■ ANNOTATION

Desmoid tumours (extra-abdominal), a surgeon's nightmare

THE CURRENT PHILOSOPHY FOR THEIR TREATMENT

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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.[1,2] They affect between five and six people per million worldwide per year, accounting for 3% of all soft-tissue tumours.[1,3,4] The peak incidence is in patients aged between 30 and 40 years, with a female predominance.[5-7] They can occur in any anatomical location and are classified according to the site of origin, as extra-abdominal, in the abdominal wall, or intra-abdominal. Extra-abdominal desmoid tumours arise in the chest wall, breast, limb girdles (mostly pericapsular), upper or lower limbs, and head and neck.[7,8] The most common site is the abdominal wall, followed by the chest wall, paraspinal trunk, mesentery, breast, limbs and girdles.[4] They may be multifocal but are generally confined to one limb.[7]

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.[9] The remaining minority, between 5% and 10%, are associated with familial adenomatous polyposis (Gardner Syndrome), characterized by germline mutation of the APC gene.[10] 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.[11] 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.[12,13]

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.[14,15] Stabilization or spontaneous regression has been reported in both retrospective and prospective series.[16–20] About half of these tumours do not

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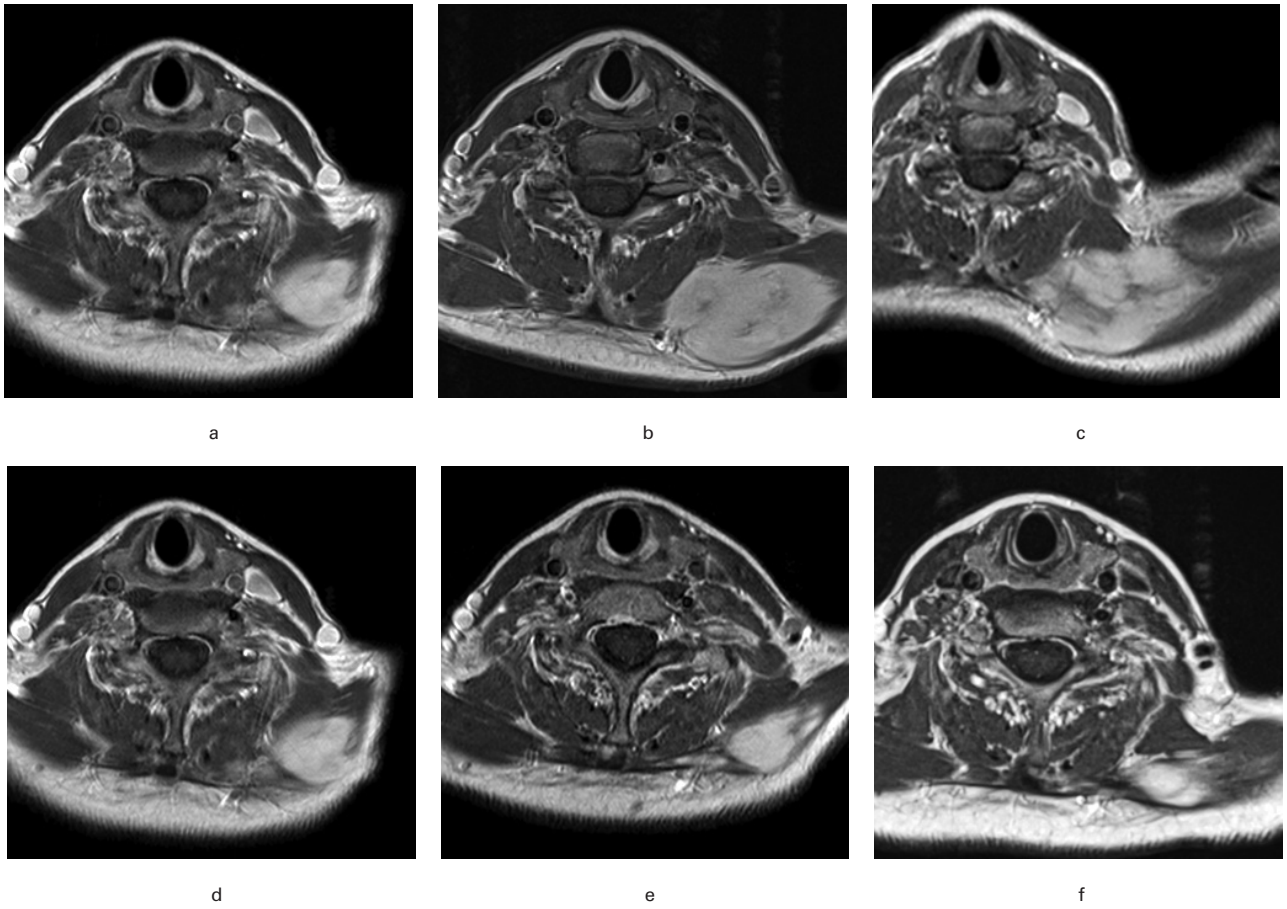

