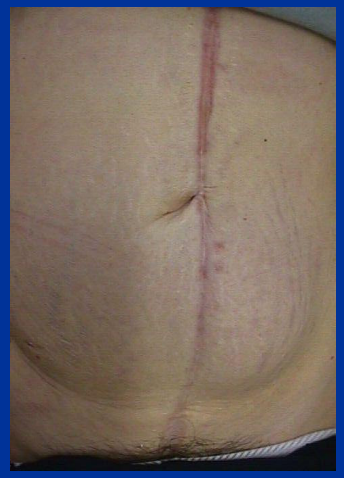
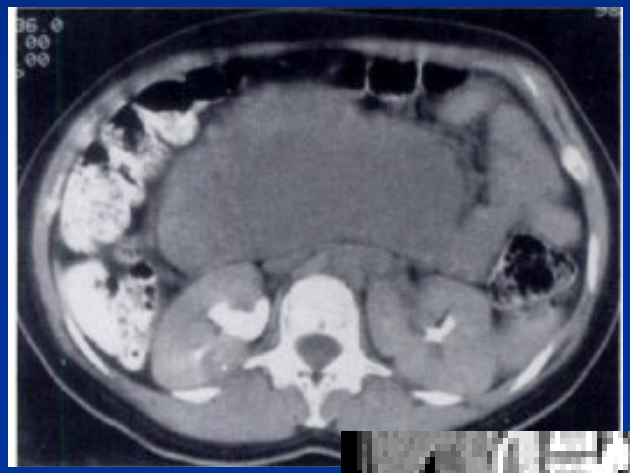
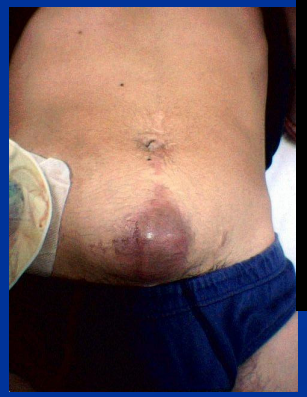
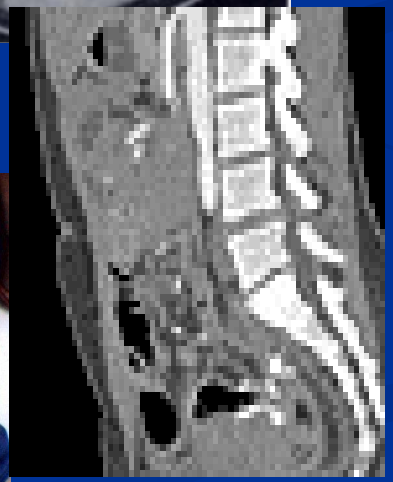
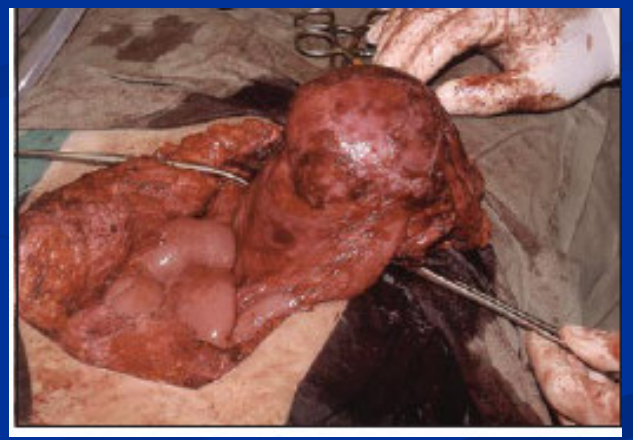
DESMOIDI











L. Bertario

Background

- **Desmoid tumors are histologically benign fibrous neoplasms** originating from the musculoaponeurotic structures throughout the body. The term desmoid, coined by Muller in 1838, is derived from the Greek word *desmos,* which means tendonlike.

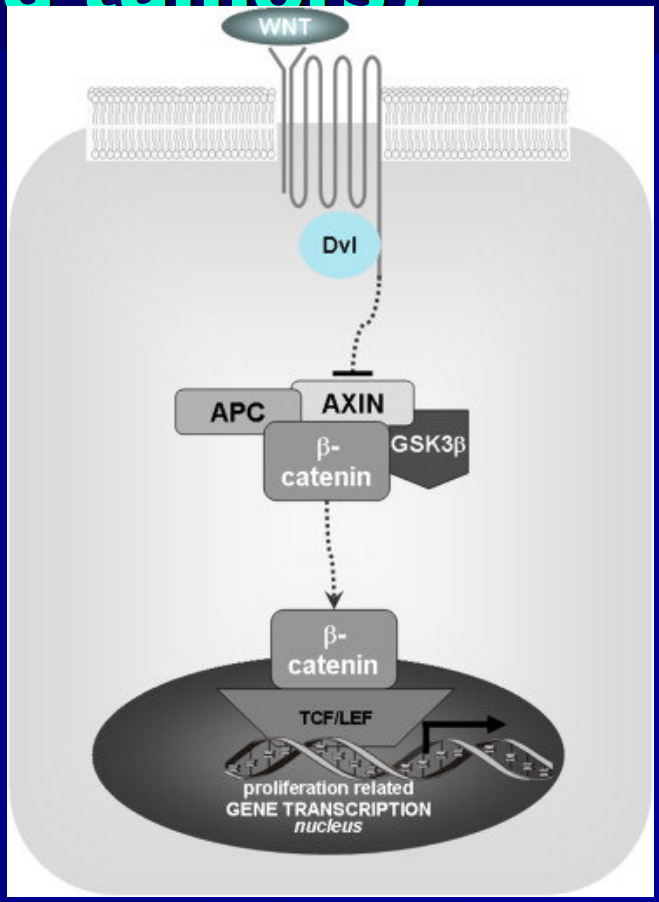
- **Desmoid tumors often appear as infiltrative, usually well-differentiated, firm overgrowths of fibrous tissue, and they are locally aggressive**. The synonym aggressive fibromatosis describes the marked cellularity and aggressive local behavior. **This course and the tendency for recurrence make the treatment of these relatively rare fibrous tumors challenging.**

- Peripheral desmoid tumors
  - Peripheral desmoid tumors are firm, smooth, and mobile.
  - They often adhere to surrounding structures.
  - The overlying skin is usually unaffected.
  - The presence of such a soft tissue growth should alert the clinician to delve more deeply into the family history for evidence of familial polyposis coli and Gardner syndrome.
  - Extra-abdominal desmoid tumors are rare and may be first evident as gradually increasing leg swelling.

- Intra-abdominal desmoid tumors may be seen. Extra-abdominal desmoid tumors may also be seen (rarely) in the urological system, including in the bladder and scrotum.
  - Intra-abdominal desmoid tumors remain asymptomatic until their growth and infiltration cause visceral compression.
  - Symptoms of intestinal, vascular, ureteric, or neural involvement may be the initial manifestations.

The role of APC and beta-catenin in the aetiology of aggressive fibromatosis (desmoid tumors)

- Aggressive fibromatosis is a benign neoplastic proliferation of fibroblastic cells surrounded by abundant collagen fibers, forming an invasively growing mass lacking the capability to metastasize. Mutations in either the APC or β-catenin genes are likely to be a major driving force in the formation of these desmoid tumors.



D.J. Lips Eur J Surg Oncol. 2008

CTNNB1 mutations are highly common (85%) in desmoid tumors. Patients harboring CTNNB1 (45F) mutations are at particular risk for recurences (67%)

Alexander J.F *(Am J Pathol 2008*

EPIDEMIOLOGY

Patients with familial adenomatous polyposis (FAP) have an increased risk of developing desmoid disease

- **Incidence from 3.6 to 13% have been reported by various polyposis registries**
- **Between 3.5 to 32% of FAP patients are estimated to be affected by desmoids**

Sporadic desmoids

- **2-4 cases / 1,000,000 / yr.**
- **Mainly in women :**

  female / male from 2:1 to 5:1
- **Peak incidence :**

  30 years of age

Table 1
Types of aggressive fibromatosis

Sporadic disease			
Sporadic (idiopathic) aggressive fibromatosis	Somatic mutations APC and/or β-catenin		• Variable phenotype
Inherited disease			
Familial adenomatous polyposis (FAP)	Germline mutations APC	10—15% penetrance	• Predominance of GI disease in clinical phenotype • Late onset (3rd—4th decade) • Mainly mesentery
Familial infiltrative fibromatosis (FIF)/ Hereditary desmoid disease (HDD)	Germline mutations APC	~100% penetrance	• Predominance of desmoid disease in clinical phenotype • Early onset (1st—2nd decade) • Mainly in proximity axial skeleton

APC, adenomatous polyposis coli; GI, gastrointestinal.

