Desmoid tumours are a rare fibroblastic proliferation of monoclonal origin, arising in deep soft-tissues. Histologically, they are characterized by locally aggressive behaviour and an inability to metastasize, and clinically by a heterogeneous and unpredictable course. Desmoid tumours can occur in any anatomical site, but commonly arise in the limbs. Despite their benign nature, they can be extremely disabling and sometimes life-threatening, causing severe pain and functional limitations. Their surgical management is complex and challenging, due to uncertainties surrounding the biological and clinical behaviour, rarity, and limited available literature. Resection has been the first-line approach for patients with a desmoid tumour but, during the last few decades, a shift towards a more conservative approach has occurred, with an initial ‘wait and see’ policy. Many medical and regional forms of treatment are also available for the management of this condition, and others have recently emerged with promising results. However, many areas of controversy remain, and further studies and global collaboration are needed to obtain prospective and randomized data, in order to develop an appropriate shared stepwise approach.

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Introduction
Desmoid tumours, also known as desmoid fibromatosis or aggressive fibromatosis, are locally aggressive but non-metastasizing deep-seated (myo)fibroblastic neoplasms with infiltrative growth and a propensity for local recurrence. They affect between five and six people per million worldwide per year, accounting for 3% of all soft-tissue tumours. The peak incidence is in patients aged between 30 and 40 years, with a female predominance.

Most of these tumours (> 90%) are sporadic and usually harbour activating mutations in exon 3 of the beta-catenine coding gene (CTNBB1 gene), mostly including T41A, S45F, and S45P. The remaining minority, between 5% and 10%, are associated with familial adenomatous polyposis (Gardner Syndrome), characterized by germline mutation of the APC gene. Sporadic desmoid tumours are mainly located in the abdominal wall or extra-abdominally.

Familial cases are classically located intra-abdominally, involving the mesentery and/or intestinal wall, and are more aggressive and frequently multifocal. Patients with a desmoid tumour may be asymptomatic, or have severely limited function due to chronic pain, deformity, gastrointestinal symptoms or complications when located intra-abdominally, and psychological problems, contributing to a general decrease in the quality of life.

These tumours are characterized by an extremely variable and unpredictable clinical course, so much so as to be hardly considered a single condition. Therefore, at least two different types of desmoid tumour can be described: those with indolent behaviour and an asymptomatic course, characterized by a natural tendency to regress spontaneously or remain stable, and those which are locally aggressive with extensive complications including the infiltration of neurovascular structures and impairment of vital organs, leading to life-threatening conditions.

Stabilization or spontaneous regression has been reported in both retrospective and prospective series. About half of these tumours do not
grow after the time of the diagnosis, and in between 40% and 50% of patients they reduce in size and sometimes disappear even after an initial progression (Figure 1).19,21

Uncertainty surrounding the biological and clinical behaviour, combined with the limited availability of relevant information because of the rarity of this condition, makes the surgical management of these patients difficult. However, surgery has been the first-line approach for patients with a resectable desmoid tumour, sometimes resulting in unnecessary complications and extensive resections including amputations. The rate of local recurrence is high even after a resection with adequate margins. A rate of local recurrence of between 20% and 60% at five years has been reported in retrospective studies.22-25

Recently, a deeper knowledge of this enigmatic condition has gradually developed, with a shift towards more conservative management, based on an initial ‘wait and see’ policy. This may allow an understanding of the biological and clinical behaviour of each case, potentially discriminating between indolent and aggressive tumours. This policy also allows a tailored approach to treatment, limiting the risk of over-treatment and related morbidity.26

The most recent guidelines published by the Desmoid Tumour Working Group in 2020 advise active surveillance, defined as the continuous monitoring of patients with an initial MRI or CT scan, performed within one or two months, and then at three-to-six-monthly intervals.6,27 Surveillance should begin after a histological diagnosis and radiological evaluation and should be discontinued in favour of active treatment only in patients with persistent progression and/or increasing symptoms. The first year after diagnosis is critical, because most lesions progress during this time, while the probability of starting active treatment decreases with the passage of time, given that we allow a period of observation before starting an active treatment because desmoid tumours can spontaneously regress even after an initial progression.17,19,20 The guidelines describe a stepwise approach and advocate surveillance as the first line of management for most, if not all, patients. Several retrospective series have supported the use of surveillance, documenting the natural

