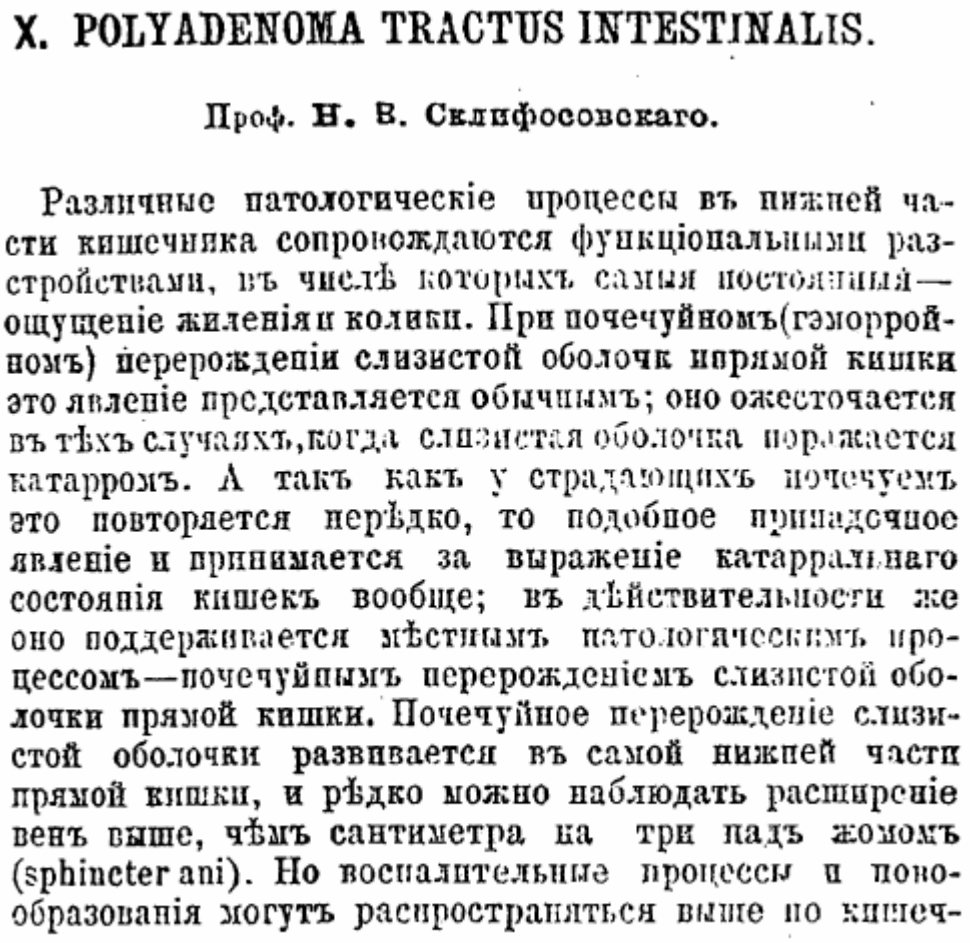
LA POLIPOSI ADENOMATOSA
FAMILIARE (FAP):
un modello per lo studio della
familiarità neoplastica

Modena, 10 dicembre 2008

Poliposi Adenomatosa Familiare definizione e diagnosi

Romano Sassatelli
ASMN Reggio Emilia

La storia



X. POLYADENOMA TRACTUS INTESTINALIS.

Проф. Н. В. Склифосовскаго.

Различные патологическіе процессы въ нижней части кишечника сопровождаются функціональными разстройствами, въ числѣ которыхъ самыя постоянныя—ощущеніе жиленія и колики. При почечуйномъ(гэморройномъ) перерожденіи слизистой оболочк ипрямой кишки это явленіе представляется обычнымъ; оно ожесточается въ тѣхъ случаяхъ,когда слизистая оболочка поражается катарромъ. А такъ какъ у страдающихъ почечуемъ это повторяется нерѣдко, то подобное припадочное явленіе и принимается за выраженіе катарральнаго состоянія кишекъ вообще; въ дѣйствительности же оно поддерживается мѣстнымъ патологическимъ процессомъ—почечуйнымъ перерожденіемъ слизистой оболочки прямой кишки. Почечуйное перерожденіе слизистой оболочки развивается въ самой нижней части прямой кишки, и рѣдко можно наблюдать расширеніе венъ выше, чѣмъ сантиметра на три надъ жомомъ (sphincter ani). Но воспалительные процессы и новообразованія могутъ распространяться выше по кишеч-

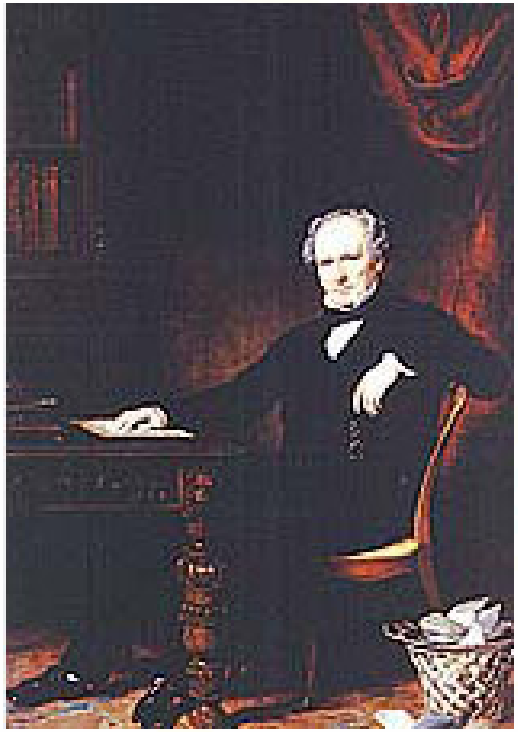
Figure 1. The first article on FAP by Sklifasowski [9].

Menzel D. “De excrescentiis verrucoso cristosis copiose in intestini crassi dysenteriam passi observatis” Acta Med Berol 1721

Sklifalowski NW; Vrac 1881

Figure 2. The old St. Mark's Hospital at City Road.

- 1925, Lockart-Mummery:
  - distinzione adenomi/flogosi
    - l'eredità è per i polipi
- Il primo Registro Poliposi al mondo…



- 1924, Coffey, prima proctocolectomia
- 1927, Cockayne, la FAP è ereditata in modo autosomico dominante
- 1927, Jungling, raccomanda la sigmoidoscopia ai figli di affetti
- 1933, Nissen, prima proctocolectomia con anastomosi ileoanale
- 1939, Lockart-Mummery & Dukes: descrizione di 10 famiglie del SMHPR
- 1943, Fitzgerald: odontomi

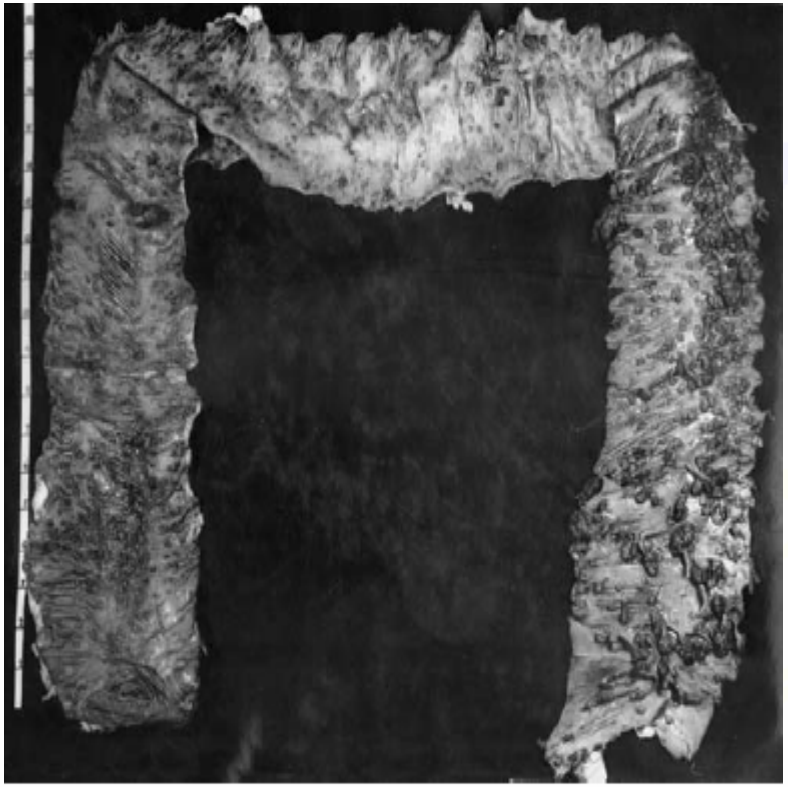


Figure 4. Old colectomy specimen from St. Mark's Hospital.

- 1948, Lloyd-Davies, prima IRA
- 1950, Halsted poliposi gastrica in FAP descritta con gastroscopia con aspetto classico di poliposi ghiandolare fundica

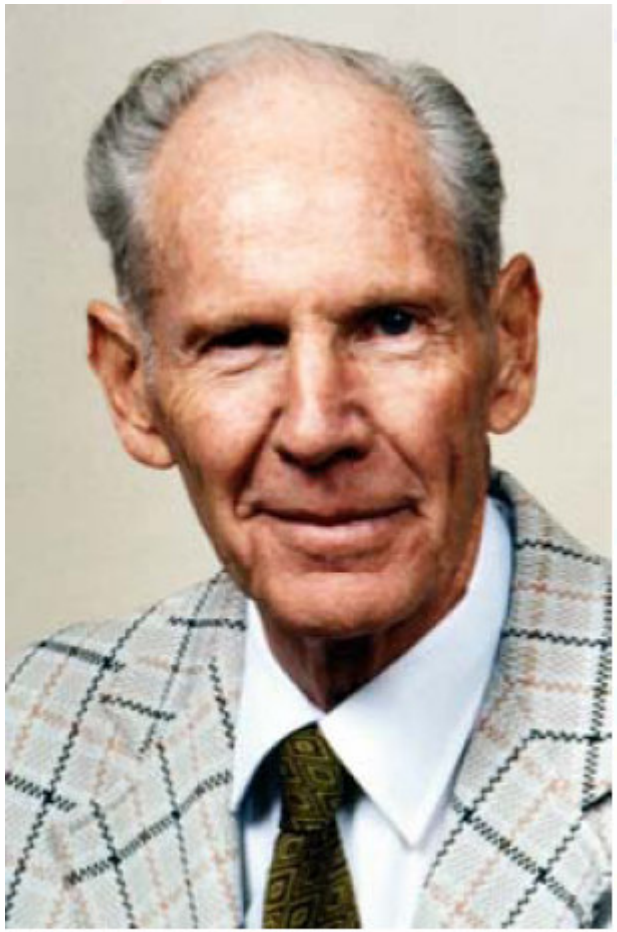


Figure 5. Eldon Gardner.

- 1951, Gardner descrive la sindrome (adenomatosi, desmoidi, tumori ossei, cisti sottocutanee)
- 1951, Dukes descrive 156 casi in 41 famiglie del SMHPR
- 1955, Reed & Neel: frequenza di 1:8,300
- 1956, Lockart-Mummery: sorveglianza del retto dopo IRA
- Dukes, se a 40 anni RS negativa, probabilità di malattia quasi nulla
- 1960, Veale esaminare tutti i familiari
- 1962, BC Morson e la classificazione istopatologica dei polipi colorettali

Figure 6. H. J. R. Bussey in the Polyposis Registry.

Anni ’70, I Registri

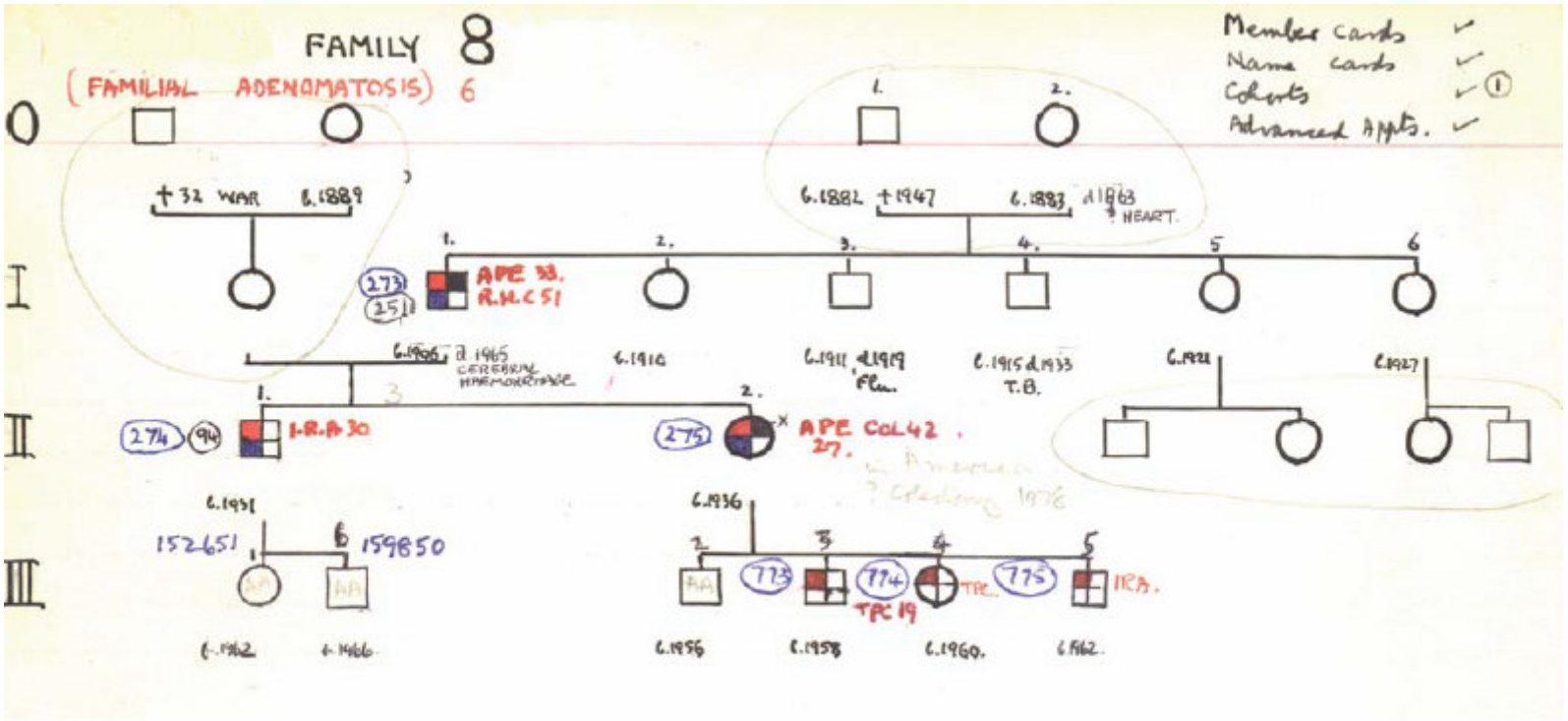
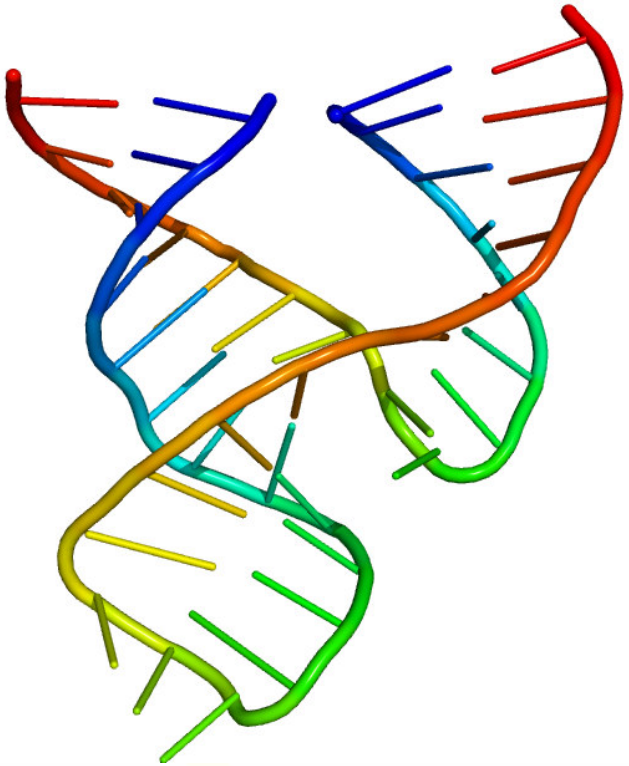
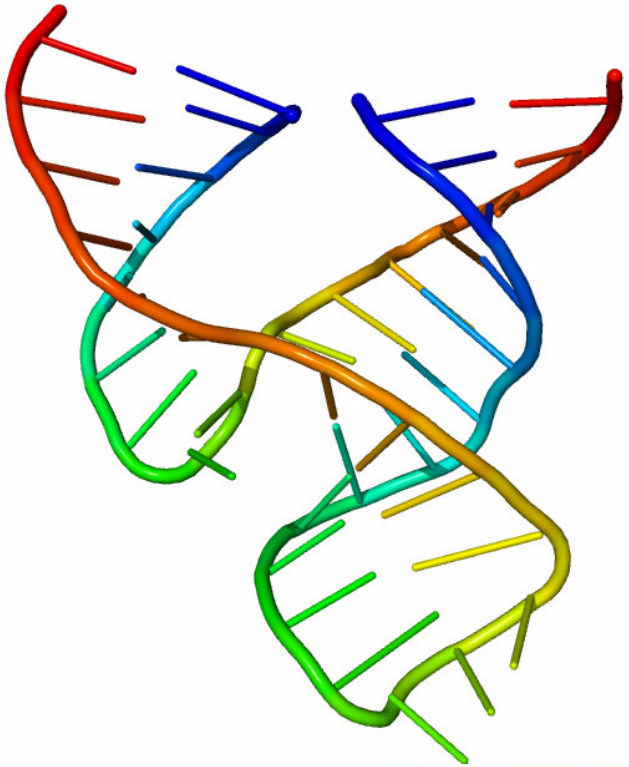


Figure 7. One of Dr. Bussey polyposis pedigrees.

- 1975, Utsunomiya, osteomi mandibolari
- 1977, YAO: adenomi duodenali
- 1977, Watanabe: poliposi ghiandolare fundica
- 1979, Hamilton: adenomi ileali post-colectomia
- 1980, Parks e Utsunomiya:colectomia con pouch e mucosectomia
- 1980: Blair&Tremple:CHRPEs
- 1981: Baron&Lee: TC per desmoidi
- 1981: Waddel:FANS e tamoxifen per desmoidi
- 1983: Kingston: hepatoblastoma
- 1986 Bülow: primi dati di sopravvivenza
- 1986, Herrera: possibile associazione a delezione di 5q
- 1985: The LCPG
- 1987, Bodmer, Leppert: localizzazione 5q 21-22



- 1989, Spigelman: stadiazione lesioni duodenali
- 1991, Groden, Kinzler The APC gene
- 1992, min mouse; Spirio: forma attenuata
- 1993, Nugent: adenomi nella pouch; nasce EuroFAP; Giardiello: sulindac; noi: polipi digiunali con PE
- 1994, Lynch: doxorub+dacarb desmoidi; Hoener: adk IAA; Lynch: AFAP
- 1995, Rubinfeld: apc protein; Chung: pancreas-sparing duodenectomy
- 1997, Milsom: VL colectomia IRA
- 2000, Steinbach, celecoxib per adenomi duodenali e colorettali



- 2002, Groves, carcinoma duodenale; Costamagna: VCE
- 2003, Sieber, Sampson: MAP; Burn:CAPP-1; LCPG+ICG-HNPCC:InSiGHT
- 2004,Bülow:storia naturale degli adenomi duodenali
- 2005-2008:…

It would be difficult to find a more promising field for the exercise of cancer control than a polyposis family, because both diagnosis and treatment are possible in the precancerous stage and because the results of the surgical treatment are excellent"

Dukes CE, 1958

Poliposi Adenomatosa Familiare

- Oltre 100 adenomi nel colon-retto
- Autosomica dominante
- Legata a mutazioni di APC (frequenza del gene 1:10.000 nati) identificabili nel 70-85% dei casi
- 15-20% dei casi: ***de novo,*** mosaicismo nel 15% dei casi
- Attenuata nell'8% dei casi

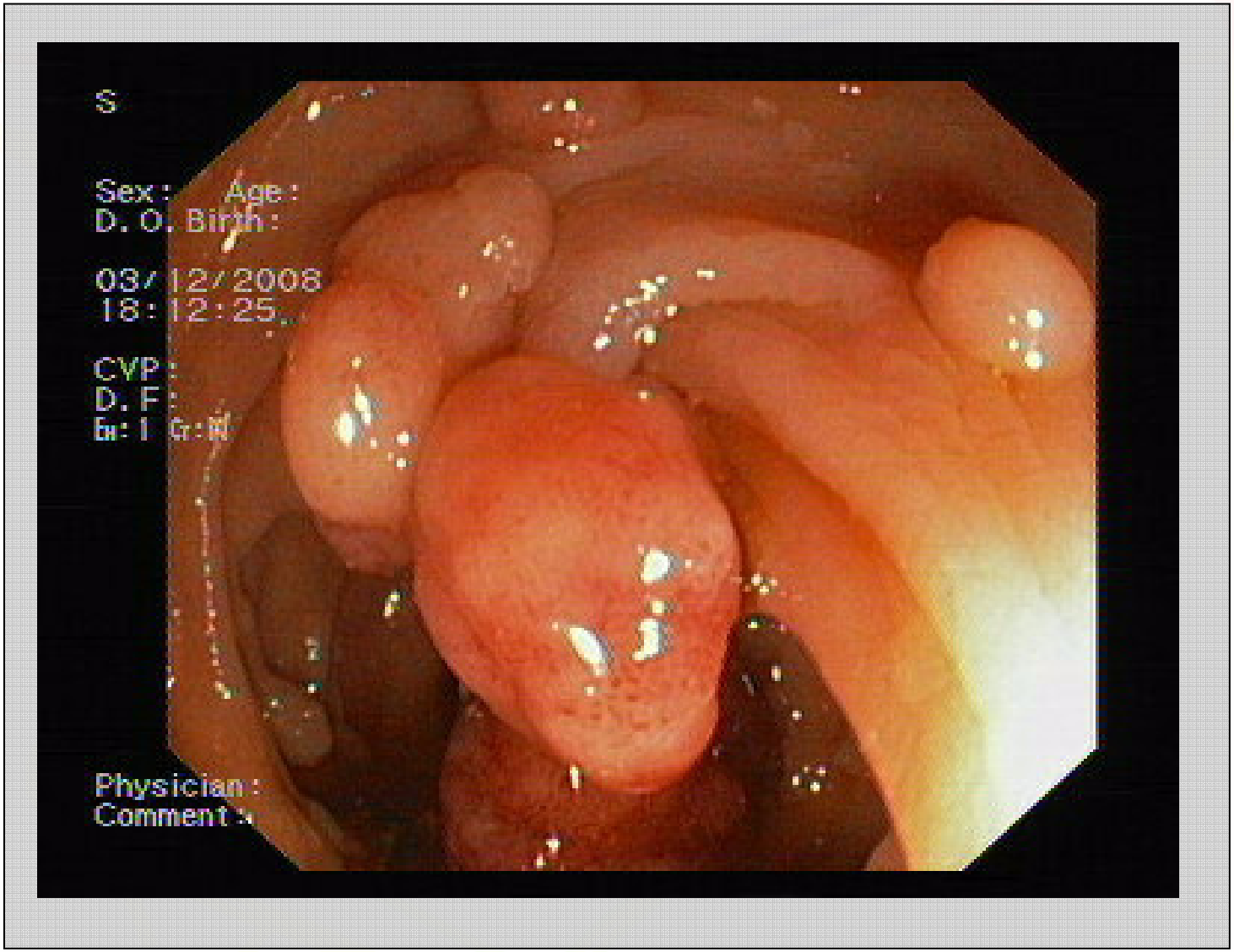
Poliposi Adenomatosa Familiare

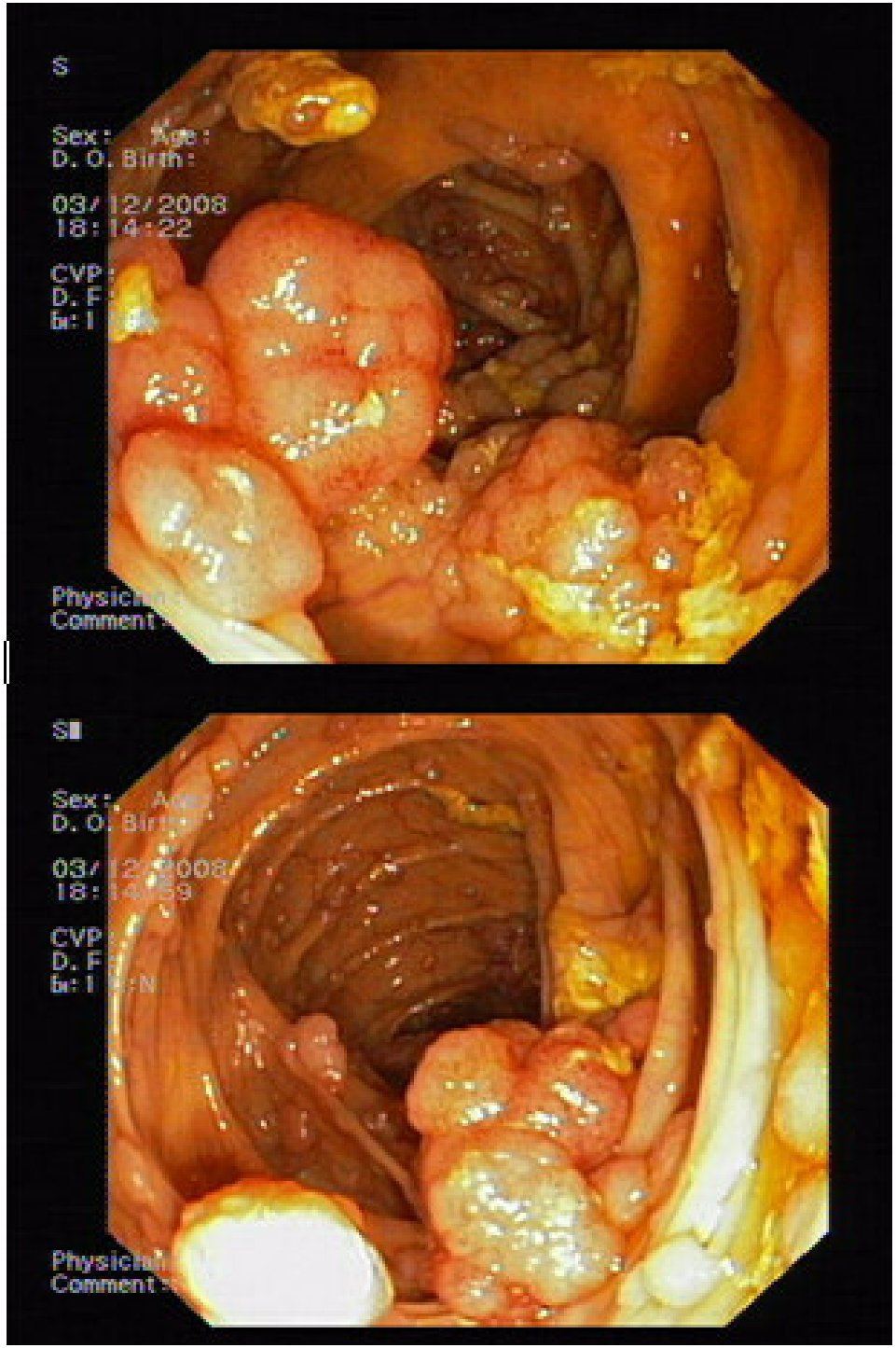
- Senza intervento chirurgico: cancro colorettale a 40-50 anni di età
- Manifestazioni extracolorettali (duodeno, stomaco, ileo, pancreas)
- Manifestazioni extraintestinali (retina, epidermide, ossa, mesentere, surrenali, tiroide, cervello, fegato)

