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Review

The management of desmoid tumours: A joint global consensus-based guideline approach for adult and paediatric patients

The Desmoid Tumor Working Group[1]

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KEYWORDS
Desmoid tumour;
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CTNNB1;
Gardner syndrome;
Medical therapy;
Radiotherapy;
Surgery;
Patient advocacy groups;
SPAEN;

Abstract Desmoid tumor (DT; other synonymously used terms: Desmoid-type fibromatosis, aggressive fibromatosis) is a rare and locally aggressive monoclonal, fibroblastic proliferation characterised by a variable and often unpredictable clinical course. Previously surgery was the standard primary treatment modality; however, in recent years a paradigm shift towards a more conservative management has been introduced and an effort to harmonise the strategy amongst clinicians has been made. We present herein an evidence-based, joint global consensus guideline approach to the management of this disease focussing on: molecular genetics, indications for an active treatment, and available systemic therapeutic options. This paper follows a one-day consensus meeting held in Milan, Italy, in June 2018 under the auspices of the European Reference Network for rare solid adult cancers, EURACAN, the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) as well as Sarcoma Patients EuroNet (SPAEN) and The Desmoid tumour Research Foundation (DTRF). The meeting brought

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Treatment algorithm

together over 50 adult and pediatric sarcoma experts from different disciplines, patients and patient advocates from Europe, North America and Japan.

1. Introduction

1.1. General issues and epidemiology

Desmoid tumour (DT) is a rare monoclonal, fibroblastic proliferation characterised by a variable and often unpredictable clinical course. In the International Classification of Diseases (ICD) it is classified as D48.1. According to the World Health Organisation (WHO), DT is a "clonal fibroblastic proliferation that arises in the deep soft tissues and is characterised by infiltrative growth and a tendency toward local recurrence but an inability to metastasise," even though it may be multifocal in the same limb or body part [1]. DT is a distinctly rare entity (incidence 5–6 cases per 1 million of the population per annum [2]) with a peak age of 30–40 years [3]. DT may occur at abdominal, intra-abdominal, and extra-abdominal locations and approximately 5–10% arise in the context of familial adenomatous polyposis (FAP). Efforts to standardise the management of this disease have been undertaken in recent years [4,5].

A global consensus meeting involving experts from Europe, North America and Japan was organised to further define the appropriate clinical management of DT, reducing inconsistent care around the world and suboptimal outcomes for many patients. The focus of the meeting was to discuss the molecular genetics of this disease, the indications for an active treatment as well as available systemic treatment options. The consensus was reached by: an initial evidence-based systematic literature search that was performed by an independent institute involving methodological experts and an analysis of the identified literature according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) followed by the consensus meeting. The meeting involved sarcoma experts with expertise in both adult and paediatric DT patients from Europe, North America and Japan, as well as patients and patient advocates from Sarcoma Patients EuroNet (SPAEN) and the USA-based Desmoid tumour Research Foundation (DTRF). The meeting was held on June 18, 2018 in Milan, Italy, under the auspices of the European Reference Network for rare solid adult cancers, EURACAN, and with the support of the patient advocacy groups DTRF, "SOS desmoid" Germany and SPAEN.

1.2. Methodology

1.2.1. Literature search

In advance of the consensus meeting a literature search was performed to elicit data upon which consensus recommendations were based. All literature searches (MEDLINE and EMBASE) were performed in January 2018. We only searched for English and German articles; no other limitations were applied in the search strategy. In addition, we requested that the guideline panel members cross-check the references of all included articles and systematic reviews on similar topics to identify articles that might have been missed by the search strategy. For the five different topics the following predefined inclusion criteria to select studies were applied:

Pathology and molecular genetics	
Patients	Patients with sporadic desmoids
Exposure	β-catenin mutated desmoids (*CTNNB1* T41A, S45F, S45P, S45N)
Comparison/Control	Wild-type desmoids
Outcomes/End-points	RFS, PFS
Study types	Comparative studies with at least two arms (at least 20 patients)
Indications for an active treatment	
Patients	Patients with sporadic (β-catenin mutated versus wild-type) and FAP-associated desmoids
Intervention	Active treatment (surgery, radiotherapy, medical therapy)
Comparison/Control	No intervention/watch and wait
Outcomes/End-points	RFS, PFS, side-effects, health-related quality of life (HRQoL)
Study types	Comparative studies with at least two arms (at least 20 patients)
Hierarchy of medical therapies	
Patients	Patients with sporadic and FAP-associated desmoids
Intervention	Medical therapies (antihormonal therapies, NSAIDs, interferon, imatinib, nilotinib, sorafenib, pazopanib, PF-03084014, chemotherapy: methotrexate, vinblastine, vinorelbine, doxorubicin, dacarbazine, cyclophosphamide, pegylated liposomal doxorubicin)
Comparison/Control	No intervention
Outcomes/End-points	RFS, PFS, side-effects, HRQoL
Study types	Comparative studies with at least two arms (at least 20 patients)

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(*continued*)

Pain control and physical therapy	
Patients	Patients with sporadic and FAP-associated desmoids
Intervention	Pain medication, physical therapy
Comparison/Control	No intervention
Outcomes/End-points	RFS, PFS, side-effects, HRQoL
Study types	Comparative studies with at least two arms (at least 20 patients)
Radiotherapy	
Patients	Patients with sporadic and FAP-associated desmoids
Intervention	Radiotherapy
Comparison/Control	No intervention/surgery only
Outcomes/End-points	RFS, PFS, side-effects, HRQoL
Study types	Comparative studies with at least two arms (at least 20 patients)

Abbreviations: RFS, recurrence-free survival; PFS, progression-free survival; QoL, quality of life.

