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*Announcement - Call for Papers*

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## Reviews

Review

## Desmoid Tumors in Familial Adenomatous Polyposis

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**Abstract.** Familial adenomatous polyposis (FAP) is a cancer syndrome caused by a germline mutation in the adenomatous polyposis coli (APC) gene. It is characterized by the presence of hundreds of colonic polyps, which have a high tendency to undergo malignant transformation. Among associated lesions in FAP, desmoid tumors represent a common possible life-threatening condition that requires special attention. They are rare tumors occurring with a particularly high incidence in FAP, especially after surgery. In agreement with Knudson's 'two-hit' theory, the inactivation of the residual APC gene in FAP is a critical step in the development of both colorectal cancer and desmoids. Several lines of evidence show that germline mutations affect the functional domains of the APC gene that are responsible for interactions of the transcript with  $\beta$ -catenin, whereas somatic second mutations involve the downstream region of the gene. Hence, an understanding of the molecular pathways underlying desmoid progression in FAP could be important for research and a valid resource for the early prevention and tailored treatment of this disease. In this review, we provide an updated insight into desmoids in FAP syndrome, from molecular pathogenesis to the main issues in management, with special attention given to genetic and molecular features of these tumors.

Desmoid tumors (DTs) owe their name to the Greek word *desmos*, which refers to the tendon-like aspect of these tumors at histological evaluation (1). Desmoids are slowly proliferating, non-metastasizing tumors with a highly invasive capacity, which can be life-threatening in the case of intra-abdominal retroperitoneal localization. They are usually present in familial adenomatous polyposis (FAP) syndrome as extra- and intra-abdominal manifestations (2). Extra-abdominal DTs originate from muscle-aponeurotic structures, usually part of the abdominal wall, while intra-abdominal DTs develop in mesenteric folds or in retroperitoneal tissue in the form of 'aggressive fibromatosis', a precursor lesion of mesenteric or retroperitoneal DTs characterized by the thickening of the mesentery in whitish plaques originating from muscle-aponeurotic structures leading to invasively growing masses (3, 4). Histopathologically, DTs are poorly circumscribed masses that infiltrate the surrounding soft-tissue structures and are made of a myxoid stroma containing uniform, elongated, spindle cells with rare mitotic figures (5). No differences are found between extra- and intra-abdominal DTs, neither in their histology nor in their clinical behavior.

DTs are an increasing issue in patients affected by FAP, representing the first cause of death once preventative proctocolectomy has been performed (6). This is because despite their benign nature, they can be infiltrative and multifocal, causing significant morbidity and mortality (7).

Germline mutations in the adenomatous polyposis coli (APC) gene (OMIM 611731) are responsible for most cases of FAP and are the main predisposing factors for formation of desmoids. As in colorectal polyps of FAP, according to Knudson's 'two-hit' theory (8), germline and somatic inactivation of the APC gene are the fundamental step in the molecular pathways involved in the onset of

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desmoids (9). However, in the case of desmoids, other factors such as family history, abdominal surgery, female sex, pregnancy and estrogen therapy, have been associated with their development, indicating the likely contribution of other modifier genes in the pathogenesis of DTs (10). Given the genetically determined germline alterations in FAP, the knowledge of the biological factors determining the disease plays a remarkable role, since early molecular screening and prophylactic colectomy have increased patient survival over the last years (11, 12). In this review, we describe the key epidemiological, pathogenetic and clinical data related to desmoids in FAP, with a particular focus on genetic factors and genotype–phenotype correlations reported to date.

### Epidemiology

FAP is a hereditary cancer syndrome that is caused by the germline mutation in the *APC* gene, which is transmitted in an autosomally dominant manner with nearly 100% penetrance (13). Reported incidence ranges from 1:6,850 to 1:23,700 live births (14, 15), and affected patients develop hundreds to thousands of small adenomatous polyps in the colon (16). Polyps originate throughout the colon typically from the second decade of life and evolve into colorectal carcinoma in almost 100% of cases within 40 years of age, accounting for fewer than 1% of all colorectal cancers (16, 17).