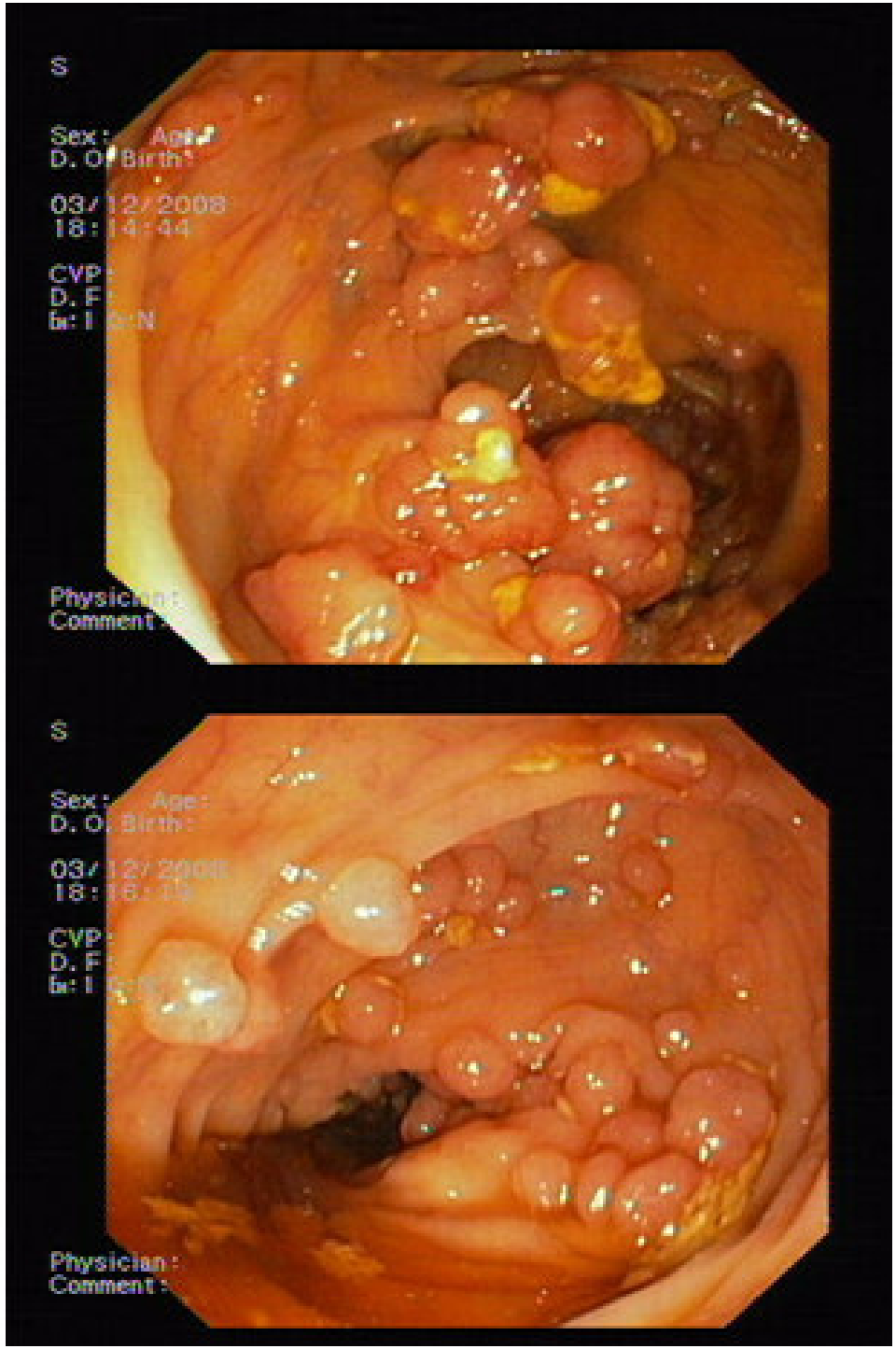
Colon-retto

- Adenomi
  - Centinaia (***intermediate***) insorgenza in 2°-3° decade di vita
  - Migliaia, oltre 5000 (***profuse***) insorgenza in 1° - 2° decade di vita

  - ***Attenuated***, < 100


S
Sex:
Age:
D. O. Birth:
03/12/2008
18:12:25
CVP:
D. F:
Physician:
Comment:

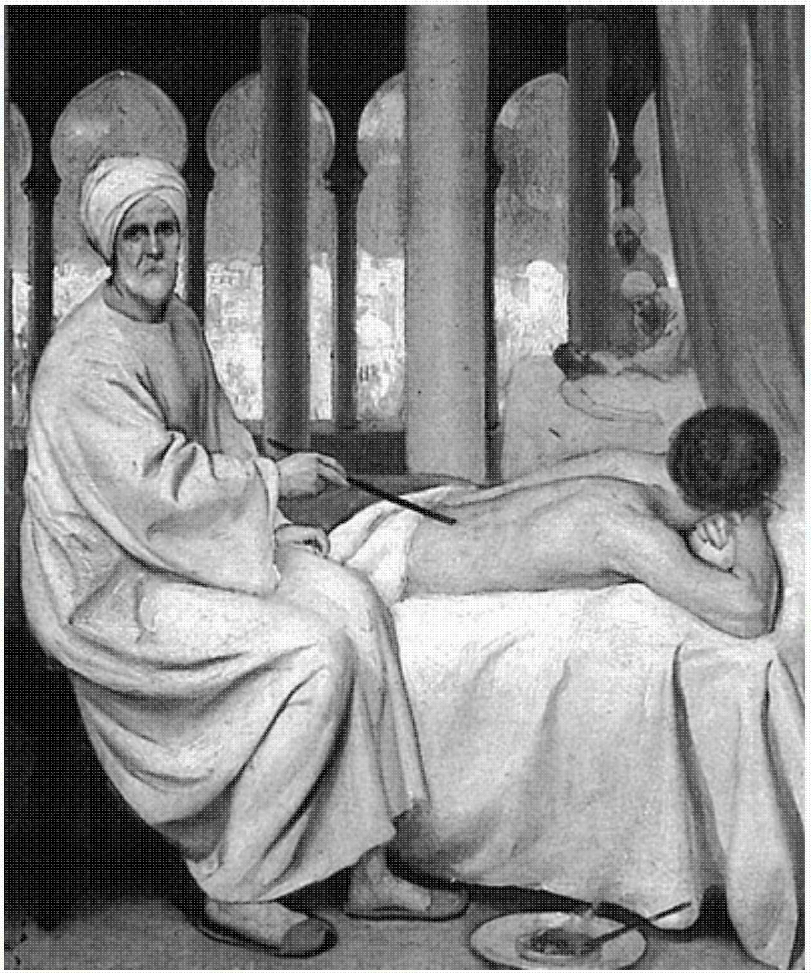

S
Sex:
D. O. Birth:
03/12/2008
18:14:22
CVP:
D. F:
Physician:
Comment:


S
Sex:
D. O. Birth:
03/12/2008
18:14:44
CVP:
D. F:
Physician:
Comment:

S
Sex:
D. O. Birth:
CVP:
D. F:
Physician:
Comment:

S
Sex:
D. O. Birth:
CVP:
D. F:
Physician:
Comment:

Trattamento, prevenzione



Abu al-Qasim Khalaf bin Abbas Al-Zahrawi – Albucasis (A.D. 936-1013)

e poi sorveglianza…

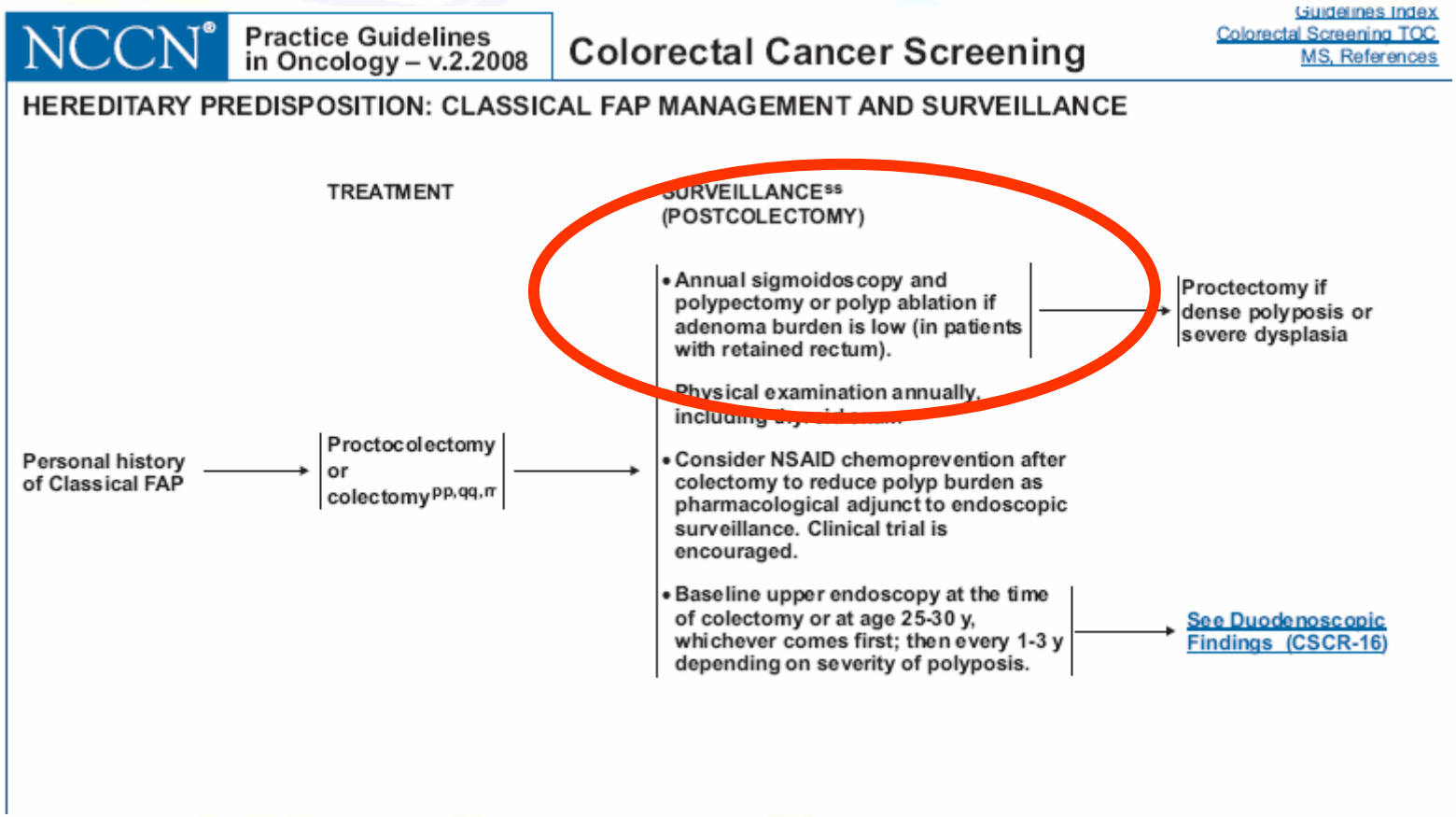
GUT ONLINE

Guidelines for the clinical management of familial adenomatous polyposis (FAP)

H F A Vasen, G Möslein, A Alonso, S Aretz, I Bernstein, L Bertario, I Blanco, S Bülow, J Burn, G Capella, C Colas, C Engel, I Frayling, W Friedl, F J Hes, S Hodgson, H Järvinen, J-P Mecklin, P Møller, T Myrhøi, F M Nagengast, Y Parc, R Phillips, S K Clark, M Ponz de Leon, L Renkonen-Sinisalo, J R Sampson, A Stormorken, S Tejpar, H J W Thomas and J Wijnen

Gut 2008;57;704-713; originally published online 14 Jan 2008;
doi:10.1136/gut.2007.136127

Retto residuo



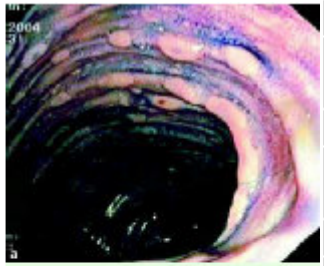
IAA

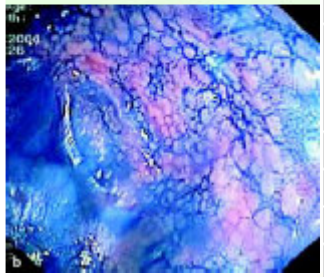
Tab. 1 Summary showing timescale, methods of surveillance and therapeutic indications

	Start of follow-up	*Timetable for surveillance*	*Methods of surveillance*	*Therapeutic indications Endoscopy*	*Surgery*
Ileo-anal anastomosis	6 months after surgery	After 1 year and then every 2 years	General anaesthesia at first, indigo-carmine	Adenomas > 1 cm or high grade dysplasia*	Cancer invading the sub-mucosa
Ileo-rectal anastomosis	6 months after surgery	Annually	General anaesthesia, indigo-carmine	All adenomas (cancer prevention)	Cancer invading the sub-mucosa
Duodenum and proximal jejunum	After 25 years at the latest	Every 2 or 3 years	General anaesthesia, indigo-carmine, lateral and axial vision	Adenomas > 1 cm or high grade dysplasia*	Cancer invading the sub-mucosa, Spigelman stage IV*

expert opinion recommended in cases of numerous adenomas, adenomas which are large or in cases of high grade dysplasia

*expert opinion recommended





Studies	Patients with adenomas	Degree of dysplasia	Mean adenoma size, mm	Mean time since colectomy, years
IPAA				
Shepherd et al. [14]	2/12	LGD	–	1
Myrhøj et al. [15]	1/1	LGD	2 – 3	12
Nugent et al. [16]	7/38	LGD	–	4
Church et al. [17]	1/1	–	2 – 20	6
Wu et al. [18]	11/26	–	3 – 20	–
Parc et al. [19]	30/85	1 HGD 21 LGD	< 5	7
Thompson et al. [20]	14/33	–	1 – 3	7
Beveridge et al. [21]	2/2	–		4 – 10
Present series	17/23	1 HGD 16 LGD	5.2	4.7
IRA				
Hamilton et al. [9]	7	–	–	1 – 25
Jarvinen et al. [10]	1/5	–	–	–
Burt et al. [11]	6/11	–	1 – 5	0.25 – 15
Bertoni et al. [12]	9/17	–		
Present series	10/21	2 HGD 8 LGD	3.3	16.4

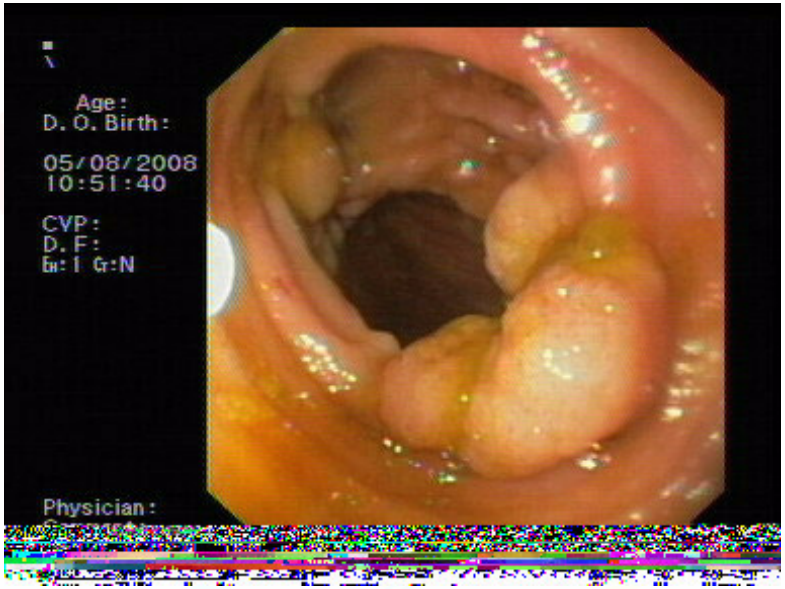
Endoscopic surveillance of the ileoanal pouch following restorative proctocolectomy for familial adenomatous polyposis

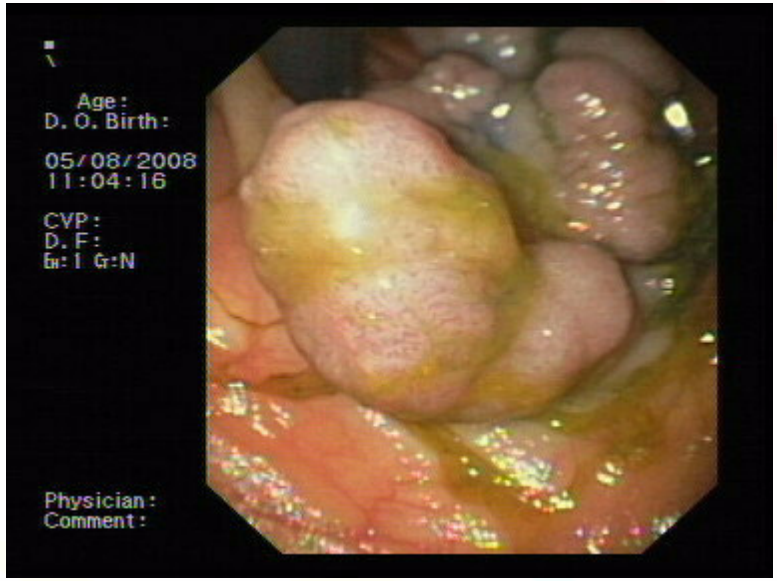
Authors D. P. Hurlstone[1], B. P. Saunders[2], J. M. Church[3]

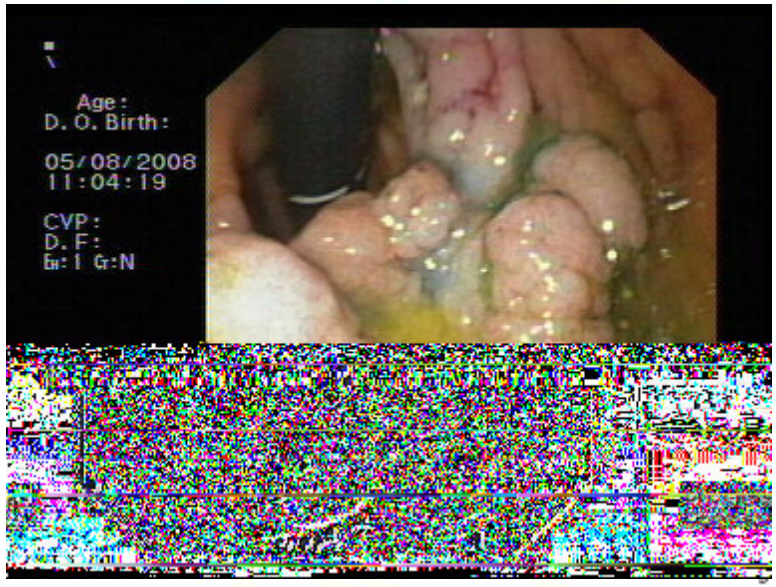
Institutions [1] Gastroenterology and Liver Unit, Royal Hallamshire Hospital, Sheffield, UK
[2] Wolfson Unit for Endoscopy, St. Mark's Hospital, London, UK
[3] Department of Colorectal Surgery, Cleveland Clinic Foundation, Cleveland, Ohio, USA

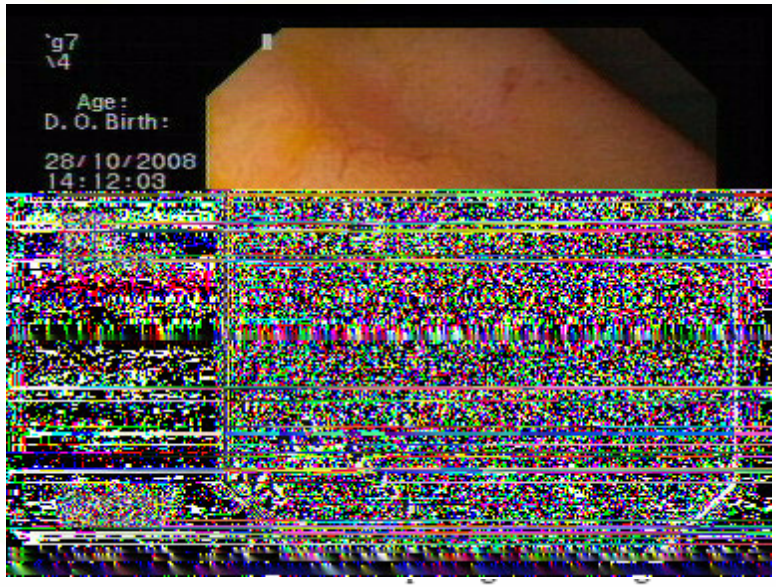
The "true" incidence and natural history of IPAA neoplasia in FAP are not clearly defined. However, Parc et al. [5] and Wu et al. [6] have shown a 35% and 42% incidence, respectively, of recurrent ATZ and cuff adenoma in FAP patients at a median follow-up of 66 months; Parc and colleagues reported an incidence of pouch adenomas of 7% at 5 years, 35% at 10 years, and 75% at 15 years after IPAA formation [5]. It is in this last group that endoscopic local control of pouch intraepithelial neoplasia can potentially fail, the only alternative therapeutic option then being pouch excision. However, pouch excision carries a risk of significant co-morbidity, a requirement for permanent ileostomy, and an overall mortality rate of 2–5%. Hence, surveillance pouchoscopy in this group of patients has now been adopted by many centers, where endoscopic local control of intraepithelial neoplasia is the preferred management.

ATZ: anal transition zone









pooling of dye precludes adequate mucosal imaging. It is important that retroflexion views of the IPAA be performed in addition to en face imaging, to limit the possibility of missed pathology at the distal margin of the ileoanal anastomosis, which cannot be viewed adequately using conventional forward-viewing endos-

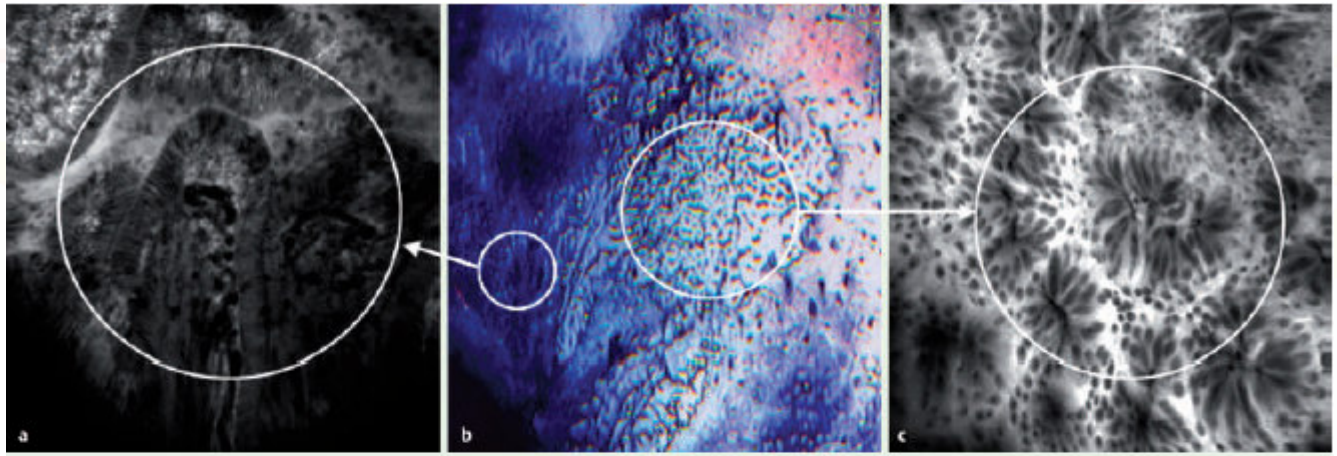


Fig. 4 **a** Confocal laser scanning endomicroscopy using intravenous fluorescein sodium 10% (50 µm *z*-axis). The circled mucosal area adjacent to the "unmasked" lesion shows normal villous architecture. In vivo intraepithelial lymphocytes can be resolved in addition to mucin-containing goblet cells within the brush border. The afferent and efferent villous capillary loops can also be resolved, with single red cells seen within (black spots). The intravillous stroma is also clearly resolved. **b** Indigo carmine 0.5 % chromoscopy shows the unmasking of a significant lesion according to SURFACE guidelines. Further characterization in this example used confocal laser scanning endomicroscopy. **c** Laser scanning endomicroscopy of the surface epithelium using topical acroflavin shows colonic crypts arranged with a regular architecture and hexagonally orientated cellular crypt structure. Early crypt fusion and elongation typical of hyperplasia is shown. This is a nonneoplastic architecture. No further endoscopic intervention is required.