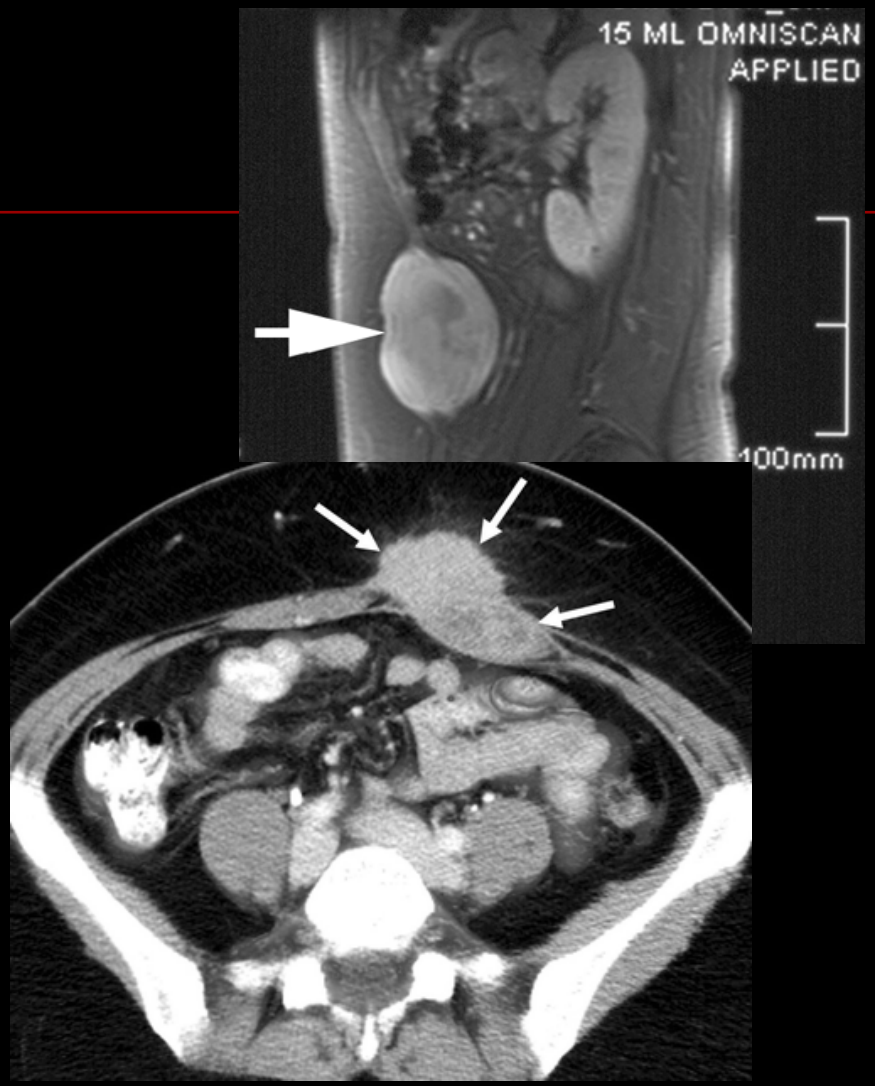
Table 3
Prevalence of extracolonic manifestations in FAP patients (Vasen [4], Bertario [27])

Extracolonic manifestations	Prevalence (%)
CHRPE[a]	70–75
Osteoma and dental abnormalities	70–90
Upper GI tumours	
Duodenal adenoma	50–90
Fundic gland polyposis	40–50
Gastric antrum adenoma	5–20
Epidermoid cysts and lipoma	25–50
Desmoids	10–15
Other malignancies	
Thyroidcarcinoma, hepatoblastoma, brain tumours	3

[a] Congenital hypertrophy of the retinal pigment epithelium.

Desmoid Risk factors

- **Trauma / abdominal surgery**
- Pregnancy
- Oral contraceptive
- Family history for desmoid
- **Specific APC gene mutation**
- Sex



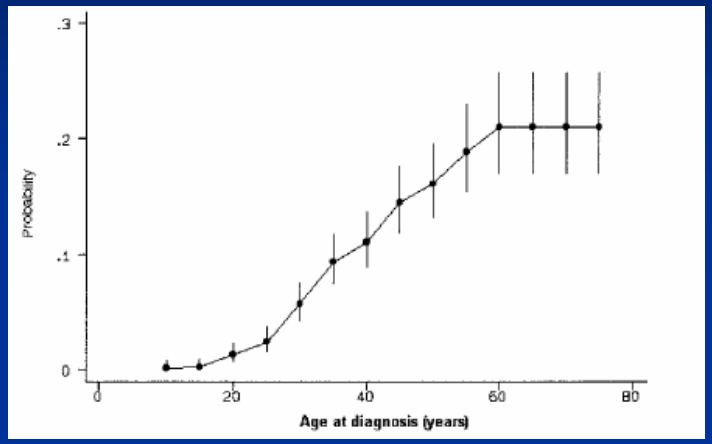
Mortality/Morbidity FAP

- **The principal cause of mortality is colorectal cancer**, which develops in all patients unless they are treated. The mean age at which colorectal cancer develops in patients with classic FAP is 39 years. Patients with adenomatous polyposis itself often are asymptomatic.

- ***The second reported lethal complication of FAP is diffuse mesenteric fibromatosis and is referred to as a desmoid tumor***. It involves intra-abdominal organs and vessels, causing gastrointestinal obstruction and constriction of veins, arteries, and ureters. **Desmoid tumors are reported in 4-32% of patients. Even after the appropriate surgical treatment of FAP, 20% of patients may develop desmoid tumors after colectomy**. Studies have found a correlation between specific *APC* mutation sites and desmoid tumor development. *Risk factors include a positive family history*. **The mortality from these tumors is 10-50%.** The second most common malignancy in patients with FAP is adenocarcinoma of the duodenum and the papilla of Vater. It affects as many as 12% of patients.

- Rarer cancers associated with FAP include medulloblastomas (Turcot syndrome), hepatoblastoma, thyroid cancer, gastric cancer, pancreatic cancer, and adrenal cancer

Age & Desmoids



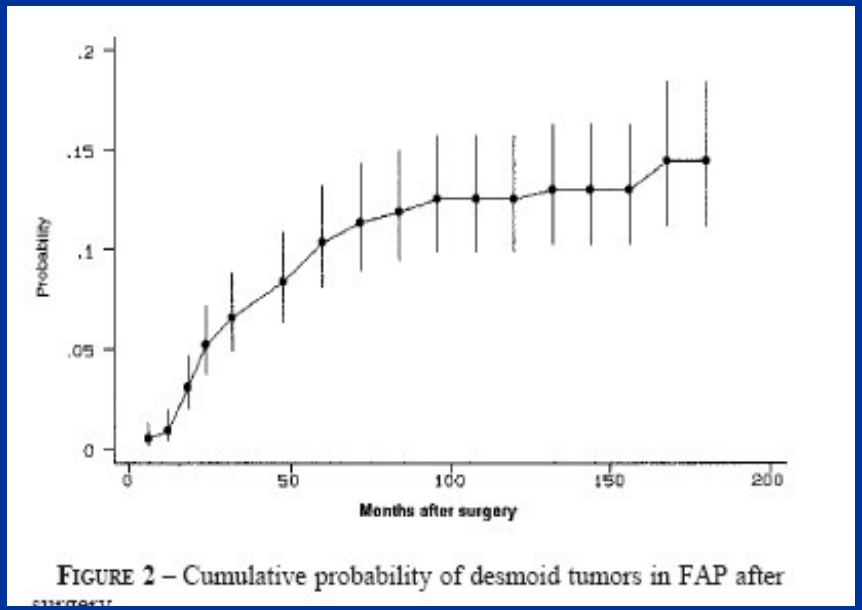
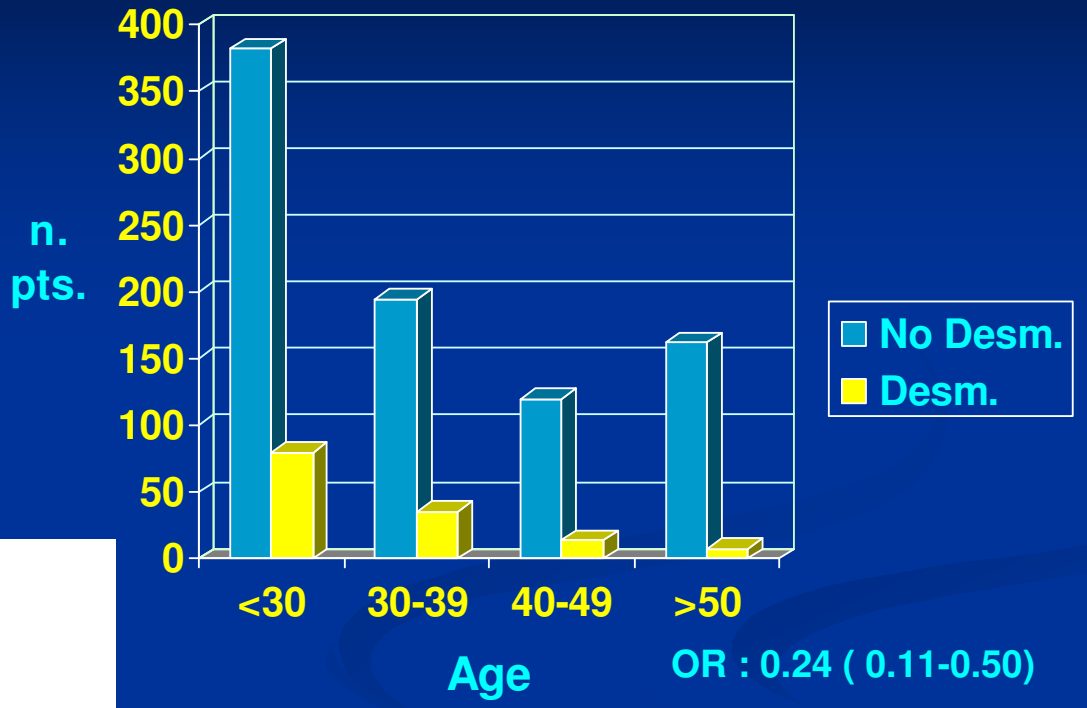