Titles/abstracts of all articles were screened by two reviewers independently. Subsequently, the full text of all potentially relevant articles was obtained and screened by two reviewers independently. Randomised controlled trials (RCTs) were assessed for risk of bias with the Cochrane risk of bias tool, while non-randomised studies were assessed with the Newcastle–Ottawa scale for cohort studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). All assessments were performed by two reviewers independently. All descriptive data (patient characteristics, intervention/exposure, comparison, setting, study design) were extracted in previously piloted standardised tables. Data on outcomes (measurement, follow-up, results) were extracted directly into RevMan or GRADEpro/GTD software. Data extraction was performed by one reviewer and verified by a second. Meta-analyses were performed in case of the absence of clinical heterogeneity. For meta-analysis a standard inverse variance random effects model was used and pooled relative risks with 95% CI for all outcomes were calculated. Statistical heterogeneity was quantified with I-square. The quality of evidence was graded and "Summary of findings" tables were prepared using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach [6]. One author graded the quality of evidence and prepared the "Summary of findings" tables and a second author verified all ratings and entries.

After removing duplicates the search in the electronic databases resulted in 2489 hits. 2390 articles were excluded based on titles/abstracts. The titles/abstracts of 99 articles seemed potentially relevant and were assessed against the inclusion criteria in detail. Finally, 40 articles (39 studies) were included. The study selection process is illustrated in the flow chart in Fig. 1.

This position paper adheres to the European Organisation for Research and Treatment of Cancer (EORTC) Policy 19 on "Guidelines, Expert Opinions, and the use of EORTC Results in Promotional Material on Cancer Care" (http://www.eortc.org/app/uploads/2017/03/POL019.pdf). It received formal EORTC Board approval on September 28, 2018.

1.2.2. Consensus meeting

To develop recommendations a consensus group meeting was organised in Milan, Italy, in June 2018. Representatives from all disciplines involved in treatment and care of patients with DT participated in the meeting including specialists in pathology, molecular biology, radiology, orthopedic surgery, general surgery, radiotherapy, medical oncology, paediatric oncology and supportive oncology, joining from main European, North American and Japanese sarcoma centres. Additional participants were European and North American patient representatives. Based on the literature review and the discussion, the Desmoid Tumour Working Group reached consensus about key aspects of the management of DT patients requiring a systematic approach summarised in this position paper.

2. Pathology and molecular genetics

See online supplements (Fig. 2).

Diagnosis of DT should be confirmed by an expert soft tissue pathologist. CTNNB1 mutations and APC mutations are mutually exclusive in DT, thus, detection of a somatic CTNNB1 mutation can help to exclude a syndromic condition. Vice versa, CTNNB1 wild-type status in DT, especially in an intra-abdominal tumour, should raise suspicion for FAP, with more extensive diagnostic clinical work-up (e.g. colonoscopy or germline testing). Therefore, our group gives a strong recommendation to perform a mutational analysis in DT biopsy specimens to confirm diagnosis and guide the work-up when appropriate.

3. Indications for active treatment

Several papers have addressed the role of active treatments in the management of DT. The definition of these active treatments has been the following: surgery, radiotherapy and systemic treatment. Comparisons have been conducted to understand if any initial strategy is superior to others for long-term disease control. It has to be taken into account that a potential post-biopsy increase in size or pain may be due to bleeding from the biopsy rather than true tumor growth.