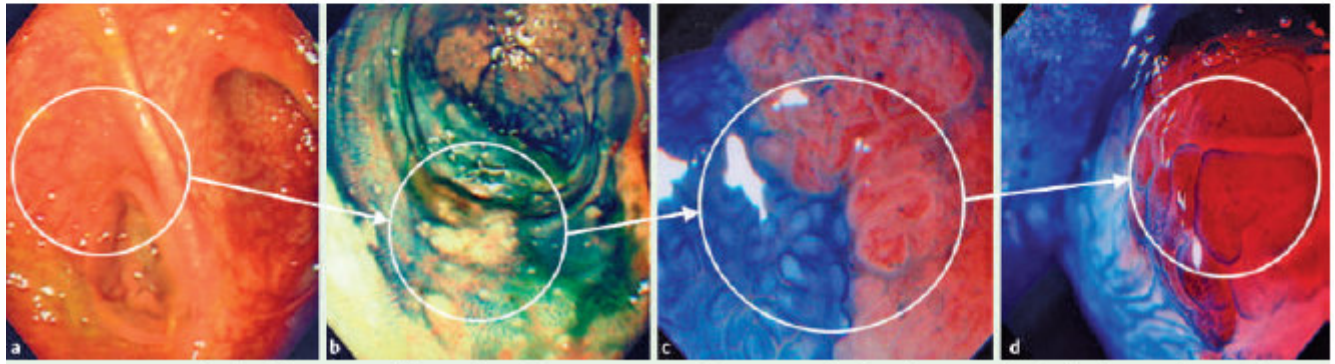


Fig. 5 **a** Conventional white-light imaging of the apical pouch reservoir. **b** Mucosal appearances of the pouch segment circled in **a**. A flat (Paris type 0–IIa) lesion is unmasked according to SURFACE guidelines. **c** High-magnification 0.5 % chromoscopy imaging (×80) shows a neoplastic type III/IV of the circumscribed neoplastic crypt (circled in **c**). A neoplastic Kudo type IV crypt is evident. In vivo diagnosis shows a Paris 0–IIa low-grade tubulovillous adenoma. There is no evidence of an invasive type V crypt. Endoscopic mucosal resection would be the endoluminal intervention of choice.

Sorveglianza ileo e pouch

- Diminutive intraepithelial neoplastic lesions less than 5 mm in diameter should be ablated by APC after representative cold biopsies have been taken.
- If there are multiple diminutive lesions (too numerous to meaningfully resect), representative biopsies should be taken, with any larger lesions snare-resected and retrieved for histology.
- Paris type 0-II/Is [9] intraepithelial neoplastic lesions less than 5 mm in diameter (in the absence of endoscopic atypia) should undergo en bloc EMR or APC ablation (with preablation biopsy). All resected specimens should be retrieved where possible; multiple lesion retrieval is facilitated by using an atraumatic Roth net. Transanal resection for larger, distally located lesions can also be considered as an alternative to EMR. A clinical example of EMR in the IPAA is shown in the accompanying video supplement.
- Paris type Ip and Isp (pedunculated/subpedunculated) intraepithelial neoplastic lesions less than 5 mm in diameter should undergo snare polypectomy unless they are so numerous that that is not feasible.

Table 1. Paris Workshop Guidelines for the Gross Morphologic Classification of Colorectal Lesions

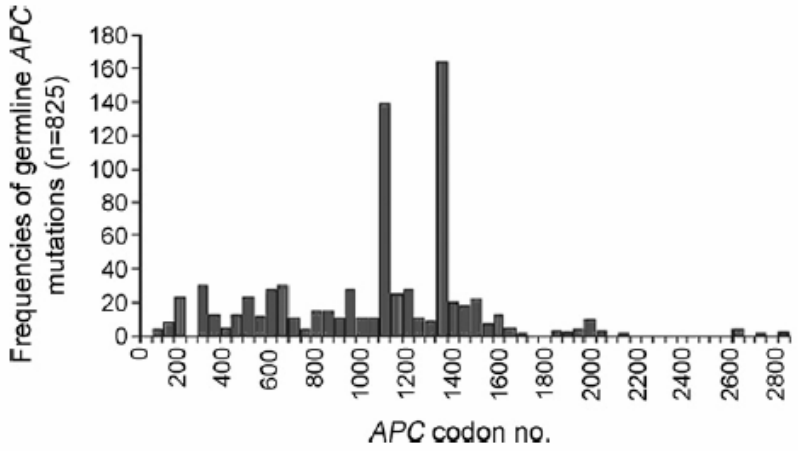
Endoscopic appearance	Paris class		Description
Protruded lesions	Ip		Pedunculated polyps
	Ips		Subpedunculated polyps
	Is		Sessile polyps
Flat elevated lesions	0–IIa		Flat elevation of mucosa
	0–IIa/c		Flat elevation with central depression
Flat lesions	0–IIb		Flat mucosal change
	0–IIc		Mucosal depression
	0–IIc/IIa		Mucosal depression with raised edge

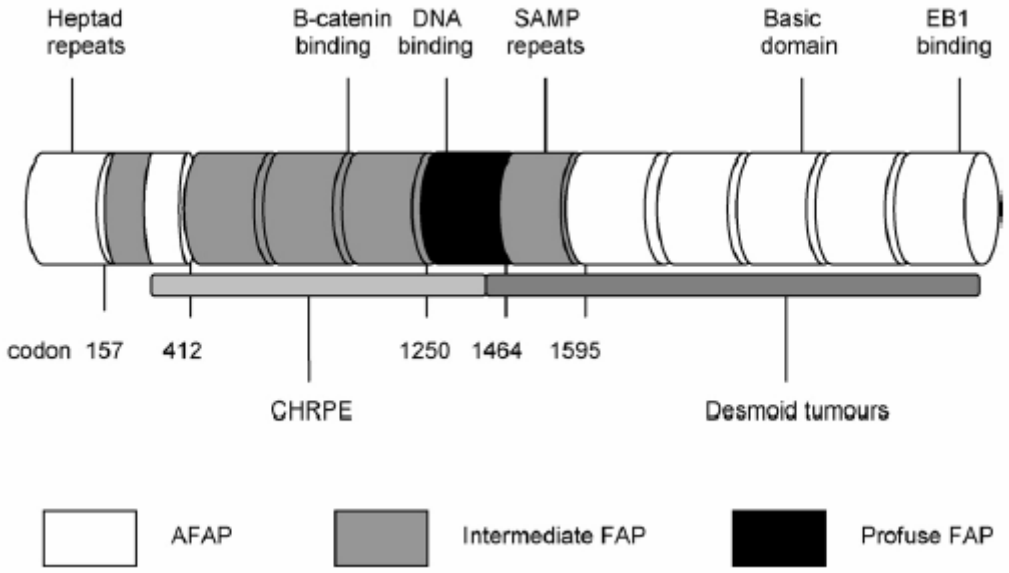
Care for:

1. Diameter exceeding 20 mm.
2. Margin of an elevated and depressed lesion (Paris 0–IIa + IIc) presenting as a smooth "circle" (without indents).
3. No or asymmetrical "lift" at submucosal injection.

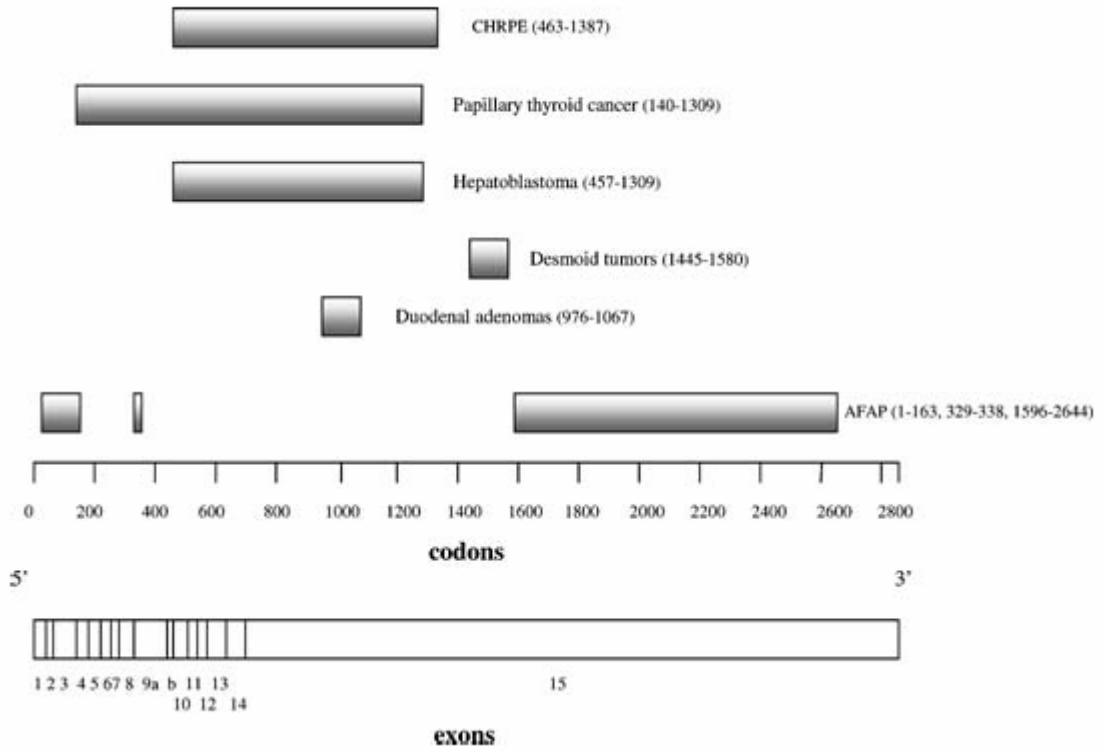
Hurlstone DP et al. Endoscopic surveillance of the ileoanal pouch ... Endoscopy 2008; 40: 437–442

Clinica , genetica

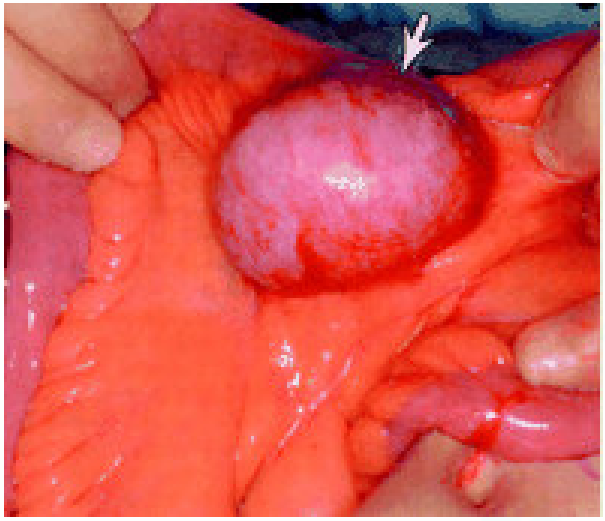


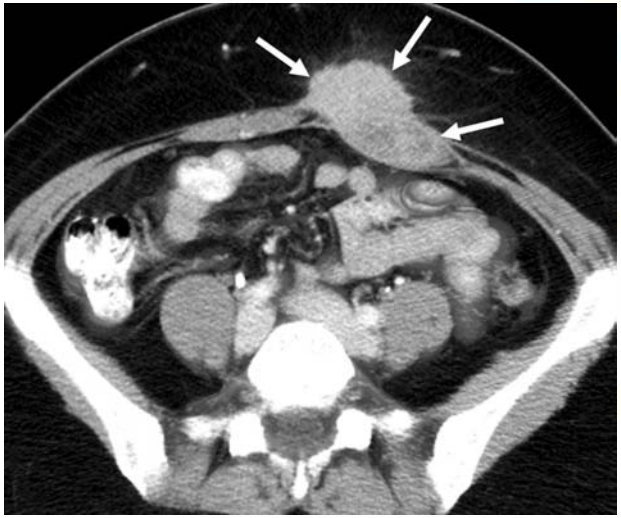


Clinica , genetica



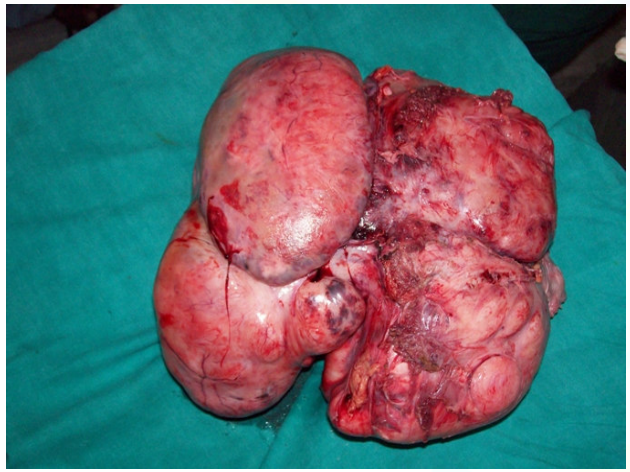
Desmoidi

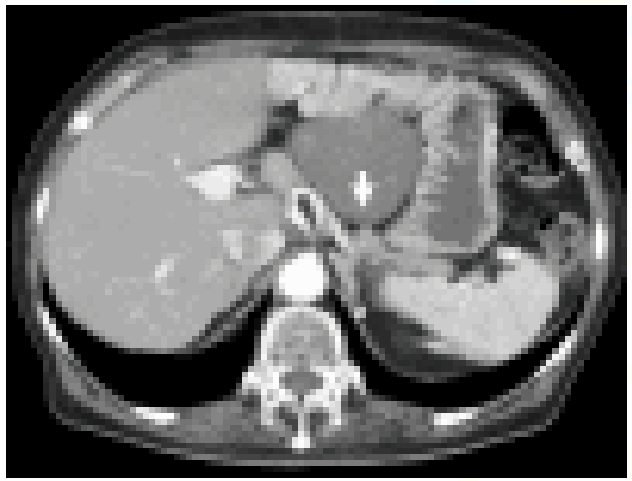




- Neoplasie mesenchimali, malignità locale, seconda causa di mortalità
- RR circa 1000, picco 30 anni
- Rischio assoluto 21%, 1444-1578
- Aspetto molto variabile sheet ► mass
- Localizzazione addominale e parietale
- Massima incidenza a due anni dall'intervento (fattore scatenante)
- FH + anche disgiunta da mutazioni APC, sesso femminile, gravidanze

Desmoidi





- Ostruzione, compressione ureteri, ischemia, ascessi, perforazioni
- 10% aggressivi fino a grosse dimensioni
- Sulindac+ tamoxifen; Cht (oncology paradox)
- Chirurgia solitamente no (recidiva, sanguinamento, short bowel)
- Sorveglianza-gestione
  - CT-MRI se 1444-1578
  - Delay surgery se fattori rischio

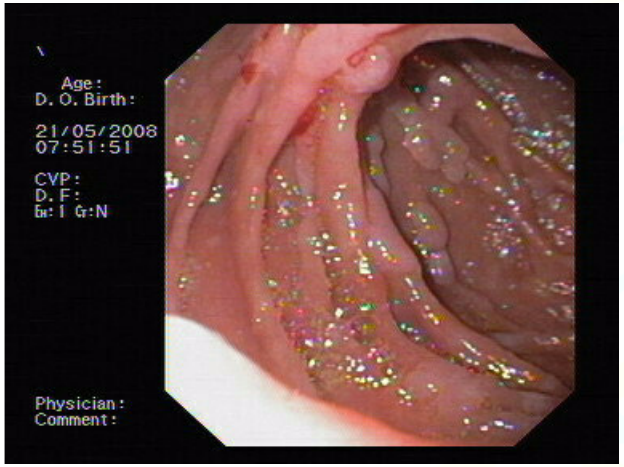
MANAGEMENT OF DESMOID TUMOURS

QUESTION: *what is the appropriate treatment of desmoid tumours?*

CONCLUSION: *non-randomised, non-controlled studies suggest that sulindac in combination with tamoxifen is effective in FAP patients with intra-abdominal desmoids and desmoids located at the abdominal wall (category of evidence III). Also small non-controlled studies indicate that chemotherapy or radiotherapy may be of benefit in those with progressive growing desmoids (category of evidence III).*

The role of surgery of (intra)-abdominal-(wall) tumours is controversial (category of evidence III)

Polipi e cancro del duodeno



- Polipi presenti nel 90%, avanzati nel 43-50% dei casi (60-70 anni)
- Età media diagnosi 40 anni
- Cancro: terza causa di morte (8.2%), età media 47-50 anni, RR 100-330 rischio cumulativo 3-4.5% (fino a 10%, periampollare) entro 60a
- Circa 2/3 papilla e regione periampollare
- Frequenti microadenomi(12%)

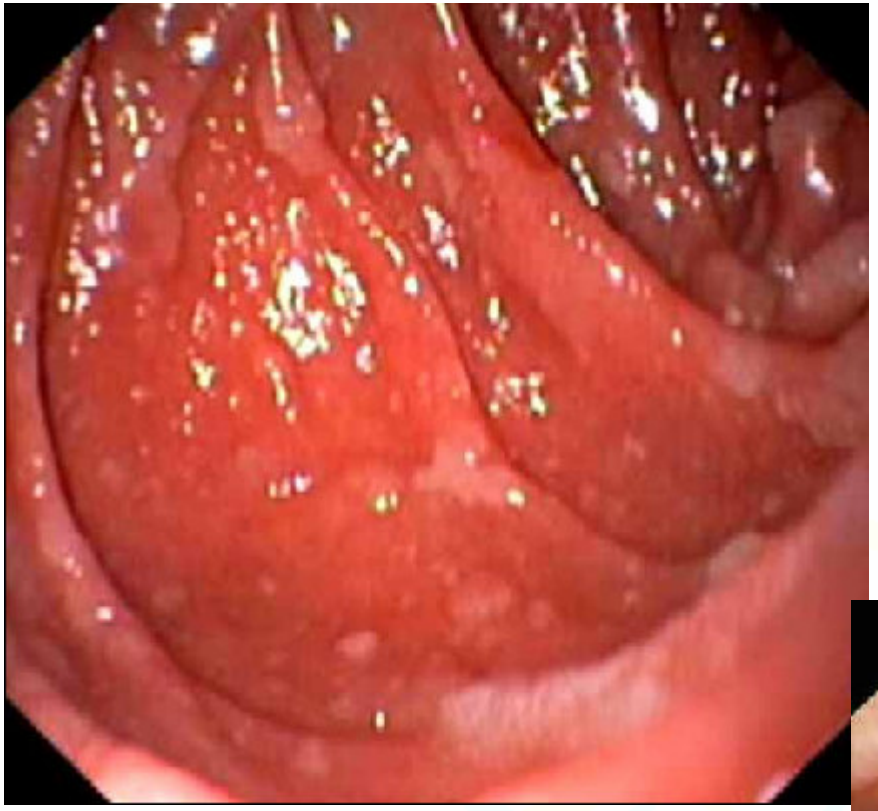
Table 5 Spigelman classification for duodenal polyposis in familial adenomatous polyposis

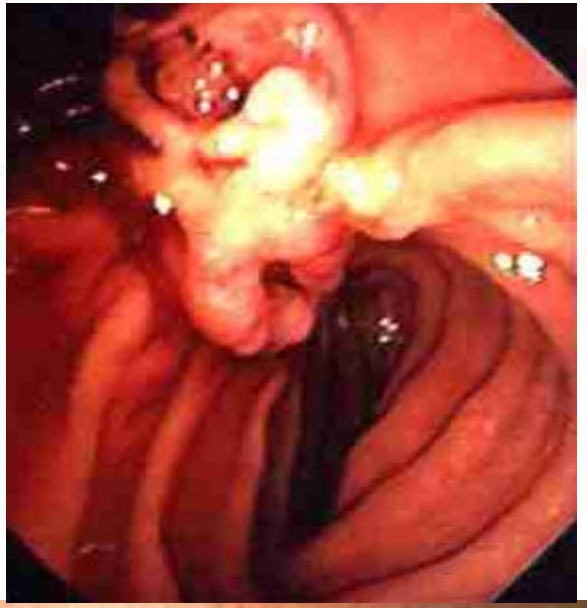
Criterion	1 point	2 points	3 points
Polyp number	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild*	Moderate*	Severe†

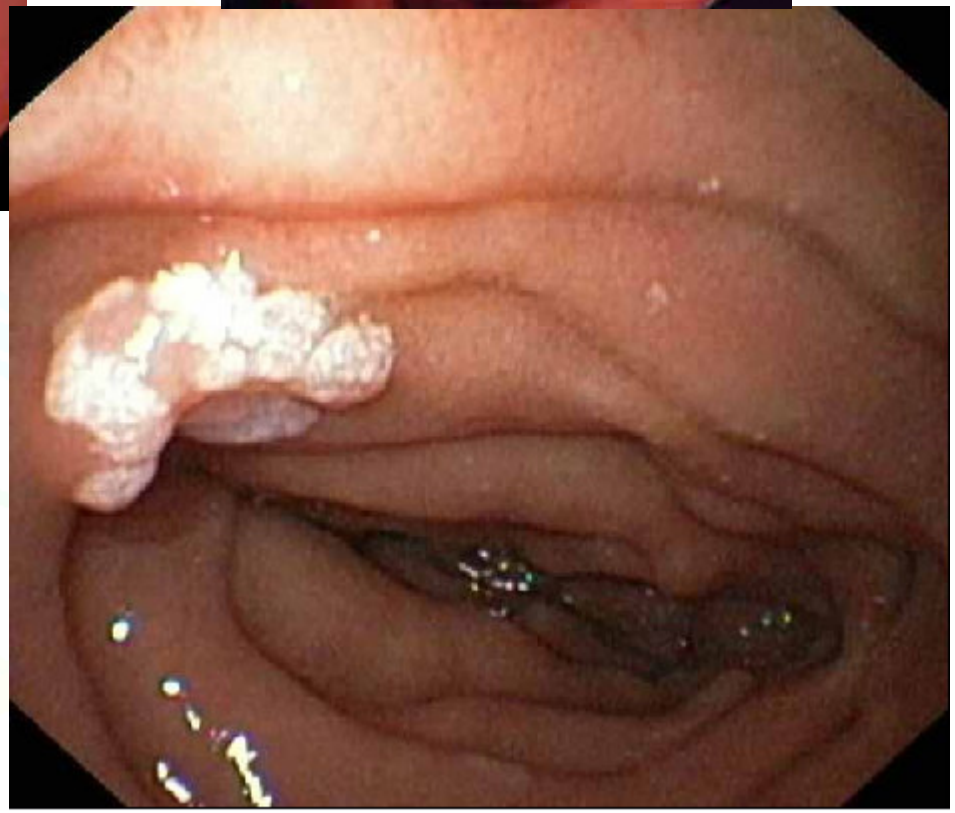
Stage 0, 0 points; stage I, 1–4 points; stage II, 5–6 points; stage III, 7–8 points; stage IV, 9–12 points.

*A low degree of dysplasia according to current classification.

†A high degree of dysplasia.







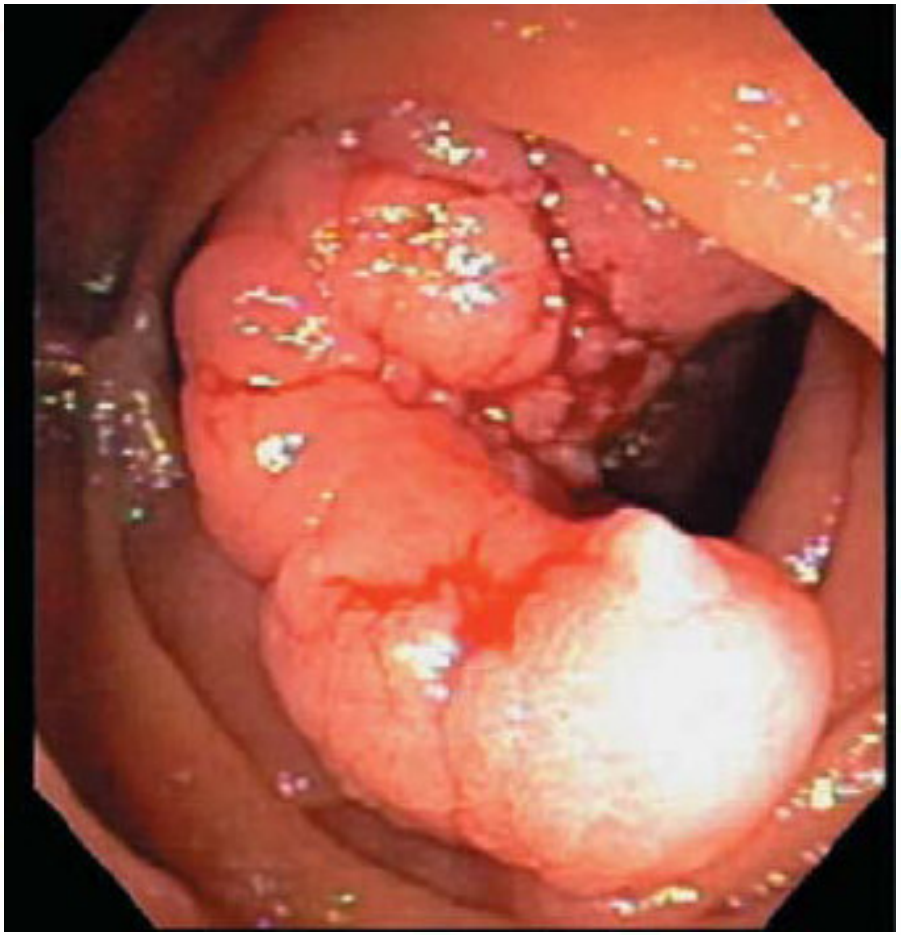


Table 6 The progression of duodenal polyposis in familial adenomatous polyposis

Author	Groves	Saurin	Bulow
Year of publication	2002	2004	2004
Subjects	99	35	368
Mean age (years)	42	37	25
Sex (% male)	55	57	49
Mean follow-up (years)	10	4	7.6
Spigelman stage IV			
at initial examination	9.6%	14%	7%
at last follow-up	14%	35%	15%
Duodenal cancer during follow-up	6*	0	4†

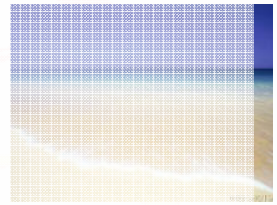
*Spigelman stage at previous endoscopy: II, III, IV, IV, IV, IV.
†Spigelman stage at previous endoscopy: II, III, IV, IV.