Example of the spontaneous regression of a desmoid tumour. A 48-year-old female presented with a mass in the left shoulder, without any associated symptoms. a) An MRI scan showed a swelling measuring about 5 cm in diameter at the level of the trapezius muscle. A biopsy confirmed the diagnosis of a desmoid tumour. Active surveillance was initiated with clinical and diagnostic monitoring, every one to two months. b) The MRI scans during the first year showed a significant increase in the size but, considering the location and the persistently absent symptoms, the patient did not receive active treatment. c) There was a subsequent spontaneous arrest of growth and stabilization, d) about two years after the diagnosis. Further MRI scans after e) another six months and f) a year.
especially in distal sites, had the worst prognosis.\textsuperscript{16,17,31} Further local recurrence in several studies, and tumours in the limbs, were seen in patients treated with surveillance or surgically.\textsuperscript{16} The site of the tumour was identified as a prognostic factor for event-free survival primarily (two-year EFS, 25%). In contrast, a better outcome was achieved in those initially managed with active treatment.\textsuperscript{19} Among patients with a tumour in an unfavourable site, a significantly higher risk of over-treatment could be based on at least three consecutive assessments documenting progression and possibly not earlier than one year after diagnosis. However, when the tumour is close to a critical structure, such as in the mesentery or head and neck, with a risk of severe morbidity, an early decision to recommend surgery could be made.\textsuperscript{32} Several systemic forms of treatment and different local options are currently available. An important consideration is that initial surveillance does not apparently reduce the efficacy of subsequent active treatment.\textsuperscript{6}

According to the Joint Global Consensus-Based Guideline Approach, the site of the tumour is the main factor which guides decisions about the type of active intervention, while also considering the risk of complications and the patient’s age.\textsuperscript{32} For extra-abdominal desmoid tumours, systemic treatment should be the first option. Medical forms of treatment include hormones (tamoxifen or toremifene), nonsteroidal anti-inflammatory drugs, low-dose chemotherapy (methotrexate and vinblastine/vinorelbine or oral vinorelbine alone), liposomal doxorubicin, anthracycline-based chemotherapy alone or in combination with dacarbazine, and tyrosine-kinase/vascular endothelial growth factor inhibitors.\textsuperscript{6,7,27,32}

There is currently insufficient comparative information to define a unique sequence of systemic medical treatments or a preference towards one or another. Thus, clinical practice is based on experience, balancing the risks and benefits of medical treatment, starting with a treatment with fewer side effects and related morbidity, and moving towards more toxic treatments if this fails. Evidence about the efficacy and the anti-tumour activity of anti-inflammatory and hormonal treatment is lacking, and these forms of treatment should be reserved for tumours in non-critical sites and/or in patients with few symptoms.\textsuperscript{27,33,34} Patients with more symptoms or an aggressive tumour are eligible for low-dose methotrexate with vinblastine or vinorelbine, which usually achieves long-term control with a favourable profile of side effects and acceptable toxicity. These are given intravenously, usually weekly, but the effectiveness of a biweekly regimen has also been reported.\textsuperscript{35} At least one year of treatment is indicated, ideally with more than 40 cycles, and repeating it in case of relapse. The response to treatment usually occurs several months after it has started but can then continue even after it has finished.\textsuperscript{36,37} Oral vinorelbine can be an additional effective and convenient option with an excellent toxicity profile.\textsuperscript{38}