The syndrome is characterized by an increased risk of extra-intestinal neoplasias: gastric and duodenal polyps, thyroid and pancreatic cancer, adrenal cortical adenoma, hepatoblastomas, CNS medulloblastoma or glioblastoma (Turcot syndrome) (17, 18). Other manifestations include congenital hypertrophy of the retinal pigment epithelium, supernumerary teeth, cutaneous lipomas and cysts (17, 19). DTs are a typical finding in FAP syndrome, where they affect 10-15% of patients (5). Differently from sporadic DTs, FAP-associated DTs are mainly intra-abdominal (80% of cases) or at the abdominal wall (10-15%), while extra-abdominal DTs account for about 5% of patients, with no differences in location from sporadic DTs (3, 20).

The incidence of DTs in the general population is 2-4 new patients per million, corresponding to 0.03% of all newly diagnosed cases and 3% of all soft-tissue neoplasms (5).

DTs can be diagnosed at all ages, but the peak incidence is after the third decade, with 80% of diagnoses made before 40 years of age (21). The incidence of DTs in FAP is 800- to 1,000-fold higher than in the general population (22): DTs occur in between 10% (23) and 15% of patients with FAP (6).

Nonetheless, their incidence is presumably underestimated, mostly because of their extremely pleomorphic presentation, starting from flat to massive solid lesions (24), so that occasional intraoperative observations suggest a possible incidence of 21-31% (25). Even though sporadic DTs occur

more frequently and earlier in females, in FAP-associated DTs, these differences are less significant (25). Evidence describes a correlation between estrogen levels and desmoids (especially in pregnant women), but estrogen-receptor positivity is variable in tumor samples (26-28). A family history of DTs arising in first-degree relatives is associated with a 25% risk of developing DTs (16). In particular, individuals with mutations of the *APC* gene beyond codon 1,444 are at a 12-fold higher risk of developing DTs (29); in some reports, *APC* mutations are associated with a 65% risk of developing mesenteric DTs (30). A peculiar risk factor for the development of DTs is surgical trauma: most DTs develop within 5 years after surgery (22, 23), in particular 68-83% DTs after abdominal operations, mostly within 24 months (11). Any possibly protective role of minimally invasive surgery is still to be determined (11).

### Biological Basis

The gene responsible for FAP is *APC*, which maps at the long arm of chromosome 5 (5q21) (31). The coding region of the *APC* gene consists of 2843 codons and is organized into 15 exons. The protein encoded by the *APC* gene has three domains: an oligomerization domain and an Armadillo region at the amino-terminal region; a central domain containing repeats of 15-20 amino acid sequences, responsible for binding to proteins of the *zonula adherens*; a carboxy-terminal region that includes a basic domain and a binding site for the end-binding-1 (EB1) and human disk Lg (hDlg) proteins (32) (Figure 1). The APC protein plays a key role in cell–cell adhesion, in the stabilization of the microtubule cytoskeleton, cell-cycle regulation, apoptosis and in the transduction of signals belonging to wingless-type mouse mammary tumor virus integration site family (WNT) pathway (32, 33). When the WNT pathway is activated,  $\beta$ -catenin accumulates in the cytoplasm and undergoes post-translational modifications, acquiring the ability to diffuse to the nucleus, where it interacts with the T-cell factor (TCF)/lymphoid enhancer-binding factor-1 (LEF1). This leads to the transcription of WNT target genes such as *c-MYC*, cyclin D1, E-cadherin or peroxisome proliferator-activated receptors, which are involved in cell development and proliferation, as well as carcinogenesis, cancer cell invasion and migration (32, 33). On the contrary, in the absence of WNT ligands, the APC protein is complexed with Axin, casein kinase 1 (CK1), and glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) and promotes the proteolytic degradation of  $\beta$ -catenin (Figure 2).