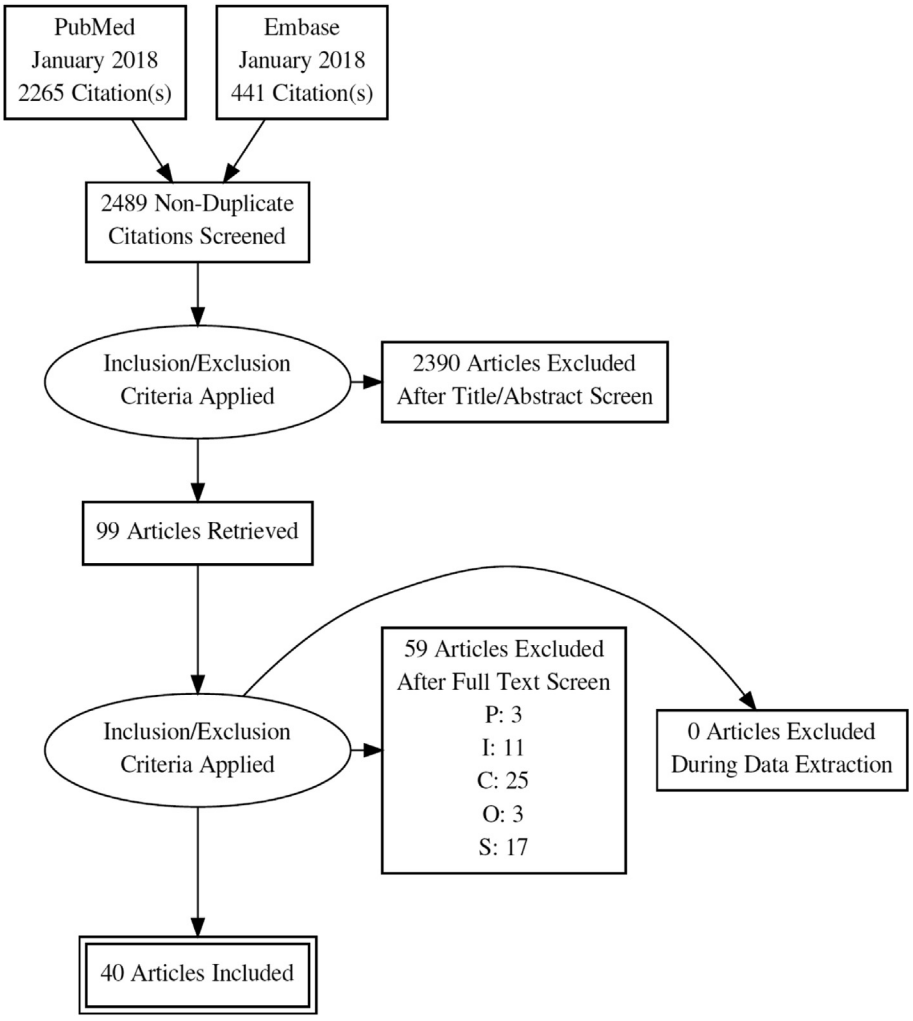


Fig. 1. Flow-diagram of the study selection process. Abbreviations: P, patients; I, intervention; C, comparison; O, outcome; S, study type.

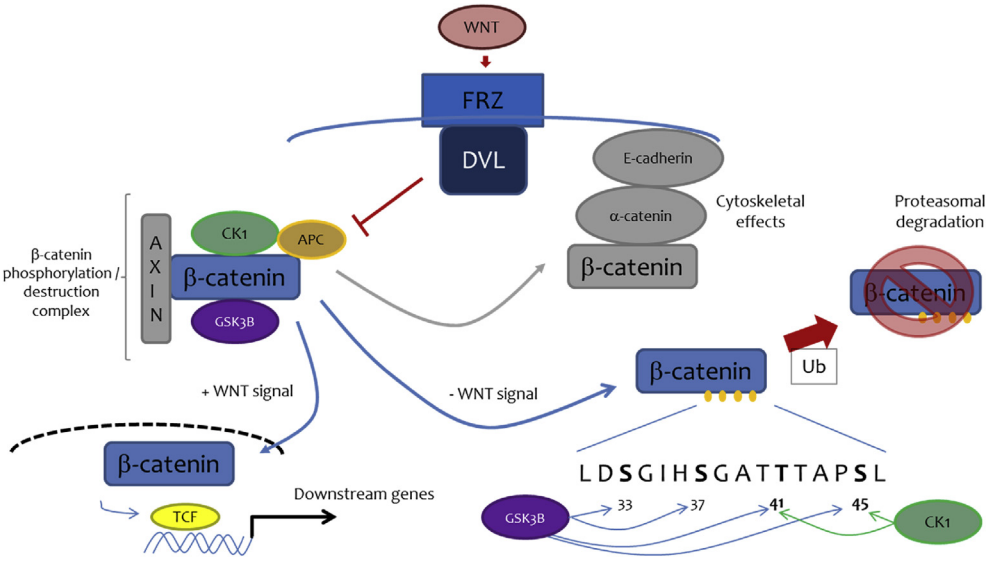


Fig. 2. Either *APC* loss or *CTNNB1* mutation can lead to DT development.

3.1. Surgery compared to observation

One of the most recent and largest series comparing initial surgery to initial observation was reported by Penel *et al.* [7]; "*very low" according to GRADE*. The results did not show any difference in event-free survival (EFS, 53% versus 58%; $p = 0.415$) and long-term disease control between patients undergoing surgery and those managed with a conservative approach. In addition, anatomic location seemed to influence the course of the disease. Among patients with favourable locations, defined as abdominal wall (AW), intra-abdominal (IA), breast, digestive viscera and lower limb, the 2-year EFS was similar in patients treated by surgery (70%) and non-surgically (63%; $p = 0.41$). Among patients with unfavorable locations, defined as chest wall, head & neck and upper limb, the 2-year EFS was significantly better in those patients managed non-surgically (52%) compared to those who underwent initial surgery (25%; $p = 0.001$). Likewise, Salas *et al.* showed a benefit of a surveillance approach although they did not perform a true comparison between groups [8]; "*very low" according to GRADE*. Other reports focussed on specific anatomical sites: mesenteric (FAP and sporadic patients [9]; "*very low" according to GRADE*), AW [10]; "*very low" according to GRADE*, extra-abdominal (EA including extremity/girdles, head & neck, and trunk [11]; "*very low" according to GRADE*) and abdominal (including both IA and AW [12]; "*very low" according to GRADE*). In both AW and EA sites, an initial non-surgical approach was shown to be safe, although surgery was offered as an option in a few selected cases. In fact, for AW the switch to surgery or to medical therapy at 3 years was 16% and 25%, respectively. After a median follow up of 97 months, only 1 out of 41 patients recurred after R1 resection [10]. Similarly for EA, the RFS at 5 years was 80% with switch to surgery in 5%, to medical therapy in 51% and spontaneous regression in 20% [11].

As shown for adults, a 5-year PFS for paediatric patients was 27% in the observation group and 41% in the surgery group ($p = 0.12$ [13]; "*very low" according to GRADE*). Park *et al.* observed a statistically superior PFS in the surveillance group ($p = 0.005$) compared to the surgical group [14]; "*very low" according to GRADE*.