Fig. 1

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.

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 availabilty 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

history of this condition, for which a natural arrest of growth is not uncommon.[16,17,28] Between two-thirds and half of the patients managed in this way have been reported to have achieved a stable condition in the medium term. A similar progression-free survival has been reported when comparing patients managed with surveillance with those managed medically, using mainly hormonal treatment and chemotherapy.[16,17,28]

Three prospective European studies (Italian, NCT 02547831;[19] Dutch, Netherlands Trial Register NTR4714;[20] and French, NCT 01801176[29]) have recently assessed the role of surveillance in the management of patients with a desmoid tumour. The Italian multicentre observational study involved 108 patients and reported a three-year treatment-free survival of 65.9%, with one-third of all patients undergoing active treatment after an initial period of surveillance. Only one patient was treated surgically. Spontaneous regression was seen in 60 patients (56%), as an initial event in 27 (25%) and in 33 (31%) after initial progression. These data suggest that the initial surveillance could be continued to reduce the risk of over-treatment.

The Dutch (GRAFITI) trial showed comparable results, reporting that only 31 patients (30%) managed initially with surveillance started active treatment after a median period of 33.7 months.[20] A stable condition was reported in 33 patients (32%), and a partial or complete response was reported in 29 (28%).[20] Both the Dutch and Italian studies investigated possible predictive factors for the failure of surveillance which could be used as criteria for the early selection of patients for this form of management or active treatment. A larger size of tumour emerged as a predictor of failure of surveillance in both series. A significant correlation between tumours of larger size and the presence of the S45F mutation was reported, and this specific mutation was an independent predictor for switching to active treatment.[20] Tumours in limbs have a significantly higher probability of being large, carrying a S45F mutation, and hence requiring active therapy.[19]

Another large prospective French study identified the site of the tumour as a major prognostic factor for event-free survival (EFS), also classifying the sites as favourable (abdominal wall, breast, intra-abdominal, and lower limb) and unfavourable (head and neck, thoracic wall and upper limb), according to the tendency of the tumour to progress locally.[30] Among patients with a tumour in an unfavourable site, a significantly better outcome was achieved in those initially managed with surveillance (two-year EFS, 52%) compared with those who underwent surgery primarily (two-year EFS, 25%). In contrast, considering favourable sites, similar oncological outcomes were seen in patients treated with surveillance or surgically. The site of the tumour was identified as a prognostic factor for local recurrence in several studies, and tumours in the limbs, especially in distal sites, had the worst prognosis.[16,18,31] Further studies are required to clarify the criteria which are related to an increased risk of progression, in order to identify which patients require more careful surveillance or early active management (Supplementary Table i).[19]

Progressive symptoms and/or enlargement of the tumour are the main indications for discontinuing surveillance in favour of active treatment.[6] A decision about the need for surgery should 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.[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.[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.[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.[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.[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.[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.[36,37] Oral vinorelbine can be an additional effective and convenient option with an excellent toxicity profile.[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.[6,27,39] Liposomal doxorubicin has been reported to have a significantly satisfactory rate of response with an acceptable toxicity.[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.[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%.[21] 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,[45] 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.[32] The clinical activity of this antiangiogenic agent in progressive desmoid tumours was documented in the DESMOPAZ trial, including 72 patients, in which the proportion of patients in whom the condition did not progress at six months was 83.7%.[46] 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.[6]