Molecular alterations in this proteolytic complex or in any other components of this pathway increase the cellular level of  $\beta$ -catenin and subsequent transcription of WNT target genes. In particular, *APC* mutations and the effect on WNT signaling are responsible for the genesis of colorectal cancer, either sporadic or in the context of FAP, through the alteration of intercellular adhesion and destabilization of the cytoskeleton (34).

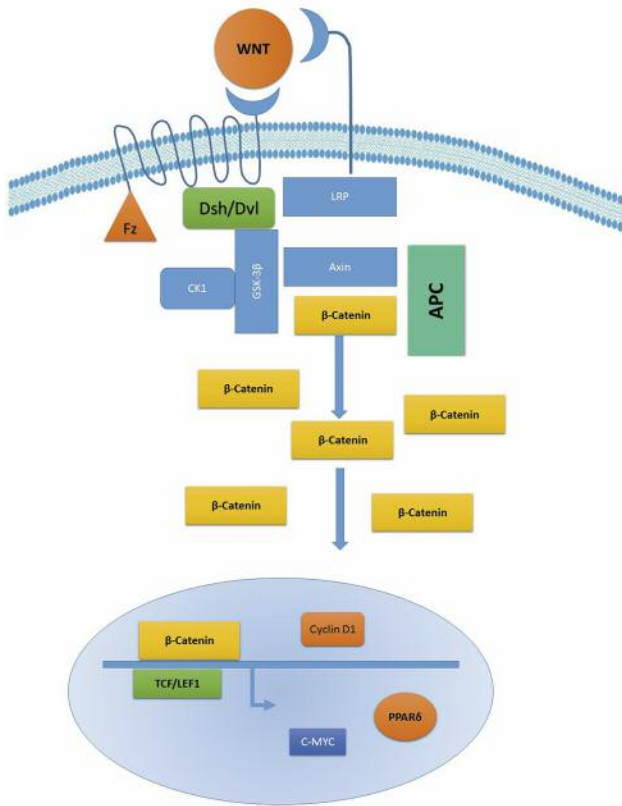


Figure 1. Schematic representation of the wingless-type (WNT) mouse mammary tumor virus integration site family signaling pathway. Adenomatous polyposis coli (APC) is a tumor-suppressor gene playing a key role in the WNT signaling pathway where it binds and controls the degradation of  $\beta$ -catenin within the cell cytoplasm. In the presence of a WNT signal, lipoprotein receptor-related protein (LRP) interacts with frizzled receptors (Fz), leading to activation of dishevelled complex (Dsh/Dvl) which blocks the APC-axin-casein kinase 1 (CK1)-glycogen synthase kinase 3 (GSK3 $\beta$ ) complex from phosphorylating  $\beta$ -catenin, resulting in an accumulation of stabilized cytosolic  $\beta$ -catenin. Stabilized  $\beta$ -catenin is able to enter the nucleus, where it interacts with T-cell factor (TCF)/lymphoid-enhancing factor-1 (LEF1), leading to the transcription of specific WNT target genes. PPAR $\delta$ : Peroxisome proliferator-activated receptor-delta. C-MYC: v-myc avian myelocytomatosis viral oncogene homolog.

### APC Gene Mutations and Genotype-Phenotype Correlations

A striking correlation exists between the position of the germline mutation of the APC gene and the phenotypic expression of FAP. It is known that mutations occurring in the 5' region of the gene (codons 97-157) determine an attenuated form of FAP, characterized by a smaller number of polyps (usually fewer than 100), and later onset of symptoms (35). Conversely, downstream mutations are