Sorveglianza duodeno

QUESTION: *does periodic examination of the upper gastrointestinal tract lead to detection of duodenal polyposis in an early stage?*

CONCLUSION: *prospective follow-up studies on the natural history of duodenal polyposis have demonstrated that the adenomas progress slowly to cancer. Because the conversion from adenomas to carcinoma may take more than 15–20 years, current screening protocols of the upper gastrointestinal tract usually detect duodenal disease at a premalignant stage (category of evidence III).*

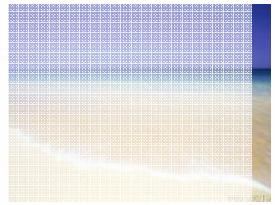
Sorveglianza duodeno



QUESTION: *does treatment of premalignant duodenal lesions lead to a reduction of mortality related to duodenal cancer?*

CONCLUSION: *screening of the duodenum in patients with FAP may lead to the identification of patients with advanced duodenal disease (Spigelman stage III/IV). Intensive surveillance and treatment of such patients may lead to reduction of duodenal cancer-related mortality (category of evidence III/IV). In young patients (<40 years) with advanced disease (stage III/IV), local surgery (duodenotomy and polypectomy) might be of benefit to postpone major surgery. In older patients with stage IV disease at repeated examinations, there is an indication for duodenectomy (category of evidence IV, grade of recommendation C).*

Sorveglianza duodeno



QUESTION: *what is the appropriate protocol in terms of timing, type of investigation and surveillance interval?*

CONCLUSION: *the Mallorca group recommends that surveillance of the upper gastrointestinal tract be initiated between age 25 and 30 years. The suggested protocol is shown in table 7* (category of evidence IV, grade of recommendation C).

Table 7 Recommended surveillance interval between upper gastrointestinal endoscopic examination in relation to Spigelman classification

Spigelman classification	Surveillance interval (years)
0/I	5
II	3
III	1–2
IV	Consider surgery ?

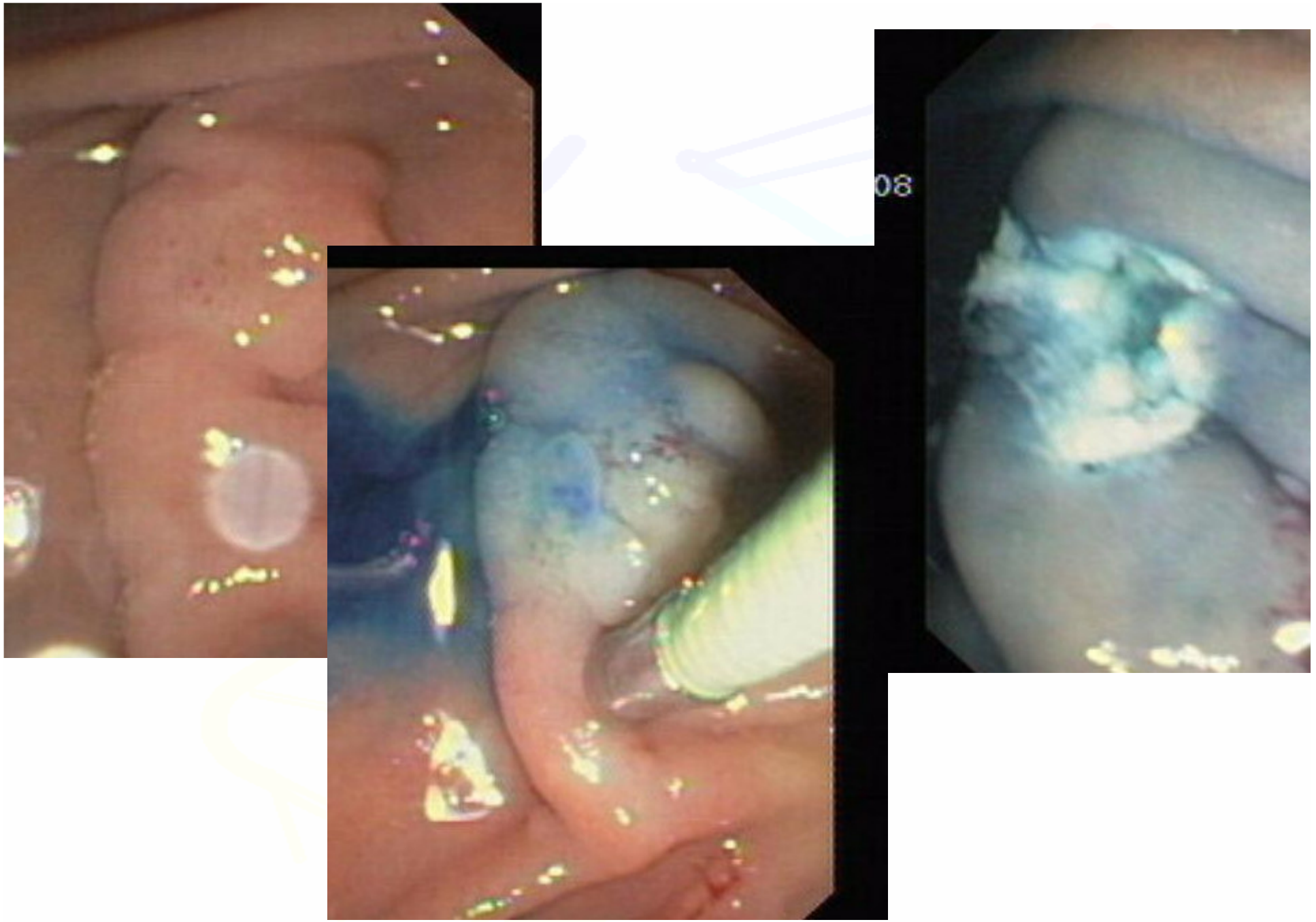


Table 1. Comparison between EUS and CT for periampullary tumor staging (tumor size and lymph node metastases) in 48 patients.

	Tumor size		Lymphnode metastases	
	EUS	**CT**	**EUS**	**CT**
Sensitivity	100%	68%	61%	33%
Specificity	75%	50%	100%	92%
Accuracy	98%	67%	84%	68%

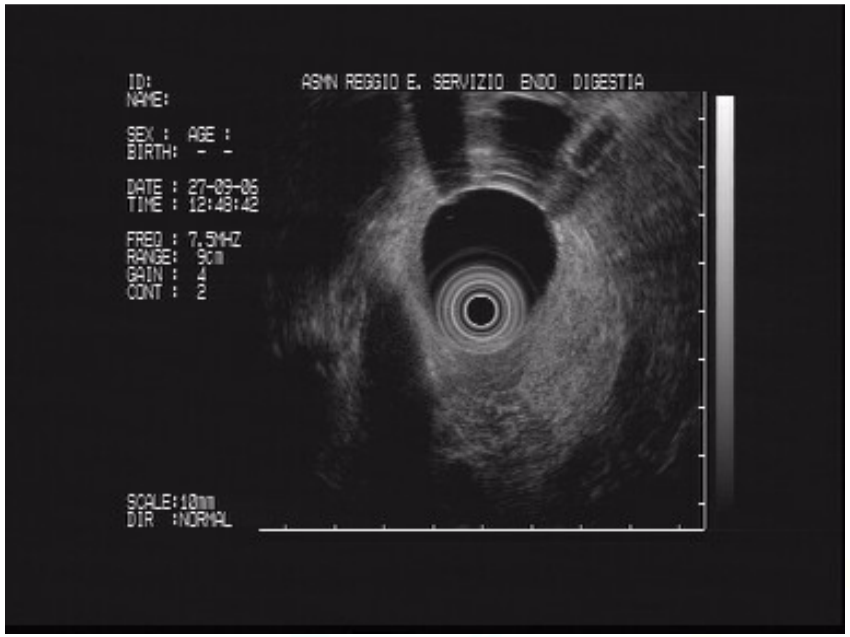
Modified from [23]

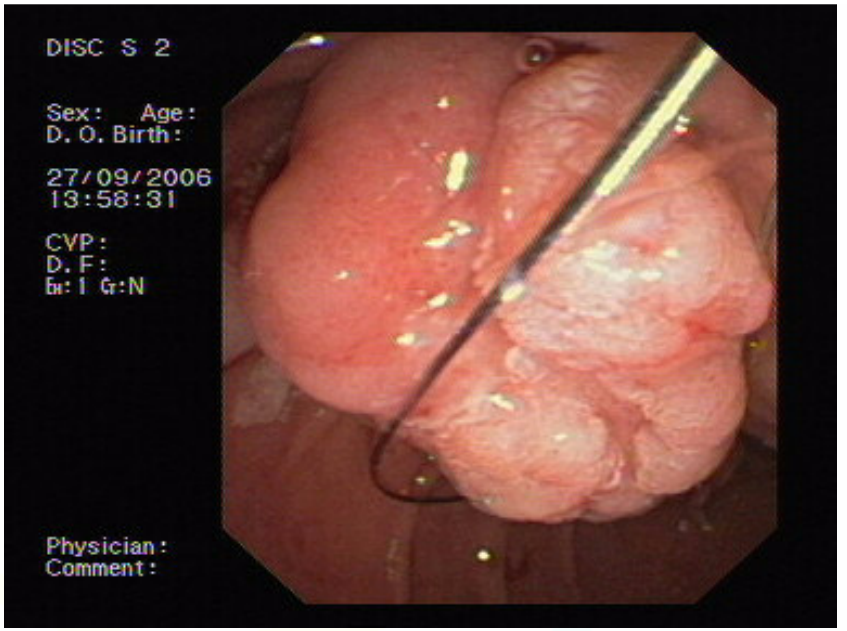
23. Rivadeneira DE, Pochapin M, Grobmyer SR, Lieberman MD, Christos PJ, Jacobson I, Daly JM. Comparison of linear array endoscopic ultrasound and helical computed tomography for the staging of periampullary malignancies. Ann Surg Oncol 2003; 10:890-7. [PMID 14527907]

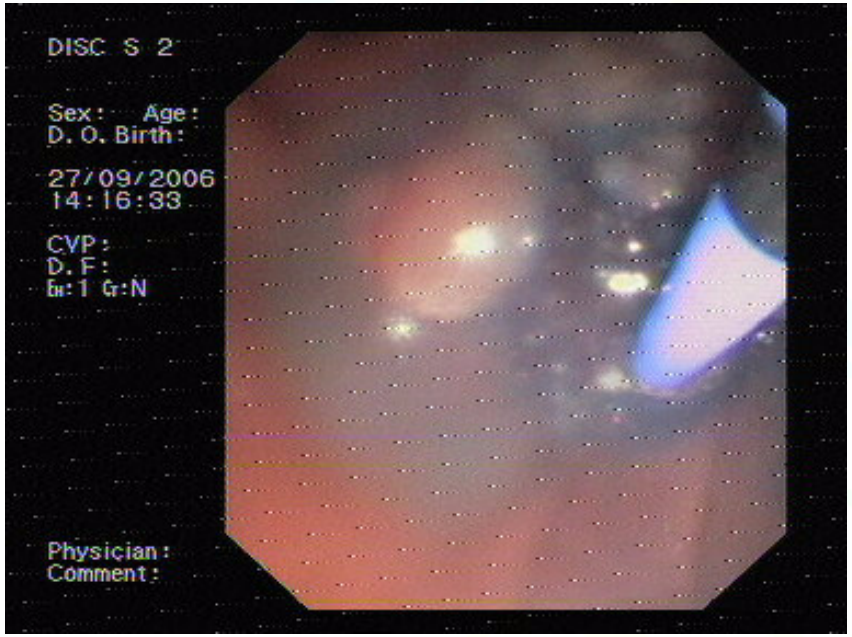
Table 3. Criteria of endoscopic resectability.

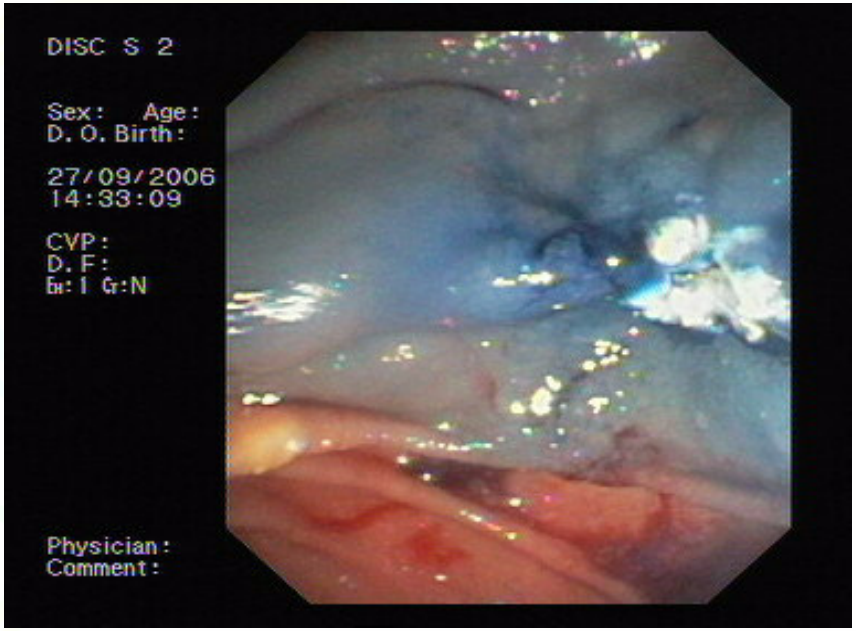
	Size	No malignant aspect [a]	Positive lifting sign	Benign histology at biopsies [b]	No invasion of the biliary and pancreatic ducts	Carcinoma in situ [c]
Binmoeller *et al*., 1993 [16]	<4 cm	Yes	-	Yes	-	Excluded
Desilets *et al*., 2001[10]	<4 cm	Yes	Yes	-	Yes	Excluded
Norton *et al*., 2002 [12]	Indifferent	-	-	-	-	Included
Cheng *et al*., 2004 [1]	<4.5cm	Yes	-	Yes	-	Excluded

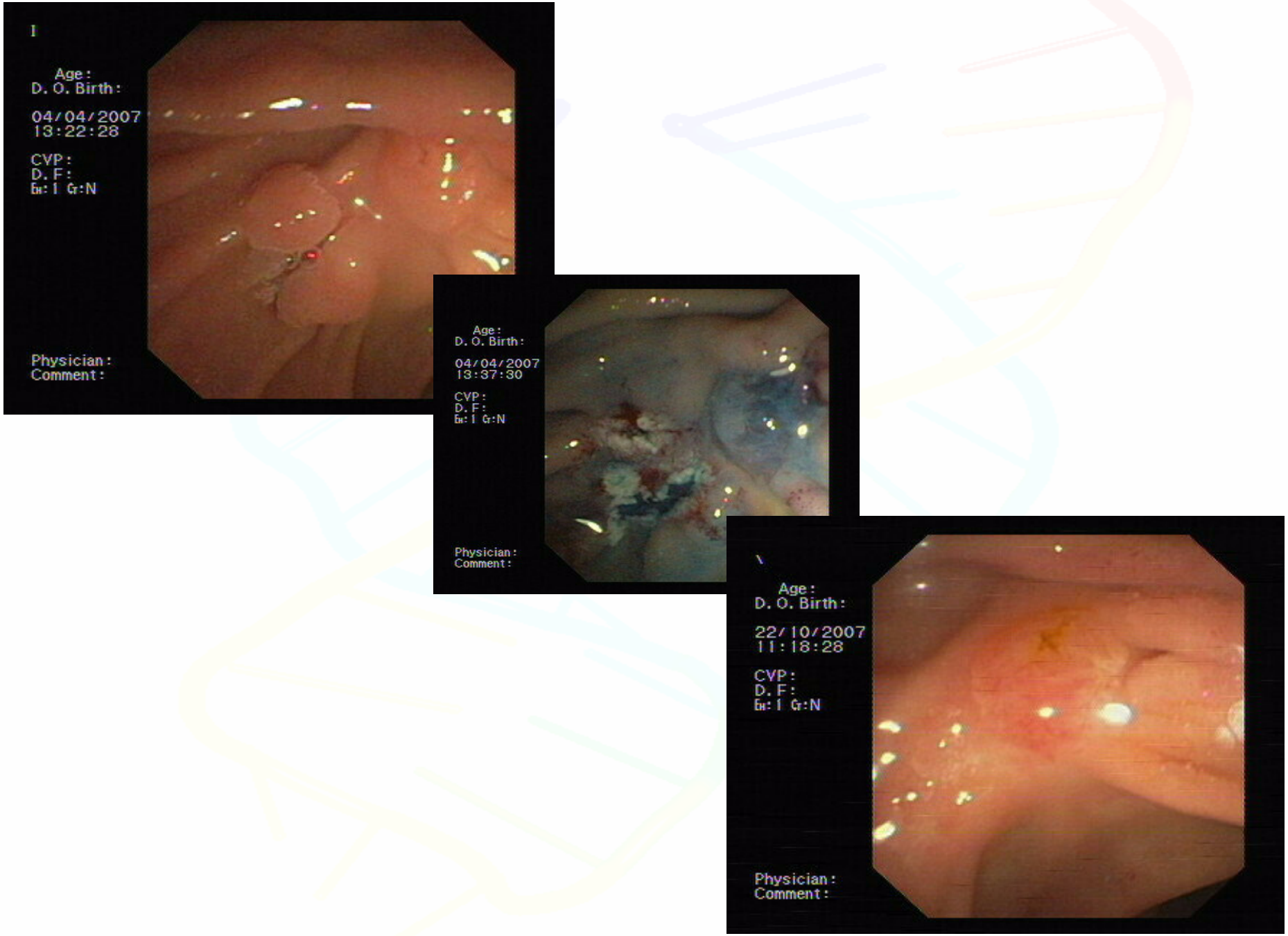
[a] Regular margins, no ulceration, soft consistency
[b] Minimum 6 biopsies
[c] No invasion of muscolaris mucosae

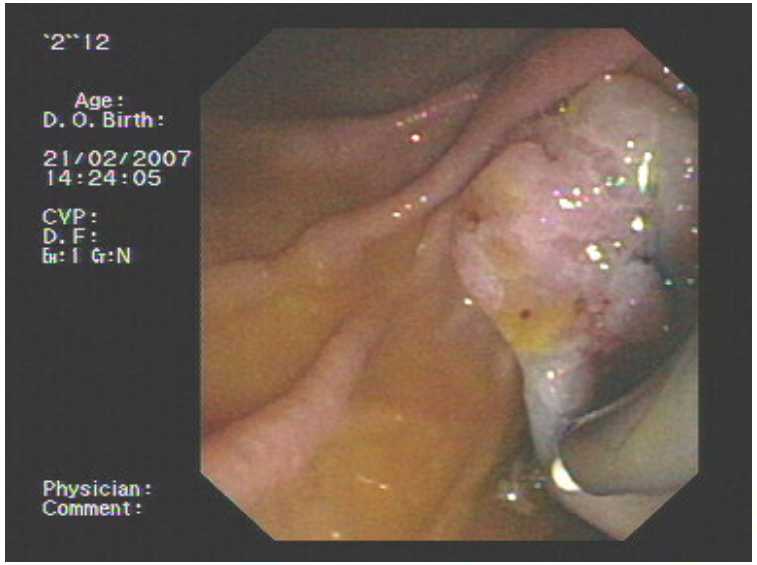

ID:
NAME:
ASMN REGGIO E. SERVIZIO ENDO DIGESTIA
SEX : AGE :
BIRTH: - -
DATE : 27-09-06
TIME : 12:48:42
FREQ : 7.5MHZ
RANGE: 9cm
GAIN : 4
CONT : 2
SCALE:10mm
DIR :NORMAL

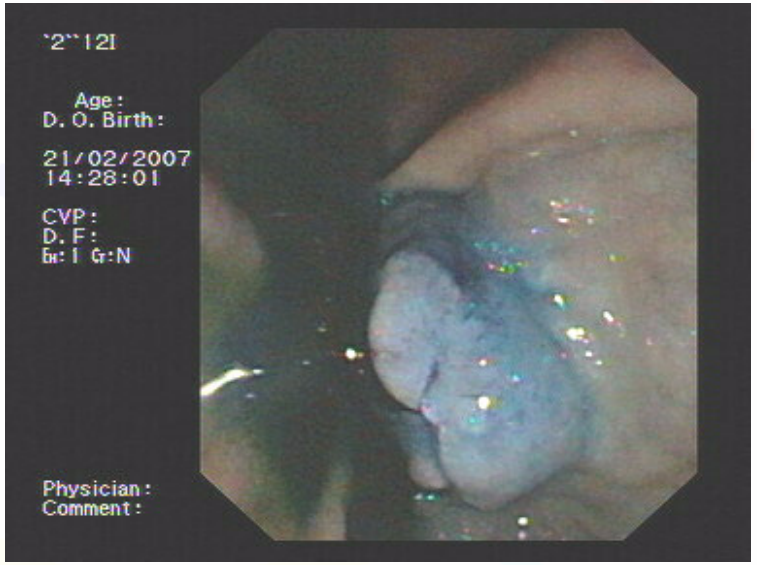

DISC S 2
Sex: Age:
D. O. Birth:
27/09/2006
13:58:31
CVP:
D. F:
Bx: 1 Gr:N
Physician:
Comment:

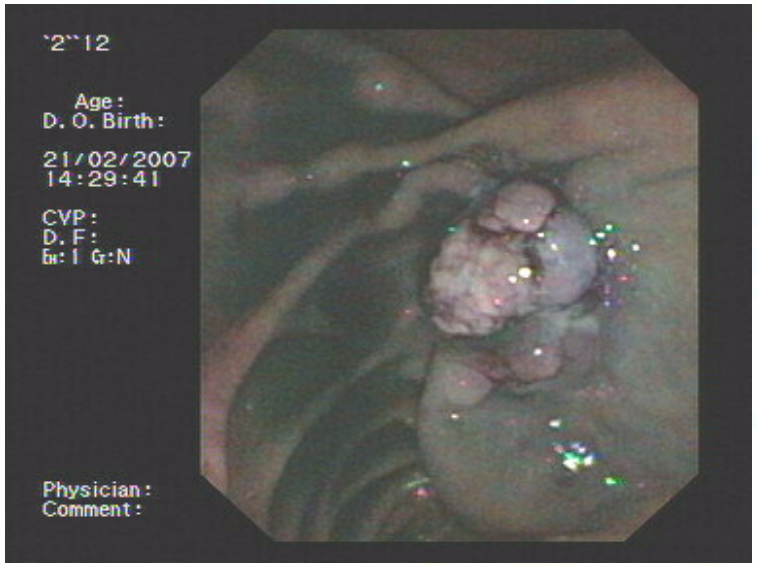

DISC S 2
Sex: Age:
D. O. Birth:
27/09/2006
14:16:33
CVP:
D. F:
Bx: 1 Gr:N
Physician:
Comment:

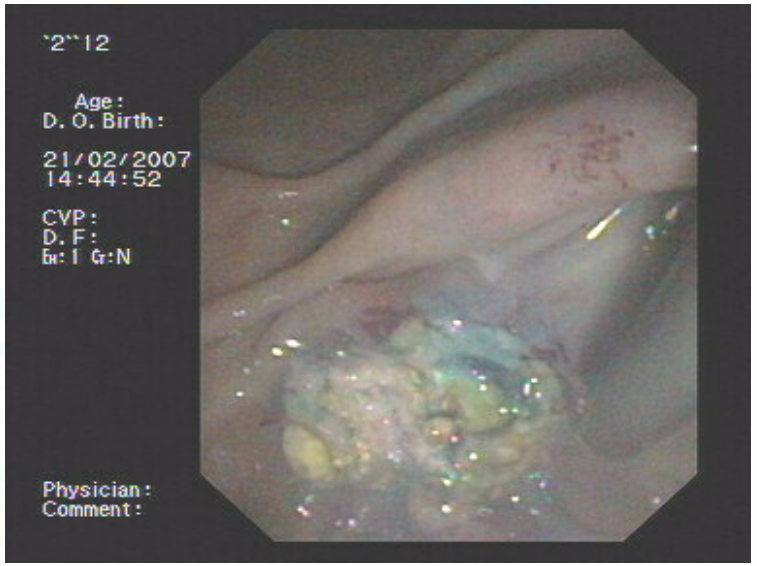

DISC S 2
Sex: Age:
D. O. Birth:
27/09/2006
14:33:09
CVP:
D. F:
Bx: 1 Gr:N
Physician:
Comment:

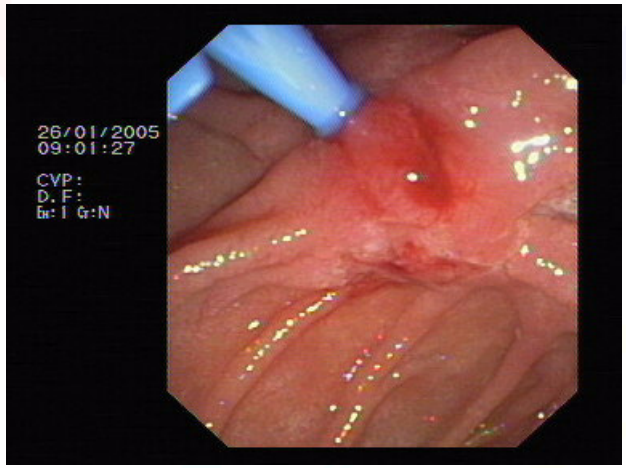

I
Age :
D. O. Birth :
04/04/2007
13:22:28
CVP :
D. F :
En: I Gr:N
Physician :
Comment :
Age :
D. O. Birth :
04/04/2007
13:37:30
CVP :
D. F :
En: I Gr:N
Physician :
Comment :
\
Age :
D. O. Birth :
22/10/2007
11:18:28
CVP :
D. F :
En: I Gr:N
Physician :
Comment :

