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REVIEW

Capturing Patient Voice to Improve Outcomes That Matter to Patients with Desmoid Tumor

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Abstract: Desmoid tumors (DT) are rare, intermediate-grade sarcomas characterized by locally aggressive growths that commonly occur intra-abdominally, in the abdominal wall, or in the extremities. Desmoid tumors are 2-3–fold more common in females than males, with most patients aged <40 years at diagnosis. Clinical course of DT is highly variable but rarely fatal, with median overall survival >80% at 20 years. However, patient morbidity and DT symptom burden can be high. DT significantly reduce patient quality of life, imposing substantial physical, emotional, and social burdens. Pain, fatigue, and insomnia are common symptoms; disfigurement, mobility restrictions, and, rarely, the need for amputation may also result. Despite its limited impact on survival, patients with DT may have anxiety and depression levels commensurate with those associated with malignant sarcomas. Thus, DT impose an array of significant, long-term morbidities on a young patient population. In order to evaluate the impact of these morbidities, patient-reported outcome (PRO) tools are used, which assess outcomes of importance to patients that extend beyond traditional oncology endpoints. General or oncology-related PROs can be used; although currently, the only DT-specific, validated PRO measure is the GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale (GODDESS©), consisting of an 11-item DT Symptom Scale (DTSS) and a 17-item DT Impact Scale (DTIS). DTSS and DTIS were secondary endpoints in DeFi, a randomized phase 3 trial of nirogacestat; blinded, pooled data from DeFi were used to validate GODDESS reliability and responsiveness as a PRO measure in DT. Another DT-specific PRO measure, the Desmoid-Type Fibromatosis Quality of Life (DTF-QoL) questionnaire, has been developed but not validated. As novel DT therapies continue to be developed, incorporating DT-specific PRO measures into clinical trials will be key to capturing patient voice, improving outcomes of importance to this unique patient population, and assisting patients and providers in selecting optimal treatment.

Keywords: patient-reported outcomes, PRO, GODDESS, quality of life, fibromatosis, rare disease

Introduction

Desmoid tumors (DT), also known as desmoid-type fibromatosis or aggressive fibromatosis, are intermediate-grade sarcomas characterized by locally aggressive and infiltrative growths that do not metastasize.[1,2] They may be multifocal, with common anatomical sites for DT comprising the abdominal wall, extra-abdominal locations (limbs, pelvic girdle, chest wall, and head and neck), and intra-abdominal locations (mesentery and pelvis).[3] The majority of cases are sporadic, but approximately 5–10% of DT are associated with familial adenomatous polyposis (FAP).[4]

Among the factors that define the DT patient population are its rarity (incidence of up to 6 individuals per 1 million annually)[1,5,6] and its more frequent (2- to 3-fold) occurrence in females than in males.[6–8] Desmoid tumors are most commonly diagnosed in adulthood, with the majority of patients being less than 40 years of age at diagnosis.[6,7] Thus, the DT population includes a significant number of women of childbearing age.

The clinical course of DT is highly variable and often unpredictable.[1,5,9] Initial growth is frequently followed by stabilization,[10] and a 20–30% rate of spontaneous regression has been described.[1] Local recurrence rates after treatment can be high, with rates of 30% reported in patients with head and neck DT.[11] Mortality with DT is low; overall survival (OS) among patients with DT 20 years after diagnosis has been reported to be >80%.[12]

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Although DT are rarely fatal, the morbidity and long-term patient burden associated with them can be quite sizable. Symptoms associated with DT depend to a large extent on tumor location, but fatigue and pain are common.[13] Among the symptoms most disturbing to patients are disfigurement/altered appearance, nerve pain, and decreased range of motion.[14]