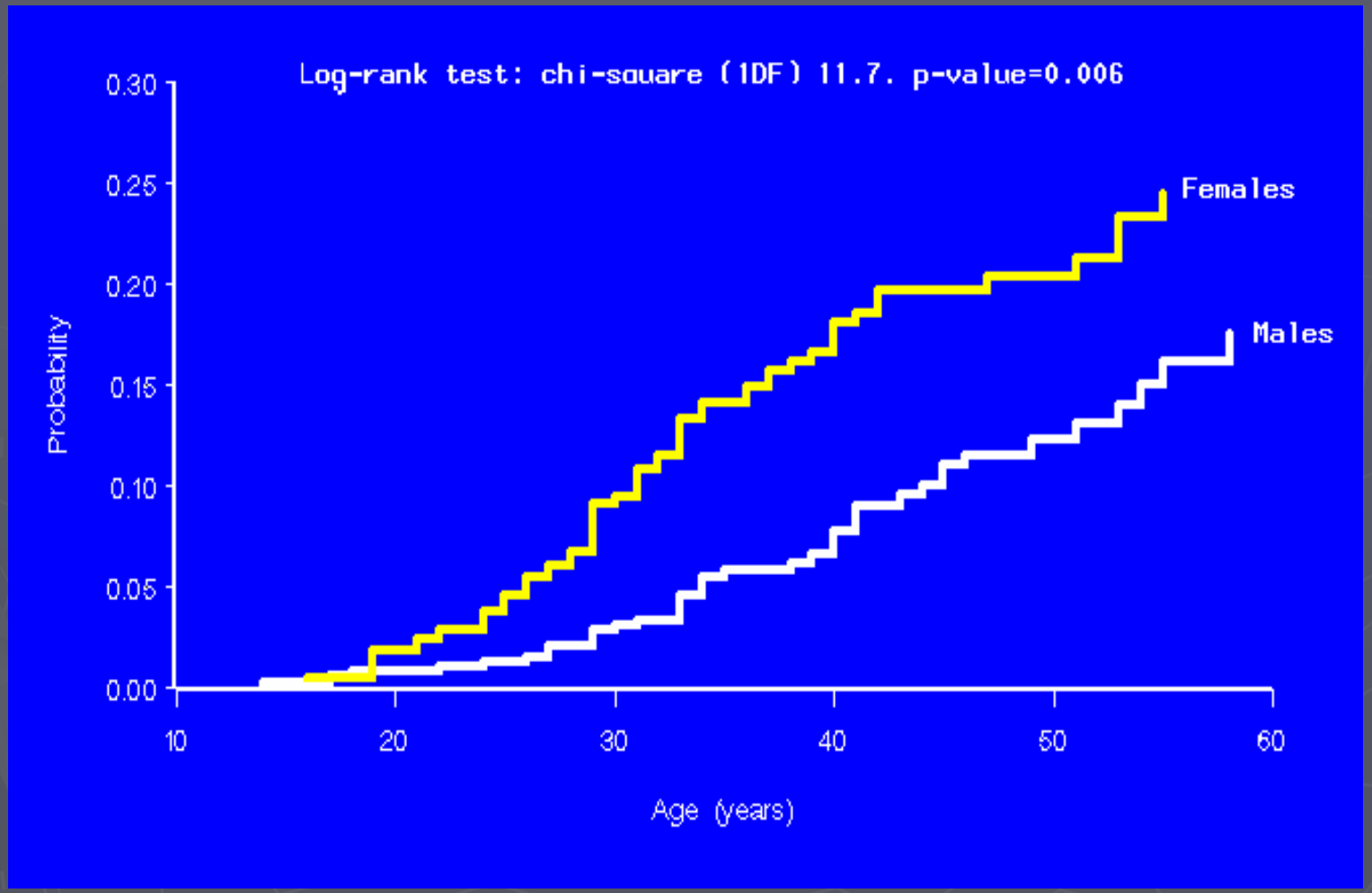
FIGURE 2 – Cumulative probability of desmoid tumors in FAP after



73% desmoids < 40 yrs age

Bertario L Int J Cancer 2001

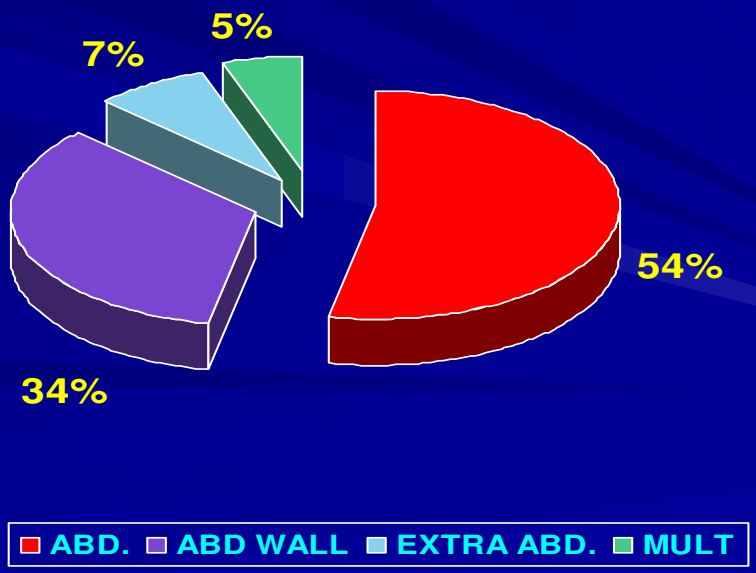
Cumulative life-time risk of desmoid tumours in FAP



