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Guidelines

Desmoid tumors located in the abdomen or associated with adenomatous polyposis: French intergroup clinical practice guidelines for diagnosis, treatment, and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, ACHBT, SFR)

Nicolas Benech[a,*], Sylvie Bonvalot[b], Armelle Dufresne[c], Afshin Gangi[d], Cécile Le Péchoux[e], Daniel Lopez-Trabada-Ataz[f], Alexandra Meurgey[g], Nayla Nicolas[h], Daniel Orbach[i], Nicolas Penel[j], Sébastien Salas[k], Jean-Christophe Saurin[a], Thomas Walter[l], Thierry Lecomte[m], Olivier Bouché[n], on behalf of the Thésaurus National de Cancérologie Digestive (TNCD), Société Nationale Française de Gastroentérologie (SNFGE), Fédération Francophone de Cancérologie Digestive (FFCD), Groupe Coopérateur multidisciplinaire en Oncologie (GERCOR), Fédération Nationale des Centres de Lutte Contre le Cancer (UNICANCER), Société Française de Chirurgie Digestive (SFCD), Société Française d'Endoscopie Digestive (SFED), Société Française de Radiothérapie Oncologique (SFRO), Association de Chirurgie Hépato-Bilio-Pancréatique et Transplantation (ACHBT), Société Française de Radiologie (SFR)

[a] *Service d'Hépato-Gastroentérologie, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon 69003, France*
[b] *Surgical Department, Institut Curie, Paris, France*
[c] *Département d'Oncologie Médicale, Léon Bérard Cancer Center, 28, rue Laennec, Lyon 69373 CEDEX 08, France*
[d] *Interventional Radiology, University Hospitals of Strasbourg, Strasbourg University, Strasbourg 67200, France*
[e] *Département d'Oncologie Radiothérapie, Gustave- Roussy Cancer Campus, 114, rue Edouard- Vaillant, Villejuif 94800, France*
[f] *Service d'Oncologie Médicale, Hôpital Saint-Antoine, 184, rue du Faubourg Saint-Antoine, Paris 75012, France*
[g] *Department of Biopathology, Léon Bérard Cancer Center, 28, rue Laennec, Lyon 69373 CEDEX 08, France*
[h] *Department of Radiology, Institut Curie, Paris, France*
[i] *SIREDO Oncology Center (Care, Innovation and Research for Children, Adolescents and Young Adults with Cancer), Institut Curie, Paris, France*
[j] *Centre Oscar Lambret and Lille University, Lille, France*
[k] *Oncology Unit, AP-HM, Aix-Marseille University, Marseille, France*
[l] *Service d'Oncologie, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon 69003, France*
[m] *Department of Hepatogastroenterology and Digestive Oncology, CHU de Tours, Tours, France*
[n] *Department of Digestive Oncology, CHU Reims, Reims, France*

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ABSTRACT

Introduction: Desmoid tumor (DT) of the abdomen is a challenging and rare disease. The level of evidence available to document their treatment is relatively low, however, recent publications of prospective studies have allowed to precise their management.
Methods: This document is a summary of the French intergroup guidelines realized by all French medical and surgical societies involved in the management of DT located in the abdomen or associated with adenomatous polyposis. Recommendations are graded in four categories (A, B, C and D), according to the level of evidence found in the literature until January 2021.
Results: When the diagnosis of DT is suspected a percutaneous biopsy should be performed when possible. A molecular analysis looking for pathogenic mutations of the *CTNNB1* and *APC* genes should be systematically performed. When a somatic pathogenic variant of the *APC* gene is present, an intestinal polyposis should be searched. Due to a high rate of spontaneous regression, non-complicated DT should first benefit from an active surveillance with MRI within 2 months after diagnosis to assess the dynamic

Abbreviations: DT, Desmoid tumor; FAP, Familial adenomatous polyposis.

* Corresponding author.
E-mail address: nicolas.benech@chu-lyon.fr (N. Benech).

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of tumor growth. The treatment decision must be discussed in an expert center, favoring the less toxic treatments which can include broad spectrum tyrosine kinase inhibitor or conventional chemotherapy (methotrexate-vinblastine). Surgery, outside the context of emergency, should only be considered for favorable location in an expert center.

Conclusion: French guidelines for DT management were elaborated to help offering the best personalized therapeutic strategy in daily clinical practice as the DT therapeutic landscape is complexifying. Each individual case must be discussed within a multidisciplinary expert team.

1. Introduction

1.1. Methods

Due to the rarity of desmoid tumors (DT) and the variability of its clinico-radiological presentation, the level of evidence available to document their management is relatively low. However, recent publications of prospective studies have qualitatively enriched the literature on this topic. A writing multidisciplinary committee originating from 9 medical societies (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, ACHBD, SFRO, SFR) and gathering experts from different specialties involved in the management of DT and familial adenomatous polyposis (digestive surgeons, pathologists, radiation oncologists, medical oncologists, gastroenterologists, and radiologists) was designated to review recent literature (Medline database queried with the keywords " *desmoid tumor* " or " *desmoid fibromatosis* " until 01/01/2021) and write a first document after interactive discussions. This initial document was then reviewed, modified, and validated by a review committee and the last version was finally validated by the steering committee of the Thesaurus National de Cancérologie Digestive (TNCD). The present article is a summary of the French guidelines published in July 2021 on the website of the SNFGE society www.tncd.org.

These recommendations have been graded into 4 categories (grade A–D) according to the GRADE system, with only expert opinion (agreement or not, grade D) when no scientific evidence was validated (Table 1) [1]. All the statements in the present article completely match the original full guidelines.