Accurate differential diagnosis poses a significant challenge in DT management. Because of its rarity and many histological and clinical similarities to other soft-tissue sarcomas, misdiagnosis rates for DT may be as high as 30–40% during an initial work-up,[1,8,13] which can result in additional treatments (eg, surgical excision) and delays for patients in receiving appropriate disease management. Other challenges are related to the assessment of treatment efficacy. For example, while the traditional endpoints of OS and progression-free survival (PFS) used in trials of malignant tumors are meaningful, they do not fully capture outcomes of importance to patients with DT, whose survival is longer and whose age of onset is generally younger compared with cancer patient populations. Among patients with DT, efficacy outcomes such as OS, PFS, and objective response rates are commonly used but are far from the only outcomes of importance. Further, patients can experience periods of stable disease, in which patients are not progressing but do not achieve complete or partial response to treatment. For these reasons, treatment goals for DT must extend beyond clinical and radiographic benefits to encompass improvements in symptoms most meaningful to patients. These, in turn, can only be assessed using patient-reported outcome (PRO) measures that are specifically designed to assess key items, such as pain, insomnia, fatigue, functioning with daily activities, and overall quality of life (QoL).[4,9,14] A more in-depth look at DT burden and assessment is presented below.

Unique Disease Burden of Desmoid Tumor

As previously noted, morbidity in patients with DT is closely related to the tumor site. Depending on where they are located, DT may infiltrate or obstruct adjacent organs, blood vessels, and muscles, or they may compress nerves.[9] Further, DT located in extremities may restrict joint movement, causing serious limitations in physical activity. In rare cases, DT or iatrogenic injury due to repeated surgical tumor resection can result in the need for limb amputation.[15] Desmoid tumor symptoms and sequelae, therefore, vary considerably between individual patients.

Commonly reported symptoms of DT include nerve and muscle pain, disfigurement/altered appearance, decreased range of motion, fatigue, and insomnia.[14,16] Notably, these cannot be quantified through clinicians' reports and other biomedical measures but must be assessed by patients.[17] In one study of 27 patients with DT, patients rated pain as the most debilitating symptom, and dependence on painkillers was identified as a significant concern.[18] In a separate study of 382 patients with DT, pain was significantly associated with tumor size ($P = 0.013$), tumor site ($P < 0.001$), functional impairment ($P = 0.001$), and poor QoL ($P < 0.001$).[19] Further, the magnitude of symptom burden varies widely among patients, with one recent study of 235 patients with DT identifying 31% as highly symptomatic.[16] Of note, high symptom burden was independently associated with poorer health-related QoL (HRQoL) in a multivariate analysis.

Many factors are responsible for the significantly reduced QoL and activities of daily living associated with DT, which carries substantial physical, emotional, and social burdens.[9,20] Quality of life was assessed via focus groups and interviews in a sample of 27 patients with DT using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30),[18] a standard QoL instrument commonly used in cancer trials in which higher scores represent either a higher (better) level of functioning or higher (worse) symptoms.[21,22] Scores for all functional scales in patients with DT were low, indicating below average function: physical, role, social, cognitive, and emotional functions were 74.4, 55.8, 52.8, 70.1, and 56.9, respectively.[18] The global QoL scale was similarly low, at 56.9. Symptom scales were high (pain, 59.0; insomnia, 56.9; fatigue, 53.6), indicating a considerable symptom burden. Conclusions may be limited by the fact that EORTC QLQ-C30 was not specifically designed to address DT and was not validated in this population, although the trends observed appear to be clear.

A prospective study also used the EORTC QLQ-C30 along with other questionnaires to compare QoL in 102 patients with DT with an equal number of healthy controls.[23] Global health status per EORTC QLQ-C30 was significantly poorer in those with DT (65.6 vs 81.4; $P < 0.0001$) (Figure 1A). All functional scales were also significantly ($P < 0.0001$) poorer for patients with DT except for cognitive functioning. Among symptom scales, fatigue ($P < 0.0001$), pain ($P < 0.0001$), insomnia ($P = 0.0002$), and financial difficulties ($P < 0.0001$) were significantly worse for patients with DT (Figure 1B). Anxiety and depression were compared using the Generalized Anxiety Disorder Assessment (GAD-7)[24] and Patient

