
K (61)	55.7 (37.0, 74.5)	32.8 (18.4, 47.2)	1.6 (0.0, 4.9)	—	—	26.2 (13.4, 39.1)
L (27)	59.3 (30.2, 88.3)	22.2 (4.4, 40.0)	3.7 (0.0, 11.0)	—	—	29.6 (9.1, 50.2)
P value	0.264	0.062	<0.001	0.342	0.081	<0.001

Detection of adenoma, HP, and SSA differed significantly by endoscopist. Classification of HP and SSA differed significantly by pathologist. Endoscopy and pathology practices should consider educational interventions to improve serrated polyp detection and standardize classification.

Sindromi poliposiche amartomatose

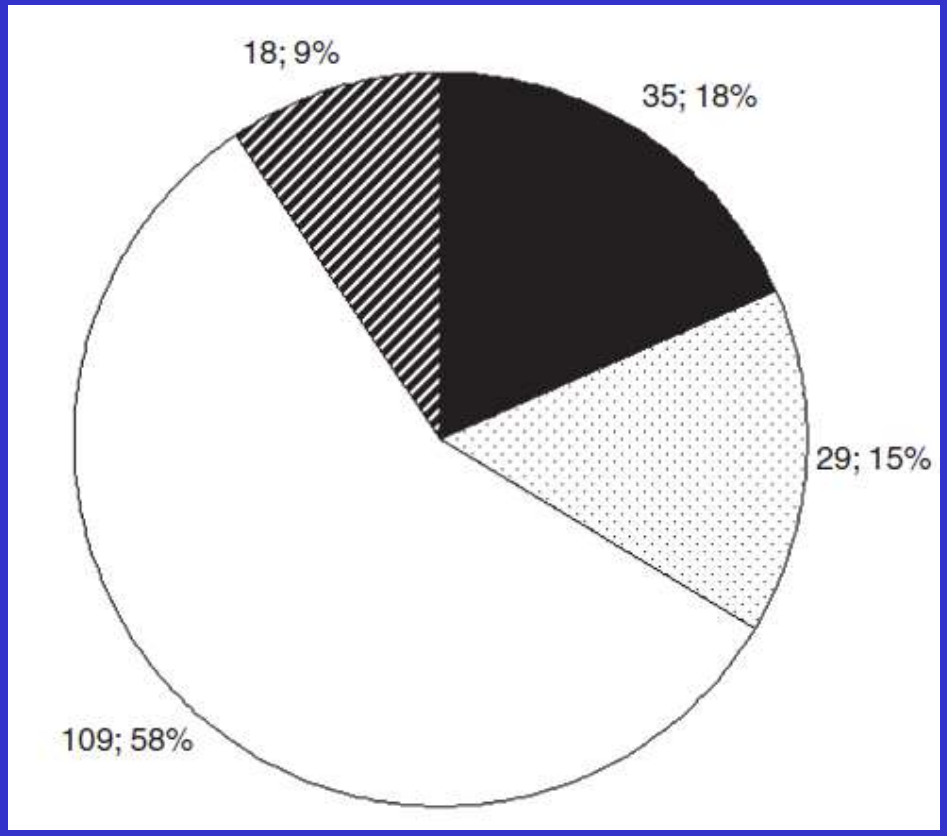
Diagnosi clinica spesso insidiosa >> casi e famiglie "perse"

- Casi de novo
- Assenza stimmate cutanee
- Storia familiare spesso misconosciuta

Multiple colorectal adenomas: Clinical features

- **Less than 100 polyps, mostly adenomas**
- **Polyps distribution may concern only a part of the large bowel**
- **Late age at onset if compared to classical FAP**