1.2. Definition

DT is defined histologically by a fibroblastic monomorphic proliferation of soft tissues, classified as intermediate tumors in the WHO 2020 classification, with local malignancy (infiltrating, invasive tumor), without metastatic potential [2]. All locations are possible: abdominal wall, limbs and girdles, head and neck, breast, pelvic, retro-peritoneal, and mesenteric tumors.

1.3. Epidemiology

DT are rare with around 400 cases / year in France, affecting mainly women (2/3 of DT), with an annual incidence estimated at 5–6 cases / million inhabitants according to NETSARC (French network of referral centers for the management of sarcomas and soft tissue tumors). The median age at diagnosis ranges from 35 to 44 years (range 6–90 years), with less than 2% of cases diagnosed before the age of 15 [3,4].

In this article we focused on the diagnosis, treatment, and follow-up of:

- DT of the abdominal wall (around 30% of cases),
- Intra-abdominal and mesenteric DT (around 20%),
- DT associated with familial adenomatous polyposis (FAP- 15 to 20% of DT).

1.4. Molecular characteristics

More than 90% of DT are sporadic and linked to a somatic gene activating variant in exon 3 of the *CTNNB1* gene (T41A, S45F, S45P, essentially), which is pathognomonic in a context of fibromesenchymal tumor.

The absence of a somatic pathogenic variant of the *CTNNB1* gene, particularly in case of intra-abdominal DT, justifies searching for a syndromic form linked to inactivating mutations or deletions of the tumor suppressor gene *APC*.

The pathogenic variants of the *CTNNB1* and *APC* genes are mutually exclusive. DT without *CTNNB1* or *APC mutation* are extremely rare and are linked to other mechanisms of deregulation of the signaling pathway [5–8]. These " *wild-type* " forms should be considered with caution and differential anatomopathological diagnoses must be excluded with re-evaluation in an expert center [6].

2. Diagnosis and pre-therapeutic explorations

2.1. Usual clinical forms and contexts of discovery

With a median size at diagnosis of 5.5 cm (range: 1–55 cm), DT are mostly revealed by a mass syndrome sometimes painful and

Table 1
Grade of recommendations according to the GRADE system [1].

Grade	Quality of evidence	Definition
A	High	Strongly recommended based on highly robust scientific evidence (e.g. several randomized controlled trials/meta-analysis) Further research is very unlikely to change our confidence in the estimate of effect
B	Moderate	Usually recommended based on scientific presumption (e.g. one randomized controlled trial) Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
C	Low	Option based on weak scientific evidence (e.g. one or several non-randomized trials) Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
D	Very low	Expert opinion (agreement or not) Any estimate of effect is very uncertain

inflammatory of soft tissue or the abdominal wall (rectus abdominis in particular) [3]. In cases of abdominal wall location, the association with pregnancy or postpartum (up to 18 months) is also common with painful outbreaks that may be punctuated by menstrual cycles requiring the elimination of endometriosis.

DT frequently develop following surgery, especially in patients with FAP, with the development of multiple lesions of the abdominal wall and mesentery within 18 months or more after a prophylactic colectomy [4,9].

In rare situations, the diagnosis is made after surgery in the context of an acute complication:

- Perforation / abscess in the digestive tract of a mesenteric mass.
- Digestive obstruction on mass syndrome.
- Ureterohydronephrosis of pelvic and mesenteric masses.

The course is unpredictable and characterized within 2 years after diagnosis by spontaneous regression (30–50%), local progression (∼ 20–30%) or stability in lesion size (∼ 30%), [10].

2.2. Imaging

Imaging plays an essential role in diagnosis, local extension assessment, preoperative planning, and follow-up of DT. Scalability and locoregional extension, potentially very aggressive, are the most important criteria to evaluate in order to orientate the treatment (surveillance, surgery or medical treatment) and require frequent radiological re-evaluation [11]. These tumors have no metastatic potential and therefore it is not necessary to do a remote extension assessment (https://www.nccn.org/professionals/physician_gls). Tumor measurements can be performed in 1, 2 or 3 dimensions even if RECIST 1.1 remains the reference for therapeutic trials. The change in density / signal can also be used to judge the degree of fibrosis [12].

2.2.1. Parietal abdominal locations

MRI can best assess the limits and degree of infiltration of the tumor into the muscles. The lesion develops along the muscle fascia which can give a "comet tail" appearance. Extension along the fascia is an important part of surgical planning. The MRI signal of the lesions is a function of the size of the collagen fibrosis contingent (in T2 and T1 hypo signal of the low level of its low water content and which is enhanced weakly and late after injection of contrast product) compared to the contingents of young fibrosis and myxoid extra-cellular matrix (in T2 hypersignal, T1 hypo / isosignal and enhancing homogeneously; [13]. Once the diagnosis has been established, injection of contrast medium is not necessary for radiological monitoring.

On ultrasound, when performed, the DT appear as more or less well-defined tissue masses within a muscle or along an aponeurosis, of heterogeneous echo structure with hypoechoic components and a posterior attenuation testifying to an intra-lesional fibrous component within an iso or hyperechoic stroma.

Although not specific, the identification of the fibrous component is a strong diagnostic argument in imaging, *a fortiori* in the event of a compatible clinical presentation, like after cesarean section or local trauma, or in the genetic context of FAP.

2.2.2. Intra-abdominal locations (retroperitoneal and mesenteric)

CT is the examination of choice for the diagnosis of complications (bowel obstruction and perforation, mesenteric ischemia). Intra-abdominal DT appear as more or less well-defined tissue lesions, with spiculated contours, heterogeneous enhancement, without necrotic contingent or intra-lesional calcification [14]. In the context of FAP, the appearance of a mesenteric or retro-peritoneal lesion exhibiting these characteristics is strongly suggestive of DT [15]. The important elements to be defined preoperatively are the size of the lesion, its relationship to the mesenteric vessels (especially the proximal branches, allowing the risk of postoperative short bowel to be assessed), its relationship to the retro-peritoneal vessels, and the degree of infiltration of the adjacent viscera (especially hail). The extent of mesenteric infiltration of the lesion is often underestimated by imaging.