If a more rapid response is needed because of an aggressively growing tumour in an unfavourable site, conventional dose chemotherapy using an anthracycline-based regimen (alone or in combination with dacarbazine) should be considered. However, given the lack of metastatic potential and the young age of many patients, the toxicity profile, including acute side effects and severe irreversible long-term morbidity such as cardiotoxicity and treatment-induced malignancy, should always be carefully balanced.\textsuperscript{6,27,34} Liposomal doxorubicin has been reported to have a significantly satisfactory rate of response with an acceptable toxicity.\textsuperscript{40} Imatinib, a tyrosine kinase inhibitor, is characterized by a high rate of stabilization of the condition but by a limited rate of associated shrinking of the tumour, which is why it is not recommended in patients who need urgent relief of symptoms.\textsuperscript{41–44}
Sorafenib and Pazopanib, tyrosine-kinase/vascular endothelial growth factor inhibitors, are widely used in the treatment of desmoid tumours, particularly in patients with a progressive, refractory, or life-threatening tumour, given their potentially more rapid activity. In a phase III trial, involving 49 patients who received Sorafenib (400 mg tablet once daily), 16 (33%) had a satisfactory response and the two-year progression-free survival was 81%. The condition progressed in only six patients (12%). The median time to an objective response was 9.6 months (interquartile range 6.6 to 16.7) and the earliest partial response, according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, occurred at 2.2 months. If Sorafenib is not available, or patients are resistant to it, Pazopanib can be a viable alternative, having a similar activity profile. The clinical activity of this antiangiogenic agent in progressive desmoid tumours was documented in the DESMOPOZ trial, including 72 patients, in which the proportion of patients in whom the condition did not progress at six months was 83.7%. Tyrosine kinase inhibitors have a limited risk of acute side effects, especially when given in low doses, but may induce hypertension and/or hypothyroidism. The potential long-term toxicity is of fundamental importance in the choice of treatment, because most patients are young with a normal life expectancy, but long-term data are currently lacking.

Among newer forms of systemic treatment, Niragacestat (PF-03084014), an orally available, reversible gamma-secretase inhibitor, seems to have high clinical activity and a good safety profile, leading to prolonged control. A global phase III randomized double-blind trial (DeFi) included 142 patients with random assignment to a Niragacestat group (n = 70) or to a placebo group (n = 72). Niragacestat significantly reduced the risk of progression, showing a significant improvement in progression-free survival compared with the placebo group (hazard ratio 0.29 (95% confidence interval 0.15 to 0.55); p < 0.001). Among secondary endpoints, there were also significant improvements in the objective response rate, symptomatology, and health-related quality of life and a manageable safety profile. Promising data also emerged from a Phase II/III randomized study (RINGSIDE) on the safety profile of another gamma-secretase inhibitor (AL 102). Finally, the role of Tegavivint (BC2059), a beta-catenin inhibitor, represents a possible therapeutic approach for these patients. A first in-human phase I clinical trial is currently ongoing (NCT03459469) (Supplementary Table ii).

Several local forms of treatment are available. Radiotherapy may be used for extra-abdominal desmoid tumours, especially those in the girdles and head and neck. It can be delivered at a moderate dose (i.e. 50 Gy) as definitive treatment in patients not eligible for surgery or systemic treatment in the elderly after failure of medical treatment, or in patients with tumours close to vital structures. Satisfactory control is obtained in up to 70% of patients, but with serious long-term side effects, including fibrosis and radiation-induced tumours. Radiotherapy is rarely, if ever, used as the initial treatment or in young patients, while it may be considered more often in the elderly, especially when other options are not available or suitable.

Isolated limb perfusion with tumour necrosis factor α and melphalan seems to be a valid option in patients with locally advanced progressive desmoid tumours in the limbs, especially distally, sometimes representing a limb-saving strategy. Achieving effective local control can prevent operations that would result in significant loss of function, or amputations. In terms of efficacy, limb perfusion is a valid alternative to radiotherapy for desmoid tumours in the limbs, with the advantage of a more favourable local and systemic toxicity profile.

Percutaneous ablation, including radiofrequency ablation and cryotherapy, has also recently emerged as an option for the treatment for desmoid tumours. Cryoablation, an interventional radiological technique, based on repeated cycles of freezing and spontaneous thawing of the tumour, is gaining popularity, thanks to its efficacy both as first-line and as salvage treatment and its low morbidity. Cryodesmo-01, a prospective phase II trial, including 50 patients, reported a progression-free rate at 12 months of 85.6%, including a complete response in 28.6%, partial response in 26.2%, and a stable condition in 31%. Cryoablation was reported to be highly effective in relieving symptoms, resulting in an improvement in the quality of life and a decrease of analgesic intake, with an acceptable safety profile. Finally, chemoembolization may also be a possible regional form of treatment, for example using doxorubicin-eluting microparticles, although limited data are available (Supplementary Table iii).