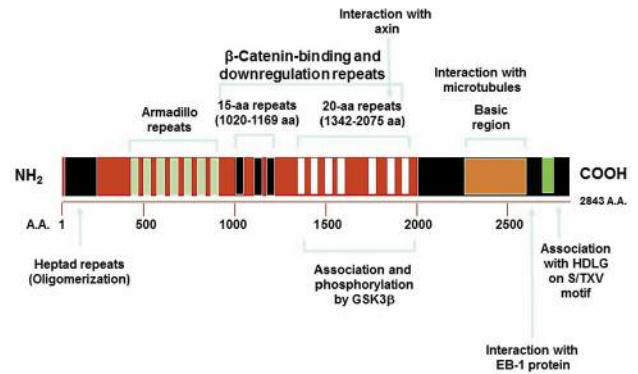


Figure 2. Schematic representation of main functional domain of adenomatous polyposis coli (APC) protein. EB-1: End binding protein 1; HDLG: human homolog disc large protein; GSK3 $\beta$ : glycogen synthase kinase 3 $\beta$ ; aa: amino acids.

responsible for a more aggressive phenotype (36, 37). Moreover, specific regions of the gene have been associated with extracolonic manifestations of FAP. More specifically, germline mutations falling between codons 1445 and 1578 have been strictly linked with desmoid onset (38).

However, the onset of extracolonic manifestations in patients with FAP are not only attributed to the position of the germline mutation. In particular, the presence of non-genetic risk factors indicates the likely contribution of other modifier genes influencing the occurrence of desmoids, irrespectively of the mutational status of APC (10).

Similarly to the molecular pathogenesis of colorectal adenomas in FAP, the critical step for the development of FAP-associated desmoids is the inactivation of the residual APC allele, according to Knudson's two-hit theory. In 1993, Miyaki *et al.* detected two different APC genetic alterations in each of eight DTs from patients with FAP, hypothesizing a mechanism of two-hit inactivation, with somatic mutations more frequently involving codons 1452-1470 and germline mutations mainly concentrated at codons 1309-1311 (13). In 1995, our group analyzed the structure of the APC gene both in normal and desmoid tissues from three unrelated patients with FAP. We confirmed the presence of somatic mutations in the allele that was not affected by the germline mutation. As the resulting protein was truncated near or slightly beyond codon 1444 in the investigated samples, as previously observed (12), we hypothesized that this event could induce dysregulation of the molecular pathways underlying the growth of fibroblastic cells (9). Lamlum *et al.* observed that DTs with germline APC mutations proximal to codon 1400 showed a 'second hit' somatic mutation distal to codon 1425 suggesting the presence of a 'desmoid gene mutation cluster' distal to codon 1425 in the APC gene (39). Our previous results on DTs are consistent with this

Table I. Results of mutational analysis carried out on germline (peripheral blood) and somatic line (desmoid tumor) cells from six patients with familial adenomatous polyposis (FAP). Mutational screening was performed in our laboratory using direct sequence analysis (ABI 3130 Genetic Analyzer, Life Technology).

Patient	Gender	Age, years		Mutation		
		At diagnosis of FAP	At desmoid resection	Germline	Somatic	Desmoid localization
#2	M	25	66	3927delAAAAGA (cod1309)	3927delAAAAGA (cod1309) 4593delT (cod1531)	Limited mesenteric fibrosis
#3	F	20	40	1629delT (cod543)	1629delT (cod543) 4313dup34bp (cod1438)	Abdominal wall desmoid
#4	F	33	46	1504G>T (Gly502Stop)	1504G>T (Gly502Stop) 4681delA (cod1561)	Abdominal wall desmoid
M	F	20	44	3927delAAAAGA (cod1309)	3927delAAAAGA (cod1309) 4367ins2bp (cod1456)	Abdominal wall desmoid
#8	M	23	65	3927delAAAAGA (cod1309)	3927delAAAAGA (cod1309) 4463delT (cod1488)	Mesenteric and retroperitoneal fibrosis
#15	F	22	38	2072delA (cod691)	2072delA (cod691) 4373del16bp (cod1458)	Mesenteric desmoid