Non-surgical strategies have also been proposed to FAP patients showing comparable PFS at 10 years compared to surgery (33% and 49%, respectively; $p = 0.16$). Moreover, none of these DTs could be removed entirely. For EA and AW lesions, the PFS at 10 years after surgery was 63% [15,16]; "*very low" according to GRADE*.

In summary, management of asymptomatic patients with initial observation, independently of tumour site and size, can be proposed but only under the supervision of an experienced team in connective tissue tumours from a reference centre. To better reflect what we actually do, we hereby introduce the term "active surveillance" and will use this from now on. However, the risk of progression may be higher for larger tumours. Surgery may still be considered as a second-line treatment for AW tumours as morbidity and risk of recurrence are limited, while other modalities should be preferred for DT located at other sites. Clearly, patients need to be referred to centres with experience in DT to minimize the risk of active surveillance and avoid unnecessarily debilitating or mutilating surgery when possibly needed. Surgery by surgeons without significant experience in the management of DT is strongly discouraged. Similarly, referral to experienced multidisciplinary teams is recommended at the time of initial diagnosis, for optimal advice on safety of an initial observation strategy.

3.2. Surgery plus radiotherapy compared to surgery alone

Retrospective studies [17–28]; "*very low" according to GRADE* have been published on the combination of surgery plus radiotherapy compared to surgery alone. While some reduction in the anticipated absolute risk of recurrence after surgery has been observed with the addition of radiotherapy (37% versus 25%), this reduction is not statistically significant (RR 0.69, 95% CI 0.41–1.17). As surgery is less frequently undertaken for DT, the combination of surgery and radiation is currently rarely employed. However, it can still be considered once surgery is offered to patients with recurrent disease, especially if a further recurrence would be difficult to treat. The level of evidence for adjuvant radiotherapy is low and this strategy is not devoid of risk in this young patient population (radiation-induced sarcoma).

3.3. Radiotherapy compared to radiotherapy and surgery

Retrospective data comparing radiotherapy alone to the combination of radiotherapy and surgery [29–32]; "*very low" according to GRADE* have predominantly been reported in the past. Based on these studies, the anticipated absolute risk of progressive disease after radiotherapy alone is similar to the recurrence rate after surgery plus radiotherapy (23% versus 22%). More recently, moderate dose definitive radiotherapy has been employed as an alternative to surgery for symptomatic/growing tumours located at critical sites such as head & neck, scapular girdle, etc. This modality can be a valid alternative to surgery and can be used if medical therapies are not available or not active.

3.4. Radiotherapy compared to surgery

Summarising the data comparing radiotherapy to surgery [33]; "*very low" according to GRADE*, the anticipated absolute risk of progressive disease after radiotherapy alone is 19% versus 29% after surgery

alone, however, not being statistically significant (RR 0.65, 95% CI 0.35–1.22).

In summary, when active management for DT is required, surgery as first-line therapy can be considered, provided expected surgical morbidity is limited. This is particularly true for abdominal wall locations. Wide (R0) microscopic margins resection should be the goal, but positive (R1) microscopic margins can be accepted when function or cosmesis is an issue. However, if positive microscopic margins can be anticipated, other managements than surgery should be preferred. In addition, if R1 resection is obtained in first-line management, there is insufficient evidence to recommend either perioperative radiotherapy or re-operation. Although the risk of a local recurrence seems to be lower after combined modality, the difference between surgery alone and surgery plus perioperative radiotherapy is not statistically significant. When surgery is not an option and active management is required, moderate dose definitive radiotherapy has also been shown to provide adequate local control in a majority of progressive patients and could be considered if medical therapies are not available or not active.

3.5. Initial medical treatment compared to observation

Similar results have been observed comparing initial observation to initial medical therapy [11]. Patients undergoing initial observation did not fare any worse than those initially treated by medical therapy, either with hormonal or chemotherapy [34]; "*very low" according to GRADE*. Of note, patients not progressing for 2 years were very unlikely to need any further active treatment [34].

Similar results were obtained in paediatric patients. The European paediatric Soft tissue sarcoma Study Group (EpSSG) showed a difference in the 5-year PFS between the observation (n = 54) and the chemotherapy group (n = 53) (27% and 43%, respectively) but without statistical significance ($p = 0.13$) [13]; "*low" according to GRADE*. An initial observation strategy did not compromise outcomes when compared with a more aggressive approach. Notably, with this conservative strategy more than half of the patients avoided surgery (and its sequelae) and radiotherapy.