Among newer forms of systemic treatment, Nirogacestat (PF-03084014), an orally available, reversible gamma-secretase inhibitor, seems to have high clinical activity and a good safety profile, leading to prolonged control.[47–50] A global phase III randomized double-blind trial (DeFi) included 142 patients with random assignment to a Nirogacestat group (n = 70) or to a placebo group (n = 72).[51] Nirogacestat 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).[52] Finally, the role of Tegavivint (BC2059), a beta-catenin inhibitor, represents a possible therapeutic approach for these patients.[6,53] 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.[54,55] 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.[56–58]

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.[8,59,60] 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%.[61] 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).[62]

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.[27] 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%.[25,31] Using an initial period of surveillance may allow surgery to be avoided in 90% of patients with sporadic extra-abdominal desmoid tumours.[28] 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.[63] 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.[17] Wide microscopic

margins (R0) should be the primary goal, but resection that causes loss of function and/or aesthetic integrity cannot be justified.[27] Positive microscopic margins (R1) can be considered acceptable to ensure function- and cosmesis-sparing surgery. Neither perioperative radiotherapy nor reoperation is required.[27] The role of the status 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.[22,26,64] However, the role of surgery currently is predominantly limited to the management of postoperative 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 limiting 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.

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Supplementary material

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

References

1. **WHO Classification of Tumours Editorial Board**. Soft Tissue and Bone Tumours: Desmoid fibromatosis. In: *WHO Classification of Tumours*. Vol 3. Lyon, France: IARC Press, 2020: 93–95.
2. **Sbaraglia M**, **Bellan E**, **Dei Tos AP**. The 2020 WHO Classification of Soft Tissue Tumours: news and perspectives. *Pathologica*. 2021;113(2):70–84.
3. **Penel N**, **Coindre J-M**, **Bonvalot S**, **et al**. Management of desmoid tumours: A nationwide survey of labelled reference centre networks in France. *Eur J Cancer*. 2016;58:90–96.
4. **Penel N**, **Bonvalot S**, **Bimbai A-M**, **et al**. Lack of prognostic value of CTNNB1 mutation profile in desmoid-type fibromatosis. *Clin Cancer Res*. 2022;28(18):4105–4111.
5. **Howard JH**, **Pollock RE**. Intra-abdominal and abdominal wall desmoid fibromatosis. *Oncol Ther*. 2016;4(1):57–72.
6. **Kasper B**, **Raut CP**, **Gronchi A**. Desmoid tumors: to treat or not to treat, that is the question. *Cancer*. 2020;126(24):5213–5221.
7. **Spolverato G**, **Gronchi A**. Desmoid Tumors. In: Leong SP, Nathanson SD, Zager JS, eds. *Cancer Metastasis Through the Lymphovascular System*. Cham, Switzerland: Springer, 2022: 619–627.
8. **Colak C**, **Hull C**, **Simpfendorfer C**, **Ilaslan H**, **Forney M**. Extra-abdominal desmoid fibromatosis: cryoablation versus traditional therapies. *Clin Imaging*. 2022;88:9–16.
9. **Colombo C**, **Belfiore A**, **Paielli N**, **et al**. β-Catenin in desmoid-type fibromatosis: deep insights into the role of T41A and S45F mutations on protein structure and gene expression. *Mol Oncol*. 2017;11(11):1495–1507.