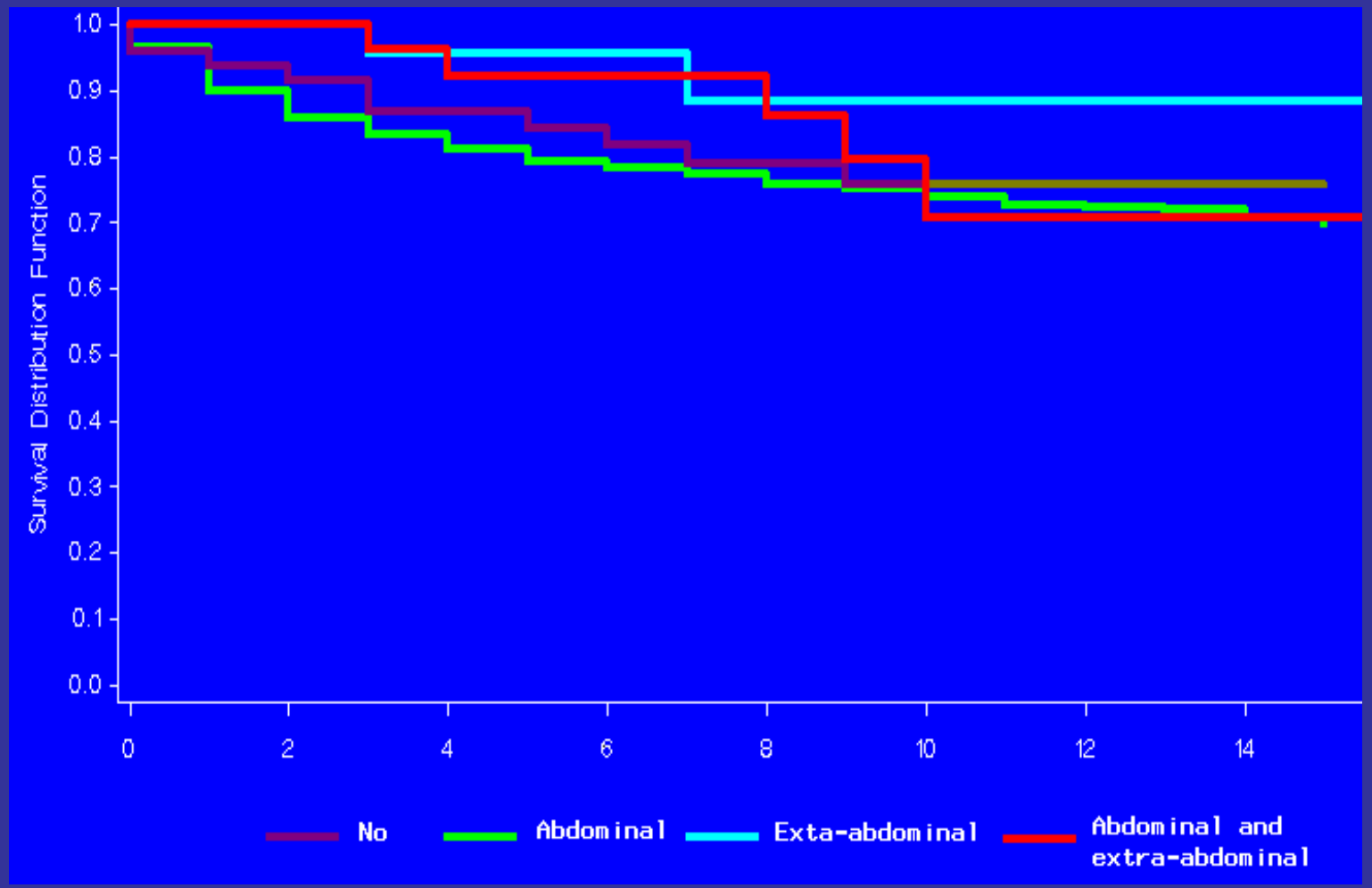
Register Hereditary Colorectal Tumours

- n. 1417 FAP pts.
- n. 170 FAP pts with Desmoids. (12%)
- Cumulative risk : 20%
- n. 15 deaths x desmoids (9%)
  - *n. 12 intra abd.*
  - *n 1 intra abd + abd. Wall*
  - *n. 2 Multiple*

- 37% PTS. MULTIPLE DESMOIDS
- 90% DESMOIDS CORRELATED TO a SURGICAL SITE



Life table analysis of survival



Familial Adenomatous Polyposis

Polymnia Galiatsatos, M.D., F.R.C.P(C),[1] and William D. Foulkes, M.B., Ph.D.[2]

(Am J Gastroenterol 2006;101:385–398)

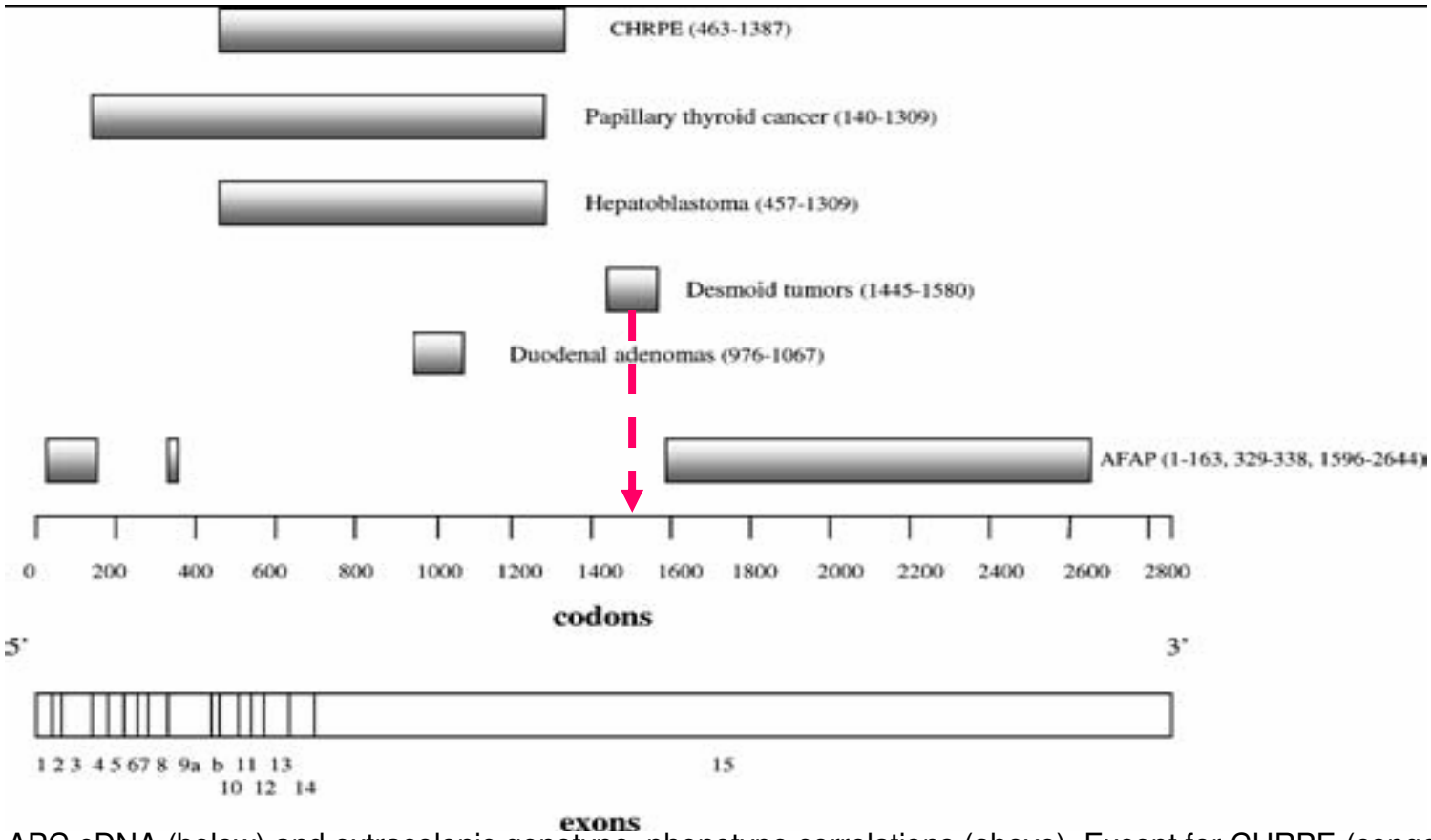
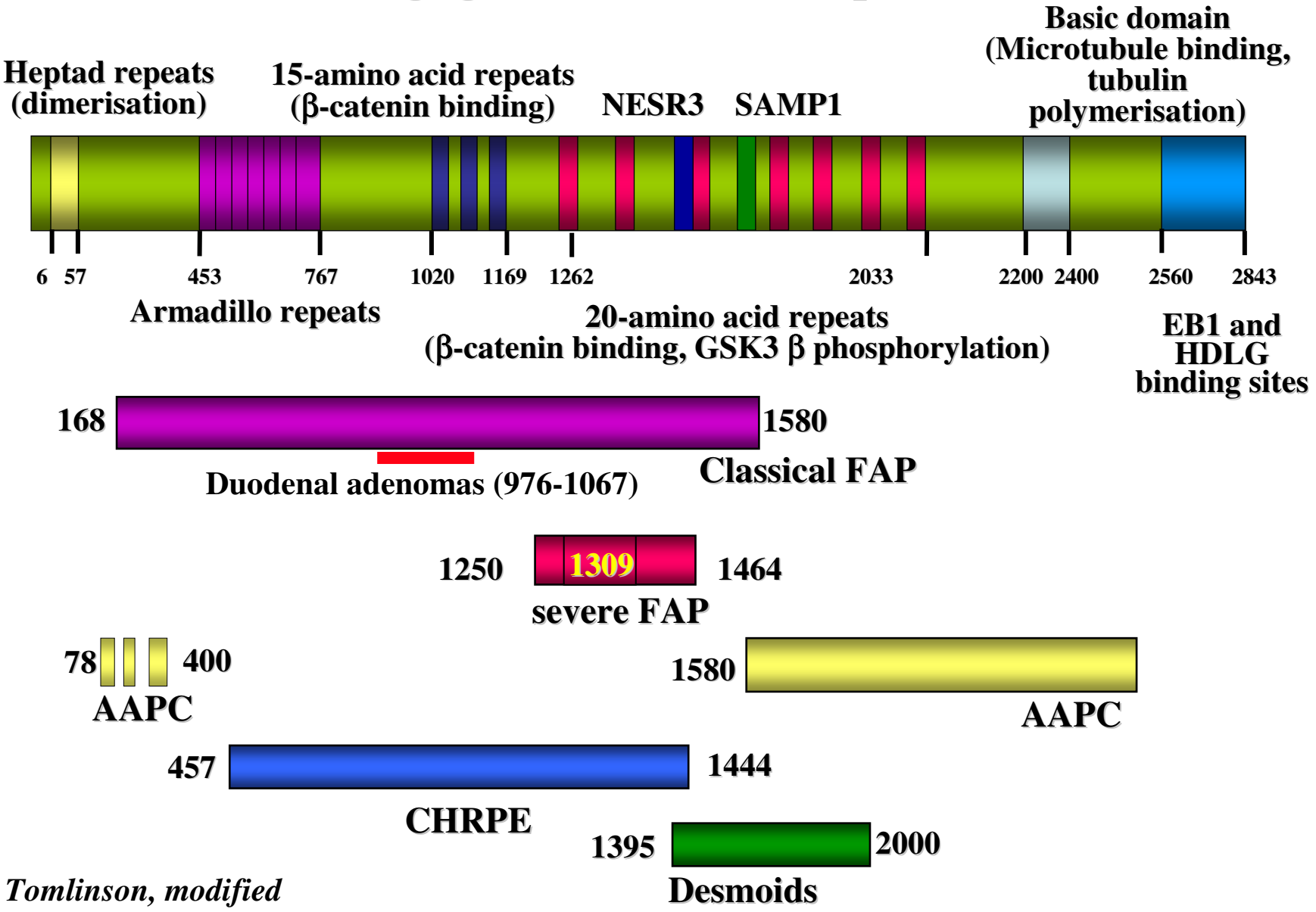