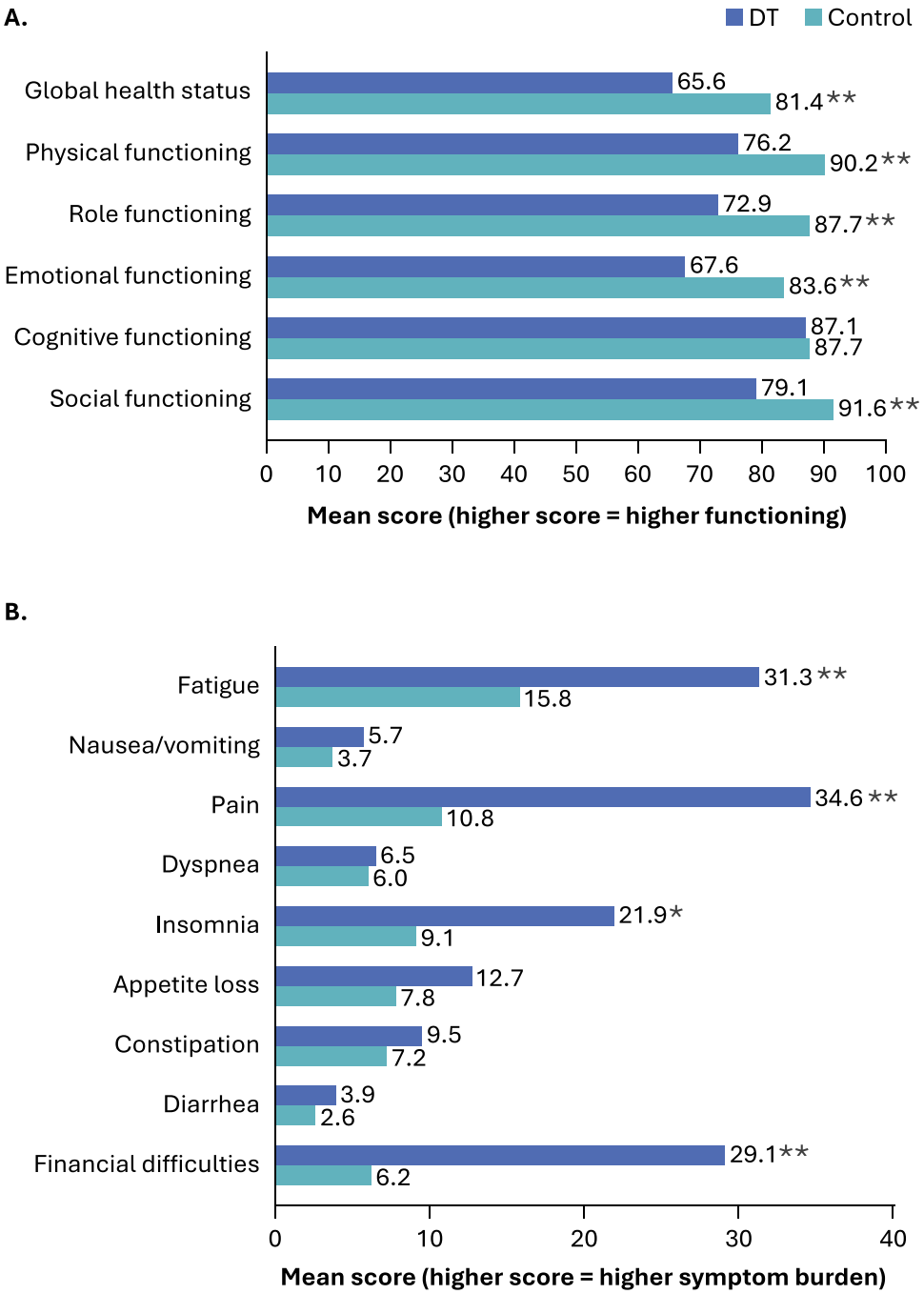

Figure 1 Mean EORTC QLQ-C30 scores in patients with DT (n=102) versus healthy controls (n=102).[23] (**A**) Global health and functional scales, with higher scores representing higher functioning. (**B**) Symptom scales, with higher scores representing higher patient symptom burden. *Indicates $P = 0.0002$, and **Indicates $P < 0.0001$.