10. **Salas S**, **Chibon F**, **Noguchi T**, **et al**. Molecular characterization by array comparative genomic hybridization and DNA sequencing of 194 desmoid tumors. *Genes Chromosomes Cancer*. 2010;49(6):560–568.
11. **Cuomo P**, **Scoccianti G**, **Schiavo A**, **et al**. Extra-abdominal desmoid tumor fibromatosis: a multicenter EMSOS study. *BMC Cancer*. 2021;21(1):437.
12. **von Mehren M**, **Benjamin RS**, **Bui MM**, **et al**. Soft tissue sarcoma, version 2.2012: featured updates to the NCCN guidelines. *J Natl Compr Canc Netw*. 2012;10(8):951–960.
13. **Garcia-Ortega DY**, **Martín-Tellez KS**, **Cuellar-Hubbe M**, **et al**. Desmoid-type fibromatosis. *Cancers (Basel)*. 2020;12(7):1851.
14. **Gronchi A**, **Colombo C**, **Le Péchoux C**, **et al**. Sporadic desmoid-type fibromatosis: a stepwise approach to a non-metastasising neoplasm--a position paper from the Italian and the French Sarcoma Group. *Ann Oncol*. 2014;25(3):578–583.
15. **Gounder MM**, **Thomas DM**, **Tap WD**. Locally aggressive connective tissue tumors. *J Clin Oncol*. 2018;36(2):202–209.
16. **Bonvalot S**, **Eldweny H**, **Haddad V**, **et al**. Extra-abdominal primary fibromatosis: aggressive management could be avoided in a subgroup of patients. *Eur J Surg Oncol*. 2008;34(4):462–468.
17. **Fiore M**, **Rimareix F**, **Mariani L**, **et al**. Desmoid-type fibromatosis: a front-line conservative approach to select patients for surgical treatment. *Ann Surg Oncol*. 2009;16(9):2587–2593.
18. **van Houdt WJ**, **Husson O**, **Patel A**, **et al**. Outcome of primary desmoid tumors at all anatomic locations initially managed with active surveillance. *Ann Surg Oncol*. 2019;26(13):4699–4706.
19. **Colombo C**, **Fiore M**, **Grignani G**, **et al**. A prospective observational study of active surveillance in primary desmoid fibromatosis. *Clin Cancer Res*. 2022;28(18):4027–4032.
20. **Schut A-R**, **Timbergen MJM**, **van Broekhoven DLM**, **et al**. A nationwide prospective clinical trial on active surveillance in patients with non-intraabdominal desmoid-type fibromatosis: The GRAFITI trial. *Ann Surg*. 2023;277(4):689–696.
21. **Gounder MM**, **Mahoney MR**, **Van Tine BA**, **et al**. Sorafenib for advanced and refractory desmoid tumors. *N Engl J Med*. 2018;379(25):2417–2428.
22. **Gronchi A**, **Casali PG**, **Mariani L**, **et al**. Quality of surgery and outcome in extra-abdominal aggressive fibromatosis: a series of patients surgically treated at a single institution. *J Clin Oncol*. 2003;21(7):1390–1397.
23. **Phillips SR**, **A'Hern R**, **Thomas JM**. Aggressive fibromatosis of the abdominal wall, limbs and limb girdles. *Br J Surg*. 2004;91(12):1624–1629.
24. **Lev D**, **Kotilingam D**, **Wei C**, **et al**. Optimizing treatment of desmoid tumors. *J Clin Oncol*. 2007;25(13):1785–1791.
25. **Janssen ML**, **van Broekhoven DLM**, **Cates JMM**, **et al**. Meta-analysis of the influence of surgical margin and adjuvant radiotherapy on local recurrence after resection of sporadic desmoid-type fibromatosis. *Br J Surg*. 2017;104(4):347–357.
26. **Gronchi A**, **Colombo C**, **Le Péchoux C**, **et al**. Sporadic desmoid-type fibromatosis: a stepwise approach to a non-metastasising neoplasm--a position paper from the Italian and the French Sarcoma Group. *Ann Oncol*. 2014;25(3):578–583.
27. **Desmoid Tumor Working Group**. The management of desmoid tumours: A joint global consensus-based guideline approach for adult and paediatric patients. *Eur J Cancer*. 2020;127:96–107.
28. **Colombo C**, **Miceli R**, **Le Péchoux C**, **et al**. Sporadic extra abdominal wall desmoid-type fibromatosis: surgical resection can be safely limited to a minority of patients. *Eur J Cancer*. 2015;51(2):186–192.