An initial "active surveillance" approach does not appear to influence the efficacy of subsequent treatments when needed. Thus, being cautious and avoiding potential harm in experienced hands, this approach is now considered the first step after diagnosis in majority of the patients. Neither surgery nor other forms of active treatments are proposed as primary therapy at diagnosis. Considering the biology and unpredictable course of the disease, active treatments should be considered only in case of persistent progression. Progression at a single assessment, especially in the absence of specific symptoms and in non-critical anatomic sites, should not per se be considered as an indication to start an active treatment immediately. Active surveillance means that patients need to be continuously monitored with a first MRI (or alternatively CT if MRI is not possible) within 1-2 months, then in 3-6 months intervals. A decision towards an active treatment should be postponed until the occurrence of subsequent progression or increase of symptoms burden, assessed with at least two further assessments and possibly not before one year from diagnosis in the absence of fulfilling RECIST progressive disease. In fact, this policy avoids overtreatment in patients who could spontaneously regress and discourages treatment for stable and pauci-symptomatic patients. However, when the disease is located close to a critical structure that may pose significant problems to the patient's life (such as mesenteric or head & neck DT) an earlier decision towards an active therapy may be taken simply because there is a potentially higher risk of morbidity prior to disease stabilisation. As depicted in the treatment algorithm in Fig. 3, the type of further treatment is generally guided according to the anatomical site and the decision should be made with the patients in a stepwise approach: For abdominal wall DT, surgery is still the first option in case of progression. For intra-abdominal/retroperitoneal/pelvic DT, systemic therapy should be considered as the first treatment option. For extremity/girdles/chest wall DT, again surgery should not be the first treatment option unless the expected morbidity is very low (and only following MDT discussion); medical therapy should be administered preferably. Besides surgery, radiotherapy and medical therapy, isolated limb perfusion (ILP) may be part of the further treatment strategy in this location. For head & neck/intrathoracic DT, medical therapy is generally considered the first line option. However, in selected conditions (elder age, patient intolerance/preference, comorbidities, lesion growing rapidly and threatening vital organs, etc.) radiotherapy is a reasonable and effective first line alternative.

FAP-associated DT (Gardner syndrome) seems to be more aggressive and multifocal and, therefore, tends to be treated more aggressively in terms of medical management. Act with caution regarding performing a biopsy; however, currently there are insufficient data to totally exclude performing a biopsy. In the setting of a confirmed APC mutation, a mesenteric mass may likely be a DT, particularly if the patient had prior surgery. FAP patients should be jointly managed by sarcoma specialists and experts in gastrointestinal cancer. Surgery should be performed by an experienced surgeon; small bowel transplantation should be discouraged.

There is a lack of evidence that paediatric patients need to be treated differently compared to adults. Thus, the management approach is very similar to that of adult patients and should follow the same treatment algorithm.

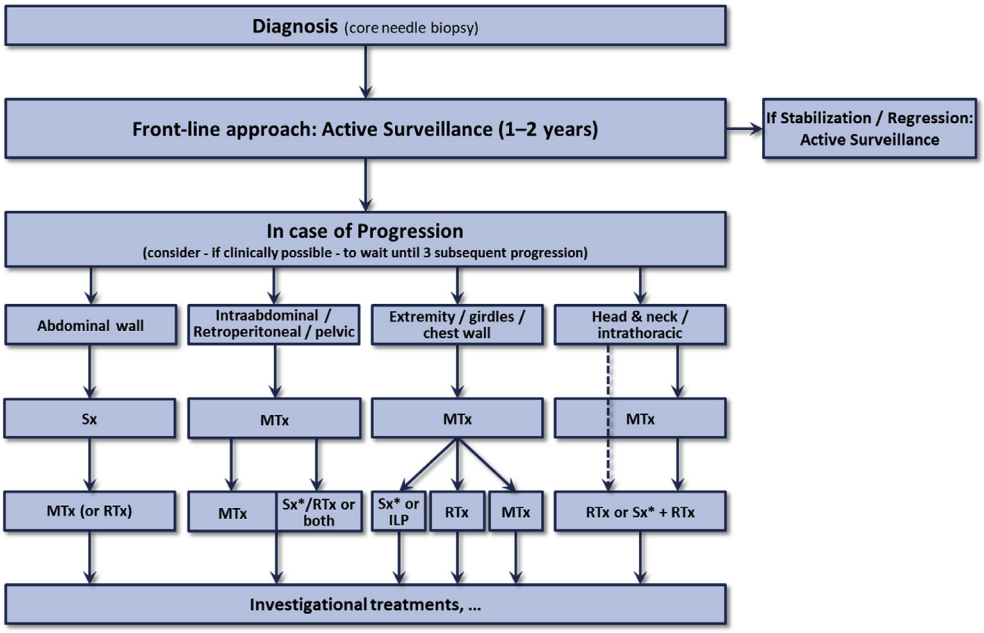
4. Available medical therapies in different indications

The independent literature search regarding systemic treatment options did not reveal any evaluable comparative studies with at least two arms being a prerequisite for an analysis according to GRADE (Grading of Recommendations Assessment, Development and Evaluation). Therefore, IFOM extracted from the initial search results all single-arm studies and provided them in a list. We then defined the following quality criteria/credits for the final analysis and interpretation of the available data: (1) n $\geq$ 20 patients, (2) confirmation of the histological diagnosis of a DT, (3) study evaluation according to a predefined statistical analysis plan, (4) definition of primary and secondary end-points as well as (5) response evaluation according to RECIST or WHO. The literature search revealed 22 publications meeting the first criterion of inclusion of at least 20 patients and forming the basis for the following chapter on systemic treatment recommendations.

Systemic treatment options for DT comprise anti-hormonal therapies, non-steroidal anti-inflammatory drugs (NSAIDs), tyrosine kinase inhibitors (TKIs), and "low-dose" or conventional chemotherapeutic regimens including liposomal doxorubicin [35,36].