Anatomical distribution of colorectal adenomas in MCRAs



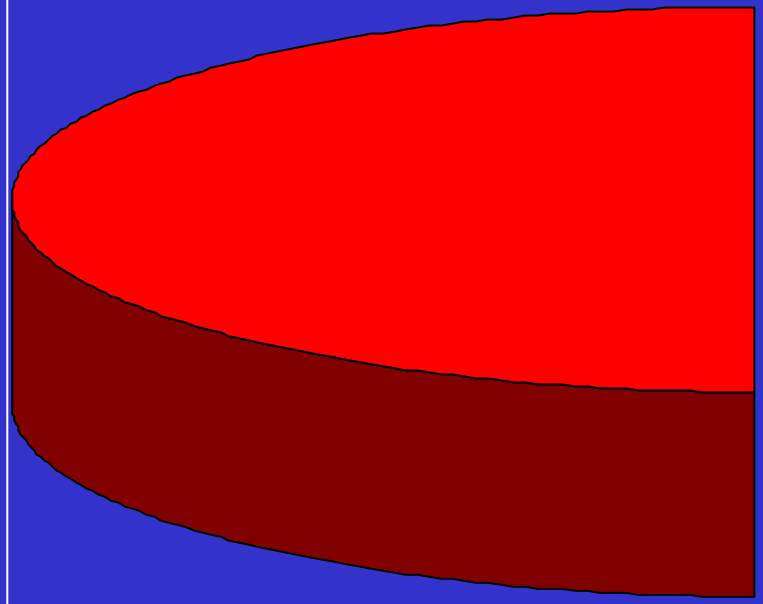
Knudsen Al et al. Colorectal dis 2010

Genotypes of MCRAs patients

APC mut. **MutYH biallelic mut** **Wild type**

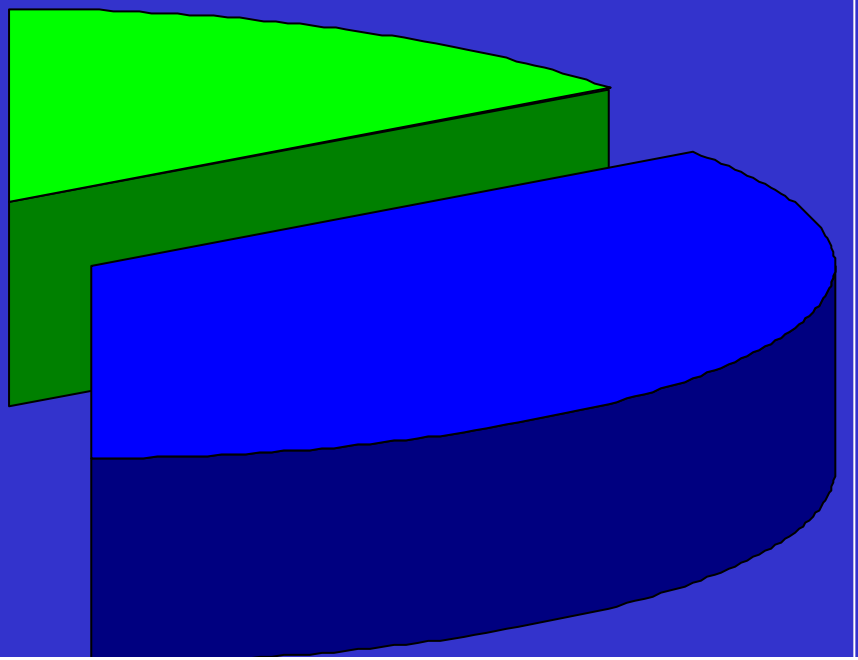
MCRAs: median polyps number: 27-33

age= 50-53 years



A-FAP: median polyps number: 19-48

age= 37-38 years



MAP: median polyps number: 36-53; age= 44-46 years

Urso EDL et al Surg Endosc 2013

Knudsen Al et al Colorectal Dis 2010

Ponz de Leon et Tech Coloproctology 2013

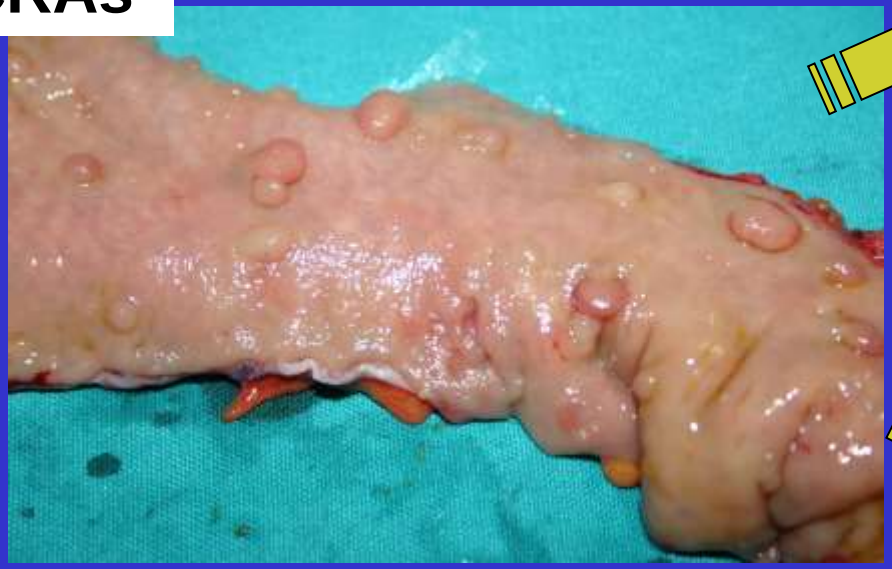
Thirlwell C et al Br J cancer 2007

Nielsen M et al J Med Genet 2005

Classical FAP

Colectomy with IRA or IPAA

MCRAs



Endoscopic polypectomies and **surveillance**

Segmental colonic resection

Colectomy with IRA/IPAA

Indications for surgical treatment

- Symptoms: hemorrhage, anemia
- Malignancy or Risk of malignancy

Risk of cancer is the key of the treatment decision

AIM

- Estimate the cancer risk
- Find clinical and molecular factors associated to increased cancer risk

Estimate the cancer risk

Reference	**Patients N°**	**Genotypes** : APC mut/MutYH double mut/wt	**Colon Cancer incidence** APC mut/MutYH double mut/wt **(%)**	**Comment**
Sieber OM et al. NEJM,2003	152	0/6/146 *	**0/50/14**	3-100 polyps
Morak M et al Clin Genet, 2010	33	0/33/0	**not tested/33/0**	only APC negative patients
Knudsen AL et al. Colorectal Dis, 2010	196	69/not tested/127	**11/ not tested/38**	MutYH not tested