29. **Bonvalot S**, **Montreff T**. Peripheral Primitive Fibromatosis (WS-RT Fibro). ClinicalTrials.gov. 2016. https://clinicaltrials.gov/ct2/show/NCT01801176 (date last accessed 12 May 2023).
30. **Penel N**, **Le Cesne A**, **Bonvalot S**, **et al**. Surgical versus non-surgical approach in primary desmoid-type fibromatosis patients: a nationwide prospective cohort from the French Sarcoma Group. *Eur J Cancer*. 2017;83:125–131.
31. **Salas S**, **Dufresne A**, **Bui B**, **et al**. Prognostic factors influencing progression-free survival determined from a series of sporadic desmoid tumors: a wait-and-see policy according to tumor presentation. *J Clin Oncol*. 2011;29(26):3553–3558.
32. **Gronchi A**, **Jones RL**. Treatment of desmoid tumors in 2019. *JAMA Oncol*. 2019;5(4):567–568.
33. **Quast DR**, **Schneider R**, **Burdzik E**, **Hoppe S**, **Möslein G**. Long-term outcome of sporadic and FAP-associated desmoid tumors treated with high-dose selective estrogen receptor modulators and sulindac: a single-center long-term observational study in 134 patients. *Fam Cancer*. 2016;15(1):31–40.
34. **Libertini M**, **Mitra I**, **van der Graaf WTA**, **et al**. Aggressive fibromatosis response to tamoxifen: lack of correlation between MRI and symptomatic response. *Clin Sarcoma Res*. 2018;8:13.
35. **Nishida Y**, **Hamada S**, **Urakawa H**, **et al**. Desmoid with biweekly methotrexate and vinblastine shows similar effects to weekly administration: a phase II clinical trial. *Cancer Sci*. 2020;111(11):4187–4194.
36. **Palassini E**, **Frezza AM**, **Mariani L**, **et al**. Long-term efficacy of methotrexate plus vinblastine/vinorelbine in a large series of patients affected by desmoid-type fibromatosis. *Cancer J*. 2017;23(2):86–91.
37. **Li S**, **Fan Z**, **Fang Z**, **et al**. Efficacy of vinorelbine combined with low-dose methotrexate for treatment of inoperable desmoid tumor and prognostic factor analysis. *Chin J Cancer Res*. 2017;29(5):455–462.
38. **Mir O**, **Honoré C**, **Chamseddine AN**, **et al**. Long-term outcomes of oral vinorelbine in advanced, progressive desmoid fibromatosis and influence of *CTNNB1* mutational status. *Clin Cancer Res*. 2020;26(23):6277–6283.
39. **Garbay D**, **Le Cesne A**, **Penel N**, **et al**. Chemotherapy in patients with desmoid tumors: a study from the French Sarcoma Group (FSG). *Ann Oncol*. 2012;23(1):182–186.
40. **Constantinidou A**, **Jones RL**, **Scurr M**, **Al-Muderis O**, **Judson I**. Pegylated liposomal doxorubicin, an effective, well-tolerated treatment for refractory aggressive fibromatosis. *Eur J Cancer*. 2009;45(17):2930–2934.
41. **Heinrich MC**, **McArthur GA**, **Demetri GD**, **et al**. Clinical and molecular studies of the effect of imatinib on advanced aggressive fibromatosis (desmoid tumor). *J Clin Oncol*. 2006;24(7):1195–1203.
42. **Chugh R**, **Wathen JK**, **Patel SR**, **et al**. Efficacy of imatinib in aggressive fibromatosis: Results of a phase II multicenter Sarcoma Alliance for Research through Collaboration (SARC) trial. *Clin Cancer Res*. 2010;16(19):4884–4891.
43. **Penel N**, **Le Cesne A**, **Bui BN**, **et al**. Imatinib for progressive and recurrent aggressive fibromatosis (desmoid tumors): an FNCLCC/French Sarcoma Group phase II trial with a long-term follow-up. *Ann Oncol*. 2011;22(2):452–457.
44. **Kasper B**, **Gruenwald V**, **Reichardt P**, **et al**. Imatinib induces sustained progression arrest in RECIST progressive desmoid tumours: final results of a phase II study of the German Interdisciplinary Sarcoma Group (GISG). *Eur J Cancer*. 2017;76:60–67.
45. **Eisenhauer EA**, **Therasse P**, **Bogaerts J**, **et al**. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247.
46. **Toulmonde M**, **Pulido M**, **Ray-Coquard I**, **et al**. Pazopanib or methotrexate-vinblastine combination chemotherapy in adult patients with progressive desmoid tumours (DESMOPAZ): a non-comparative, randomised, open-label, multicentre, phase 2 study. *Lancet Oncol*. 2019;20(9):1263–1272.