2.2.3. Extra-abdominal locations associated with FAP

DT associated with FAP can be multifocal, intra and / or extra-abdominal. The extra-abdominal locations are mainly located at the level of the wall (rectus abdominis muscles, stoma opening). In children, adolescents and young adults, FAP can be revealed by the presence of a lumbar para-vertebral DT classically called "Gardner's fibroma". In these para-vertebral locations, infiltration of the adjacent bone (giving an appearance of bone *scalloping*) is a sign of progressive local aggressiveness. As for sporadic DT, the diagnostic workup as well as the radiological follow-up of DT in patients with FAP is mainly done by MRI (in the case of an associated intra-abdominal lesion or intestinal tumors), or by CT scan in the context of emergency. Post-operative DT occur mainly within 5 years after colectomy. In order to detect DT with life-threatening localization, systematic annual abdominal palpation should be performed. In the case of personal or family history of DT, an abdominal MRI or CT-scan should be performed within 1 to 3 years after colectomy and then at 5 to 10 years intervals or in the case of suggestive abdominal symptoms [16].

2.3. Pathological diagnosis

In accordance with the guidelines of the European Society of Medical Oncology (ESMO) and the European consensus, the standard is to proceed when possible (tumor size, location) to a percutaneous biopsy with coaxial needles of sufficient size (14 or 16 G), because the diagnosis cannot be made on cytology but requires a histological examination [17,10]. A molecular analysis in search of a pathogenic variant of the β-catenin (*CTNNB1*) or *APC* gene must be carried out systematically [6]. Pathological review within a sarcoma pathology proofreading network when available is also recommended systematically (for example in France: https://netsarc.sarcomabcb.org).

In a patient with polyposis and most often with previous subtotal colectomy or a colo-proctectomy, the appearance of a mesenteric mass, possibly at the level of the ileal pouch *meso*, is very suggestive of DT [18]. In this situation, a biopsy should only be performed in the case of a strong suspicion of a differential diagnosis such as lymphoma or carcinoma. In particular, surgical biopsy should be strictly limited in this situation as it can increase the risk of DT progression. If it is large enough, it is necessary to perform a percutaneous biopsy, which approach is discussed between the radiologist and the surgeon. The endoscopic route (with an endoscopic ultrasound) is discussed depending on the location when the percutaneous route is not possible. It has the drawback of bringing only little material, which limits the possibilities of diagnosis and molecular biology. If a percutaneous / endoscopic biopsy is not possible, either a surgical biopsy, by laparoscopic route if possible, or monitoring by imaging (MRI or PET-scan - for differential diagnosis) sholud be considered in this context. A disadvantage of surgical biopsy is that it can lead to an evolutionary flare, and must therefore be limited to situations where the differential diagnosis with possible lymphoma or carcinoma cannot be clarified by imaging and markers. An immediate diagnostic resection is not recommended because of its functionally detrimental nature in these patients with previous heavy surgery.

In sporadic cases, the parietal, retro-peritoneal or mesenteric mass is revealed by non-specific digestive signs or a mechanical complication. Outside of an emergency context, the performance of

a percutaneous biopsy, which is the standard when it is anatomically possible (tumor size, location), must be discussed in a multidisciplinary team. If percutaneous or endoscopic biopsy is not possible, and the lesion is immediately amenable to surgery without extensive digestive damage, and a lymphoma has been ruled out, a curative resection can be discussed avoiding any break-in of the tumor that would be detrimental in the event of sarcoma. If the tumor is unresectable and the percutaneous biopsy not feasible, we refer to a surgical biopsy, if possible, under laparoscopy, in order to determine the histology and to guide a possible medical treatment. The extemporaneous examination is a source of error because it does not allow immunohistochemical or molecular biology analysis. It is therefore important to avoid making any potentially crippling decision on the basis of this examination [19] .

2.4. When and how a genetic cause or a familial polyposis should be suspected?

In the context of adenomatous polyposis, only patients carrying a pathogenic variant of the *APC* gene are likely to develop DT. *Polyposes* linked to the *MUTYH* gene are not affected by this phenotypic manifestation. In patients with a constitutional mutation of the *APC* gene, the cumulative risk of developing DT is approximately 10%, with a sex ratio close to 1, [20]. The contributing factors are clearly a history of abdominal surgery (65–85% of series), and a spectrum of pathogenic variants of the *APC* gene downstream of codon 1440 of exon 15 (familial forms of DT, genotype-phenotype correlation; [21]. Two retrospective studies suggested a statistical link between the development of DT and a previous heavier surgery such as colo-proctectomy with ileo-anal anastomosis versus a subtotal colectomy with ileo-rectal anastomosis [22,23].

In the situation of finding DT without a family or personal history of colorectal adenomatous polyposis, the data are much less substantiated. The largest retrospective study was published in 2019, from a danish cohort. It studied 626 patients with DT, with a diagnosis of polyps in 26 patients (4.1%) [24]. In this study, 161 patients had performed a colonoscopy in the absence of personal or family history of polyposis, among whom 6 patients (4%) were diagnosed with an adenomatous polyposis. The discovery of a polyposis was statistically associated with age (<40 years), an abdominal or retro-peritoneal location of the DT, the presence of multiple stumors and with a family history of polyposis. Two older studies published in 1986 and 2016 report a frequency of 1.3% (1/75, rectoscopy or radiological examination of the colon) to 4.7% (3/63, rectoscopy and genetic test) of polyposes [25,26]. The latter study also found a higher frequency of young cases (<40 years), abdominal tumors and multiple tumors in the familial polyposis group, with a sex ratio close to 1, unlike sporadic tumors.