Health Questionnaire-9 (PHQ-9).[25] Both anxiety ($P = 0.04$) and depression ($P = 0.001$) were significantly more common in patients with DT, with 50% of these patients reporting some degree of depression.[23]

Another study examining anxiety and depression in DT carried out a longitudinal analysis that compared 94 patients with DT with 402 patients with malignant sarcoma using the Distress Assessment and Response Tool (DART),[26] a validated (but non-DT specific) questionnaire that includes PRO measures from PHQ-9 for depression and GAD-7 for anxiety.[20] Interestingly, investigators found that anxiety and depression in patients with DT were significantly ($P = 0.01$) greater in patients with abdominal wall DT than in the sarcoma group, and among patients with DT outside of the abdominal wall, distress levels were equivalent to those of patients with malignant sarcomas. Emotional symptoms,

including anxiety and depression, were heightened in approximately one-third of patients and persisted for >6 months following treatment. Thus, the more favorable survival prognosis associated with DT does not appear to alleviate patient anxiety or lessen depression.

Clearly, DT impose an array of significant and varying morbidities on a relatively young, predominantly female patient population. Given its lack of significant mortality, treatment goals for managing DT require a more long-term focus than those for malignant diseases. Consequently, meaningful improvements in the lives of patients with DT cannot be measured by survival endpoints such as PFS alone but require a more multidimensional assessment.

Patient Voice and Perspectives with Desmoid Tumor

The value of PROs in clinical trials is well established; depending on the type of trial, they may be included as primary, secondary, or exploratory/tertiary endpoints.[27] Importantly, their use in clinical trials has increased over time.[27] While there may be challenges including PRO data in product labeling due to guidance from the US Food and Drug Administration (FDA),[28] approximately 26% of FDA-approved drugs between 2016 and 2020 included PRO-related labeling statements, of which 20% were based on PRO measures specifically developed to support key clinical endpoints (eg, the Psoriasis Symptom and Sign Diary for guselkumab).[29] An earlier analysis indicated that a still higher percentage of drugs approved by the European Medicines Agency (47% [EMA] vs 19% [FDA] from 2006–2010) carried a PRO label claim.[30]

One example of the use of PROs to support label claims among anticancer agents is the myelofibrosis drug ruxolitinib. Since treatment effects of ruxolitinib in pivotal trials could not be sufficiently captured by spleen volume reduction (the primary endpoint) and OS (a secondary endpoint), improvements in patient outcomes were assessed as an additional secondary endpoint through a PRO measure called Total Symptom Score (TSS) derived from a novel questionnaire, the modified Myelofibrosis Symptom Assessment Form.[31] The significant >50% reduction in TSS in the ruxolitinib arm at week 24 (46% vs 5% for placebo; $P < 0.0001$) indicated improvements meaningful to patients and became an essential part of product approval.[32] Ruxolitinib extended the median overall survival of patients with myelofibrosis to approximately 7 years.[33] The decades-long median survival associated with DT further increases the importance of PROs in supporting treatment benefits.

The management of patients with DT has undergone a profound transformation in recent years. The treatment paradigm has shifted away from surgery, which was associated with high morbidity and frequent tumor recurrence, to watch and wait/active surveillance as the primary treatment modality in the majority of patients.[4,15,34] Minimally invasive local therapies, including cryoablation, are being utilized and studied with increasing frequency.[35] Radiation is reserved for use after careful discussion in a tumor board, given the risk of secondary malignancies.[4] Systemic therapies, including tyrosine kinase inhibitors and cytotoxic chemotherapy, are also often recommended, though until recently none carried a specific regulatory approval for the treatment of DT.[4] This changed in late 2023 when nirogacestat—a targeted, oral, small molecule gamma secretase inhibitor—was approved by the FDA for the treatment of progressive DT requiring systemic therapy.[36,37] This is the first agent to receive regulatory approval for the treatment of DT.[38]