4.1. Anti hormonal therapies/Non-steroidal anti-inflammatory drugs (NSAIDs)

Anti hormonal agents such as tamoxifen or toremifene have been frequently used alone or in combination with NSAIDs. The retrospective analysis from Fiore *et al.* (3 credits) included 44 patients (median age 41 years) with radiologically progressive disease (no RECIST progression required) and/or symptomatic deterioration being treated with toremifene 180 mg daily (20 for radiological progression, 16 for pain and 8 for both). In 28 patients, toremifene was offered as first-line therapy while in 11 patients after tamoxifen failure. Progression-free survival (PFS) was 90% at 12 and 24 months. According to RECIST, partial response (PR), stable disease (SD) and disease progression (PD) were observed in 25%, 65% and 10% of the patients, respectively. Symptomatic relief was achieved in 75% of all patients. Adverse events (AEs) grade 2 were reported in ten patients (23%) and included four patients with amenorrhea/dysmenorrhea, three with vaginal discharge and one each with vertigo, palpitations, and fatigue; no grade 3 or above AEs were observed [37]. Quast *et al.* (1 credit) reported outcomes on a cohort of 134 patients (64 with FAP-associated and 70 sporadic DT) treated with combination of sulindac and high-dose selective estrogen modulators, either tamoxifen, raloxifene or toremifene, at a single institution. Patients were scanned every six months during the first two years of therapy, and then every 12 months until sustained stable disease or death. Response was defined as dimensional stabilisation or regression of the DT between two CT or MRI scans; no formal response criteria were applied. Even though 114 (85%) patients showed regressive or stable DT, the definition for initiating treatment remains unclear [38,39]. The only



Abbreviations: Sx: Surgery; Sx*: Surgery is an option if morbidity is limited; MTx: Medical treatment; RTx: Radiotherapy; ILP: Isolated limb perfusion.

Fig. 3. Treatment algorithm.

prospective data evaluating the combination of high-dose tamoxifen and sulindac is from a phase II study in the paediatric patient population. Over a 5 year period, Skapek *et al.* (5 credits) enrolled 59 evaluable patients less than 19 years of age who had a measurable DT that was recurrent or not amenable to surgery or radiotherapy. Twenty-two (37%) of the patients were treatment naïve; 37 (63%) of the patients had recurrent disease. Six of these 37 patients had received prior systemic chemotherapy and 15 had prior radiotherapy. Tamoxifen and sulindac were both dosed at 3 mg/kg twice daily (maximum daily dose of 300 mg). No life-threatening toxicity was reported; however, 12 of 30 (40%) females developed ovarian cysts, eleven of which were asymptomatic. Only ten patients (17%) completed the planned one year of therapy without disease progression or discontinuation of treatment. tumour responses, defined by WHO criteria, included four patients with PR and one with a complete response (CR) for an overall response rate (ORR) of 8%. The estimated 2-year progression-free and overall survival rates were 36% and 96%, respectively. There were three deaths due to progressive disease in mesenteric locations [40]. Beside retrospective case series showing some evidence of activity, some with response rates of 25% with prolonged disease control in as many as 90% of patients, the only prospective phase II study evaluating antihormonal therapy plus NSAID showed limited activity as measured by WHO response criteria and PFS rates. Moreover, a recently published paper found no clear relationship between size, MRI signal changes and symptom changes with tamoxifen treatment [41]. Therefore, there is no evidence to consider antihormonal therapies and NSAIDs in patients with DT.

4.2. Tyrosine kinase inhibitors (TKIs): imatinib, nilotinib, sorafenib, pazopanib

The TKI imatinib was evaluated in three prospective, non-randomised studies meeting the criterion of at least 20 treated patients. Chugh *et al.* (5 credits) enrolled 51 patients (median age 34 years, range 12–67 years) who had unresectable disease or in whom surgical resection would lead to significant functional impairment. Progressive disease (PD) was not a required study inclusion criterion. Participants received imatinib twice daily 300 mg, 200 mg or 100 mg based on bovine serum albumin (BSA) $\geq$1.5 m^2, 1–1.49 m^2 or <1.0 m^2, respectively. The 1-year progression-free survival (PFS) rate was 66%; the overall response rate (ORR) was 6% (3 of 51). Best tumour response was achieved after 19, 22 and 26 months of treatment. Over a third of patients required a dose reduction, and five patients discontinued therapy due to toxicity [42]. The second phase II trial, reported by Penel *et al.* (5 credits), analysed 35 evaluable adult patients with unresectable and progressive (no RECIST progression required), symptomatic DTs who received imatinib 400 mg/day for one year. FAP was diagnosed in six cases. The PFS rates at 3, 6 and 12 months were 91%, 80% and 67%, respectively. The ORR was 11% (4 of 35). Eleven patients (31%) stopped therapy prior to one year for reasons other than progressive disease [43]. The most recent phase II study evaluating imatinib in patients with DT was conducted by the German Interdisciplinary Sarcoma Group (GISG) (5 credits). Thirty-eight patients (median age 44 years, range 19–80) with tumour progression as defined by RECIST within the last 6 months prior to study enrolment received imatinib 800 mg daily (planned for 2 years). The progression arrest rate after 6 months of imatinib treatment was the primary end-point and was reached in 65% of patients; the ORR was 19%. More than 60% of patients required at least one dose reduction [44]. All three prospective, single-arm, phase II trials demonstrated activity of imatinib with high rates of disease stabilisation (60–80%) despite rather low response rates (6–19%) and with the expected well-known toxicity profile of imatinib. However, the lack of randomisation in a disease with the possibility of spontaneous disease regressions makes it difficult to determine the definitive role of imatinib in this condition. Imatinib should clearly not be the treatment of first choice if DT remission is intended.

Of note, eight patients who failed imatinib on the GISG study and subsequently treated with nilotinib demonstrated a progression arrest rate at 3 months of 88% (7/8) that was sustained until the end of the study at 24 months [44].