The molecular biology of tumors can be of help to identify a genetic background as a mutation of *CTNBB1* / β-catenin seems to exclude the presence of associated FAP (82 cases, 0 polyposis). This exclusive nature of *CTNNB1* mutation is reported in another pediatric series of 44 DT (29 *CTNNB1* mutated cases, 0 polyposis). We can therefore propose a decisional algorithm presented in Fig. 1 for the identification of FAP patients during the initial management of DT [27].

2.5. Recommendations for pre-therapeutic explorations

- MRI is the standard imaging modality for desmoid tumors (recommendation: grade D, experts' agreement)
- The abdomino-pelvic CT-scan is the examination of choice in the event of a surgical complication. It can also be used to allow better visualization of vascular relationships, especially for intra-abdominal locations (recommendation: grade D, expert's agreement).
- The extent of mesenteric infiltration of the lesion is often underestimated by imaging
- Ultrasound of the soft parts for patient monitoring is an alternative in the context of pregnancy or for small parietal lesions (recommendation: grade D, experts' agreement).
- Indications of biopsy:
- A percutaneous microbiopsy (no cytology) should be performed, when possible (14 or 16 G needle), (recommendation: grade D, expert's opinion).
- A molecular analysis seeking for a somatic pathogenic variant of the *CTNNB1* gene should be carried out systematically as a first-line evaluation (recommendation: grade D, experts' agreement).
- If this search is negative, it is necessary to search for a constitutional pathogenic variant of the *APC* gene (recommendation: grade D, experts' agreement).
- A desmoid tumor without an *APC* / *CTNNB1* mutation should suggest a differential tumor diagnosis (recommendation: grade D, experts' agreement).
- Proofreading in an expert center for sarcoma pathology is systematically recommended (recommendation: grade D, experts' opinion).
- The surgical biopsy is likely to induce tumor progression and should be limited to situations where the differential diagnosis with possible lymphoma or carcinoma cannot be specified (recommendation: grade D, experts' agreement).
- In a context of FAP linked to the proven *APC* gene, if a highly suggestive imaging is carried out in an expert center, it is acceptable not to perform a biopsy of the initial tumor, in particular if it may be potentially morbid (recommendation: grade D, experts' opinion).
- Indication of specific exploration to search for familial adenomatous polyposis:
- It is recommended to seek for FAP associated with a DT in the following cases (recommendation: grade C):
  - Familial history of adenomatous polyposis
  - Male
  - Age < 40 years
  - Presence of clinical signs suggestive of Gardner syndrome: osteoma, epidermal skin cysts, anomaly on the fundus, etc.
  - DT of multiples locations
  - Absence of somatic pathogenic variant of *CTNNB1* with histological confirmation of the diagnosis
  - Association with a somatic pathogenic variant of the *APC* gene.

Diagnostic strategy for FAP identification after the discovery of a DT is summarized in Fig. 1.

3. Treatments

3.1. Rationale for active surveillance in " first line "

Active surveillance of DT was first offered to patients who presented limbs recurrences with no possibility of conservative surgery [28]. Disease stabilized in more than half of patients making possible to avoid a mutilating surgery. Initial surveillance was then proposed to patients with a resectable DT [29–32] and it was also showed that more than half of the tumors stabilized or regressed spontaneously. After three years, the risk of evolution is very low, apart from an additional external parameter such as pregnancy [30]. This strategy has been evaluated in different locations, including intra-abdominal [33] with confirmation of these results in increasingly large retrospective studies, having more hindsight [3]. More recently, a randomized phase III clinical trial comparing sorafenib to placebo in selected patients with

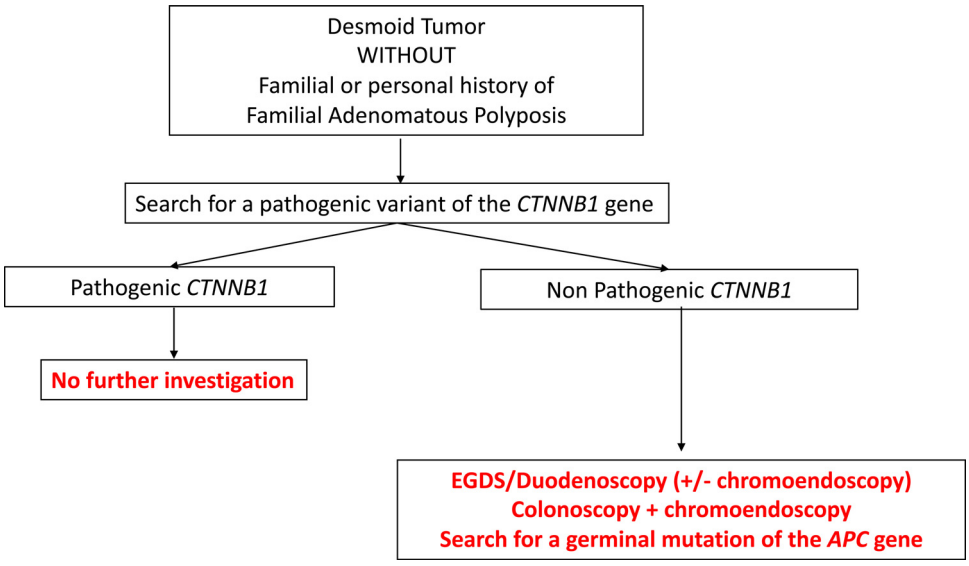

Fig. 1. Diagnostic strategy for familial adenomatous polyposis identification after the discovery of a desmoid tumor. EGDS: Esophagogastroduodenoscopy.

a progressive DT (i.e. recurrence or evolution confirmed by subsequent examinations) showed that even in the placebo group, the two thirds of tumors stabilized or exhibited regression, of which 20% were significant according to RECIST1.1 (reduction of at least 30% in the sum of the diameters of the target lesions; [34]). The ESMO guidelines and the European consensus now recommend to start with active surveillance or medical therapy alone in advanced DT, depending on the symptomatology [17,10].