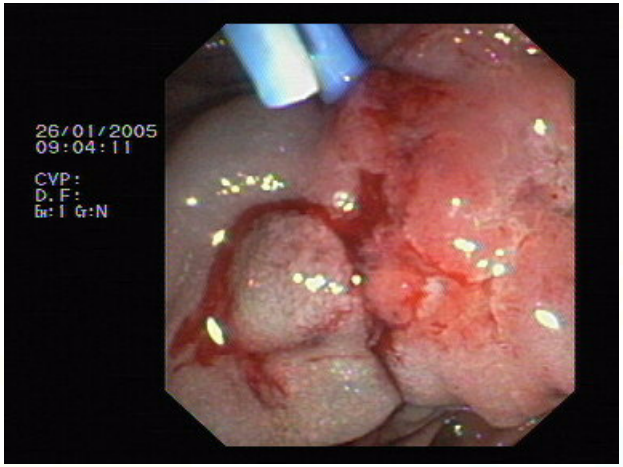

`2``12
Age:
D. O. Birth:
21/02/2007
14:24:05
CVP:
D. F:
Br: I Gr:N
Physician:
Comment:

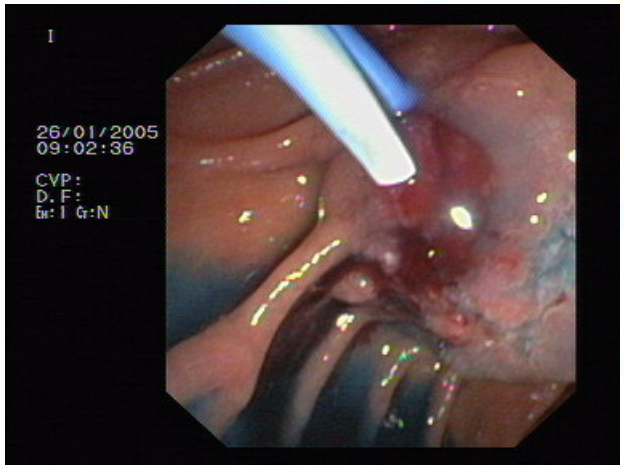

`2``12I
Age:
D. O. Birth:
21/02/2007
14:28:01
CVP:
D. F:
Br: I Gr:N
Physician:
Comment:

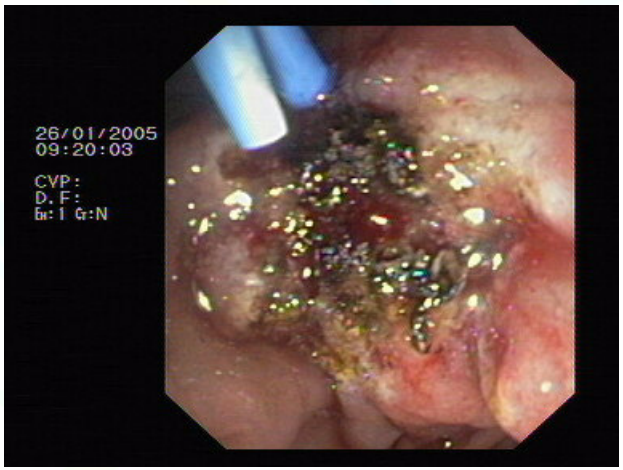

`2``12
Age:
D. O. Birth:
21/02/2007
14:29:41
CVP:
D. F:
Br: I Gr:N
Physician:
Comment:

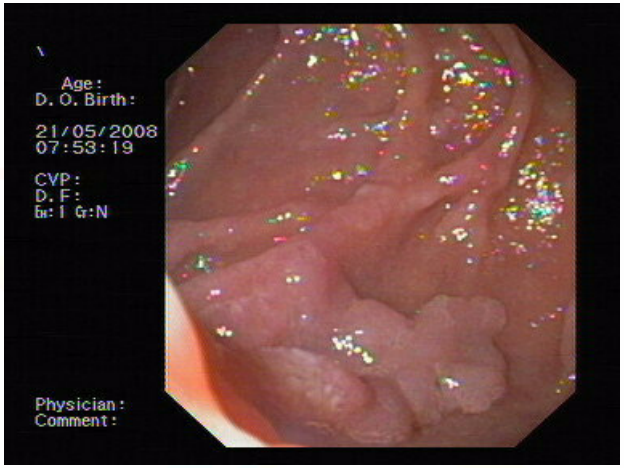

`2``12
Age:
D. O. Birth:
21/02/2007
14:44:52
CVP:
D. F:
Br: I Gr:N
Physician:
Comment:

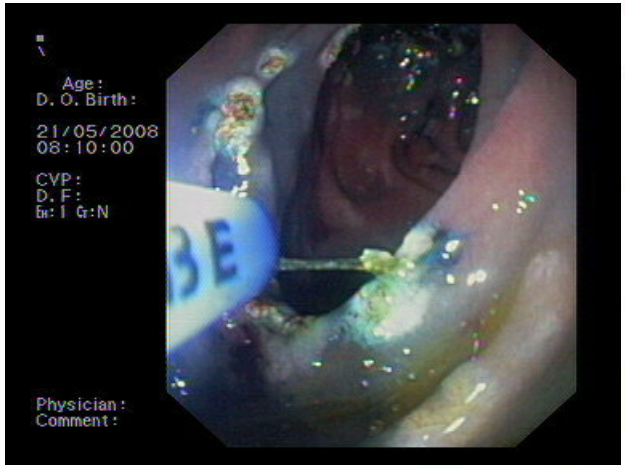

26/01/2005
09:01:27
CVP:
D.F:
En:1 Gr:N

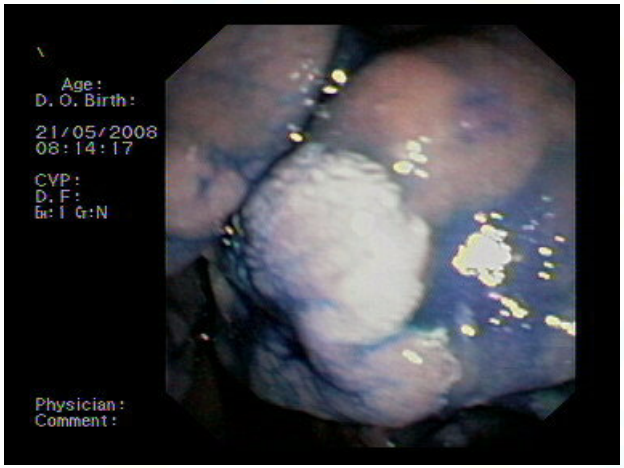

26/01/2005
09:04:11
CVP:
D.F:
En:1 Gr:N

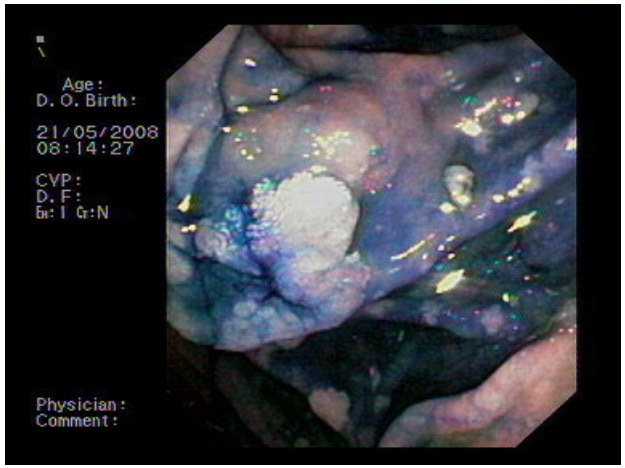

I
26/01/2005
09:02:36
CVP:
D.F:
En:1 Gr:N

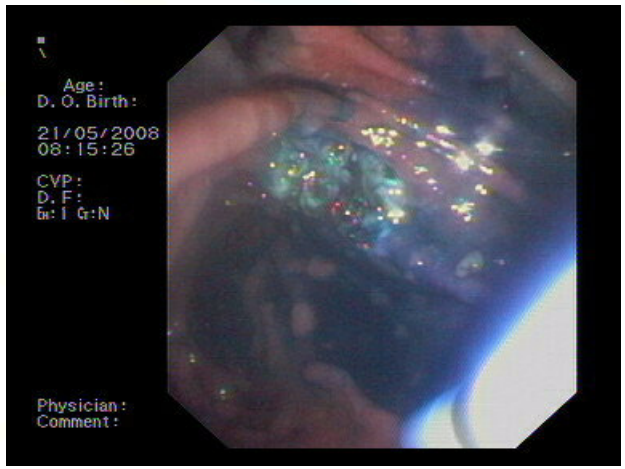

26/01/2005
09:20:03
CVP:
D.F:
En:1 Gr:N

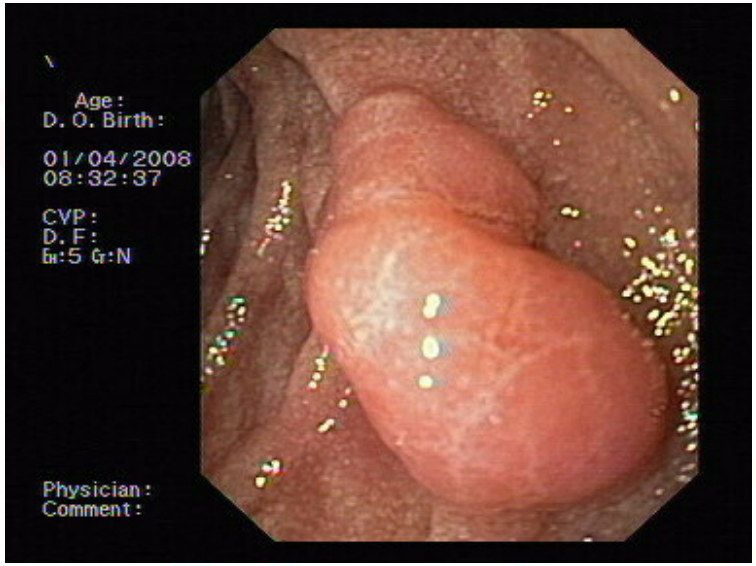

Age :
D. O. Birth :
21/05/2008
07:53:19
CVP :
D. F :
En: I Gr:N
Physician :
Comment :

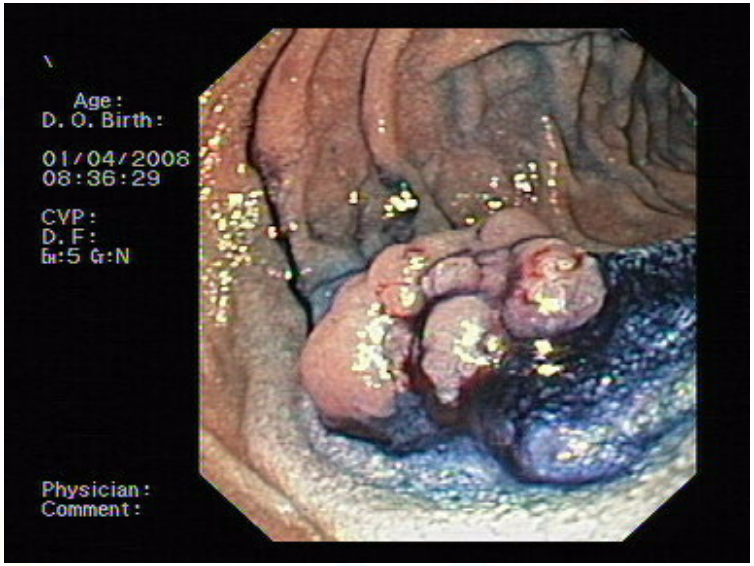

Age :
D. O. Birth :
21/05/2008
08:10:00
CVP :
D. F :
En: I Gr:N
Physician :
Comment :

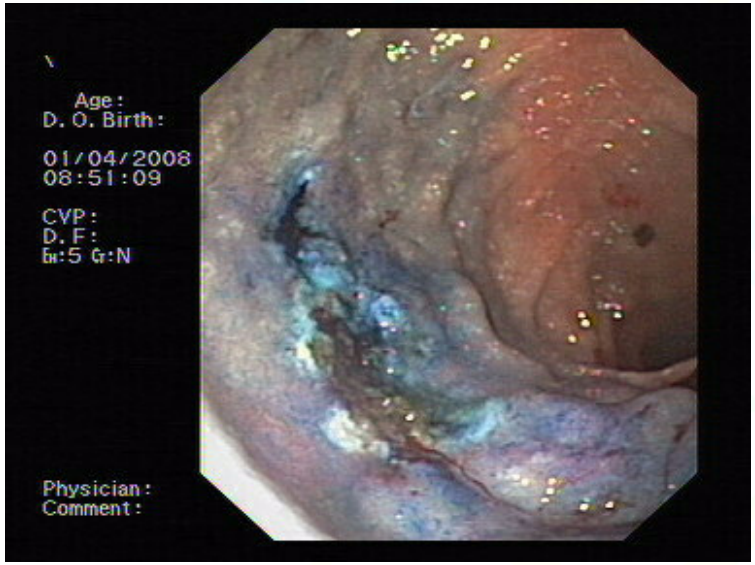

Age :
D. O. Birth :
21/05/2008
08:14:17
CVP :
D. F :
En: I Gr:N
Physician :
Comment :


Age :
D. O. Birth :
21/05/2008
08:14:27
CVP :
D. F :
En: I Gr:N
Physician :
Comment :


Age :
D. O. Birth :
21/05/2008
08:15:26
CVP :
D. F :
En: I Gr:N
Physician :
Comment :


Age :
D. O. Birth :
01/04/2008
08:32:37
CVP :
D. F :
En:5 Gr:N
Physician :
Comment :


Age :
D. O. Birth :
01/04/2008
08:36:29
CVP :
D. F :
En:5 Gr:N
Physician :
Comment :


Age :
D. O. Birth :
01/04/2008
08:51:09
CVP :
D. F :
En:5 Gr:N
Physician :
Comment :

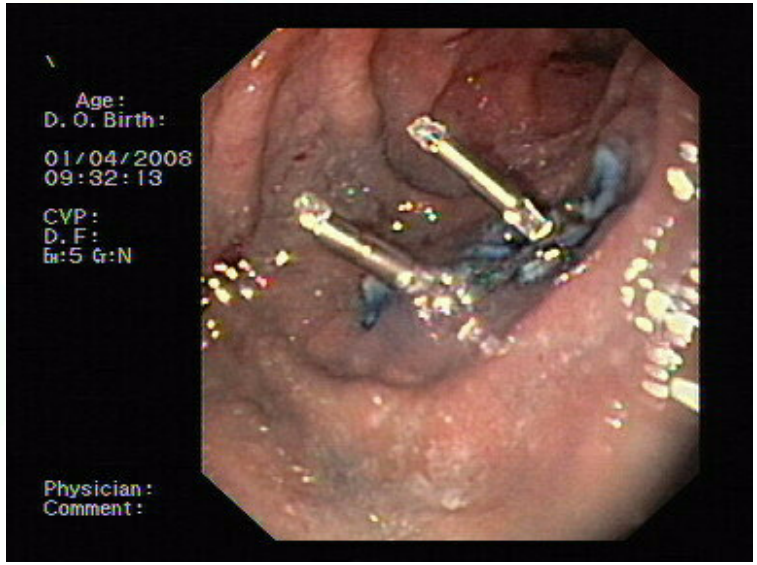

Age :
D. O. Birth :
01/04/2008
09:32:13
CVP :
D. F :
En:5 Gr:N
Physician :
Comment :

Table 4 Endoscopic treatment for duodenal neoplastic lesions

Author	Treatment	Follow up	Patients	Outcome	Postoperative
Soravia[52]	Endoscopic resection nos	4–34 months (mean 18)	6 FAP	Recurrence of duodenal adenomas in all 5 surviving patients	1 patient died of acute pancreatitis after endoscopic ampullectomy
Bertoni[53]	Snare papillectomy	18 months	2 FAP	Recurrence in 1 patient, successfully retreated	1 oozing-type haemorrhage and 1 mild pancreatitis, controlled by conservative measures
Morpurgo[44]	Snare polypectomy (3) argon plasma therapy (2)	6–24 months (mean 19)	5 FAP	Recurrence in 3 patients	No postoperative complications
Alarcon[46]	Snare polypectomy and thermal contact ablation	14–83 months (mean 43.5)	3 FAP	Recurrence in 3 patients	NS
Heiskanen[5]	Snare excision (5), YAG laser coagulation (1)	0.4–15.1 years (median 6.8)	6 FAP	No significant difference in Spigelman stage preoperative and at latest endoscopy	Patient treated with YAG laser developed mild pancreatitis
Norton[54]	Ampullary ablative therapy	1–134 months (median 24)	59 FAP, 32 sporadic	Return to normal histology in 44% of sporadic and 34% of FAP lesions	12 patients had mild complications, 3 severe complications: 1 duodenal stenosis, 1 postcoagulation syndrome, 1 necrotising pancreatitis
Norton[55]	Snare excision of papilla	2–32 months (median 9)	15 FAP, 11 sporadic	Recurrence rate of adenomatous tissue of 10%	2 minor bleedings, 4 mild pancreatitis, 1 duodenal perforation
Mlkvy[49]	PDT with ALA or Photofrin		4 FAP patients with duodenal polyps	Superficial necrosis and no polyp reduction after PTD with ALA. Deep necrosis and moderate polyp reduction after PDT using Photofrin.	Mild skin photosensitivity using Photofrin
Regula[48]	PDT with ALA		2 duodenal adenomas, 3 ampullary carcinomas	Superficial necrosis of adenomas and in 2 adenocarcinomas. 1 adenocarcinoma unaffected.	Side effects included mild skin photosensitivity, nausea/vomiting, and transient increases in ASAT
Loh[50]	PDT with HpD or Photofrin	3–50 months (median 5.5)	8 patients with 9 colorectal adenomas	7 adenomas successfully eradicated	No local complications
Abulafi[51]	PDT with HpD		10 patients with ampullary carcinoma unsuitable for surgery	Remission for 8–12 months in 3 patients with small tumours. In 4 patients with small tumours bulk was reduced. No improvement in patients with extensive disease	3 patients with moderate skin sensitisation

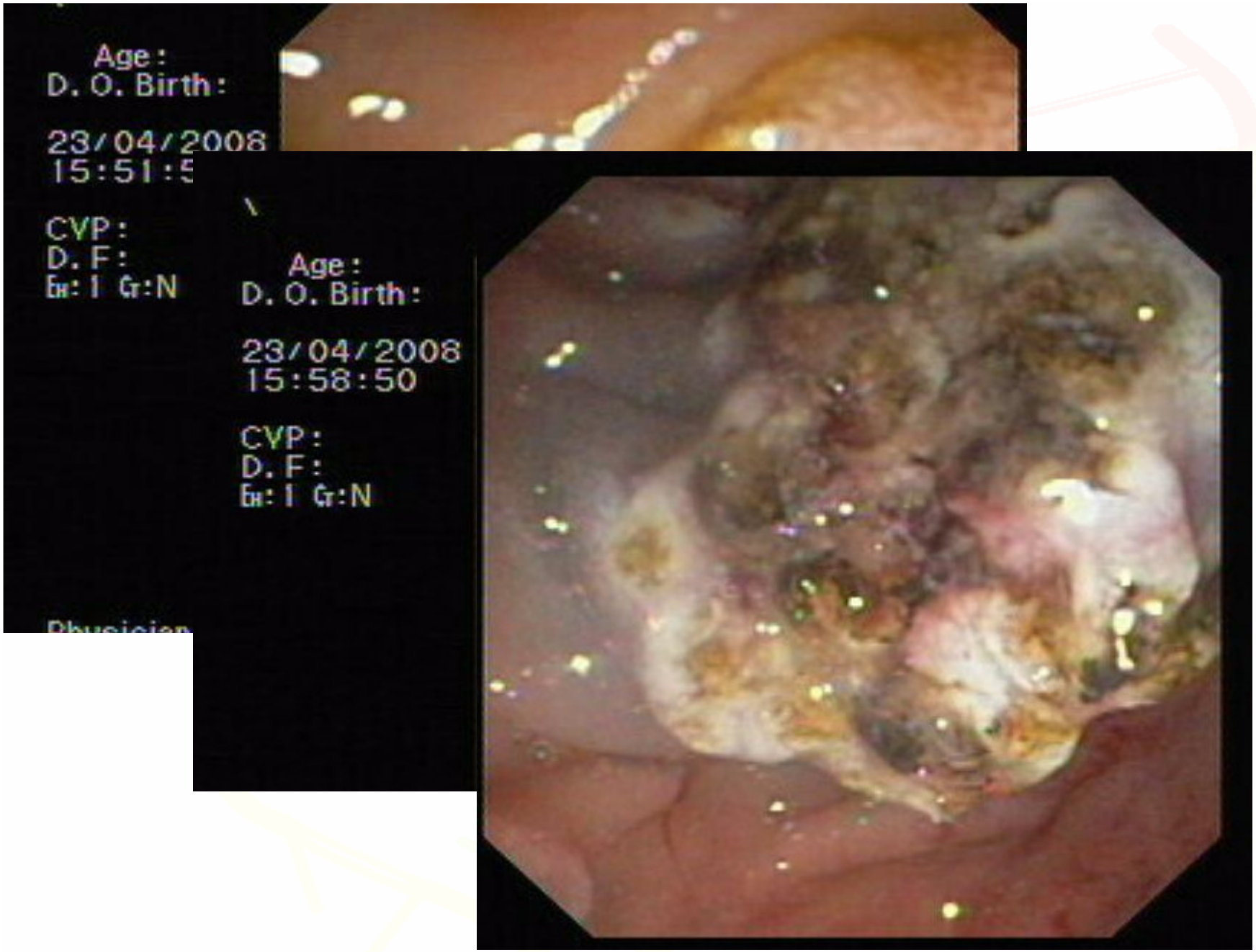
NS, not stated; PDT, photodynamic therapy; ALA, 5-aminolaevulinic acid; HpD, haematoporphyrin derivate or Photofrin; FAP, familial adenomatous polyposis.

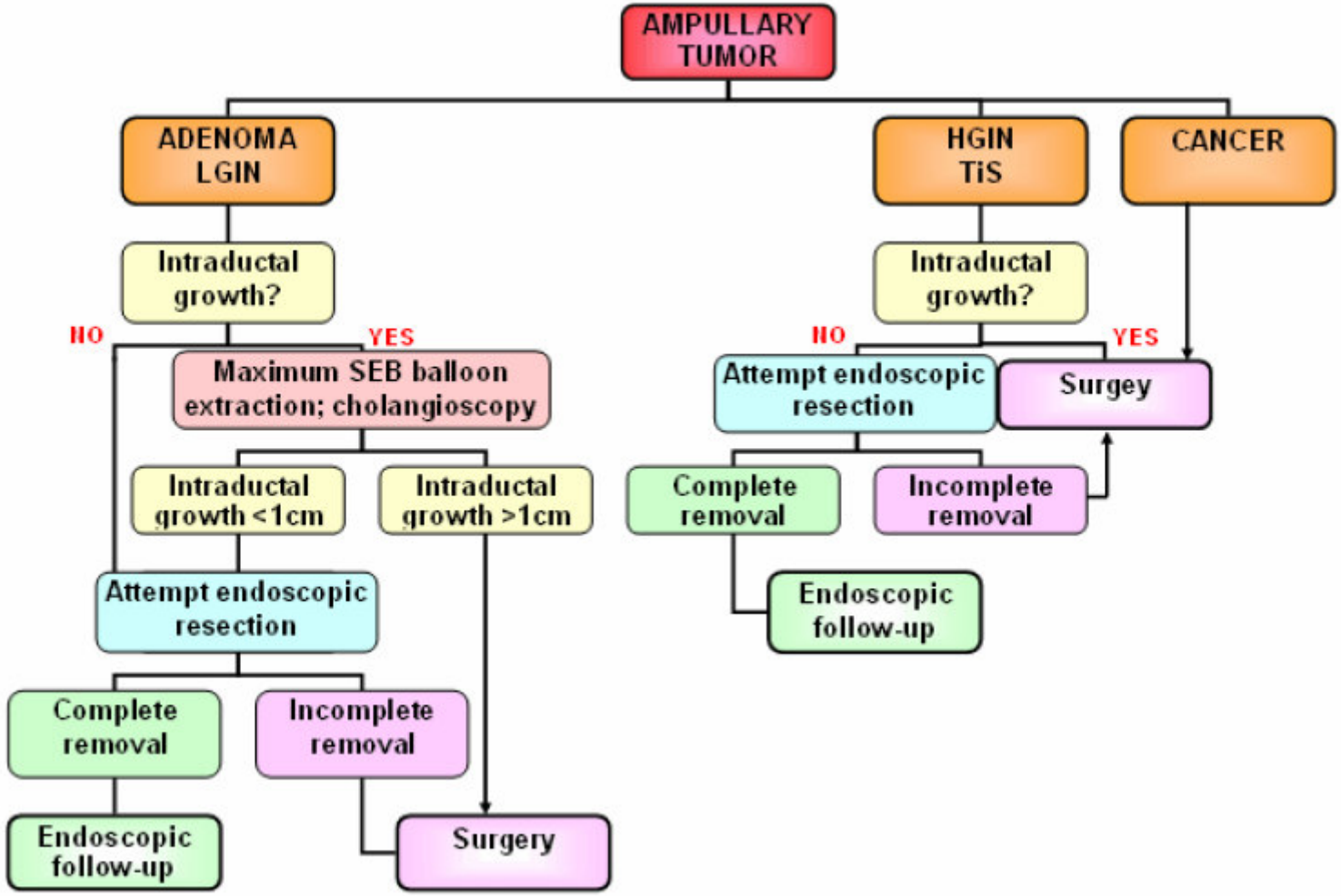
GUT ONLINE

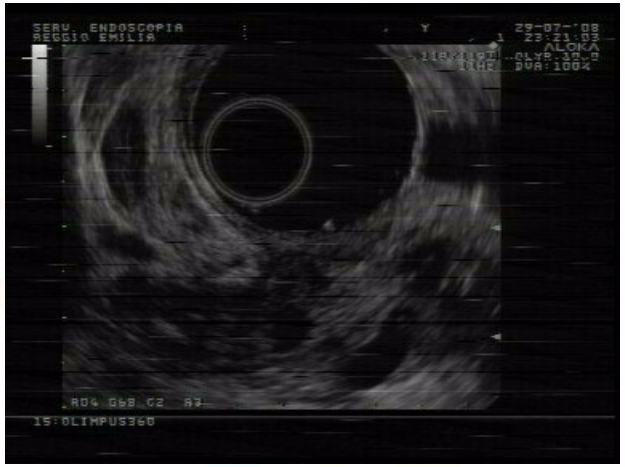
Prevention and management of duodenal polyps in familial adenomatous polyposis