M: Male, F: female, cod: codon.

hypothesis. Findings obtained by Albuquerque *et al.* support a revision of the classical double-hit theory with the introduction of the 'just-right' signaling model. In fact, analyzing 133 colorectal adenomas from six patients with FAP, they observed that in all cases, according to the type of germline mutation, somatic mutations were always selected in order to guarantee residual regulatory activity of APC, consisting of just one or two of the 20 amino acid repeats of the central domain, responsible for  $\beta$ -catenin binding and degradation repeats, in such a way to balance the nuclear levels of  $\beta$ -catenin and facilitate tumorigenesis (40). In 2009, Kohler *et al.* identified a new  $\beta$ -catenin-inhibitory domain (CID) domain located between the second (20R2) and the third repeat (20R3) of 20 amino acids of the APC gene. The authors observed that in DTs, when a germinal hit fell before position 1417, at the CID domain, the somatic mutation systematically promoted retention of the CID on the other allele. Conversely, germline mutations between codons 1429 and 1564, promoting the maintenance of CID domain, very often induced loss of the second allele, suggesting that in this case CID retention is tolerated and not counter-selected. The authors explained these different mechanisms of selective pressure assuming two alternative methods of partial regulation of the  $\beta$ -catenin level, based on the retention of repetition 20R3, which showed a strong affinity for  $\beta$ -catenin (41). Our data on DTs are also consistent with these findings, confirming that if the first germline mutation affects the domains involved in the regulation of  $\beta$ -catenin level, the second somatic mutation occurs in a downstream region of the APC gene (9, 42). Conversely, when the first germline mutation does not involve these domains, the somatic

mutation in desmoid occurs on the portion encoding for the  $\beta$ -catenin-binding site or on an upstream region (42) (Table I). More recent studies have also provided evidence of other regions of the APC gene within codons 543-713 and codons 232 and 554 related to a strong family history and a high tendency to develop DTs, irrespective of the germline APC mutation (43, 44).

### Other Molecular Markers

Data emerging from genomic analysis are proving that DTs are characterized by a high grade of genetic heterogeneity, which can arise from mutations affecting other genes. These genes are related to WNT/ $\beta$ -catenin signaling finally preventing the formation of the multiprotein complex composed of APC, axin,  $\beta$ -catenin and GSK3 $\beta$ .

A sequencing analysis performed on 42 sporadic DTs showed, for the first time, the presence of mutations in two codons of exon 3 (p.Thr41Ala, p.Ser45Phe, and p.Ser45Pro) of the  $\beta$ -catenin gene (*CTNNB1*) in 50% of cases (45). These mutations prevented phosphorylation of threonine and serine residues, promoting  $\beta$ -catenin accumulation at the nuclear level, with subsequent activation of the T-cell factor and transcription of target genes. Subsequent Sanger and whole-exome sequencing analyses, conducted on higher number of patients, revealed that mutations affecting *CTNNB1* are even more frequent (around 85-90% of cases), confirming that nuclear accumulation of  $\beta$ -catenin is a key event during the development of aggressive fibromatosis (46, 47).

Several clonal chromosomal aberrations have been documented in DTs. The main cytogenetic findings include

trisomy 8, trisomy and monosomy 20 loss of 6q, loss of 5q (harboring *APC* gene) and loss of the Y chromosome (48-51). Trisomy 8, in particular, is one of the most frequent events (about 30% of cases) and different studies have suggested that this kind of aberration may define a subgroup of patients with a high risk of recurrence (48, 50).