3.2. Surgery, indications, modalities

3.2.1. Indications and modalities of emergency surgery

Patients with surgical complication at diagnosis need to be operated on. It may be occlusion, digestive perforation, or mesenteric ischemia. If the resection of the tumor is not mutilating and requires only limited digestive resection, the treatment of the complication is done at the same time as the excision of the tumor. If the removal of the tumor would involve major digestive sacrifices, it is preferable to limit surgical treatment to the complication and to leave the tumor in place, with systematic biopsy for histological confirmation. Medical treatment will be discussed postoperatively. Patients who present a pelvic abscess or fistulizations occurring in the context of an already operated polyposes will be preferentially treated by percutaneous drainage.

In the absence of a mechanical complication, a large initial size at diagnosis or a life-threatening location (such as cervical, mediastinal, intra-abdominal and mesenteric locations) are not by themselves an immediate operative indication. Indeed, after the diagnosis provided by the biopsy, spontaneous regressions can be observed regardless of the starting size and location. However, in life-threatening locations, in particular in mesenteric locations, or when symptoms are present, a medical treatment should be discussed in an expert center [17,10,35]. Surgery ultimately has limited indication in these unfavorable situations with a large tumor volume, because both mutilating and exposing to a high risk of recurrence and complications. In addition, imaging underestimates the extension in the mesentery location and surgery is often macroscopically incomplete in these locations.

Recurrences are as likely to regress as primary tumors and they are neither an indication for immediate surgery [30,34]. Indeed, in nearly 50% of early relapse after surgery, the lesion stabilizes, or even regresses spontaneously after an initially rapid growth. Moreover, surgery has an ambiguous role on macro or microscopic remnants (which are not different from keloids on a microscopic level), because induced healing tissue factors constitute also growth factors for DT.

3.2.2. Indications and modalities of deferred surgery (" second line ")

The main potential indications for surgery are the progression or appearance of symptoms despite appropriate medical treatment. The first step in the event of progression is to verify that it is indeed a DT, in particular for retro-peritoneal locations. The molecular analysis must have been carried out with a search for the *CTNNB1* mutation of the β-catenin or *APC* gene [10]. With current sequencing techniques, non-mutated DT are very rare [6]. Cases of a diagnosis of " progressive DT " invalidated after histological review in an expert center and molecular biology analysis are frequent. This rereading must be therefore systematic, particularly if a medical treatment is planned [3].

3.2.3. When discussing surgery?

The indication for local treatment will depend on the initial size, progression kinetics, location, symptoms, and age of the patient. It is obvious that for an initial lesion of small size (2 to 3 cm) in a favorable location (abdominal wall for example), a doubling of the size of the tumor can be tolerated knowing that a secondarily slowing down, a stabilization or even a regression can occur. However, the same initial size in an unfavorable location, close to major vasculo-nervous axes, will encourage early treatment. The evolution curve is the central element of the decision. Patients should therefore be monitored closely after diagnosis, as the evolution profile must be categorized at this time. The monitoring can be then spaced in time if the tumor is indolent or stabilizes. Thus, a first check-up is recommended one or two months after the initial imaging, then three months later if the disease is stable and then six months later (Fig. 2). Medical treatment is discussed before local invasive treatment, as they can stabilize the tumor and avoid sequelae [10]. A last, the decision to operate must be taken in a multidisciplinary discussion but not too late after considering the developmental curve of DT.