Figure 2. APC cDNA (below) and extracolonic genotype–phenotype correlations (above). Except for CHRPE (congenital hypertrophy ofthe retinal pigment epithelium), most lesions can occur with mutations anywhere along the APC gene, but are more likely in the locationsillustrated. AFAP = attenuated FAP. Adapted from Fearnhead *et al*. (7), Foulkes (8), Bertario *et al*. (84), and Cetta *et al*. (92).

APC protein domains and FAP phenotype association with (truncating) germline mutation position



by Ian Tomlinson, modified

Correlations between mutation site in APC and phenotype of familial adenomatous polyposis (FAP): A review of the literature

M.H. Nieuwenhuis [a], H.F.A. Vasen [a,b,*]

	codon	Authors
Desmoid tumours	1924, 1962	Eccles 1996, Scott 1996
	1445–1578	Caspari 1995
	1444–1560	Davies 1995, Gebert 1999
	1403–1987	Dobbie 1996, Heinimann 1998, Moisio 2002
	1395–1493	Wallis 1999
	1310–2011	Bertario 2003

- **The occurrence of desmoids in FAP has been linked to mutations at the 3 end of the APC gene , in general downstream codon 1400. *This correlation does not always appear to be consistent.***

Critical Reviews in Oncology/Hematology 61 (2007) 153–161

Conclusions
Desmoid Risk Factors

Factors	OR	95 % CI
Osteoma	2.06	1.26 - 3.38
Sex	2.55	1.56 -418
Apc mutations Yes v. No	9	3.2 - 25
Apc >1444	25	7.5 - 88

Mutations of adenomatous polyposis coli (APC) gene are uncommon in sporadic desmoid tumours

16 sporadic and four FAP-related desmoids were analysed in order to investigate the possible involvement of APC in non-syndromic cases also.

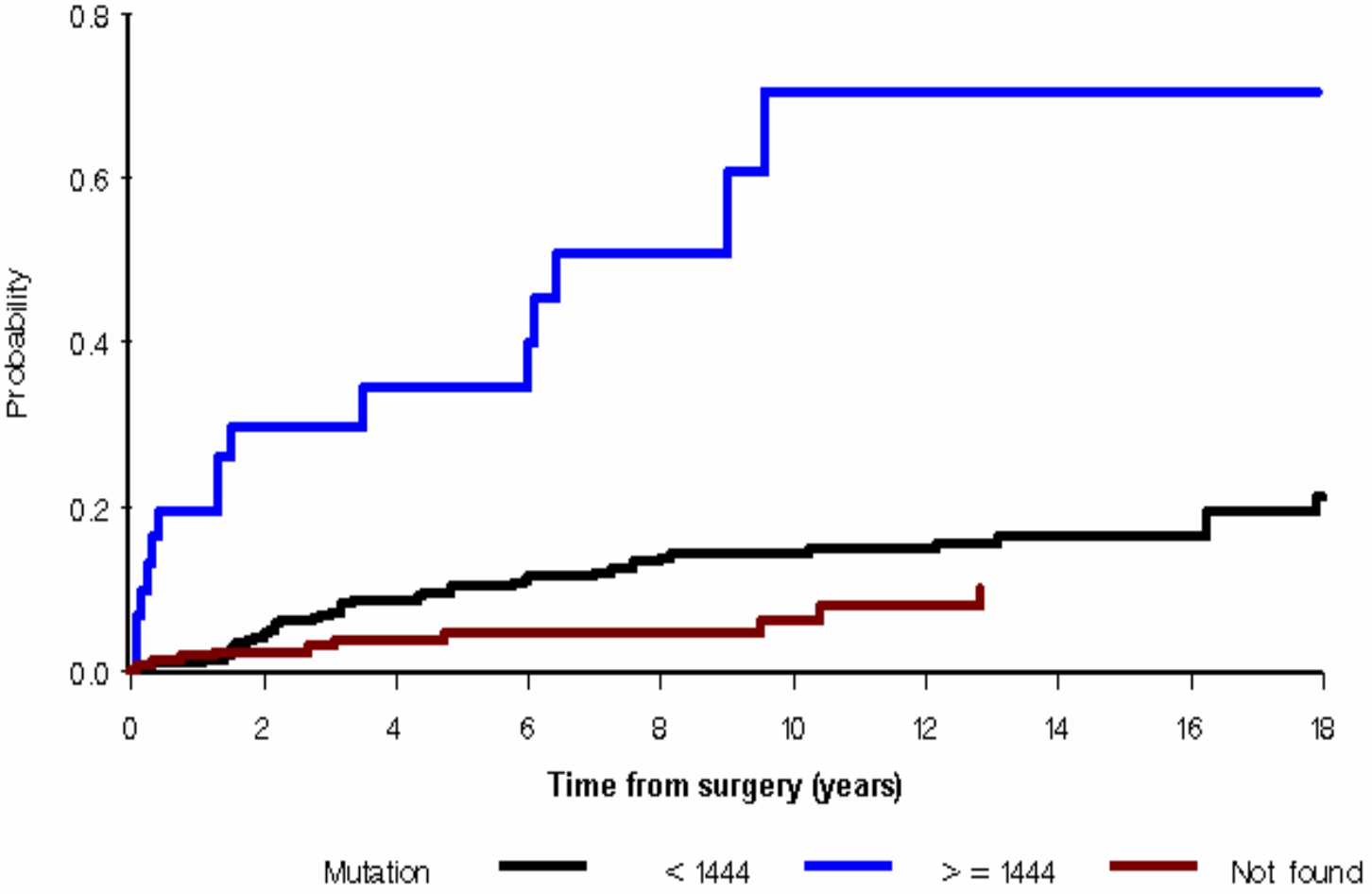
Somatic mutations were found in three FAP-associated desmoids (75%) and two sporadic tumours (12.5%). In one of the latter cases, both alleles were affected.