Further progress in the identification of potential non-invasive biomarkers for DTs derives from recent studies conducted on microRNAs, a class of small non-coding RNAs regulating gene expression at a post-transcriptional level, whose deregulation has been correlated to cancer development. A group of 15 differentially expressed microRNAs was identified in progressive and non-progressive DTs, suggesting the potential prognostic value of these molecules (52). In a subsequent study, Walton *et al.* compared microRNA levels in serum of two independent cohorts of patients with FAP with and without DTs. They found a number of differentially expressed microRNAs, with overexpression of miR 34a-5p being independently associated with the presence of desmoids in both cohorts. Interestingly, *CNN1B1* is predicted to be a direct target of miR-34a-5p by *in silico* analysis, while *LEF1*, a transcription factor of WNT signaling, is a validated target of this microRNA (53).

### Clinical Presentation

The presentation of DTs depends on the location, size and number of lesions. Extra-abdominal DTs originate from muscle-aponeurotic structures of the abdominal wall and less frequently from muscles of the extremities, the chest or the shoulder. The most typical presentation is a single painless mass, round or oval in shape, extremely hard and firm on palpation (1). Parietal infiltration can be responsible for insipid deformations; local invasion can induce pain, asthenia, paresthesia and neuropathy (7). The origin of DTs as aggressive fibromatosis determines intra-abdominal presentation of desmoids as a thickening of the mesenteric or retroperitoneal structures with hard whitish spots that can be asymptomatic for long periods (7). Frequently, the presence of these lesions is incidentally discovered in patients with FAP at the time of colectomy, influencing the scheduled surgical procedure. For example, the fashion of the ileal pouch can be precluded by the difficulty in approaching the intestinal loops as a consequence of their poor elasticity (1).

The tendency of aggressive fibromatosis to expand and infiltrate the intestinal loops or the ureter can cause small-bowel obstruction, ischemic lesions or hydronephrosis, with emergency conditions such as digestive hemorrhage, intestinal occlusion or perforation, fistula and life-threatening complications (3, 4, 54, 55). Potential morbidity can be relevant and DTs represent a major cause of death in patients with FAP (30).

The behavior of DTs is difficult to predict (56): some DTs have a prolonged stable phase (50%) or even a spontaneous resolution (10%); on the other hand, others grow aggressively up to 60 cm in size (10%) (11). Sudden enlargement of DTs is also possible usually due to liquefactive necrosis or abscess formation with peculiar complications in patients who have undergone restorative procto-colectomy with ileo-anal pouch anastomosis, who may have a deterioration of intestinal function and often require removal of the pouch and terminal ileostomy (1).

The introduction into clinical practice of prophylactic colectomy has reduced mortality from colorectal cancer in patients with FAP, and consequently intra-abdominal DTs have become the most common cause of death in up to 11% (57).

Diagnosis of DTs is based on magnetic resonance imaging, due to its superior definition of such lesions, their relation to surrounding tissues and noble structures, and technical issues for surgical planning. DTs are usually ovoid lobulated masses with irregular margins that do not respect fascial structures, without central necrosis. In T1-weighted imaging, they are isointense to the surrounding tissue whereas in T2-weighted sections they tend to be heterogeneously hyperintense. These lesions also exhibit hypercapture of the contrast medium (58, 59).

### Prophylactic Measures to Avoid the Onset of DTs

The risk of developing DTs in patients with FAP should be limited as much as possible by eliminating or reducing modifiable risk factors. Therefore, since the main precipitating factor for desmoids is surgical trauma, especially when the patient is young, prophylactic colectomy should be delayed if possible (1). In particular, this could be considered especially in patients belonging to a FAP family with evidence of DTs in more than 50% of the members, or with either an *APC* germline mutation beyond codon 1444 or with mutations of the 3' region of *APC*. Female gender must be considered as posing high risk, females have double the incidence for developing DTs compared to males (38, 60, 61). Either after surgery or in the presence of desmoid precursor lesions, it is rational to adopt measures that avoid the recurrence or the development of proper DTs. Considering the low toxicity of selective estrogen receptor modulators (SERM) (see below), their use has been proposed as a prophylactic measure. Controlled randomized studies are sparse, but in follow-up experience, none of the patients to whom raloxifene or tamoxifen were administered developed DTs (62, 63).