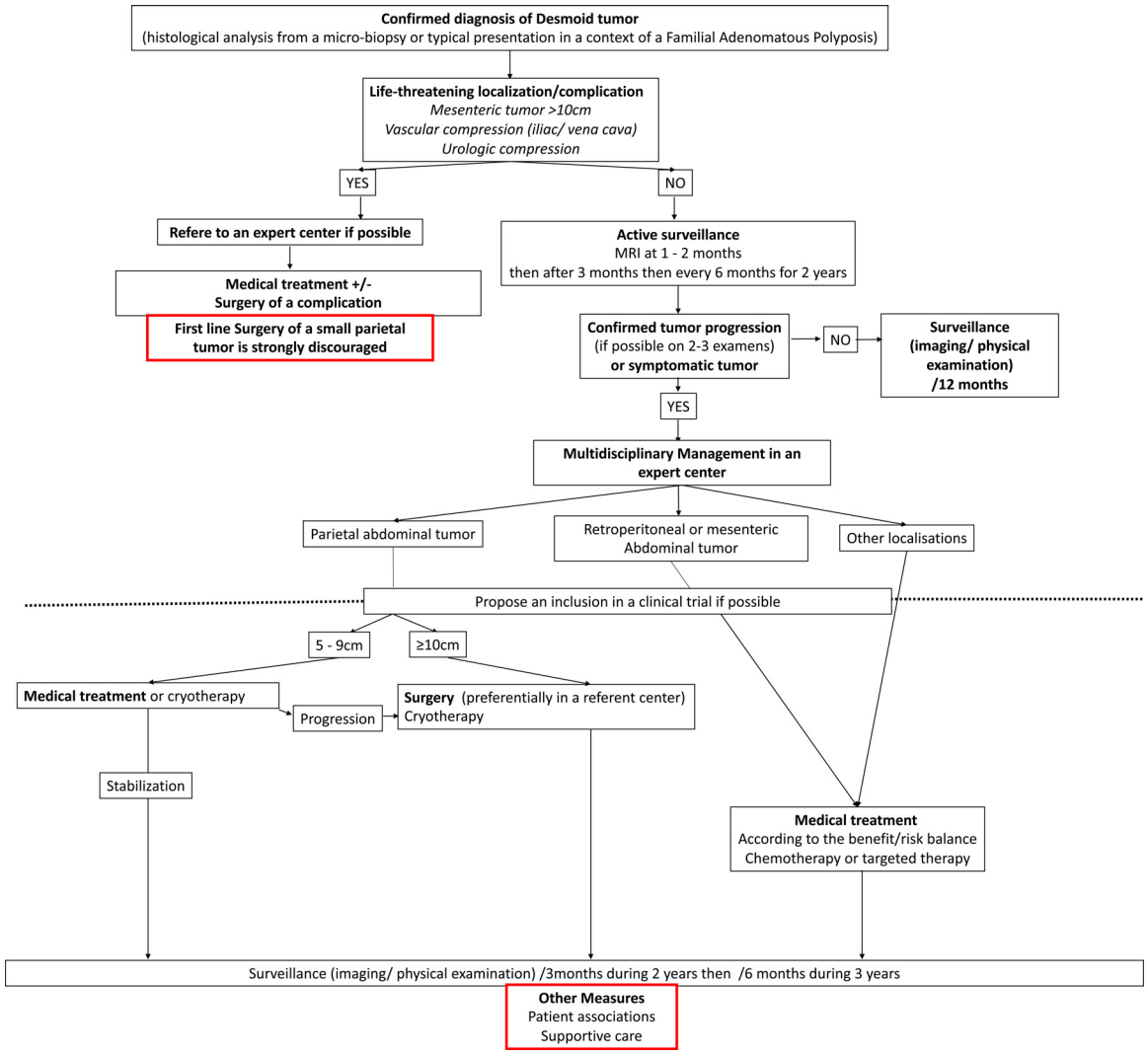

Fig. 2. Management strategy for desmoid tumors located in the abdomen and/or associated with familial adenomatous polyposis.

3.2.4. What are the best indications for surgery in case of progression?

DT of the abdominal wall represents a very good indication if the tumor progresses significantly despite medical treatment [29], in particular when the tumor is ≥ 10 cm. If the size of the lesion is between 5 and 10 cm and it remains progressive between two images, we can discuss either cryotherapy or medical treatment. If the progression continues, a parietectomy-type surgery can be proposed. Despite mutilation brought by an abdominal parietectomy in a young woman prone to be pregnant, a complete surgery is easily accessible and remains well supported. In particular if the reconstruction is of good quality, future pregnancies are possible even with an abdominal plate. Overall, between 15 and 20% of patients with DT of the abdominal wall end up undergoing surgery [36]. As the tumor most often infiltrates the muscle in its entire thickness, it is usually a parietectomy removing the affected muscle with replacement of the wall by a plate fixed behind the remaining muscles. On the microscopic level, the impact of the margins has only been studied on old series which mixed indolent and evolving DT. Moreover, the poorly limited nature of these tumors and the limited number of sections do not always allow to be retrospectively precise on the completeness of the resection. By mixing different evolutionary forms with more or less precise anatomopathological analyzes studies differ on the impact of these margins on the risk of recurrence. As regulated surgery is now aimed at progressive tumors, it is possible that having negative margins is favorable, these being found as a prognostic factor in a multicenter study [37].

Regarding lateral retro-peritoneal locations, which frequently involve the iliac vessels and the ureter, surgery should only be considered when it can be macroscopically complete and as a second-line treatment after induction medical treatment. Radiation therapy is an alternative to discuss when possible and considering the patient's age (see below; [38]).

Regarding mesenteric locations, potentially responsible for ischemia and occlusion, surgery is discussed if the medical treatment is ineffective, focusing on situations where complete excision can be performed without major functional damage. Digestive segmental resections leaving macroscopic remnants in place should only be performed on a case-by-case basis after discussion in a specialized center.

3.2.5. Recommendations regarding the use of surgery for desmoid tumors

- Surgery is not indicated in 1 st line other than in the situation of a mechanical complication (recommendation: grade A).
- In the event of a complication and a tumor that is difficult to resect or with a risk of mutilating surgery, the tumor must be

left in place and the surgical treatment limited to the complication (recommendation: grade A).
- Non-emergency surgery should be considered for favorable location (mainly parietal) in case of uncontrolled progression. Apart from these locations, the indication must be discussed in an expert center (recommendation: grade A).

3.3. Systemic treatments

For many years, multiple systemic treatments have been used with low levels of evidence based on case descriptions, retrospective series and non-randomized phase II trials. These treatments are listed here:

- Anti-inflammatory drugs including sulindac, celecoxib and meloxicam [39,40]
- Tamoxifen, LHRH agonists, anti-aromatase
- Imatinib
- Chemotherapy: doxorubicin, pegylated doxorubicin, doxorubicin-dacarbazine combination [41,10].

Two randomized trials have been published recently and allow a better evaluation of the benefit / risk of both metronomic chemotherapy association with methotrexate and vinblastine and tyrosine kinase inhibitors (sorafenib and pazopanib).