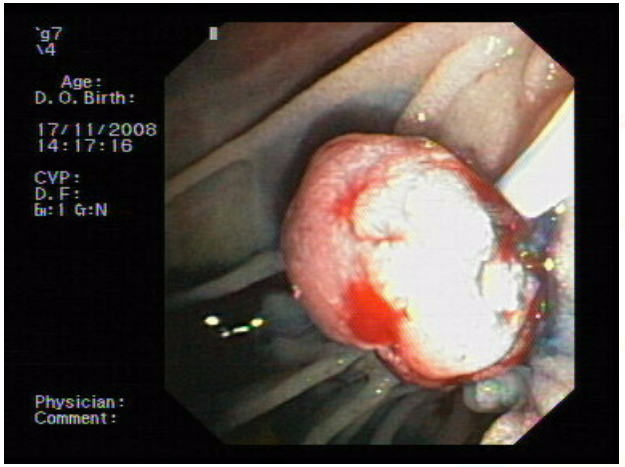
L A A Brosens, J J Keller, G J A Offerhaus, M Goggins and F M Giardiello

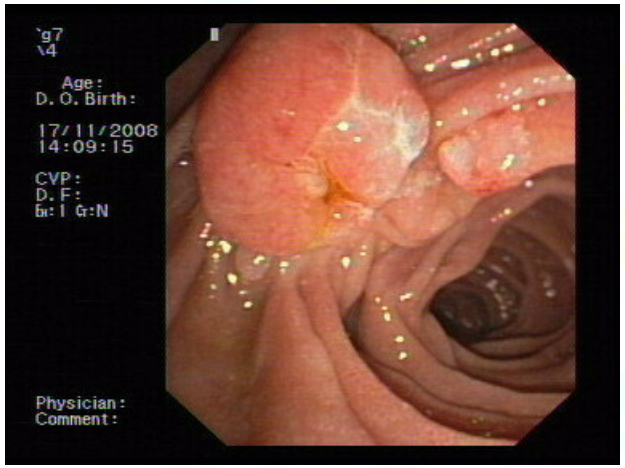
Gut 2005;54:1034-1043
doi:10.1136/gut.2004.053843

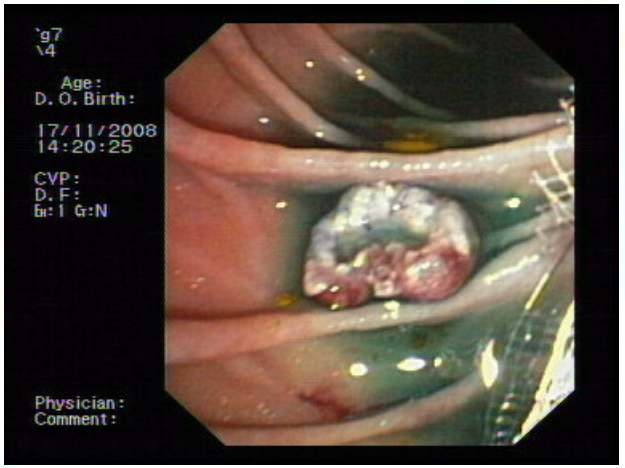

Age:
D. O. Birth:
23/04/2008
15:51:5
CVP:
D. F:
EH:1 G:N
Age:
D. O. Birth:
23/04/2008
15:58:50
CVP:
D. F:
EH:1 G:N

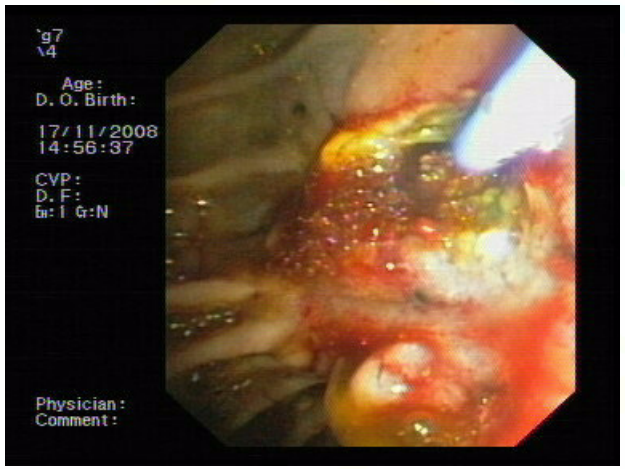

AMPULLARY TUMOR
ADENOMA LGIN
HGIN TiS
CANCER
Intraductal growth?
Intraductal growth?
NO
YES
NO
YES
Maximum SEB balloon extraction; cholangioscopy
Attempt endoscopic resection
Surgey
Intraductal growth <1cm
Intraductal growth >1cm
Complete removal
Incomplete removal
Attempt endoscopic resection
Endoscopic follow-up
Complete removal
Incomplete removal
Endoscopic follow-up
Surgery

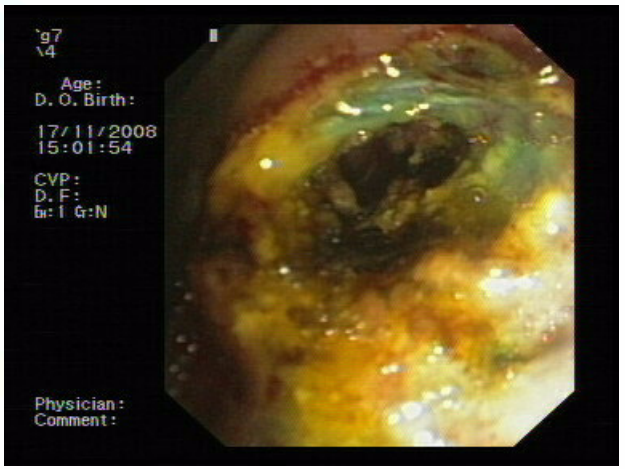

SERV. ENDOSCOPIA
REGGIO EMILIA
29-07-'08
23:23:03
ALOKA
OLYMPUS360


`g7
\4
Age:
D. O. Birth:
17/11/2008
14:17:16
CVP:
D. F:
G:I G:N
Physician:
Comment:


`g7
\4
Age:
D. O. Birth:
17/11/2008
14:09:15
CVP:
D. F:
G:I G:N
Physician:
Comment:


`g7
\4
Age:
D. O. Birth:
17/11/2008
14:20:25
CVP:
D. F:
G:I G:N
Physician:
Comment:


`g7
\4
Age:
D. O. Birth:
17/11/2008
14:56:37
CVP:
D. F:
G:I G:N
Physician:
Comment:


`g7
\4
Age:
D. O. Birth:
17/11/2008
15:01:54
CVP:
D. F:
G:I G:N
Physician:
Comment:

Acute pancreatitis after argon plasma coagulation of duodenal polyps in a patient with familial adenomatous polyposis

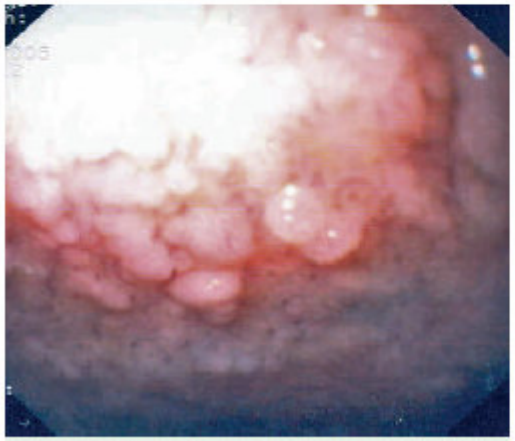


Fig. 1 This endoscopic image shows typical large flat adenomatous polyps in the superior duodenal flexure. These were found in consid-

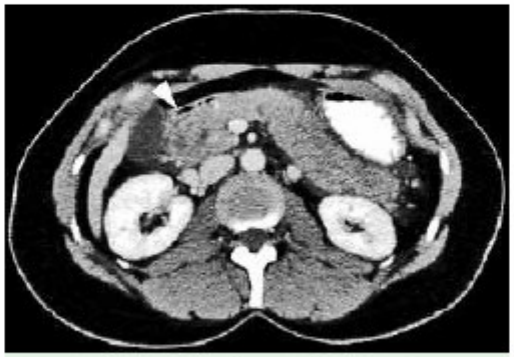


Fig. 2 A contrast-enhanced computed tomographic image showing edema of the pancreas and a small fluid collection around the pancreatic head (arrowhead).

such as hollow viscus perforation and abscess formation. To our knowledge there have been no previous reports of pancreatitis associated with APC.

Endoscopy_UCTN_Code_CPL_1AH_2AZ
Endoscopy_UCTN_Code_CPL_1AH_2AK

J. Weigt, L. C. Zimmermann, K. Mönkemüller, P. Malfertheiner
Department of Gastroenterology, Hepatology and Infectious Diseases, Otto von Guericke University Magdeburg, Magdeburg, Germany

References

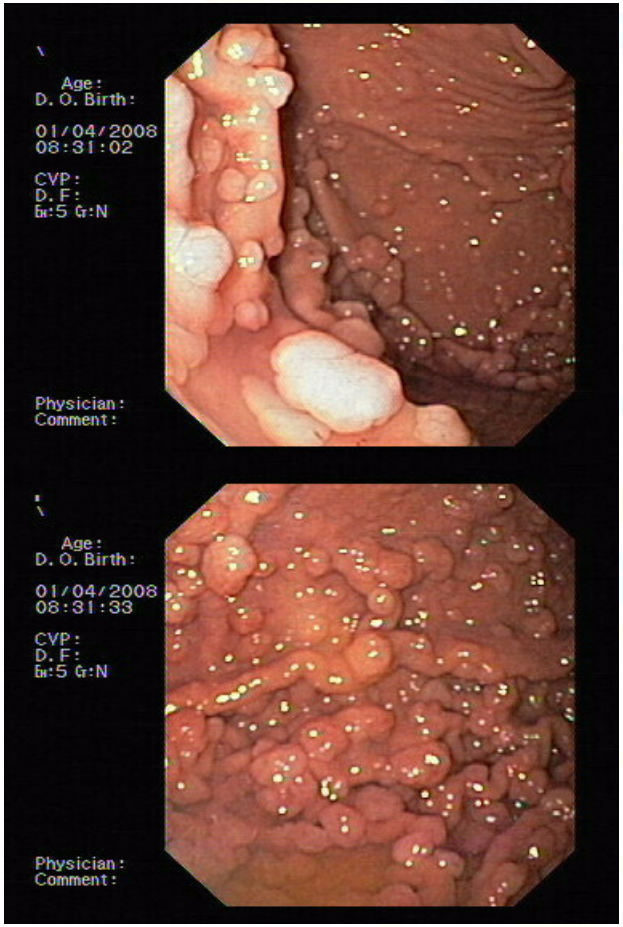
1 *Heiskanen I, Kellokumpu I, Jarvinen H.* Management of duodenal adenomas in 98 patients with familial adenomatous polyposis. Endoscopy 1999; 31: 412 – 416
2 *Bülow S, Björk J, Christensen IJ et al, and the DAF Study Group.*. Duodenal adenomatosis in familial adenomatous polyposis. Gut 2004; 53: 381 – 386
3 *Kashiwagi H, Spigelman AD.* Gastroduodenal lesions in familial adenomatous polyposis.

PHARMACOLOGICAL TREATMENT

QUESTION: *what is the role of NSAIDS in the treatment of colorectal and duodenal adenomas in FAP?*

CONCLUSION: *chemoprevention with NSAIDs can be considered in patients following initial prophylactic surgery as an adjunct to endoscopic surveillance, to reduce the rectal polyp burden. The role of selective COX-2 inhibitors in patients with FAP is controversial because of cardiovascular side effects reported for rofecoxib. Therefore, these drugs should only be considered in selected patients without cardiovascular risk factors until more data are available.*

Poliposi Gastrica



- Classica: poliposi ghiandolare fundica (corpo-fondo)
- 26-61% dei pazienti (0.8-1.9% popolazione generale, “ma effetto PPI”)
- Correlazione inversa con infezione da HP
- Displasia presente nel 25-41% dei casi
- K gastrico non così sporadico…

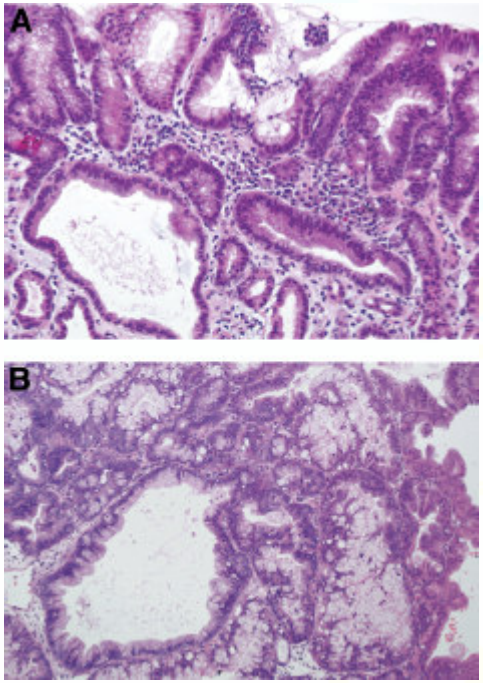
FGPs dysplasia

Fundic Gland Polyp Dysplasia Is Common in Familial Adenomatous Polyposis

LAURA K. BIANCHI,* CAROL A. BURKE,‡ ANA E. BENNETT,§ ROCIO LOPEZ,‖ HENNIE HASSON,‖ and JAMES M. CHURCH‡

*Evanston Northwestern Healthcare, Evanston, Illinois; ‡Digestive Disease Center, §Anatomic Pathology, and ‖Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio

15. Bertoni G, Sassatelli R, Nigrisoli E, et al. Dysplastic changes in gastric fundic gland polyps of patients with familial adenomatous polyposis. Ital J Gastroenterol Hepatol 1999;31:192–197.



- Numerati i FGPs
- Se FGPs +: tre aree
- Biopsia di tutti i polipi > 10 mm e irregolarità
- Biopsie : 3 (1-20 FGPs), 5 (21-30), 7 (oltre 30)
- Random antrali HP (correlazione inversa)
- Numero e dimensioni PD, Spigelman

- 75 pazienti consecutivi
- FGPs: 88%; Displasia 41 % (3% HGD)
- HP+: 1.5% FGPs

Table 4. Multivariable Regression Analysis of Factors Associated With Dysplasia

Factor	OR (95% CI)	*P* value
Acid-suppressive medications	0.14 (0.03–0.64)	.01
Duodenal polyposis stage		
Each increase in stage	2.3 (1.2–4.5)	.01
Stage IV vs stage 0	30.2 (2.2–409.7)	
Presence of antral gastritis	11.2 (1.2–103.9)	.03
Size of largest FGP		
Each increase in size range	4.0 (1.1–14.4)	.035
Size >1 cm vs size 1–4 mm	15.92 (1.2–207.2)	
Tobacco consumption	3.8 (0.79–18.6)	.096

FGPs, sorveglianza

Table 5. Endoscopic Surveillance in the Absence of Dysplastic FGPs

Duodenal polyposis	Surveillance interval	Method
Stage 0	5 y	EGD/D
Stage I–II	3 y	EGD/D
Stage III	1 y	EGD/D
	3 y	CE
Stage IV[a]	3–6mo	EGD/D
	3 y	CE

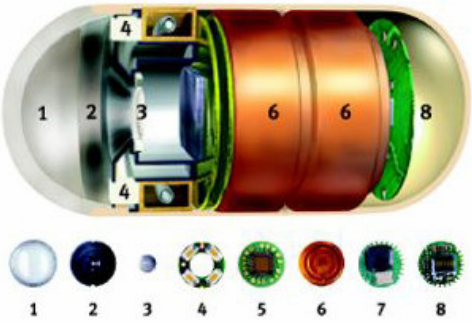
D, duodenoscopy with biopsy of the papilla; CE, capsule endoscopy.
[a]Preferred strategy is pylorus-preserving prophylactic duodenectomy, but recommend aggressive surveillance if surgical resection is not pursued.

Table 6. Endoscopic Surveillance in Individuals With Dysplastic Gastric Polyposis

Duodenal polyposis	FGP dysplasia	Surveillance interval	Method	Gastric neoplasm intervention
Stage 0–II	LGD	3 y	EGD/D	None
Stage III	LGD	1 y	EGD/D	None
		3 y	CE	
Stage IV	LGD	3–6 mo	EGD/D	None
		3 y	CE	
Stage 0–IV	HGD[a]	3–6 mo	EGD/D	Targeted polypectomy and consider chemoprevention
		3 y	CE	

D, duodenoscopy with biopsy of the papilla; CE, capsule endoscopy.
[a]Consider prophylactic gastrectomy if HGD is detected in small (<10 mm) FGPs or normal mucosa and persists for 2–3 follow-up intervals.

Oltre il Treitz



- Descrizione sporadica di neoplasie maligne del piccolo intestino,
più frequenti adenomi (50% digiuno, 84% ileo)

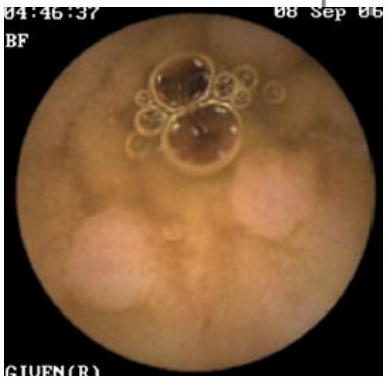


TABLE 5. Number of small-bowel polyps of 103 patients with FAP in different studies

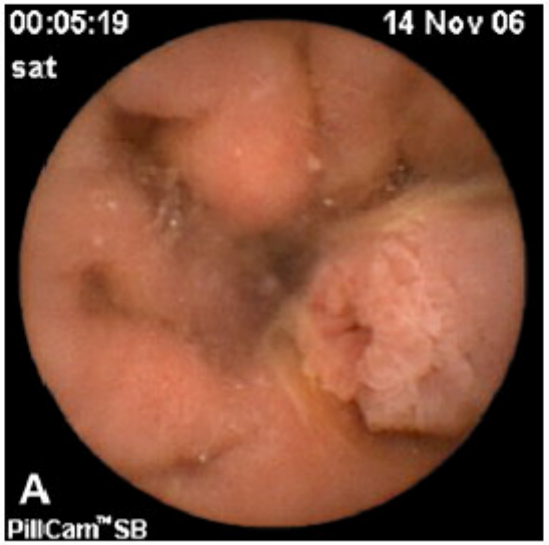
	No. patients			No. polyps
Study, y	FAP	Jejunum	Ileum	Distal jejunum ileum
Caspari et al,[20] 2004	16	4	0	0
Burke et al,[18] 2005	15	9	7	>20
Schulmann et al,[19] 2005	29	16	6	23
Mata et al,[21] 2005	20	1	2	3
Our study, 2007	23	4	5	15
Total	103	34	20	

- Con VC buona osservazione del digiuno, scadente del duodeno e della papilla; DBE con cromo ovviamente fattibile…

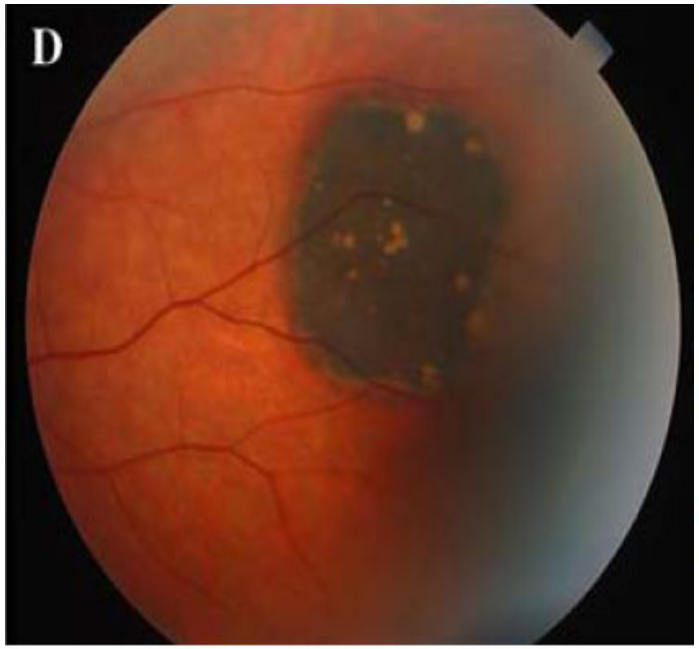
Is half-knowledge worse than ignorance?

Oliver W. Cass, MD
Department of Medicine
Hennepin County Medical Center
Minneapolis, Minnesota

Ampulla of Vater as seen on capsule endoscopy (with video)



CHRPEs



- Ipertrofia congenita dell’epitelio pigmentato retinico
- La più frequente manifestazione extraintestinale di FAP (70-80% dei pazienti) 436-1309
- Le CHRPEs bilaterali multiple sono molto specifiche per FAP (>95%); attenzione a DD

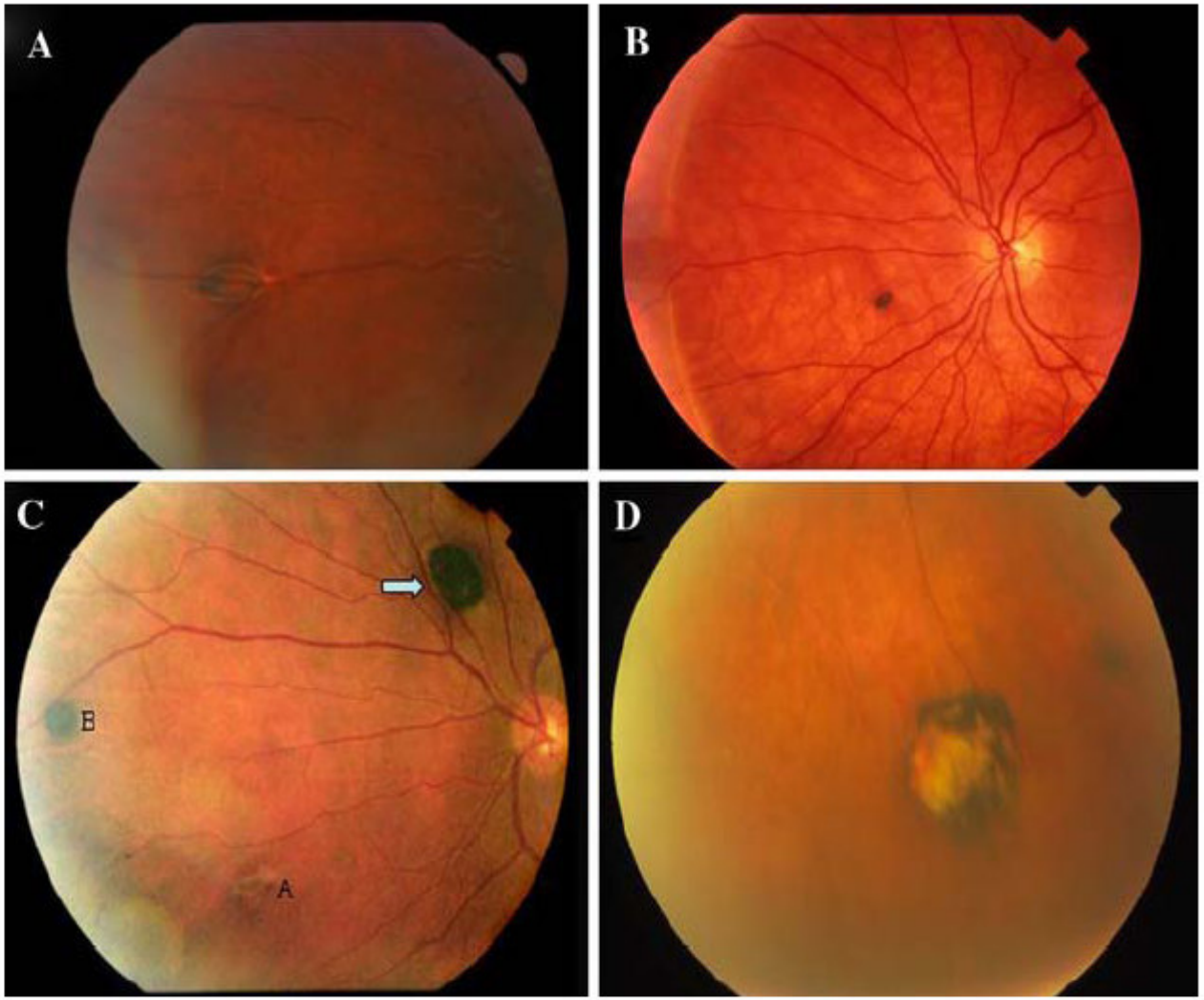
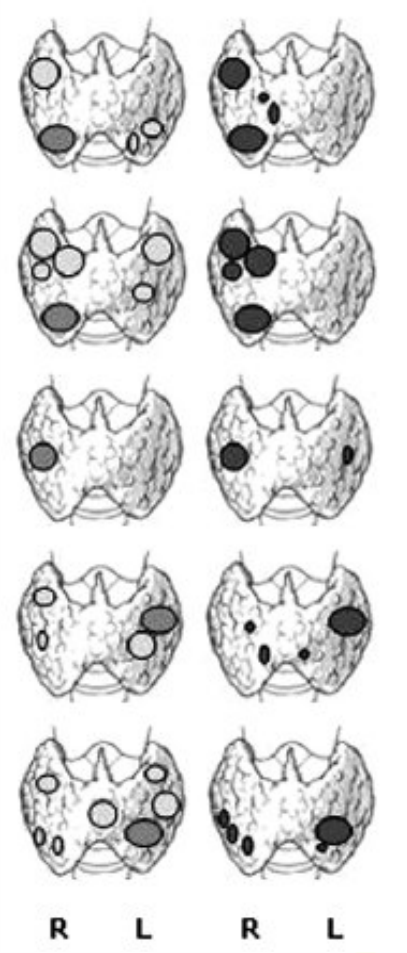