In patients with extra-abdominal desmoid tumours, surgery is reserved for secondary treatment in selected cases, after the tumour and/or symptoms have progressed during surveillance or conservative treatment, and it should be considered an option only if the expected related morbidity is limited. Surgery for desmoid tumours in the limbs or girdles has a higher rate of morbidity, potentially causing varying degrees of loss of function and cosmesis. The rate of recurrence after surgery is also reported to be unacceptably high, exceeding 40%. Using an initial period of surveillance may allow surgery to be avoided in 90% of patients with sporadic extra-abdominal desmoid tumours. Conversely, for these tumours in the abdominal wall surgery can be considered earlier, because local control can be achieved in > 90% of patients and morbidity is generally minimal.

Patients failing after a period of surveillance and possibly local ablative therapy such as cryoablation can be offered surgery, even if incisional hernias and the possibility of further pregnancies also have to be considered in the final decision. However, most patients with sporadic abdominal wall tumours who are counselled and managed appropriately will have stabilization of the tumour and subsequent regression. So, there should be no hurry to resort to surgery. Finally, early surgery can also be considered for intra-abdominal sporadic desmoid tumours, when morbidity is acceptable (depending on the involvement of the superior mesenteric vessels), because local control is also good. The risk of later surgical complications should always be considered if the tumour does not regress either spontaneously or after medical treatment.

The role of surgery for regressing and residual tumours is still much debated. Not only the role, but also the surgical strategy, has evolved with the passage of time, moving from aggressive resections with wide margins to more limited surgery with the preservation of structures and function. Wide microscopic
Margins (R0) should be the primary goal, but resection that causes loss of function and/or aesthetic integrity cannot be justified. Positive microscopic margins (R1) can be considered acceptable to ensure function- and cosmesis-sparing surgery. Neither perioperative radiotherapy nor reoperation is required. The role of the surgical margin has been investigated by various authors in retrospective studies, reporting that microscopically positive margins were not associated with a higher risk of local recurrence. However, the role of surgery currently is predominantly limited to the management of post-operative complications for tumours located intra-abdominally (bowel perforation, bleeding, intestinal obstruction), important cosmetic implications for those tumours that do not shrink after treatment (generally located to the abdominal wall, always to be balanced against the cosmetic implications of the surgery and the possible loss of function), and failure of other available options (Supplementary Table iv).

In summary, desmoid tumours are complex, with varied and unpredictable clinical and biological behaviour. Many areas of their management remain uncertain and controversial, and further studies and global collaboration are needed to provide prospective and randomized evidence. A case-by-case discussion in dedicated multidisciplinary tumour boards is mandatory and the patient’s active involvement in decision-making process is of paramount importance. Quality of life should be the main goal of treatment, both by optimizing the control of symptoms and by aiming at as much as possible the side effects of treatment, in the short and long term. Surveillance should be considered as a first step at the time of diagnosis, whenever possible. Any approach – medical, regional, or surgical – should always be chosen by balancing the benefits and risks, remembering that our duty is to treat the patient rather than the condition, looking for the overall wellbeing of the individual, without causing harm.

Take home message
- Management of desmoid tumours requires a multidisciplinary approach and should follow a step-wise approach, tailored to each patient.
- When possible, patient surveillance is recommended as the primary management strategy.
- Active therapy (medical, locoregional, surgical) is indicated in case of persistent progression of the disease or worsening of symptoms, taking into account the location of the tumour, possible complications, and the age of the patient.
- Quality of life and overall wellbeing of the patient should be the main goals during the entire decision-making process for treatment selection.

Supplementary material
Tables displaying an overview of the available evidence about different treatments for desmoid tumours.

References


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