Ponz de Leon et al. Tech Coloproctol, 2013	82	10/30/42	**30/46/45**	North Italian series
Urso EDL et al. Surgical Endosc, 2013	80	4/19/57	**43 (whole series)**	no difference in cancer incidence among genotypes
Filipe B et al. Clin Genet, 2009	52	6/18/28	**67/67/39**	
Nielsen M et al. J Med Genet 2005	170	not tested/40/130	**not tested/65/45**	APC not tested

Surgical treatment

- Complication rate: 20%
- Reintervention rate: 5-7%
- Perioperative mortality: 1-2%

Endoscopic management

- bleeding: 0.3-0.6%
- delayed bleeding: 2%
- perforation: 0.3-04%

Oncologic considerations

Risk of N+ for T1 high risk:6-15 %

Risk of N+ independent from tumor size

Veldkamp R etal Lancet Oncol 2005

Stoffel EM etal Cancer prev res 2008

Heresbach D et al Endoscopy 2008

Waye JD et al J Clin Gastroenterol 1992

Rex DK et al. Gastrointest endosc 1992

Nascimbeni R et al Dis Colon Rectum 2002

Conclusioni

- La sindromi neoplastiche ereditarie sono disponibili protocolli di sorveglianza sicuramente efficaci per diminuire il rischio di carcinoma e la mortalità cancro correlata.

- La terapia delle malattie neoplastiche ereditarie presenta invece ampi spazi di dibattito anche nelle forme (FAP) in cui la colectomia profilattica è un dato assodato

- La sorveglianza dei tumori associati al carcinoma colorettale come il carcinoma endometriale e il carcinoma duodenale sono elementi essenziali per la riduzione della mortalità cancro correlata