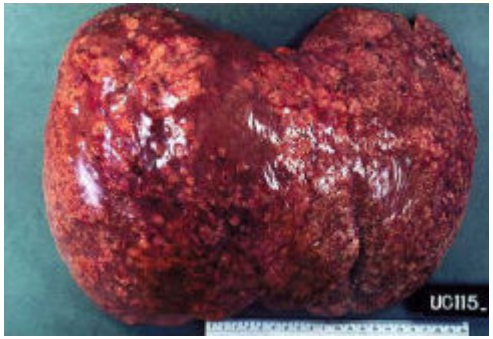
Fig. 1 Berk Classification of CHRPE: Type A: Oval, pigmented and surrounded by a depigmented halo. Type B: Round, small and pigmented without halo. Type C: Round, large and pigmented (arrow). The lesion is comparable to the size of the optic disc which is about 1.5 mm in diameter. Two other lesions are also seen (Type A and B). Type D: Round, large and depigmented

Cancro della tiroide



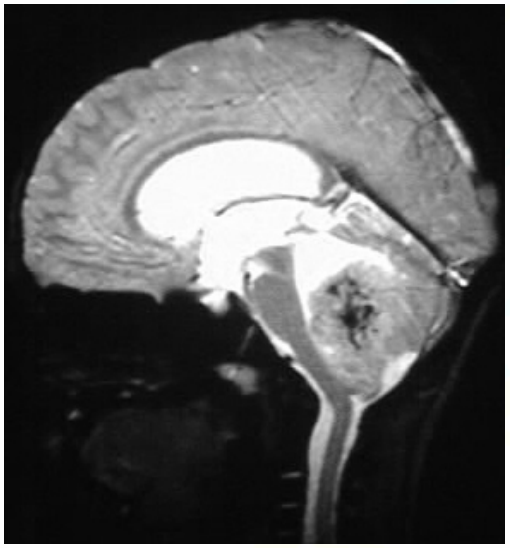
- Incidenza stimata 1-2% (12%?)
- Età media di diagnosi 25-33aa, RR 160
- Più colpite le donne (17:1); 140-1309
- Più frequente papillare (<75%) cribriforme
- Associazione CHRPEs
- Spesso multicentrici
- Sorveglianza
  - Palpazione annuale
  - Ecografia ogni 1-2 anni

Epatoblastoma



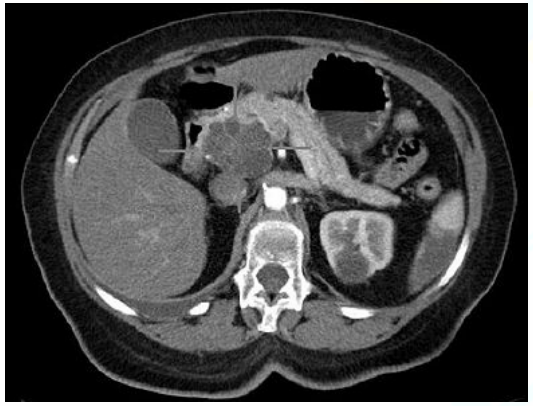
- Tumore epatico embrionale aggressivo
- Bambini 0-4 anni (fino a 16) probabilità in FAP 1:235; RR 750-7500; prevalenza 1-2%
- Rapporto M:F= 2.3:1 ; 457-1309
- Storia familiare di epatoblastoma!
- Sorveglianza (trimestrale fino a 4aa; “incrociata” con sporadici per APC?)
  - Misurazione sistematica Afp
  - Eco ± CT/MRI

Neoplasie cerebrali

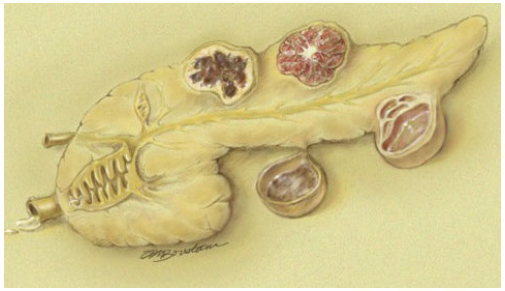


- ex-Turcot (1959) ora BTP1 MMR correlata (glio,astro)
- BrainTumorPolyposis 2: medulloblastoma (80% dei casi) associato a FAP
- 70% dei casi entro i 16 anni
- RR 90; RA: 1-2%
- Sorveglianza?
  - Controllo annuale vista?
  - Sintomi?

Neoplasie pancreatiche

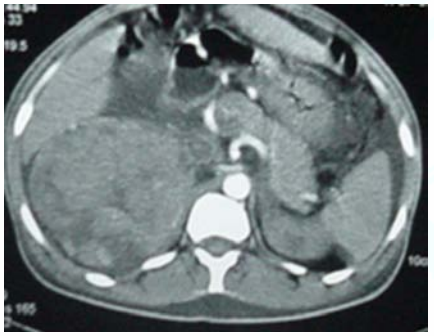


- RR 4.5% (1.1-11.4) di adk (RA $21.4X10^5$)
- Descritti: IPMN, ca cistici, papillari, acinari, delle insule



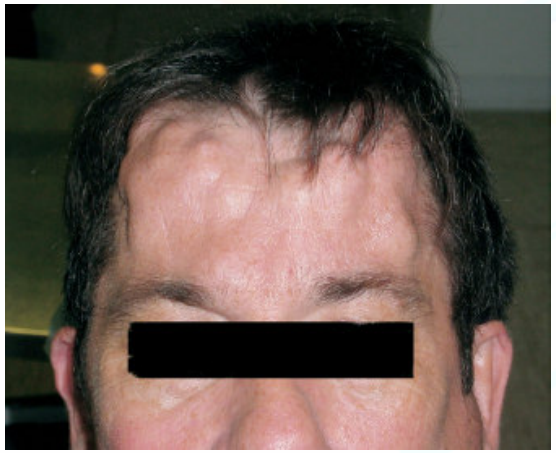
- EUS? Non evidenza di cluster familiari in FAP

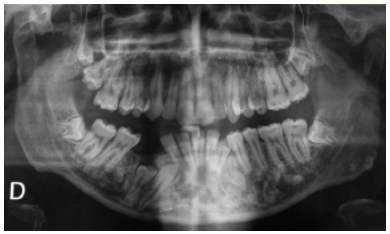
Neoplasie surrenali



- Prevalenza 7-13% di “incidentalomi” (popolazione generale 3% circa)
- Clusters familiari
- Sorveglianza
  - Iniziali segni ormonali?
  - CT
  - Intervento se > 6 cm

Osteomi, anomalie dentarie





- Osteomi 20% di FAP (popolazione generale 1-2%); 767-1578
- Anomalie dentarie (impattati soverannumerari, ec)
- Sorveglianza
  - Panoramica ogni 2 anni

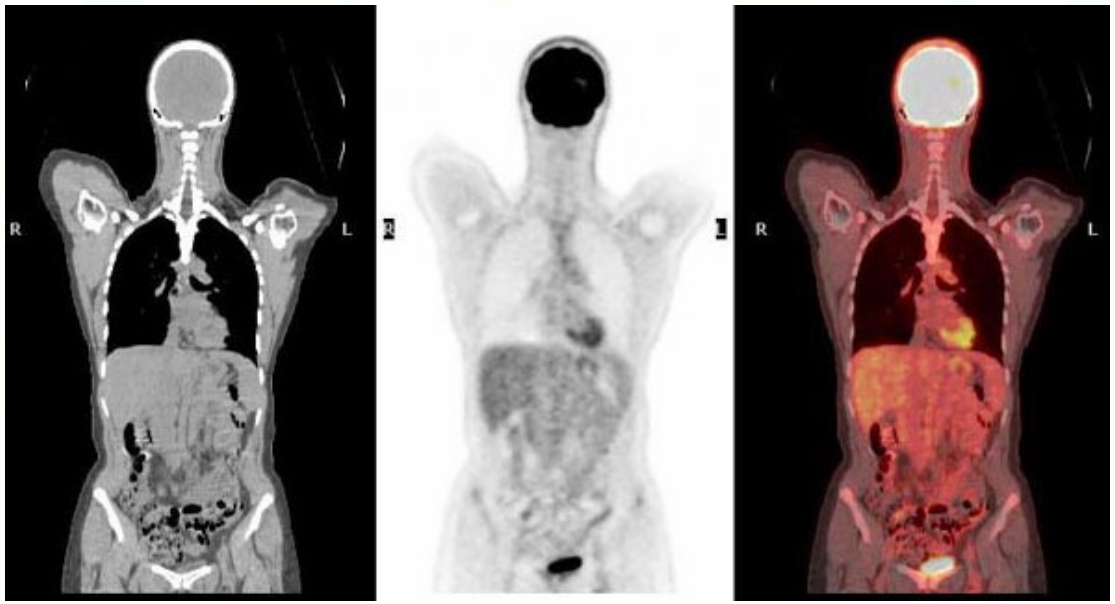
Possibile una “sorveglianza globale” ?

Ability of FDG-PET to detect all cancers in patients with familial adenomatous polyposis, and impact on clinical management

Mariëtte C. A. van Kouwen[1], Joost P. H. Drenth[1], J. Han J. M. van Krieken[2], Harry van Goor[3], Pieter Friederich[1], Wim J. G. Oyen[4], Fokko M. Nagengast[1]

Conclusion: FDG-PET detected all the cancers present, and none of the patients with negative FDG-PET developed cancer. This suggests that positive FDG-PET in FAP patients should lead to further examinations to rule out cancer. In patients with negative FDG-PET a more conservative approach seems justified.

Eur J Nucl Med Mol Imaging (2006) 33:270–274
DOI 10.1007/s00259-005-1955-0



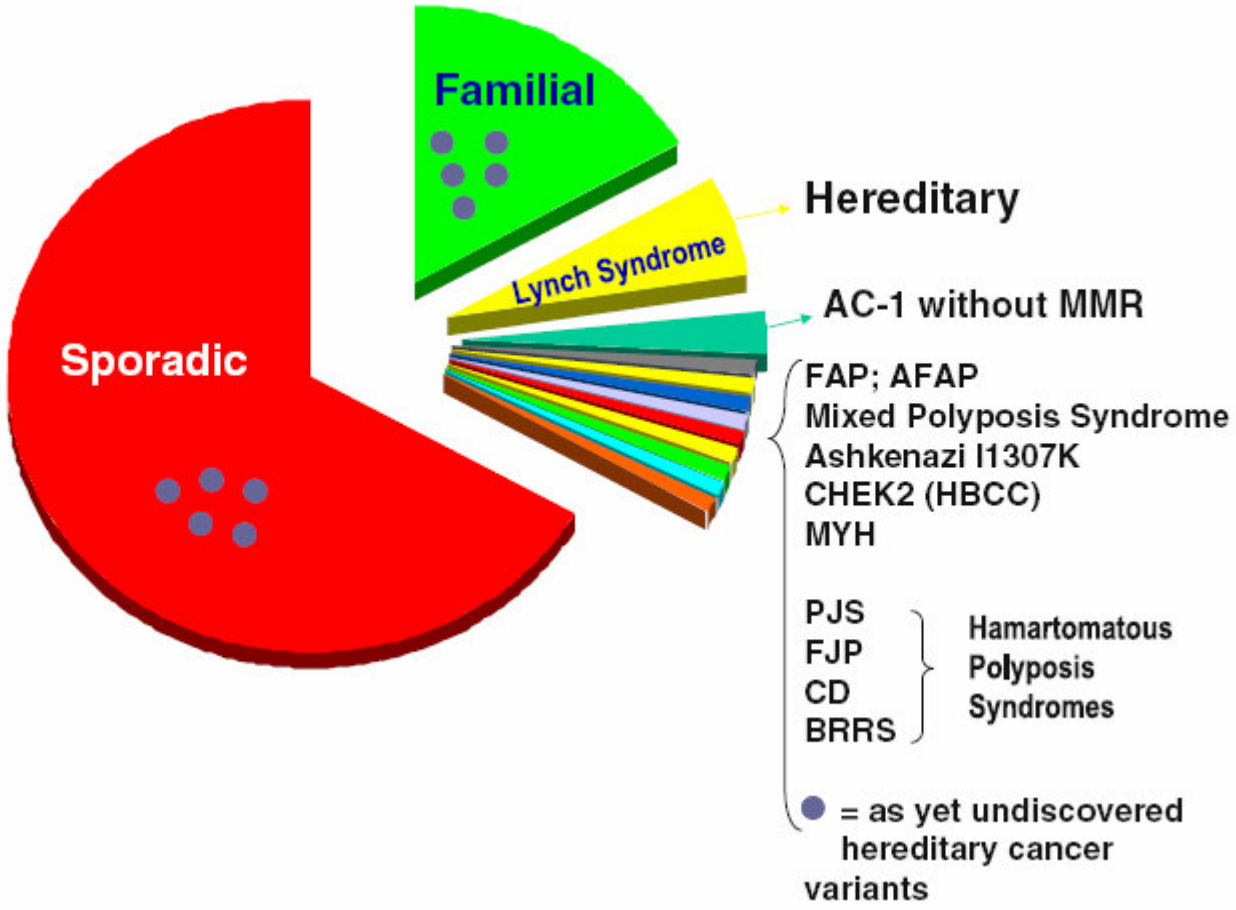
Mondo reale, PC 1988

Domanda:

"conosce qualche caso di poliposi adenomatosa familiare?"

Risposta:

"Si, decine, forse centinaia, che ho trattato endoscopicamente"



Familial Cancer (2008) 7:27–39
DOI 10.1007/s10689-007-9165-5

Attenuated Familial Adenomatous Polyposis (AFAP)

A Phenotypically and Genotypically Distinctive Variant of FAP

Henry T. Lynch, M.D., Thomas Smyrk, M.D.,† Thomas McGinn, M.D.,‡ Stephen Lanspa, M.D.,‡ Jennifer Cavalieri, R.N.,* Jane Lynch, B.S.N.,* Susan Slominski-Castor, M.S.,* Matthew C. Cayouette, B.S.,§ Ira Priluck, M.D.,‖ and Michael C. Luce, Ph.D.§*

Table 1. FAP and AFAP Colorectal Cancer Syndromes

Classical FAP	Attenuated FAP
Number of colonic adenomas Usually thousands; amost always more than 100	Usually 1–50; never more than 100
Gross morphologies of adenomas Polypoid adenomas	Slightly elevated plaque of adenomatous tissue
Histology No special history	"Flat adenomas" (see text)
Location of colonic adenomas Througout the colon	Predominance proximal to splenic flexure
CRC, location Throughout the colon	Predominance proximal to splenic flexure
CRC, average age of onset 39	55
Fundic gland polyps Constant feature	Constant feature
Extra colonic cancers Periampullary carcinoma, papillary thyroid carcinoma, sarcomas, brain tumors, small bowel cancer	Periampullary carcinoma; other cancers not yet identified
Desmoid tumors Common	Not yet identified
Congenital hypertrophy of the retinal pigment epithelium Approximately 70 percent of families	Absent to date

FAP: familial adenomatous polyposis; AFAP: attenuated FAP; CRC, colorectal cancer.

Table 1. The phenotypes of FAP and AFAP.

	AFAP	FAP
Number of adenomas	< 100	100–5000
Adenoma distribution	Rightsided, rectal sparing	Colorectal, leftsided
Age at onset of adenomatosis	35–45 years (mean age)	17 years (median age)[a]
Age at onset of CRC	55 years (mean age)	40 years (median age)[a]
Lifetime penetrance of CRC	Unknown (high?)	100%
Upper gastrointestinal adenomas	> 50%, frequent	52–84% (prevalence)[b]
Desmoid tumours	Rare?	4–13% (incidence)[c]
Other extraintestinal manifestations	Very rare?	Frequent

[a] S. Bülow, unpublished data.
[b] Bülow S, Alm T, Fausa O et al. Int J Colorect Dis 1995; 10: 43–6 [99]; Church JM, McGannon E, Hull-Boiner S et al. Dis Colon Rectum 1992; 35: 1170–3 [100].
[c] Knudsen AL, Bülow S. Familial Cancer 2001; 1: 111–9 [125].

Table 1
Classification of FAP severity

	Phenotype	No. of colorectal adenomas	Age of onset
Classical	Profuse	Thousands	1st and 2nd decade
	Intermediate	Hundred to thousands	2nd and 3rd decade
Attenuated	Attenuated	<100	4th and 5th decade

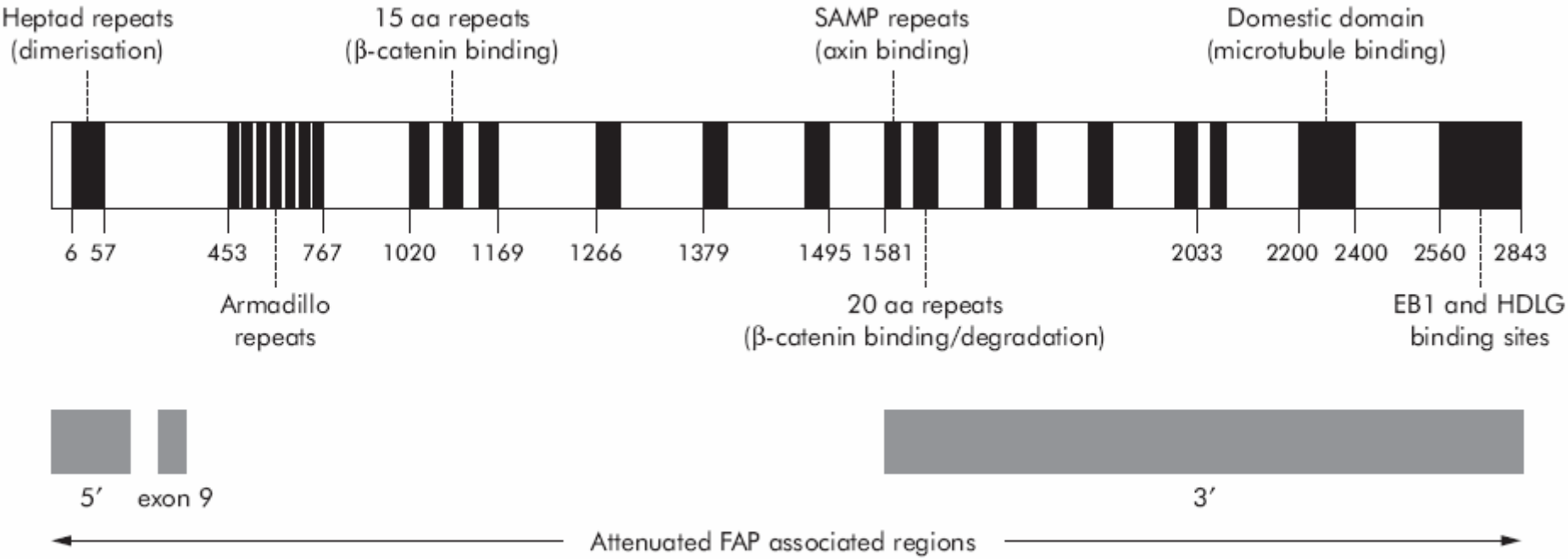
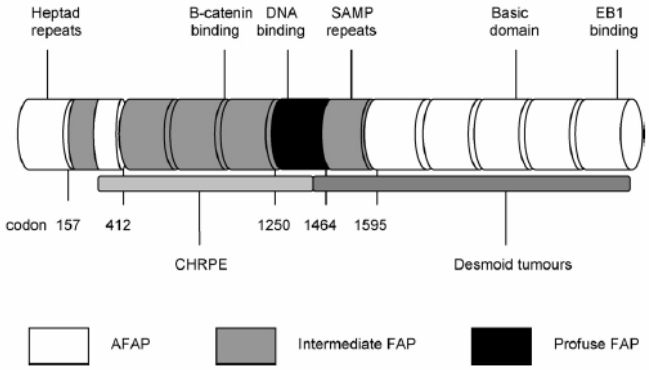


Figure 1 Representation of the adenomatous polyposis coli protein comprising important functional domains and showing regions of the protein germline mutation which are associated with attenuated familial adenomatous polyposis (FAP).



COLORECTAL CANCER

Disease severity and genetic pathways in attenuated familial adenomatous polyposis vary greatly but depend on the site of the germline mutation

O M Sieber, S Segditsas, A L Knudsen, J Zhang, J Luz, A J Rowan, S L Spain, C Thirlwell, K M Howarth, E E M Jaeger, J Robinson, E Volikos, A Silver, G Kelly, S Aretz, I Frayling, P Hutter, M Dunlop, T Guenther, K Neale, R Phillips, K Heinimann, I P M Tomlinson

A continuum between AFAP and classical FAP

An Evolving and Poorly Understood Entity

EVOLUTION OF A SYNDROME

Challenge in the differentiation between AFAP and HNPCC

Variation of a variation: Case report of attenuated familial adenomatous polyposis

AFAP: variety is the spice of life

Quindi problemi…

- Variabilità f(genetica)
- Variabilità intra(genetica)
- Difficoltà della definizione di un fenotipo
- Difficoltà del management clinico

AFAP…

- 3-100 adenomas (Sieber, 2003)
- < 100 adenomas (Hernegger, 2002)
- ≥ 10 <100 adenomas (Bouguen, 2006)
- 5-99 adenomas no detailed FH (Russell, 2006)
- < 100 adenomas (Menendez, 2008)
- 20-99 adenomas (Burt, 2004)
- ≥10 < 100 adenomas (Soravia 1998)
- 0-45/50 adenomas, even small ones (Rozen, 1999)
- ≥10 < 100 adenomas (Hes, 2008)
- < 100 + Mut + (AFAP) < 100 Mut not ident (mult)(Sieber,2002)
- …

Un poco di chiarezza

- Per quanto concerne la definizione
  (Nielsen, 2007)

- Per quanto concerne le caratteristiche cliniche
  (Burt, 2004)

Families with clinical AFAP were selected from the Dutch Polyposis Registry according to the following criteria: (a) at least two patients with 10–99 adenomas diagnosed at age >30 years or (b) one patient with 10–99 adenomas at age >30 years and a first-degree relative with colorectal cancer (CRC) with a few adenomas, and, applying for both criteria, no family members with more than 100 polyps before the age of 30 years.

Germline mutations in *APC* and *MUTYH* are responsible for the majority of families with attenuated familial adenomatous polyposis

Nielsen M, Hes FJ, Nagengast FM, Weiss MM, Mathus-Vliegen EM, Morreau H, Breuning MH, Wijnen JT, Tops CMJ, Vasen HFA. Germline mutations in *APC* and *MUTYH* are responsible for the majority of families with attenuated familial adenomatous polyposis. Clin Genet 2007: 71: 427–433. © Blackwell Munksgaard, 2007

Genetic Testing and Phenotype in a Large Kindred With Attenuated Familial Adenomatous Polyposis

RANDALL W. BURT,* MARK F. LEPPERT,† MARTHA L. SLATTERY,§ WADE S. SAMOWITZ,‖ LISA N. SPIRIO,† RICHARD A. KERBER,¶ SCOTT K. KUWADA,* DEBORAH W. NEKLASON,¶ JAMES A. DISARIO,* ELAINE LYON,‖ J. PRESTON HUGHES,# WILLIAM Y. CHEY,** and RAYMOND L. WHITE†

*Departments of Medicine, †Human Genetics, §Family and Preventive Medicine, ‖Pathology, and ¶Oncological Sciences, University of Utah, Salt Lake City, Utah; #St. Marks Hospital, Salt Lake City, Utah; and **Department of Medicine, University of Rochester, Rochester, New York

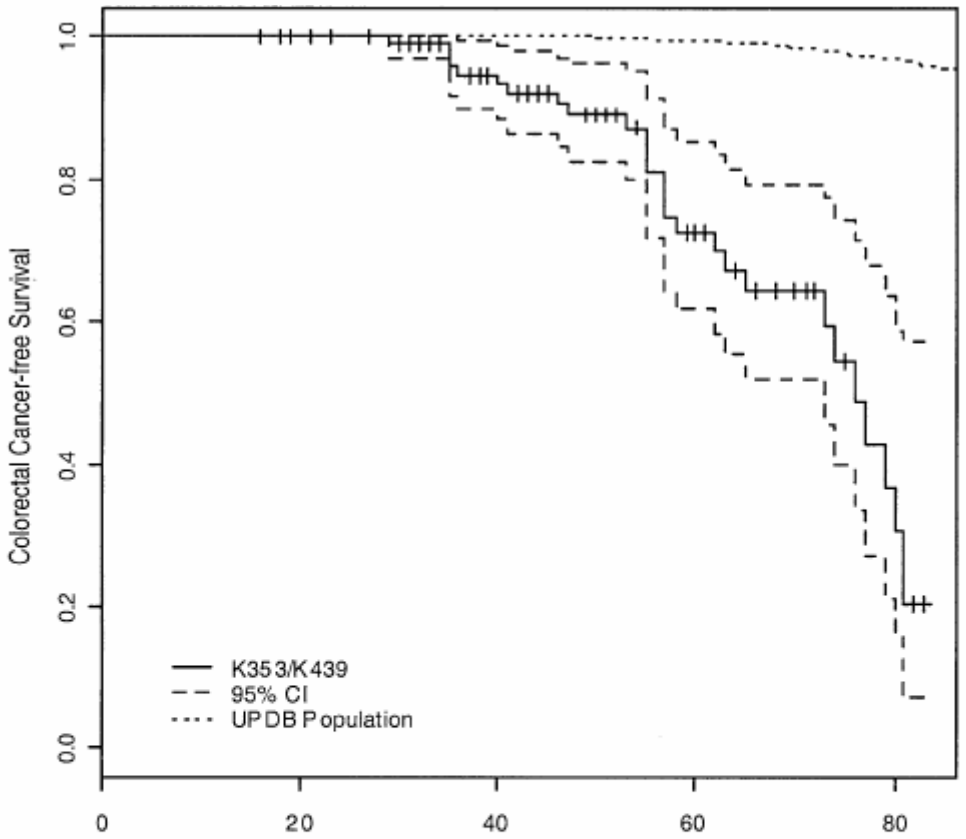


Figure 2. CRC-free survival curves by age in AFAP kindreds and the Utah Population Database. Kaplan–Meier survival curves for CRC-free survival in mutation-positive AFAP kindred members (K353/K439; *solid line*) and the Utah Population Database population (UPDB; *dotted line*) were calculated for invasive CRC as described in Methods. The 95% confidence interval (CI) for mutation-positive AFAP kindred members is indicated by the dashed line. The number of observations for CRC in the AFAP kindreds, as age progresses, are indicated. Note that the CRC-free survival at age 80 is 31% (CRC risk, 69%).