3.3.1. Cytotoxic chemotherapy

Vinca-alkaloid-based protocols are widely used for the treatment of DT, particularly in intravenous administration. In an uncontrolled phase II trial ($n = 30$), the methotrexate-vinblastine combination administered once a week for 12–18 months showed an objective response rate of 40% and stability of 60%. After a median follow-up of 75 months, the 10-year progression-free survival was of 67%, [42]. Long-term tolerance and toxicity were found acceptable. A phase II trial ($n = 38$) of the combination of methotrexate (30 mg / m²) - vinblastine (6 mg / m²) every 2 weeks in patients with progressive DT showed a progression-free survival at 5 years of 80%. The objective response rate was 51%, the rate of partial response and stable disease were 43% and 5%, respectively. The median time to obtain an objective response was 10 months. This treatment reduced the pain due to DT in 76% of cases and improved functional status in 33% of cases. Only 4 patients discontinued treatment for toxicity [43]. Mir et al. also reported a retrospective series of 90 patients treated with oral vinorelbine alone once a week (60–90 mg / m² or a fixed dose of 90 mg). Patients were heavily pretreated, with a median number of systemic treatments of 2 (0–5), and 78% of them were receiving opioids for pain management. The median duration of treatment was 6 months. The 6- and 12-month progression-free survival rates were 89% and 78%, respectively. The partial response rate was 29%, the stability rate was 57%, and the disease progression rate was 14% [44]. Low-dose vinca-alkaloid protocols can therefore be considered as an effective treatment, benefiting from a favorable evaluation of long-term toxicity, which is fundamental for these benign tumors, treated in young subjects.

Although less evaluated, anthracycline-based chemotherapy is a possible alternative with, however a significant toxicity.

3.3.2. " Targeted " therapy

Two randomized trials have evaluated the benefit of broad-spectrum tyrosine kinase inhibitors. The 1st trial is a non-comparative randomized phase II trial, evaluating on one hand pazopanib and on the other hand a methotrexate-vinblastine combination (Table 2; [45]). This study shows a certain activity of pazopanib which should be formally evaluated in a comparative test. The 2nd trial is a Phase 3 superiority comparing the effectiveness of sorafenib at the dose of 400 mg / day against placebo with 87 patients included. There was a significant advantage for sorafenib. However, it should be noted that in patients with active, threatening or painful tumors, placebo was associated with a tumor reduction in 20% of cases (against 33% for sorafenib). This trial could change practices, but there is no information on long-term toxicity and the safety reported was also moderate with 20% of patients discontinuing treatment for toxicity and a grade 3 toxicity rate of 20%. Currently, no drug has got specific reglementary authorization for this indication.

The Desmoid Working Group recommends the use in 1st place of the least toxic treatment [46]. The maximum duration of treatment is not defined for targeted therapies.

3.4. Recommendations regarding systematic treatment in desmoid tumors

Recommendations:

- There is no established therapeutic standard for progressive desmoid tumors requiring systemic treatment.
- The treatment decision must be discussed in an expert center, favoring the less toxic treatment (recommendation: grade B).

Options:

- The efficacy and safety profile (especially in the long term) of the methotrexate-vinblastine combination is well established (recommendation: grade B).
- The use of a broad-spectrum tyrosine kinase inhibitor (pazopanib or sorafenib) is an option, but their tolerance may be difficult and their long-term toxicity is not well established (recommendation: grade B).
- The use of NSAIDs can be considered for analgesic purposes (recommendation: grade B).

3.5. Local treatments

3.5.1. Radiotherapy

Radiotherapy has few indications in abdominal DT. While its use has been validated in a phase 2 study, it mainly included peripheral locations and barely more than 10% abdominal DT [38]. It can be discussed occasionally in an expert center for recurrent DT with parietal abdominal locations refractory to other validated medical treatments and / or cryotherapy- (cf . Below) and parietectomy. The other potential indication to be discussed in an expert center concern, more rarely, unresectable progressive retroperitoneal or intra-peritoneal DT despite medical treatment, for wich volume and location allow to technically consider irradiation. Protocol of irradiation has to be defined on a case-by-case basis. In all cases, this exceptional indication must be validated in an expert center, in the presence of a radiation oncologist .

3.5.2. Cryotherapy

Cryotherapy is a technique of cold thermal destruction (-40 °C) of tumors. In the case of DT, it is performed under imaging control (CT or MRI). It is offered to patients with DT accessible to a percutaneous treatment who are refractory to medical treatment (at least two lines of treatment) with tumor and / or symptomatic progression. A first prospective non-randomized study (CRYODESMO-01) has evaluated cryotherapy in the treatment of progressive DT despite medical treatment (neck, limbs, thorax, and abdominal wall locations). In this work, 86% (36/42) of tumors did not progress at 12 months and the patients had a significant improvement in functional status and pain control after treatment [47]. The place of cryotherapy in the therapeutic strategy will also be evaluated as part of a future clinical trial (CRYODESMO-02) which will take place in France and prospectively and randomly

Table 2
Summary of randomized controlled trials evaluating drug treatments in desmoid tumors. CI: Confidence Interval; HR: Hazard Ratio; PFS: progression-free survival.

Trial N	Gounder et al. 84	Toulmonde et al. 72
Population	Patients with a progressing tumor: - Increase in tumor size (≥ 10% in 6 weeks) - Unresectable tumor	Patients with a growing tumor ≥ 20% (according to RECIST 1.1) over the last 6 months
Intervention	Sorafenib (400 mg / d) until intolerance or progression	Pazopanib (800 mg / d) up to intolerance or progression or up to 12 months.
Comparator	*Matched placebo*	Methotrexate / Vinblastine IV for 52 weeks
Design	Phase 3 superiority trial (2: 1 ratio) with possible progressive crossover	Non-comparative phase 2 trial (2: 1 ratio) with cross-over
Primary endpoint	Lack of progression (PFS-RECIST 1.1 non-centralized assessment)	No progression at 6 months (PFS-RECIST 1.1, centralized assessment for the pazopanib arm)
Statistical hypothesis	1-sided $\alpha = 2.5\%$; $\beta = 10\%$; PFS (placebo) = 6 months; PFS (sorafenib) = 15 months; HR = 0.4	Pazopanib arm: 1-sided $\alpha = 5\%$, $\beta = 20\%$, H1 = 80%, H0 = 60%
Results on the primary endpoint	Median PFS not achieved in the sorafenib arm HR for progression or death in the sorafenib arm = 0.13; 95% CI: 0.05–0.31; $P < 0.001$)	6-month PFS: - pazopanib: 83.7% (95% CI: 69.3–93.2); - Methotrexate / Vinblastine: 45, 0% (95% CI: 23.1–68.5)
Conclusion	Superiority of sorafenib vs placebo	Pazopanib appears to be a promising treatment

compare medical treatment and cryotherapy, with the possibility of offering cryotherapy as the first line of treatment.