These medical therapies can be effective in controlling and reducing the growth of DTs, may have a role in preventing the development of DTs from desmoid precursors and can avoid the recurrence of DTs after surgical removal, and therefore they should be used as a first-line treatment in the majority of DTs.



## Surgical Treatment

Surgery is an important treatment for DTs in patients with FAP (NCCN 374-377). Yet some caution should be paid in performing surgery. On the one hand, the identification of DTs can influence surgical decisions, for example addressing patients to restorative proctocolectomy instead of an ileal-rectal anastomosis, because in the case of DT development, such a procedure would preclude the feasibility of a secondary pouch (29). At the same time, surgery has some limitations: contraindications to surgery, risk of recurrence and risk of *de novo* DTs. Among surgical contraindications, intra-abdominal DTs often involve small bowel, mesentery, and great vessels, so that mesenteric resection could lead to possible complications such as ischemia, fistula, hydronephrosis, and small bowel obstruction (2, 64). Small bowel obstruction in particular is a common complication, as a consequence of a wide removal of the small intestine to achieve a radical resection of mesenteric DTs, with reported incidence of between 27% and 38%, sometimes more (58%) (3, 64, 65).

The need for repeated surgery is significant, especially for intra-abdominal DTs, with rates between 75% and 85%, such that extensive resections are frequently required, even if charged with high mortality rates (3, 66). Surgical mortality rates range from 36-50% (3, 11, 54, 67, 68).

Finally, data show that surgery itself is a risk factor for desmoids: the rate of *de novo* lesions in surgically treated patients is 12.6% after restorative proctocolectomy, 13% after ileorectal anastomosis, and 13.5% after partial colectomy (69).

For all of these reasons, surgical treatment of DTs is still controversial and its benefits must be considered, including their consequences. Some authors consider surgery not advisable in relation to the possibility of a spontaneous tendency to dimensional stability or regression of DTs, their high recurrence rate even in the case of radical resection, and the risks of the surgical procedure itself (1). For example, removal of a huge mass from the abdominal wall requires a wider incision, creating a large muscle-aponeurotic defect that may require reconstruction with synthetic devices or myocutaneous flaps, in order to reduce – but not eliminate – the risk of complications such as incisional hernia or intestinal adhesions (1).

Therefore, in our experience, the treatment of intra-abdominal DTs is strictly recommended in cases in which complications occur such as small-bowel obstruction, bowel perforation, intestinal bleeding, hydronephrosis or severe deterioration of intestinal function after total colectomy (1). Long-term artificial nutrition or intestinal transplant can be necessary. It is therefore important to treat DTs when small, monitoring patients by imaging after total colectomy in order to obtain an early diagnosis. The first therapeutic approach

is medical and only patients in whom therapy is ineffective should be treated surgically, reducing in this manner the side-effects of surgery (1, 7, 54).

## Medical Treatment

Evidence for medical therapy in DTs has been proposed even if with few limited results, mainly related to the low numbers of patients and the pleomorphism in presentation and evolution of DTs (22, 54, 66). Non-steroidal anti-inflammatory drug (NSAID) therapy, in particular with sulindac, has been suggested for DTs in FAP (6, 70-72), with reports evidencing stable disease or regression in up to 29% of cases (3). The rationale for this treatment derived from the high expression of cyclo-oxygenase (COX)-1 and -2 in desmoid cells and their significant growth reduction in *in vitro* assays with anti-COX agents (73). Sulindac was the first anti-COX drug used at a daily dosage of 200-400 mg. The effect was obtained after few weeks of treatment (33, 72). More recently celecoxib, an inhibitor of COX2, has been used for its less severe gastro-intestinal side-effects compared to sulindac (74). Current data are still unsatisfactory; therefore, careful attention should be paid in the prescription of this therapy. (54).