47. **Messersmith WA**, **Shapiro GI**, **Cleary JM**, **et al**. A phase I, dose-finding study in patients with advanced solid malignancies of the oral γ-secretase inhibitor PF-03084014. *Clin Cancer Res*. 2015;21(1):60–67.
48. **Gounder MM**. Notch inhibition in desmoids: "Sure it works in practice, but does it work in theory?" *Cancer*. 2015;121(22):3933–3937.
49. **Kummar S**, **O'Sullivan Coyne G**, **Do KT**, **et al**. Clinical activity of the γ-secretase inhibitor PF-03084014 in adults with desmoid tumors (aggressive fibromatosis). *J Clin Oncol*. 2017;35(14):1561–1569.
50. **Villalobos VM**, **Hall F**, **Jimeno A**, **et al**. Long-term follow-up of desmoid fibromatosis treated with PF-03084014, an oral gamma secretase inhibitor. *Ann Surg Oncol*. 2018;25(3):768–775.
51. **Gounder M**, **Ratan R**, **Alcindor T**, **et al**. Nirogacestat, a γ-secretase inhibitor for desmoid tumors. *N Engl J Med*. 2023;388(10):898–912.
52. **Gounder MM**, **Jones RL**, **Chugh R**, **et al**. Initial results of phase II/III trial of AL102 for treatment of desmoid tumors (DT). Abstract 1488MO. *Ann Oncol*. 2022;33(suppl_7):S681–S700.
53. **Braggio DA**, **Costas C de Faria F**, **Koller D**, **et al**. Preclinical efficacy of the Wnt/β-catenin pathway inhibitor BC2059 for the treatment of desmoid tumors. *PLoS One*. 2022;17(10):e0276047.
54. **Keus RB**, **Nout RA**, **Blay J-Y**, **et al**. Results of a phase II pilot study of moderate dose radiotherapy for inoperable desmoid-type fibromatosis--an EORTC STBSG and ROG study (EORTC 62991-22998). *Ann Oncol*. 2013;24(10):2672–2676.
55. **Bishop AJ**, **Zarzour MA**, **Ratan R**, **et al**. Long-term outcomes for patients with desmoid fibromatosis treated with radiation therapy: a 10-year update and re-evaluation of the role of radiation therapy for younger patients. *Int J Radiat Oncol Biol Phys*. 2019;103(5):1167–1174.
56. **Grünhagen DJ**, **de Wilt JHW**, **Verhoef C**, **van Geel AN**, **Eggermont AMM**. TNF-based isolated limb perfusion in unresectable extremity desmoid tumours. *Eur J Surg Oncol*. 2005;31(8):912–916.
57. **Bonvalot S**, **Rimareix F**, **Causeret S**, **et al**. Hyperthermic isolated limb perfusion in locally advanced soft tissue sarcoma and progressive desmoid-type fibromatosis with TNF 1 mg and melphalan (T1-M HILP) is safe and efficient. *Ann Surg Oncol*. 2009;16(12):3350–3357.
58. **van Broekhoven DLM**, **Deroose JP**, **Bonvalot S**, **et al**. Isolated limb perfusion using tumour necrosis factor α and melphalan in patients with advanced aggressive fibromatosis. *Br J Surg*. 2014;101(13):1674–1680.
59. **Auloge P**, **Garnon J**, **Robinson JM**, **et al**. Percutaneous cryoablation for advanced and refractory extra-abdominal desmoid tumors. *Int J Clin Oncol*. 2021;26(6):1147–1158.
60. **Efrima B**, **Ovadia J**, **Drukman I**, **et al**. Cryo-surgery for symptomatic extra-abdominal desmoids. A proof of concept study. *J Surg Oncol*. 2021;124(4):627–634.
61. **Kurtz J-E**, **Buy X**, **Deschamps F**, **et al**. CRYODESMO-01: A prospective, open phase II study of cryoablation in desmoid tumour patients progressing after medical treatment. *Eur J Cancer*. 2021;143:78–87.
62. **Elnekave E**, **Ben Ami E**, **Shamai S**, **et al**. Selective intra-arterial Doxorubicin eluting microsphere embolization for desmoid fibromatosis: a combined prospective and retrospective study. *Cancers (Basel)*. 2022;14(20):5045.
63. **Bonvalot S**, **Ternès N**, **Fiore M**, **et al**. Spontaneous regression of primary abdominal wall desmoid tumors: more common than previously thought. *Ann Surg Oncol*. 2013;20(13):4096–4102.
64. **Crago AM**, **Denton B**, **Salas S**, **et al**. A prognostic nomogram for prediction of recurrence in desmoid fibromatosis. *Ann Surg*. 2013;258(2):347–353.

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