Sorafenib is an active agent and currently the best-studied TKI in DTs. After an initial retrospective study (3 credits) reporting a promising ORR of 25% and disease stabilisation and improvement in symptoms in 70% of patients treated at a dose of 400 mg oral daily [45], a phase III, placebo-controlled, randomised trial (NCT02066181) was conducted. Results were published in the New England Journal of Medicine (NEJM) in December 2018 and were included here after formal finalisation of the literature search. 87 patients (median age 39 years, range 18–72) were treated with sorafenib 400 mg daily or placebo in a 2:1 randomisation (sorafenib: 50 patients, placebo: 37 patients). Median PFS, the primary end-point of the study, was 11.3 months in the placebo group and was not reached in the sorafenib arm ($p < 0.0001$); the risk of progression could be reduced by the factor 7 in favour of sorafenib (HR = 0.14). The ORR was 33% for sorafenib; however, the placebo arm ORR was as high as 20% demonstrating spontaneous regression and giving useful information on the natural history of this disease. The

study has been unblinded due to these results. Common toxicities for sorafenib included fatigue, rash, hypertension and gastrointestinal symptoms [46]. Of note, responses were also seen in patients receiving a dose as low as 200 mg with a clear benefit in terms of reduced toxicity. Limitations of the study are the inclusion of patients with very modest increase in tumour size (10%), no central radiological review and no guidelines to assess symptoms severity suggesting that many patients included in this study would probably not have required an active treatment.

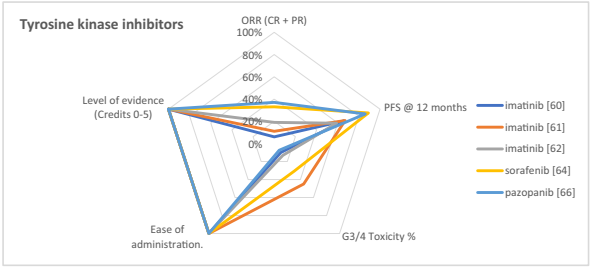
Pazopanib was also studied both retrospectively in a small series (1 credit) [47] and prospectively in a phase II randomised study (DESMOPAZ, NCT01876082) evaluating pazopanib 800 mg oral daily versus methotrexate (30 mg/m^2) plus vinblastine (5 mg/m^2) including 72 RECIST progressive DT patients (pazopanib: 48 patients, chemotherapy arm: 24 patients; median age 40 years, range 18–79). The 6-month non-progression rate was 82% for pazopanib, with response rates similar to those of sorafenib [48]. Of note, only patients with truly progressive disease based on independent review of two imaging performed at less than 6 months interval were included in this study.

Taken together, these findings show clear clinical benefit of TKIs in DT. The effect appears to be more pronounced with sorafenib and pazopanib compared to imatinib and likely achievable with even low dosages, limiting the potential adverse effects.

4.3. Chemotherapy options

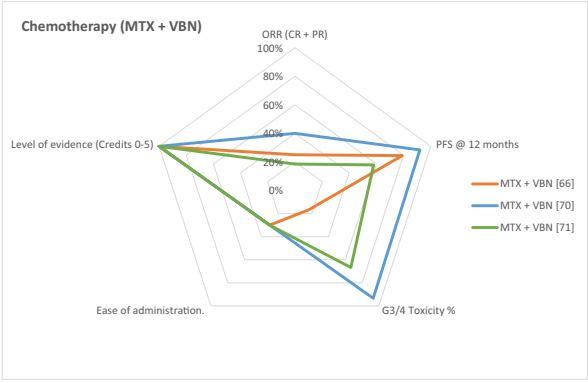
Chemotherapy options include a "low-dose" regimen with methotrexate plus vinblastine or vinorelbine, or conventional dose chemotherapy using anthracycline-based regimens as similarly instituted for the treatment of soft tissue sarcomas, and pegylated liposomal doxorubicin. Most of the published data have evaluated the "low-dose" chemotherapeutic option, mainly in retrospective series (3 credits each) [49–51] and two prospective phase II studies (5 credits each) [52,53]. Response rates are in the range of 35–40%, but usually occur as late as several months after the start of therapy. Shrinkage can continue even after treatment withdrawal, and long-term disease control is usually achieved in up to 50–70% of the patients depending on the series. Of note, at recurrence, and especially if the patients responded to the therapy, the treatment can be repeated with substantial benefit. Similar results are observed in children.

Oral vinorelbine alone has also been evaluated retrospectively. The toxicity profile was excellent, with



Treatment class	Tyrosine kinase inhibitors				
Drugs	Imatinib	Imatinib	Imatinib	Sorafenib	Pazopanib
ORR (CR + PR) [%]	6	11	19	33	37
PFS @ 12 months [%]	66	67	59	89	86
G3/4 toxicity [%]	10	45	13	31	8
Ease of administration	Oral				
Level of evidence / credits (0-5)	5				
Reference	Chugh [60]	Penel [61]	Kasper [62]	Gounder [64]	Toulmonde [66]

Abbreviations: ORR, overall response rate; CR, complete response; PR, partial response; PFS @ 12 months, progression-free survival rate at 12 months; G3/4 toxicity, grade 3/4 toxicity; level of evidence/credits (0-5): 0 = 0 %, 1 = 20 %, 2 = 40 %, 3 = 60 %, 4 = 80 %, 5 = 100 %; ease of administration: inpatient chemotherapy = 0 %, IV weekly = 30 %, IV monthly = 50 %, oral = 100 %.