DTs have proven responsiveness to anti-estrogens (75). The strict association of DTs with the endogenous hormonal environment or exogenous sex hormones is evidenced by their prevalence in females, their onset during reproductive age, their development following exposure to oral contraceptives, and the report of tumor regression during menopause. The action of estrogens is mediated by specific receptors (ER $\alpha$  and ER $\beta$ ) that are variably expressed in desmoid cells. SERMs have an action on these receptors that can be agonist or antagonist (76, 77). Tamoxifen or its chlorinated derivative tomerifen have been employed in several uncontrolled clinical studies. A positive effect was obtained in approximately 50% of the patients taking 30 mg/day (78). Higher doses of tamoxifen (120-200 mg/day) have been shown to have a greater positive effect (63-77%) (63, 79). The response to SERMs is gradual and slow, so that the result must be evaluated after at least 6-12 months. However, frequent side-effects include development of ovarian cysts and hypertrophy of endometrial epithelium. Prolonging the treatment for several years exposes females to the risk of endometrial carcinoma. Another SERM, raloxifene, has been employed with positive response (75%) and without the side-effects of tamoxifen (also if the treatment was prolonged for several years) since this drug has an anti-estrogenic effect on the endometrium (62). The eventual association of SERMs with sulindac, has had comforting results: in one report, therapy with both tamoxifen and NSAIDs induced stable disease in 46% and partial response in 30.7% (63).

Biological agents have been proposed to treat DTs: among these, imatinib is a multikinase inhibitor that has provided some significant results, with a progression-free survival of 66% at 12 months and objective tumor response in three out of 51 patients (80).

Traditional chemotherapy is a proven therapy for DTs, where different protocols have been proposed: doxorubicin and dacarbazine (81), methotrexate and vinblastine (82), doxorubicin and carboplatin or dacarbazine or ifosfamide (22).

Further ongoing studies are testing the efficacy of pazopanib (clinicaltrials.gov NCT01876082),  $\gamma$ -secretase inhibitor PF-03084014 (clinicaltrials.gov NCT01981551) and sirolimus (clinicaltrials.gov NCT01265030).

Radiotherapy may be a treatment option for DTs only in the case of extra-abdominal sites (extremities, head and neck, superficial trunk), but is not generally recommended for intra-abdominal DTs (54).

## Conclusions and Future Directions

Despite considerable advances in our knowledge, particularly with regard to the molecular mechanisms of onset and neoplastic progression, the therapeutic treatment of DTs remains controversial. The choice for the correct treatment is a main issue in patients with FAP, for whom some clinicians have even proposed a wait-and-see approach. Given the high rates of recurrence and morbidity of surgery for intra-abdominal DTs (66), and the chance that patients experience a prolonged stable phase or even spontaneous regression (83), it could be reasonable to address highly selected patients to follow-up (2, 84). With the aim of defining the indications for aggressive treatment, some proposals have been made about possible score systems that subdivide patients into risk groups according to parameters such as symptoms, maximum DT diameter, obstructive nature and evolution (56), or according to size, clinical presentation and lesion severity (56). However, all of these models lack a concrete predictive value, and are still far from real clinical applicability. General directions in patient management are: in the case of life-threatening complications, immediate referral to surgery; on the other hand, if timely diagnosed and with small dimensions, conservative treatment with eventual anti-oestrogen (and possibly sulindac-associated) therapy. In the case of progression, if lesions are at the abdominal wall, then surgery should be performed with margins if possible (66, 67, 85). In the case of progression of intra-abdominal lesions, then therapy should be chosen according to a balance between trauma of surgery and progression of disease, resorting to chemotherapy when possible, reserving surgery only for patients unfit for chemotherapy or for palliative or emergency conditions such as to relieve obstruction (54).

In conclusion, further efforts in different fields of research will be needed to develop new and alternative treatment strategies and improve the clinical management of patients suffering from DTs.

## Conflicts of Interest

The Authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in this article apart from those disclosed.

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