Giarola M. Br J Cancer. 1998

FAP-related cases	Type of mutation	Codons affected	Nucleotide Change
1	germline	1538	del(GA)
2	germline	935	TAC→TAA
	somatic	1558	ins(A)
3	germline	213	CGA→TGA
	somatic	1534	del(G)
4	germline	1464-1465	del(AGAG)
	somatic	1309-11	del(AAAGA)
Non FAP-related cases	**Type of mutation**	**Codons affected**	**Nucleotide Change**
1	somatic	1450	CGA→TGA
2	somatic	1142-1149	del23 bp
	somatic	1469	CAA→TAA

Giarola et al, British Journal of Cancer (1998) 78(5), 582587

Cumulative life-time risk of desmoid tumours in FAP



I.R.A. v. I.P.A.A. : *787 patients with diagnosis of classical FAP*

	IRA	IAA	P-value
Age	33.5-13.2	30.6-11.3	0.02
Sex (M/F)	304/236	137/110	0.9
CRC at diagnosis (Yes/No)	150/390	90/157	0.02
Stage CRC (AB/CD)	77/73	46/44	1.0
Metachronous ca. (Yes/No)	37/503 (6%)	3/244 (1%)	0.0002
Desmoids (Yes/No)	68/472	42/204	0.08
Surgical mortality (<30 days) (Yes/No)	3/537	2/245	0.07
Genotype : 1309/others	47/379	37/139	0.002
Successive surgery	60/480	3/244	<0.001

Hereditary Colorectal Tumours Registry Milan Italy

SURGERY & DESMOIDS

	OR	95% CI
IRA/ISA	17.63	2.34-132.76
IAA	24.35	3.19-185.82
Other surgery	13.99	1.77-110.61
SURGERY	19.12	2.56-142.5

Significance of Incidental Desmoids Identified During Surgery for Familial Adenomatous Polyposis

- A recent systematic study of the incidence of IADs in patients undergoing laparotomy for FAP from our own institution found unexpected and therefore subclinical. IADs to be present in 3 % of patients at the time of their first operation and in 36% of those who required a second operation

J. E. Hartley Dis Colon Rectum 2004;

Risk factors for development of desmoid tumours in familial adenomatous polyposis

- **Conclusion: No risk factor for life-threatening mesenteric DT could meaningfully modify the management of patients with FAP**
- The only modifiable factor is the type of surgical procedure, but this did not have a significant influence on the risk of DT.

J H. Lefevre British Journal of Surgery 2008

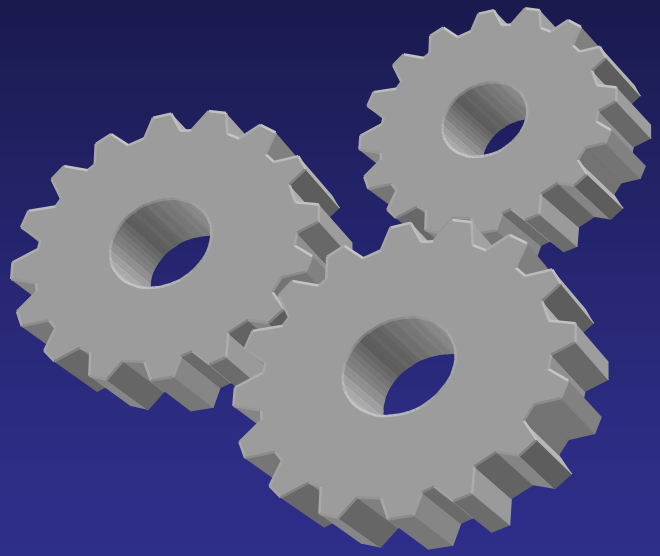
Does Early Colectomy Increase Desmoid Risk in Familial Adenomatous Polyposis?

Durno C 2007

- **Female patients were more likely to develop desmoids than male patients (17% vs 11%, P = .03)**
- **Female patients who had an early colectomy were more than 2 times more likely to develop a desmoid, compared with women who had a colectomy at >18 years (*P* .01).**
- **Female patients who had an early colectomy (<18 years) were 2.5 times more likely to develop desmoids, compared with male patients who had a late colectomy (*P* .05).**
- The prevalence of desmoids in the 5' and 3' groups was 13% and 38%, respectively (*P* .0005). *Patients with a mutation after codon 1399 were found to have 4 times greater chance of developing a desmoid.*

Delayed colectomy might be considered in young female patients with FAP to decrease the chances of developing desmoids.

TREATMENT



CONTROVERSIAL
EMPIRICAL
DIFFICULT

In the beginning there was colectomy

Desmoid clinical course

- 10% of tumours resolve spontaneously,
- 30% undergo cycles of progression and resolution
- 50% remain stable after diagnosis
- 10% progress rapidly

N. Julian Familial Cancer (2006)

Management

- Given the problems with the treatment of desmoids,there is a good case for simple observation of many tumours, particularly if asymptomatic.
- Following diagnosis, a small tumour which is not encroaching on any nearby structures may be followed up by regular clinical examination (perhaps every 6 months) with or without imaging, usually by CT
- Rapidly growing tumours, or those which are symptomatic, usually warrant treatment
- **Symptoms need to be managed**

GUT ONLINE

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

Hans F A Vasen, Gabriela Moeslein, Angel Alonso, Stefan Aretz, Inge Bernstein, Lucio Bertario, Ignacio Blanco, Steffen Bulow, John Burn, Gabriel Capella, Chrystelle Colas, Christoph Engel, Ian Frayling, Waltraut Friedl, Frederik Hes, Shirley Hodgson, Heiki Jarvinen, Jukka-Pekka Mecklin, Pal Moller, Torben Myrhoj, Fokko M Nagengast, Yann Parc, Robin Phillips, Sue Clark, Maurizio Ponz de Leon, Laura Renkonen-Sinisalo, Julian Sampson, Astrid Stormorken, Sabine Tejpar, Huw Thomas and Juul Wijnen

Gut published online 14 Jan 2008;
doi:10.1136/gut.2007.136127

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

In contrast to sporadic desmoid tumours, **the majority of the tumours associated with FAP are located in the abdominal wall or intra-abdominally.**
The options for treatment are pharmacological treatment (NSAIDs and/or anti-estrogens), chemotherapy, surgical excision or radiotherapy Evidence for the efficacy of these treatments is poor and is based on small, non-controlled studies. An additional problem for the evaluation of efficacy is that desmoids have a variable natural history with some tumors showing spontaneous regression in the absence of treatment.

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

Hans F A Vasen, Gabriela Moeslein, Angel Alonso, Stefan Aretz, Inge Bernstein, Lucio Bertario, Ignacio Blanco, Steffen Bulow, John Burn, Gabriel Capella, Chrystelle Colas, Christoph Engel, Ian Frayling, Waltraut Friedl, Frederik Hes, Shirley Hodgson, Heiki Jarvinen, Jukka-Pekka Mecklin, Pal Moller, Torben Myrhoj, Fokko M Nagengast, Yann Parc, Robin Phillips, Sue Clark, Maurizio Ponz de Leon, Laura Renkonen-Sinisalo, Julian Sampson, Astrid Stormorken, Sabine Tejpar, Huw Thomas and Juul Wijnen

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- Currently, the first line of treatment in patients with large or growing intra-abdominalor abdominal wall tumours is sulindac (300 mg) usually in combination with tamoxifen (40-120 mg) or toremifene (180 mg) (52-54;57). In patients with progressive intra-abdominal tumours that do not respond to this treatment, chemotherapy (e.g. doxorubicine and dacarbazine or methotrexate and vinblastin) or radiation therapy is indicated

GUT ONLINE

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

Hans F A Vasen, Gabriela Moeslein, Angel Alonso, Stefan Aretz, Inge Bernstein, Lucio Bertario, Ignacio Blanco, Steffen Bulow, John Burn, Gabriel Capella, Chrystelle Colas, Christoph Engel, Ian Frayling, Waltraut Friedl, Frederik Hes, Shirley Hodgson, Heiki Jarvinen, Jukka-Pekka Mecklin, Pal Moller, Torben Myrhoj, Fokko M Nagengast, Yann Parc, Robin Phillips, Sue Clark, Maurizio Ponz de Leon, Laura Renkonen-Sinisalo, Julian Sampson, Astrid Stormorken, Sabine Tejpar, Huw Thomas and Juul Wijnen

Gut published online 14 Jan 2008;
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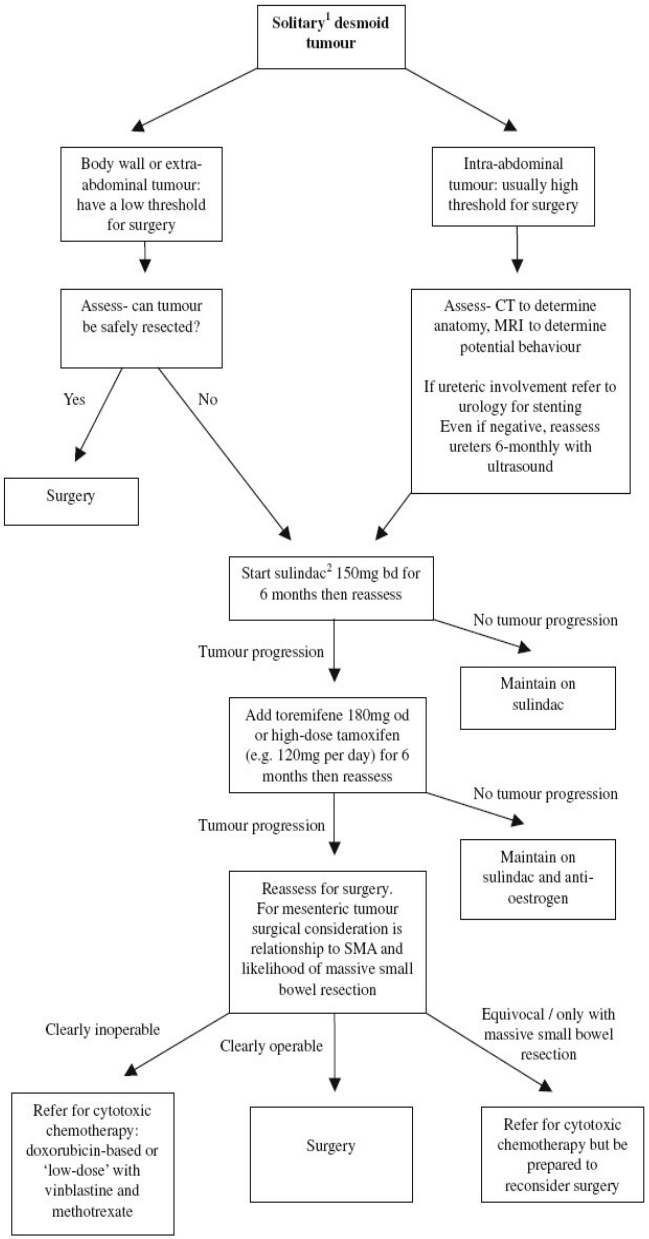
- CONCLUSION:

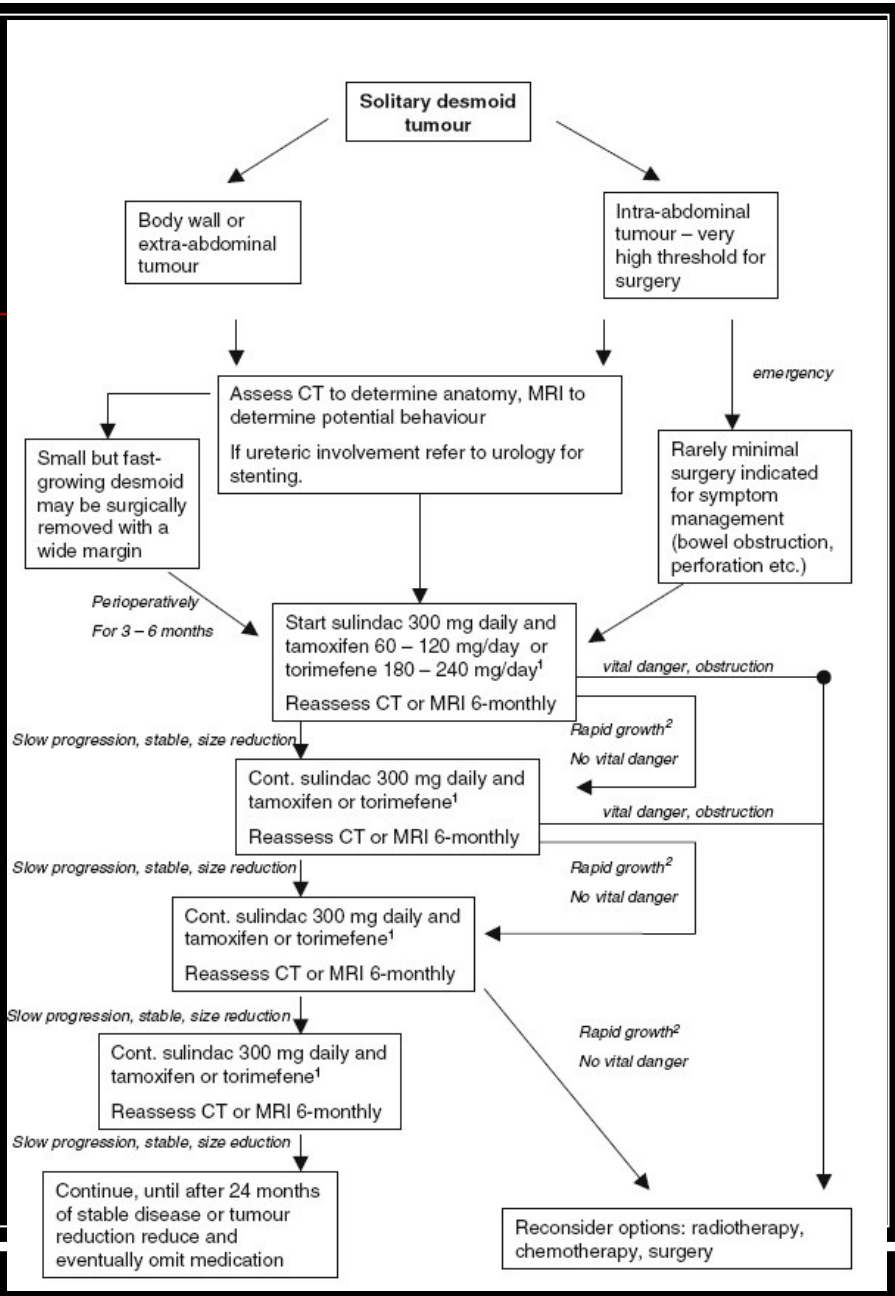
  *Non-randomised, non-controlled studies suggest that **sulindac in combination with tamoxifen is effective in FAP patients with intra-abdominal desmoids and desmoids located at the abdominal wall** (Category of evidence III). Also small non-controlled studies indicate that chemotherapy or radiotherapy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

Desmoids Dilemma

- The definition of desmoid disease has been used inconsistently.
- In some patients, desmoid tumors do not progress or are very slow growing and may not need therapy.
- There is no consistent, systematic way to evaluate the response to therapy.
- There is no single institution that will enroll enough patients to perform a randomized trial

No randomized clinical trials using these agents have been performed and their use in clinical practice is based on anecdotal experience only.


Solitary[1] desmoid tumour
Body wall or extra-abdominal tumour: have a low threshold for surgery
Intra-abdominal tumour: usually high threshold for surgery
Assess- can tumour be safely resected?
Assess- CT to determine anatomy, MRI to determine potential behaviour
If ureteric involvement refer to urology for stenting
Even if negative, reassess ureters 6-monthly with ultrasound
Yes
No
Surgery
Start sulindac[2] 150mg bd for 6 months then reassess
No tumour progression
Tumour progression
Maintain on sulindac
Add toremifene 180mg od or high-dose tamoxifen (e.g. 120mg per day) for 6 months then reassess
No tumour progression
Tumour progression
Maintain on sulindac and anti-oestrogen
Reassess for surgery. For mesenteric tumour surgical consideration is relationship to SMA and likelihood of massive small bowel resection
Clearly inoperable
Clearly operable
Equivocal / only with massive small bowel resection
Refer for cytotoxic chemotherapy: doxorubicin-based or 'low-dose' with vinblastine and methotrexate
Surgery
Refer for cytotoxic chemotherapy but be prepared to reconsider surgery


Solitary desmoid tumour
Body wall or extra-abdominal tumour
Intra-abdominal tumour – very high threshold for surgery
emergency
Assess CT to determine anatomy, MRI to determine potential behaviour
If ureteric involvement refer to urology for stenting.
Small but fast-growing desmoid may be surgically removed with a wide margin
Rarely minimal surgery indicated for symptom management (bowel obstruction, perforation etc.)
Perioperatively
For 3 – 6 months
Start sulindac 300 mg daily and tamoxifen 60 – 120 mg/day or torimefene 180 – 240 mg/day[1]
Reassess CT or MRI 6-monthly
vital danger, obstruction
Slow progression, stable, size reduction
Rapid growth[2]
No vital danger
Cont. sulindac 300 mg daily and tamoxifen or torimefene[1]
Reassess CT or MRI 6-monthly
vital danger, obstruction
Slow progression, stable, size reduction
Rapid growth[2]
No vital danger
Cont. sulindac 300 mg daily and tamoxifen or torimefene[1]
Reassess CT or MRI 6-monthly
Slow progression, stable, size reduction
Rapid growth[2]
No vital danger
Cont. sulindac 300 mg daily and tamoxifen or torimefene[1]
Reassess CT or MRI 6-monthly
Slow progression, stable, size eduction
Continue, until after 24 months of stable disease or tumour reduction reduce and eventually omit medication
Reconsider options: radiotherapy, chemotherapy, surgery

DESMOID TUMOURS: TO OPERATE OR NOT TO OPERATE

Rafi q H Abed, Adesegun Abudu, Simon Carter, Rob Grimer, Roger Tillman, Lee Jeys

The Royal Orthopaedic Hospital, Birmingham, United Kingdom

- **160 patients were studied at mean follow up of 49 months and mean age 36 years. Male to female ratio was 1:1**
- **147 patients had surgical treatment with very few having adjuvant radiotherapy. Overall recurrence rate was 41%.**
- **Recurrence was more common in females. Margins of resection had no influence on recurrence**
- **Our series experience is that recurrence is common after surgery even with radiotherapy. Surgical margins did not infl uence local recurrence. Observation alone appears to be the best policy for those with painless desmod tumours.**