Table 2. Genetic Status, Colonoscopy Examination, and CRC History of Research Subjects

Variable	Male	Female	Total
Genetic status			
Number mutation positive	83	101	184
Number mutation negative	299	327	626
Total number of subjects	382	428	810
Colonoscopy performed in 148 mutation-positive subjects			
Number of subjects	68	80	148
Average age at colonoscopy (*yr*)	40	44	42
Number with colectomy	28	39	67
Average age at colectomy (*yr*)	45	47	47
Quantifiable colonoscopy results in 120 mutation-positive subjects[a]			
Number of subjects	56	64	120
Average age at colonoscopy (*yr*)	39	43	41
Median number of adenomas	34	15	25
Cancer history in 148 mutation-positive subjects and 34 obligate mutation carriers			
Number of subjects	87	95	182
Number of subjects with CRC	10	17	27
Average age at diagnosis (*yr*)	48	63	58

[a]Precise polyp counts available.

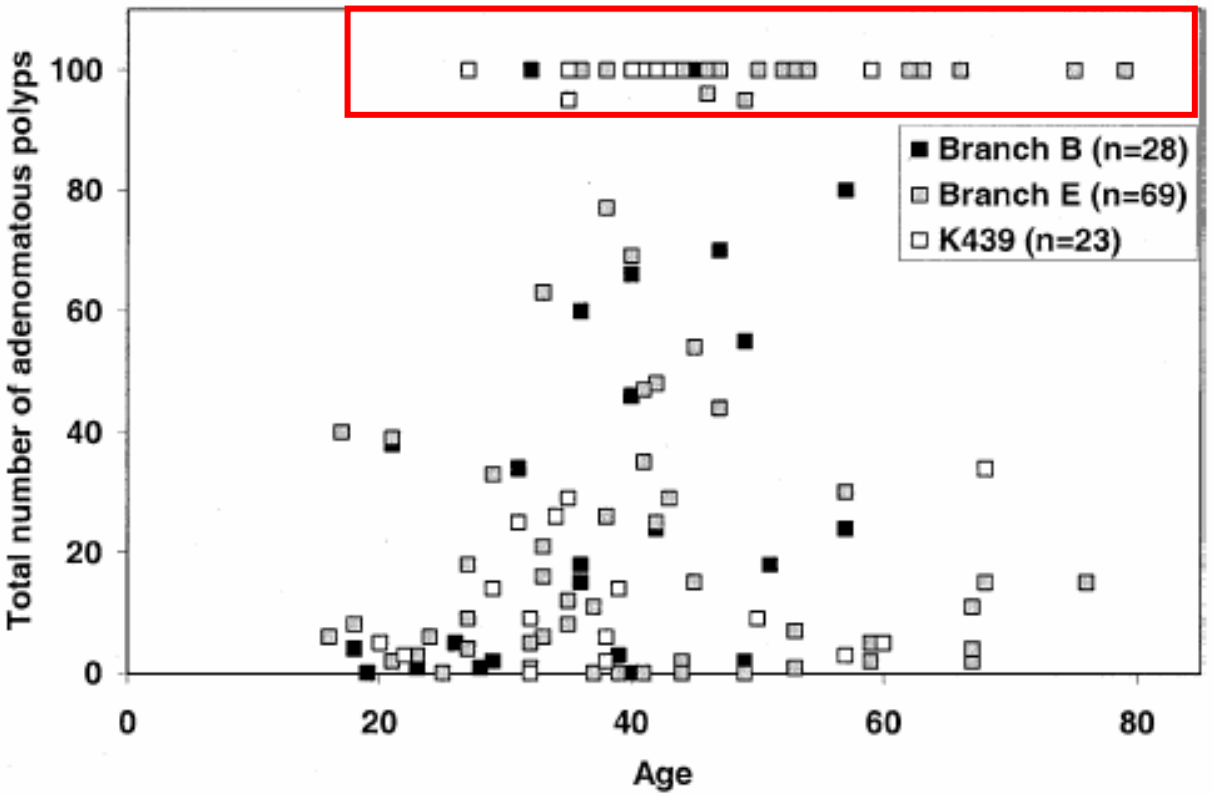


Figure 1. Number of adenomatous polyps in mutation-positive individuals as a function of age. The maximum numbers of adenomatous polyps found in the colon during a single endoscopic or surgical procedure are plotted against the age of the individual at the time of the procedure. Each individual is represented by a *square* (n = 120). *Black squares* represent individuals from K353(B). *Gray squares* represent individuals from K353(E). *White squares* represent individuals from K439. Those with 100 or more polyps were set at 100 polyps.

Table 3. Colonic Polyp Distribution in Mutation-Positive Subjects

Total no. of adenomas	No. subjects	Female-male ratio	Average age, *yr* (*range*)	Average % proximal adenomas per patient (*95% CI*)
0	9	5:4	36.2 (19–49)	NA
1–10	35	23:12	36.4 (16–67)	54 (41–66)
11–50	26	13:13	39.2 (21–76)	73 (64–82)
>50	17	8:9	48.1 (27–79)	78 (70–85)

NOTE. Patients were stratified into 4 groups based on the total number of adenomas per patient. The sex, age, and average percentage of proximal polyps per patient are shown by group. Detailed records of polyp location and number were available from 87 of the 120 individuals for this analysis.

NA, not applicable; CI, confidence interval.

Table 4. Median and Maximum Colonic Polyp Size (in mm) by Location

Colonic location	Average median size (±SD)	Number of examinations	Average maximum size (±SD)	Number of examinations
Cecum	3.3 (±5.9)	75	6.2 (±9.9)	89
Ascending	2.7 (±1.8)	79	6.7 (±9.0)	101
Transverse	4.4 (±6.4)	61	6.4 (±7.2)	83
Descending	3.3 (±2.5)	75	6.3 (±6.8)	97
Sigmoid	4.4 (±4.6)	111	5.6 (±6.1)	123
Rectum	4.4 (±4.6)	76	5.3 (±8.2)	82

NOTE. Median and maximum size of polyps were abstracted from a subset of medical records containing accurate location and size. The number of examinations includes multiple records from some participants.

Guidelines for referral to The Family Cancer Clinic at St Mark's

(ADAPTED FROM THE PUBLIC HEALTH GENETICS UNIT GUIDELINES, CAMBRIDGE)

NUMBER OF AFFECTED[1] PEOPLE IN FAMILY RELATED TO THE PROBAND	RELATIONSHIP TO THE PROBAND	TYPE OF CANCER	AGE OF RELATIVE	RISK GROUP	SCREENING REQUIRED	TYPE OF SCREENING	TO BE SEEN AT SPECIALIST GENETICS CLINIC
1	One FDR	CRC I or HRC II	>45 Years	Low	No	None	No- Reassure. Advice on diet and bowel awareness.
	One FDR	CRC	<45 Years	High/Moderate	Yes	First colonoscopy at 45 Years or when patient presents (whichever is later). Repeat 5 Yearly until 75 years.	In some cases
2	Two SDRs	CRC or HRC	>45 Years	Low	No	None	No- Reassure. Advice on diet and bowel awareness
	One FDR + One SDR(on same side of family)	CRC CRC or HRC	<70 years <70 years	Low/Moderate	Yes	Single colonoscopy at 55 Years or when patient presents (whichever is later).	No
	Two FDRs	CRC	Average <60 Average>60	High/Moderate Low/Moderate	Yes Yes	First colonoscopy at 45 Years or when patient presents (whichever is later). Repeat 5 yearly until 75 Years. Single colonoscopy at 55 Years or when patient presents (whichever is later).	Yes
	Both parents affected	CRC		Low/Moderate	Yes	Single colonoscopy at 55 Years or when patient presents (whichever is later).	No
3	Two FDRs + One FDR or SDR (but Amsterdam [2] negative)	CRC CRC or HRC		High/Moderate	Yes	First colonoscopy at 45 Years or when patient presents (whichever is later). Repeat 5 Yearly until 75 Years.	Yes
	One FDR + Two FDR or SDR (but Amsterdam [2] negative)	CRC CRC or HRC		High/Moderate	Yes	First colonoscopy at 45 Years or when patient presents (whichever is later). Repeat 5 Yearly until 75 Years.	Yes
A family history of a known hereditary colorectal cancer syndrome, or multiple colorectal polyps (polyposis coli) e.g FAP, AFAP, PJS, FJP or HNPCC (by fulfillment of modified Amsterdam criteria [2])				High	Yes	**FAP:** According to St Mark's polyposis registry protocol **AFAP:** On an individual basis **PJS AND FJP:** According to St Mark's polyposis registry protocol **HNPCC:** First colonoscopy at 25 years or when patient presents (whichever is later) and then repeated 2 yearly to 75 years. Pelvic/Renal/Stomach surveillance (as appropriate)	Yes

AFAP

In families with AFAP, a different protocol is recommended. A recent Dutch study on nine AFAP families associated with *APC* mutation reported a mean age at diagnosis of CRC of 54 years (n = 40) which is about 10–15 years later than in classical FAP. No cases of CRC were observed in individuals younger than 20 years. The youngest case of CRC was diagnosed at age 24 years.[4] In an American study of a large family with AFAP, no CRC was observed in patients under the age of 29 years.[28] Therefore, periodic examination is recommended starting from age 18–20.

Table 4 Colorectal surveillance protocol in family members at risk for (A)FAP

	Type of investigation	Lower age limit	Interval
Classical FAP	Sigmoidoscopy*	10–12 years	2 years*
AFAP	Colonoscopy	18–20 years	2 years*

*Once adenomas are detected annual colonoscopy should be performed until colectomy is planned.
(A)FAP, (attenuated) familial adenomatous polyposis.

MUTYH-ASSOCIATED ADENOMATOUS POLYPOSIS (MAP)

In 2002, Al-Tassan *et al* demonstrated a role for defective base excision repair (BER) in hereditary colorectal cancer.[5] They identified bi-allelic germline mutations in the BER gene *MUTYH* in a British family with three affected members and recesssive inheritance of multiple colorectal adenomas and carcinoma. Further studies found bi-allelic *MUTYH* mutations in 26–29% of patients with 10–100 polyps and 7–29% of patients with 100–1000 polyps.[74–76] Bi-allelic mutations have rarely been reported in patients with fewer than 10 adenomas, and in some apparently CRC-only patients.[77 78] Based on these findings, patients with more than 10 adenomas should be referred for genetic counselling, and mutation analysis of the *MUTYH* gene should be considered. Bi-allelic *MUTYH* mutations are usually

QUESTION: *which surveillance protocol should be recommended to patients with FAP due to bi-allelic MUTYH mutations?*

CONCLUSION: *the suggested surveillance protocol for MAP patients is similar to that for patients with AFAP (category of evidence III, grade of recommendation B) (see table 4).*

QUESTION: *what is the approprate surgical treatment of colonic polyposis in carriers of bi-allelic MUTYH mutations?*

Quindi…

- Molti polipi (ma non abbastanza…)
- Distribuzione prossimale
- Grosse dimensioni (abbastanza?)
- Individualizzazione del trattamento

- … **una sfida per l'endoscopista**
  - Pancolonscopia (sempre e bene)
  - Operativa complessa
  - Trattamento di lesioni duodenali
  - Valutazione accurata poliposi fundiche
  - Ma soprattutto… tutti i polipi sono uguali ma alcuni sono più uguali degli altri!

THE AMERICAN JOURNAL OF GASTROENTEROLOGY

Published by Elsevier Science Inc.

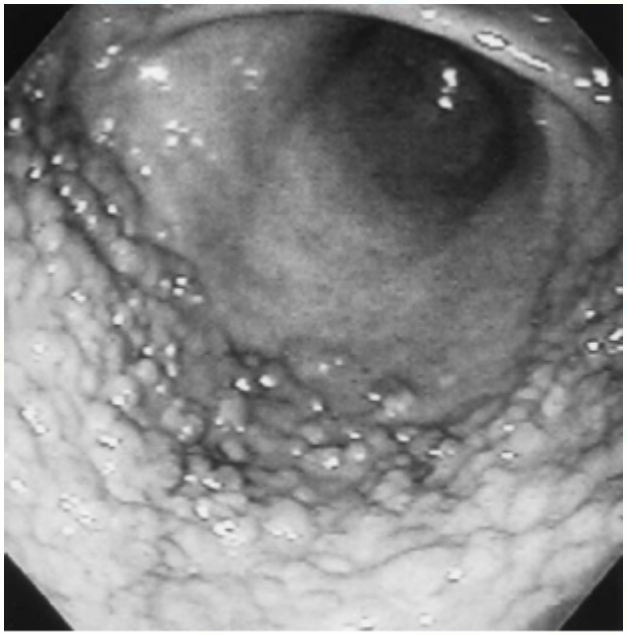
Vol. 94, No. 8, 1999
ISSN 0002-9270/99/$20.00
PII S0002-9270(99)00368-8

CASE REPORTS

Gastric Adenocarcinoma Associated With Fundic Gland Polyps in a Patient With Attenuated Familial Adenomatous Polyposis

Wolfgang T. Hofgärtner, M.D., Micah Thorp, M.D., Mark W. Ramus, M.D., Guy Delorefice, M.D., William Y. Chey, M.D., Charlotte K. Ryan, M.D., Garry W. Takahashi, M.D., and John R. Lobitz, M.D.

Departments of Medicine and Pathology, Providence St. Vincent Medical Center, Portland, Oregon; and William B. and Sheila Konar Center for Digestive and Liver Diseases and Departments of Medicine and Pathology, University of Rochester Medical Center, Rochester, New York



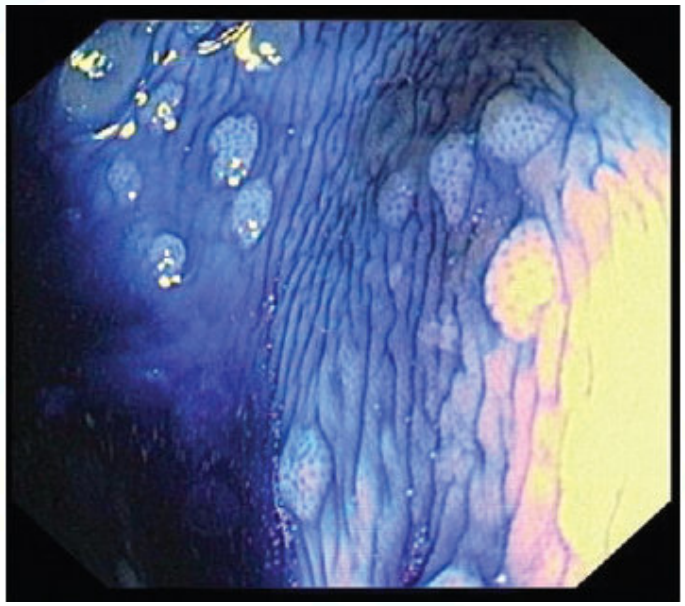
an entirely benign process. We feel that during upper gastrointestinal endoscopy in FAP patients, the area covered with fundic gland polyps requires meticulous inspection. Representative fundic gland polyps may need to be completely excised and examined histologically for the indolent presence of high grade dysplasia or malignant transformation (23).

In some kindreds with FAP or attenuated FAP, prophylactic gastrectomy may even be contemplated once dysplastic changes of fundic gland polyps have been identified. Although endoscopic ultrasound of the gastric fundus in our patient did not definitively identify any neoplastic changes, it may prove to be a useful adjunct by directing biopsies to areas of particular concern. Further investigation of FAP patients is needed to resolve the question of the malignant potential of fundic gastric polyps.

Duodenal carcinoma in MUTYH-associated polyposis

M Nielsen, J W Poley, S Verhoef, M van Puijenbroek, M M Weiss, G T Burger, C J Dommering, H F A Vasen, E J Kuipers, A Wagner, H Morreau, F J Hes

J Clin Pathol 2006;59:1212–1215. doi: 10.1136/jcp.2005.031757



GUT ONLINE

Attenuated familial adenomatous polyposis presenting as ampullary adenocarcinoma

J D Trimbath, C Griffin, K Romans and F M Giardiello

Gut 2003;52;903-904
doi:10.1136/gut.52.6.903

AFAP in screening*

- **21.04.05 – 30.03.08**
- **6200 pancolonscopie**
- **5276 persone**
- **Oltre 5 polipi in una colonscopia di cui almeno tre adenomi:**
  - **388 persone**
  - **572 colonscopie**

ADENOMI

3	**(267)**
4	**(21)**
5	**(25)**
6	**(44)**
7	**(8)**
8	**(6)**
9	**(11)**
10	**(1)**
11	**(2)**
14	**(1)**
17	**(1)**
18	**(1)**
> 50	**(1)**

* Centro Screening Reggio Emilia, dati provvisori

- Possibilità di un “continuum” di situazioni (sporadicità, forme attenuate, APC correlate, MYH correlate, HNPCC, ec)
- Possibilità di forme attenuate in polipi multipli (anche pochi!)
  - Grossi polipi? Polipi cancerizzati?
  - Necessità di approfondire l’anamnesi familiare (ma i mutanti?)
- Possibilità che una forma attenuata si “nasconda”
  - Tumori duodenali-ampollari
  - Tumori del piccolo intestino, ec
  - Polipi ghiandolari fundici (?)

Table 9. Technical Developments in Colonoscopy Directed Toward Neoplasia Detection: Are They Effective in Improving Detection and Practical?

	Effective	Practical
Methods for exposure of more mucosa		
Wide-angle colonoscopy	No	Yes
Cap-fitted colonoscopy	Yes	Yes
Colonoscopy in retroflexion	No	No
Third Eye Retroscope	NS	NS
Methods for detection of flat lesions		
Chromoendoscopy	Yes	No
Narrow band imaging	Mixed results	IS
High definition	NS	Yes
Autofluorescence	IS	NS

NS = not studied in humans; IS = insufficient data available.

Douglas K. Rex, M.D., F.A.C.G.
Indiana University Medical Center, Indianapolis, Indiana

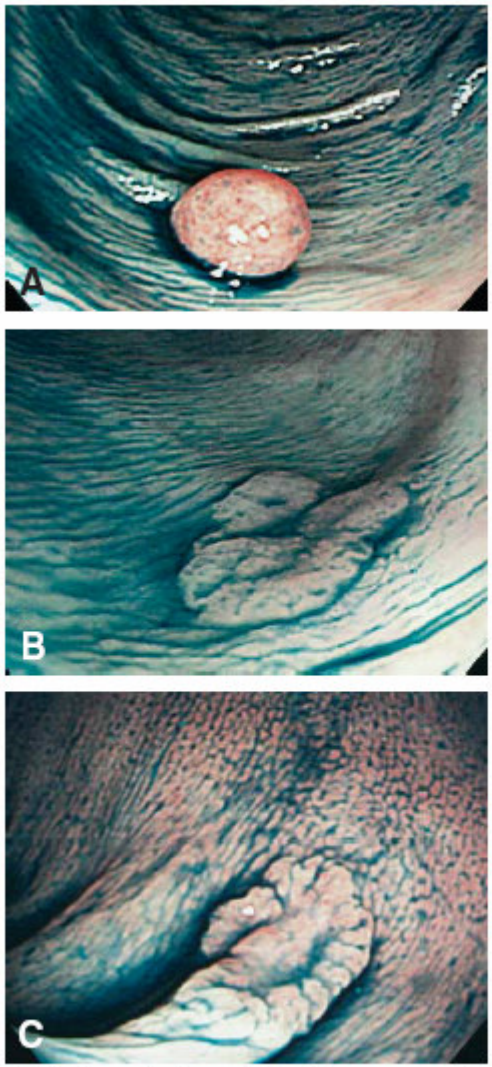


Figure 1. Endoscopic views illustrating macroscopic classification of polyps (all lesions seen after spraying with Indigo carmine dye). **A**, 6-mm diameter polypoid lesion. **B**, 8-mm diameter flat-elevated lesion. **C**, 10-mm diameter depressed lesion.

- **Nuove tecnologie**
  cromo-colonscopia ad alta magnificazione
  (Hurlstone DP, 2005
  Lecomte T, 2005; Hurlstone 2008)

Anche in AFAP!

Con magnificazione da < 100 a > 100 adenomi

Ha senso?

(wallace 1999)

Table 1.
Table Comparing Polyp Numbers Found at Standard Colonoscopy and Dye-Spray with Subsequent Histology

Age (yr)	Gender	Polyp Count by Referring Endoscopist	Dye-Spray	Actual
25	M	"Very few"	"Multiple"	>1000
32	M	6	>1000	1290
37	F	20	>1000	1250
19	F	>20	>1000	1070

Attenuated Adenomatous Polyposis Coli

The Role of Ascertainment Bias Through Failure to Dye-Spray at Colonoscopy

Marina H. Wallace, F.R.C.S, Ian M. Frayling, Ph.D., Susan K. Clark, F.R.C.S., Kay Neale, M.Sc., Robin K. S. Phillips, F.R.C.S.

From the ICRF Colorectal Cancer Unit and The Polyposis Registry, St Mark's Hospital, Harrow, United Kingdom

Table 2. Summary of the Randomized Controlled Trials Comparing Chromoscopy With White Light Endoscopy for the Detection of IN in "Sporadic" Colorectal Screening Cohorts

	Chromoscopy			Nonchromoscopy		
RCT	No. patients	Mean no. IN lesions	SD	No. patients	Mean no. IN lesions	SD
Brooker et al[15]	124	2.06	2.00	135	0.81	2.00
Hurlstone et al[16]	128	1.44	2.00	132	0.78	2.00
Lapalus et al[17]	146	1.54	2.00	146	1.05	2.00
Le Rhun et al[18]	99	1.74	2.00	99	1.05	1.80

IN, intraepithelial neoplasia; SD, standard deviation;

Nel frattempo

Preoperative and Postoperative Quality of Life in Patients with Familial Adenomatous Polyposis

Impact of Familial Adenomatous Polyposis on Young Adults: Quality of Life Outcomes

A Prospective Evaluation of Sexual Function and Quality of Life After Ileal Pouch-Anal Anastomosis

Severe dysplasia in children with familial adenomatous polyposis: rare or simply overlooked?

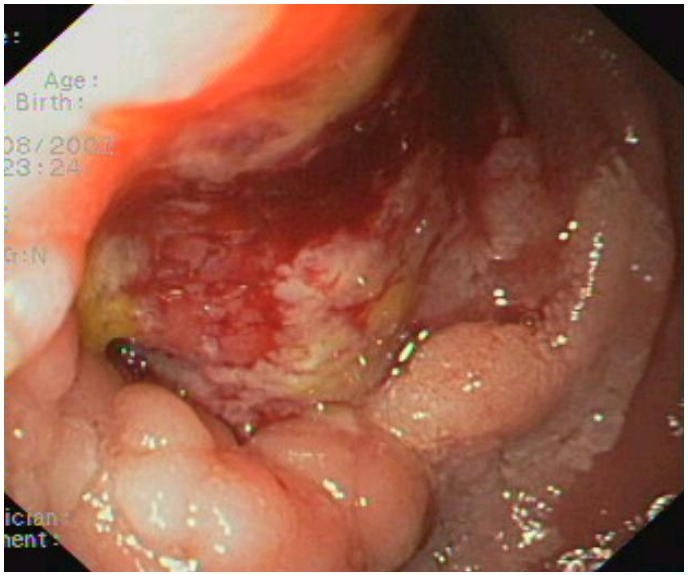
Familial Adenomatous Polyposis in Children Younger than Age Ten Years: A Multidisciplinary Clinic Experience

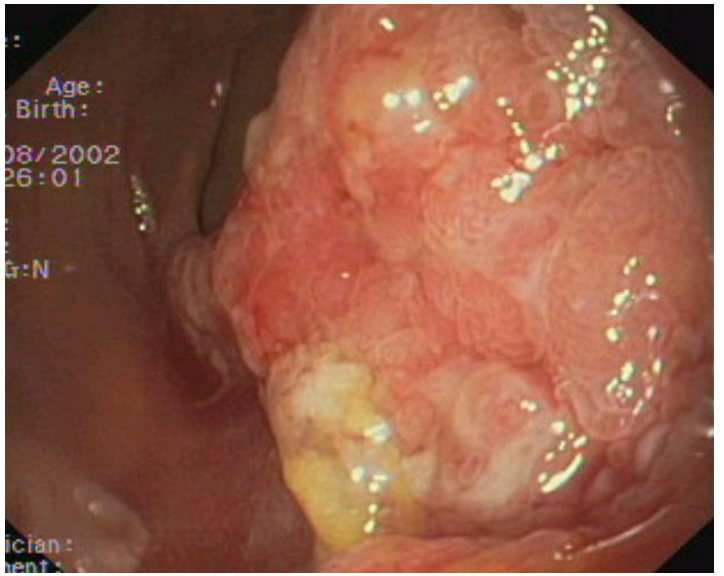
''You're One of Us Now'': Young People Describe Their Experiences of Predictive Genetic Testing for Huntington Disease (HD) and Familial Adenomatous Polyposis (FAP)

Disseminating risk information to familial adenomatous polyposis families

Is Internet Information Adequate to Facilitate Surgical Decision-Making in Familial Adenomatous Polyposis?

Colorectal Cancer Surveillance Behaviors Among Members of Typical and Attenuated FAP Families


Age :
Birth :


Age :
Birth :
08/2002
26:01
G:N

You are old, Father William, the young surgeon said,
And your colon from polyps is free.
Yet most of your sibling are known to be dead –
A really *bad* family tree.
In my youth, Father William replied with a grin,
I was told that a gene had mutated,
That all who carried this dominant gene
To polyps and cancer were *fated.*
I sought for advice from a surgical friend,
Who sighed and said – Without doubt
Your only escape from an untimely end
Is to have your intestine right *out*.
It seemed rather back luck – I was then but nineteen
–
So I went and consulted a quack,
Who took a firm grip on my dominant gene
And promptly *mutated it back*.
This, said the surgeon, is something quite new
And before we ascribe any merit
We must see if the claims of this fellow are true,
And observe what your *children* inherit!

Cuthbert Dukes