3.5.3. Recommendations for local treatment

- Radiotherapy is a treatment to be considered in exceptional indications (recommendation: grade D, experts' agreement).
- Cryotherapy treatment in an expert center is a therapeutic option currently being evaluated in tumors accessible to percutaneous treatment (recommendation: grade D, experts' agreement).

3.5.4. Clinical trials

CRYODESMO-2 study (in progress): randomized phase II evaluating medical treatment versus cryotherapy. Coordinator: Pr A. GANGI (Strasbourg)

4. Other associated measures

4.1. Supportive care

Given the pain, functional damage, the rarity of the disease, and the uncertainty about its course, the repercussions of the disease can be extremely severe, with:

- Pain;
- Functional impotence;
- Anxiety, depression;
- Professional and financial issues;
- Isolation and incomprehension.

Patients must be able to benefit from appropriate supportive care [48–51]. Resorting to support associations can help and should be offered (as an example in France: https://www.sos-desmoide.asso.fr/page/392623-actualites).

There is no direct link between pain and tumor evolution. Some tumors that have spontaneously regressed can be a source of significant pain, and some evolving tumors can be painless. Pain management may require specialized algological management.

4.2. Pregnancy and contraception

The presence of a DT is not an absolute contraindication to pregnancy. It is advisable to have, if possible, a stable disease with an evolutionary follow-up of 2 years. It should be noted that there is a risk of tumor progression in 30% of postpartum cases. Pregnancy is possible but requires monitoring by specialized interdisciplinary teams [52]. A close monitoring (every 2 to 3 months) by ultrasound is the method of choice, according to the principles of radiation protection. There is a doubt about the safety of oral contraception, particularly estrogen-based pils; so, if possible, another method of contraception should be recommended.

4.3. Risks associated with surgeries

Any direct or distant trauma (including surgery) is associated with a risk of progressive relapse. Any surgical intervention plan must be put into perspective with this risk. In the context of prophylactic colectomy for patients with FAP, laparoscopic surgery should be preferred when possible as it was found associated with a lower risk of post-operative DT [53].

4.4. Recommendations for additional therapeutics considerations

- Contact with patient association must be systematically offered if possible, as well as supportive care (pain, etc.), (recommendation: grade D, experts' agreement).
- Any surgical intervention plan must be put into perspective with the risk of a progressive outbreak (recommendation: grade D, experts' agreement).
- Any cosmetic surgery or tattoo / piercing should be discouraged (recommendation: grade D, experts' agreement).
- Pregnancy is possible and requires monitoring by trained multidisciplinary teams (recommendation: grade D, experts' agreement).
- There is a doubt about the safety of oral contraception, particularly estrogen-based; if possible, another method of contraception should be recommended (recommendation: grade D, experts' opinion).

5. Therapeutic indications

5.1. Management in adults

Management strategy for desmoid abdominal tumors and / or tumors associated with adenomatous polyposis is summarized in Fig. 2.

5.2. Specificity of care in children

- Abdominal and mesenteric locations are rare in children. Pediatric data, mainly retrospective, show that the management of pediatric desmoid tumors can similarly follow current recommendations for DT management in adult patients [54,55].

5.3. Recommendations of care in children

Recommendations:

- The primary observation strategy should be favored if the position of the tumor and its size allow this monitoring without risk for the child [56,57]; (recommendation: grade B).
- The treatments are indicated in the event of threatening tumors, located in a dangerous site or clearly progressive after a period of monitoring. Operative procedures should also be avoided as much as possible (recommendation: grade B).
- The initial biopsies should preferably be performed percutaneously (recommendation: grade B).
- Due to its absence of known long-term adverse effects, the methotrexate-vinblastine combination remains the 1st line of medical treatment in pediatrics (recommendation: grade B).

Options (recommendation: grade D, experts opinion):

- Tyrosine kinase inhibitors have not been evaluated in pediatrics, but the potential known (thyroid, cardiac) and unknown toxicities may limit their use. They should be discussed as a second-line treatment in older patients.
- Data concerning the efficacy of Hydrea © (hydroxyurea) remain to be confirmed [58].
- Hormonal and NSAID treatments have shown very modest efficacy in pediatrics (<8% response rate).

6. Evaluation and surveillance

6.1. Initial and post-treatment follow-up

- The MRI is the best examen to monitor desmoid tumors (recommendation: grade D, experts' agreement).
- The first follow-up imaging after diagnosis should be made between 1 and 2 months and then spaced out in case of tumor stability to every 3 to 6 months for the first two years and then annually (recommendation: grade D, experts' agreement).
- Post-treatment follow-up: clinical follow-up + imaging (CT / MRI) should be planned every 3 months for 2 years and then every 6 months for 3 years. After five years: assessment once a year with clinical examination +/- imaging depending on the location and initial treatment (recommendation: grade D, experts' opinion).
- The occurrence of pregnancy in patients with an existing or residual desmoid tumor after treatment should require close radiological monitoring (every 2 to 3 months) by ultrasound or MRI (recommendation: grade D, experts' agreement).

Declaration of Competing Interest

O. Bouché: Roche, Merck, Amgen, Servier, Pierre Fabre, Bayer, Grunenthal.

C. Le Pechoux: Institutional honoraria for participation to boards or scientific meetings: Amgen, Astra Zeneca, Lilly, Medscape, Nanobiotix, PrimeOncology, Roche.

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