Treatment class	Chemotherapy		
Drugs	MTX + VBN	MTX + VBN	MTX + VBN
ORR (CR + PR) [%]	25	40	19
PFS @ 12 months [%]	79	92	58
G3/4 toxicity [%]	17	93	67
Ease of administration	IV weekly		
Level of evidence / credits (0-5)	5		
Reference	Toulmonde [66]	Azzarelli [70]	Skapek [71]

Abbreviations: MTX, methotrexate; VBN, vinblastine; ORR, overall response rate; CR, complete response; PR, partial response; PFS @ 12 months, progression-free survival rate at 12 months; G3/4 toxicity, grade 3/4 toxicity; level of evidence/credits (0-5): 0 = 0 %, 1 = 20 %, 2 = 40 %, 3 = 60 %, 4 = 80 %, 5 = 100 %; ease of administration: inpatient chemotherapy = 0 %, IV weekly = 30 %, IV monthly = 50 %, oral = 100 %.

Fig. 4. Proposed 5-dimensional model for selection from available medical therapies in DT.

no grade 3–4 toxicity reported. Symptomatic relief at three months was seen in 80% of patients and best response was 32% partial response (PR), 58% stable disease (SD) and 10% disease progression (PD). Progression-free survival (PFS) rates at 3, 6 and 12 months were 98%, 92% and 88%, respectively [54]. Recent data support the use of hydroxyurea in children [55]. Two regimens, doxorubicin plus dacarbazine [56] and low-dose chemotherapy with methotrexate plus vinca alkaloids [57], have demonstrated activity in retrospective analysis in familial adenomatous polyposis (FAP)-associated DT.

Conventional dose chemotherapy using anthracycline-based regimens is another option and is expected to achieve more rapid tumour responses. It has been evaluated only in two retrospective series (3 credits each) with reported response rates of 37% (13 of 35 patients) and 54% (7 of 13 patients) [58,59]. This type of chemotherapy is usually administered for six to eight cycles, i.e. until the maximum tolerated dose of anthracycline is reached. Responses to chemotherapy observed in children is superimposable to those observed in the adult population.

Finally, the administration of pegylated liposomal doxorubicin at 40 mg/m^2 every 4 weeks has also been reported in two uncontrolled patient series (1 credit each) with a response rate of approximately 35% and an acceptable toxicity level and - importantly in this young patient population - less cardiac toxicity than conventional doxorubicin [51,60].

The evaluation of the clinical benefit in terms of pain control associated to all these drugs is more complex, as no prospective studies with a rigorous health-related quality of life (HRQoL) and pain assessment have been conducted so far.

In summary, due to the lack of comparative studies we are still not able to propose a definitive sequence of the existing systemic treatment options. Randomised data only exist for sorafenib, pazopanib and methotrexate plus vinblastine. Prospective phase II studies do exist for the administration of low-dose chemotherapy with methotrexate plus vinblastine and for the use of imatinib. In general, it is reasonable to employ less toxic therapy initially followed by more toxic agents in a stepwise fashion. Out of the variety of possible systemic treatment options, one can be chosen taking into account the (1) level of evidence, (2) overall response rate, (3) PFS rate, (4) ease of administration and (5) expected toxicity of the administered drug following a 5-dimensional model (Fig. 4). As an example, in a worst-case scenario with a mesenteric, potentially life-threatening DT there is consensus to administer more aggressive therapies.

5. Assessment of treatment effects

See online supplements.

- Assessment of treatment effects in DT remains an unresolved issue and no standard validated response criteria are available as of today.
- RECIST does not robustly identify all clinically relevant responses, though the majority of prospective trials report efficacy using RECIST.
- Integration of “tissue response” is probably needed, mainly based on MRI signal changes.
- Contrast-enhanced MRI or alternatively CT are the preferred modalities for monitoring DT. A role for Fluorodeoxyglucose (^{18}F) FDG-PET in the evaluation of patients with DT has not been demonstrated.
- Circulating tumour DNA is presently under evaluation and may become a valid biomarker of response/progression.
- HRQoL evaluation should be included in any assessment of clinical benefit; validation of a specific tool for DT patients is currently under way.
- A comprehensive consensus definition of clinical benefit from treatment of DT patients needs to be developed. Thus, validation of dedicated response criteria in DT should be included in the design of future clinical studies.

6. Pain, quality of life, fertility, pregnancy

The evidence in this clinical setting is scarce and further clinical trials must integrate HRQoL as an end-point including levels of functioning and symptoms (most importantly pain). Management of pain or functional impairment urgently needs specific research. Comprehensive programmes for DT patients should include physical, psychological and social support. A DT is not a contraindication for future pregnancies in favourable evolution and pregnant DT patients should be followed closely by obstetricians and desmoid clinicians. For further details see online supplements.

7. Which endpoints, study designs and regulatory requirements do we need for DT?

See online supplements.

Key questions

- Identify predictive factors for the failure of the active surveillance strategy.
- Provide stronger data about the risk of DT in FAP patients treated by prophylactic surgery.
- Better assess the symptomatic burden and need of supportive care in DT.
- Stimulate specific research on the symptomatic management of DT.
- Better describe the imaging changes observed during active surveillance and during treatment and better define the response or failure to treatment.
- Develop and validate specific HRQoL tools.
- Provide larger data about pregnancy, birth control and fertility in DT patients.
- Provide larger data about the specificity of paediatric patients.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organisations with which the authors are affiliated.

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.11.013.

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