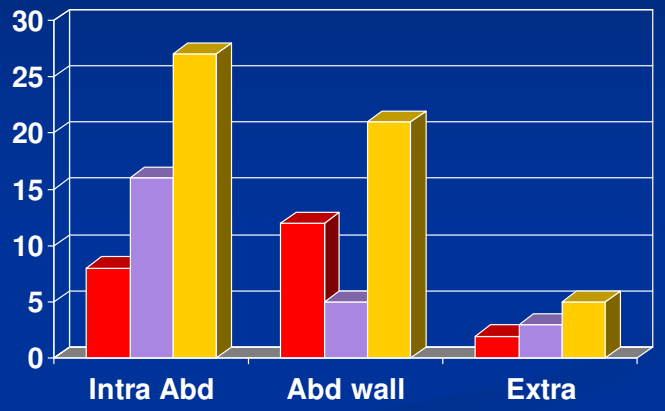
CTOS 14th Annual Meeting
November 13 — 15, 2008

Register Hereditary Colorectal Tumours
Desmoids

- INT Milan : n. 94 FAP pts

94 pts.

- **80 alive (22 DF)**
- **5 Desmoid Deaths (5%)**
- 3 CRC Deaths
- 2 Deaths O.C



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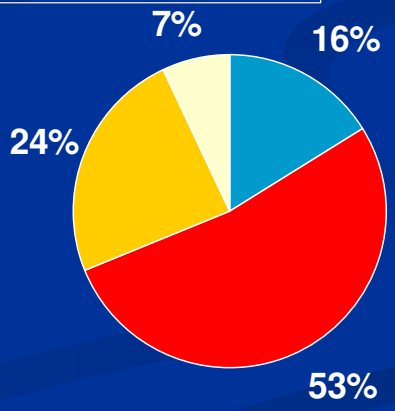

Surg. Surg/Drug Drug No ther.

DISEASES OF THE COLON & RECTUM

ORIGINAL CONTRIBUTION

A Desmoid Tumor-Staging System Separates Patients with Intra-Abdominal, Familial Adenomatous Polyposis-Associated Desmoid Disease by Behavior and Prognosis

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Table 1. Desmoid tumor staging system[8]

Stage	
I	Asymptomatic, <10 cm maximum diameter, and not growing
II	Mildly symptomatic, <10 cm maximum diameter, and not growing
III	Moderately symptomatic or bowel/ureteric obstruction, or 10 to 20 cm, or slowly growing
IV	Severely symptomatic, or >20 cm, or rapidly growing

Mildly symptomatic = sensation of mass, pain, but no restrictions; moderately symptomatic = sensation of mass, pain; restrictive but not hospitalized; severely symptomatic = sensation of mass, pain; restrictive and hospitalized.

CONCLUSION: Desmoid staging identifies tumors by prognosis and its use for designing prospective treatment studies is reasonable.

Table 4. Course of the intra-abdominal desmoid disease according to stage

Stage	*Disappeared/stable*	*Growing*	*Rapid Growth*
I	17 (81)	4 (19)	
II	28 (78)	5 (14)	
III	11 (42)	11 (42)	
IV	5 (28)	7 (39)	
P value	0.002*	38.806	

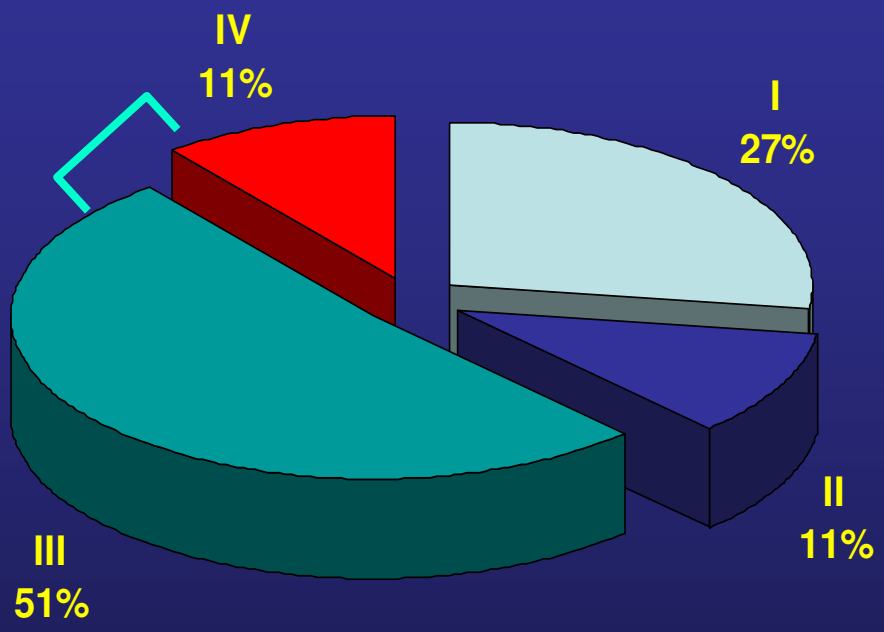
*Data are numbers with percentages in parentheses. • * Chi-squared.*

Table 6. Treatment of intra-abdominal desmoids according to stage (many patients had combinations of treatments)

Stage	*n*	*None*	*Medical*	*Surgery*	*Chemo*	*Radiation*
I	21	12	8	6	0	0
II	36	5	26	20	1	0
III	26	1	16	12	7	4
IV	18	0	15	13	5	3
Total	101	18	65	51	13	7

Intra abdominal Desmoid Staging

Stage III-IV : 5 Deaths (12%)



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Stage III: 11-20 cm slowly growing

Stage IV: > 20 cm fast growing

RHCT INT Milan

Cyclooxygenase-2 and Platelet-Derived Growth Factor Receptors as Potential Targets in Treating Aggressive Fibromatosis

Abstract

Purpose: To explore the molecular bases of potential new pharmacologic targets in aggressive fibromatosis (desmoid tumor).

Experimental Design: Tumor specimens from 14 patients surgically treated for aggressive fibromatosis (6 familial adenomatous polyposis and 8 sporadic cases), analyzed for adenomatous polyposis coli (APC) and *CTNNB1* (*β-catenin*) mutations, were further investigated for β-catenin, cyclooxygenase-2 (COX-2), platelet-derived growth factor (PDGF) receptor α (PDGFRA)/PDGF receptor β (PDGFRB), their cognate ligands (PDGFA and PDGFB), and KIT using a comprehensive immunohistochemical, biochemical, molecular, and cytogenetic approach.

Results: No *CTNNB1* (*β-catenin*) mutations were found in the familial adenomatous polyposis patients, but previously reported activating mutations were found in six of the eight sporadic patients. All of the cases carrying an altered WNT pathway showed nuclear and cytoplasmic immunoreactivity for β-catenin, whereas β-catenin expression was restricted to the cytoplasm in the sporadic patients lacking *CTNNB1* mutations. COX-2 protein and mRNA overexpression was detected in all 14 cases, together with the expression and phosphorylation of PDGFRA and PDGFRB, which in turn paralleled the presence of their cognate ligands. No *PDGFRB* mutations were found. The results are consistent with PDGFRA and PDGFRB activation sustained by an autocrine/paracrine loop.

Conclusions: Aggressive fibromatosis is characterized by WNT/oncogene pathway alterations triggering COX-2–mediated constitutive coactivation of PDGFRA and PDGFRB, and may therefore benefit from combined nonsteroidal anti-inflammatory drug + tyrosine kinase inhibitor treatment.

Signoroni S., Clin Cancer Res 2007

Hormonal Receptor analysis

All the cases were investigated for Androgen, Estrogen and Progesterone receptors expression by immunohistochemistry.

The results showed a NULL IMMUNOPHENOTYPE for **the three receptors in all cases**, in keeping with the literature

Table 5. Estrogen and progesterone receptor status in desmoid tumors.

Study	ER-α	ER-ß	PR
Fong et al., 1993	0/6	0/6	0/6
Serpell et al., 1999	0/24	-	0/24
Sorensen et al., 2002	0/72	0/72	-
Picariello et al., 2004	0/7	3/7 (42%)	-
Leithner et al., 2005	0/116	7/116 (6%)	0/116
Ishizuka et al., 2006	2/27 (7.4%)	2/27 (7.4%)	7/27 (25.9%)
Deyrup et al., 2006	0/40	40/40	-

Kotiligam D et al. Histol Histopathol 2008;23:117-126

CONCLUSIONS

The perfect is the enemy of the good.

Voltaire