A number of the systemic and local therapies used in DT have been or are currently being studied in clinical trials (Table 1). These include a trial of another gamma secretase inhibitor, AL102 (NCT04871282 [RINGSIDE])[39]; kinase inhibitors imatinib (NCT01137916[40] and NCT00287846), sorafenib (NCT02066181),[41] and pazopanib (NCT01876082 [DESMOPAZ])[42]; the chemotherapy agent nab-paclitaxel (NCT03275818 [ABRADES])[43]; high intensity focused ultrasound ablation (NCT05111964 [SarcAblate]); and cryoablation (NCT06081400 [CRYODESMO-02]). Further, there are trials that do not specify therapies (NCT02867033 [ALTITUDES][19,44] and NCT04289077 [QUALIFIED]).[45] Among all of these trials, only the nirogacestat DeFi trial NCT03785964,[46] the sorafenib trial NCT02066181,[41] and the AL102 trial NCT04871282[39] are phase 3, randomized, placebo-controlled studies.

Understanding treatment effects on pain, DT-specific symptoms, and their impact on patient lives, functioning, and overall QoL is key to informing appropriate therapy. In recognition of this, each of these studies has included one or more PRO as an endpoint, though typically not a primary one. The use of PROs as secondary endpoints in randomized trials may support or, alternatively, contradict primary endpoint findings but, in either case, may prove critical to study interpretation.[17] The value of PROs in clinical trials, of course, depends on their appropriate application and analysis. As seen in Table 1, however, there does not appear to be any standard instrument used to assess PROs in current DT trials. The majority of studies use questionnaires that are not specific to DT and have not been validated in the DT patient

Table 1 Clinical Trials for Patients with Desmoid Tumors (N≥10) and PRO Outcomes Listed on Clinicaltrials.gov as of March 12, 2024

Trial	Name	Treatment	Design	Status	Phase	N	PRO Measure	PRO Endpoint
NCT05111964	SarcAblate	HIFU	SA	R	NA	16	BPI EORTC QLQ-C30	2°
NCT01981551[47]	–	Nirogacestat	SA	C	2	17	MDASI	2°
NCT04195399	–	Nirogacestat	SA	ANR	2	35	**GODDESS** PROMIS	Other
NCT01137916[40]	–	Imatinib	SA	C	2	39	NS	2°
NCT00287846	–	Imatinib	SA	C	1/2	40	NS	2°
NCT03275818[43]	ABRADES	Nab-paclitaxel	SA	C	2	69	AQA BPI and BPI-SF	1° and 2°
NCT01876082[42]	DESMOPAZ	Pazopanib	RA, NC	C	2	72	BPI EORTC QLQ-C30	2°
NCT02066181[41]	–	Sorafenib	RA, DB, PC	C	3	87	BPI-SF LASA PRO-CTCAE	Other
NCT03785964[46]	DeFi	Nirogacestat	RA, DB, PC	ANR	3	142	BPI-SF EORTC QLQ-C30 **GODDESS** PROMIS	2°
NCT06081400	CRYODESMO-02	CT Cryoablation	RA	R	NA	150	BPI EQ-5D	2°
NCT04289077[45]	QUALIFIED	–	Obs	C	NS	156	**DTF-QoL** EORTC QLQ-C30 EQ-5D-5L	1°
NCT04871282[39]	RINGSIDE	AL102	RA, DB, PC	ANR	2/3	192	BPI-SF EQ-5D **GODDESS** PROMIS	2°
NCT02867033[19,44]	ALTITUDES	–	Obs	ANR	NA	628	EORTC QLQ-C30 HADS	2°

Notes: Desmoid tumor–specific questionnaires are shown in bold.

Abbreviations: ANR, active not recruiting; AQA, Analgesic Quantification Algorithm; BPI, Brief Pain Inventory; BPI-SF, BPI Short Form; C, completed; DB, double-blind; DTF-QoL, Desmoid-Type Fibromatosis Quality of Life questionnaire; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality Of Life Questionnaire Core-30; EQ-5D, EuroQoL-5 Dimension; GODDESS©, Gounder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale; HADS, Hospital Anxiety and Depression Scale; HIFU, high-intensity focused ultrasound; LASA, Linear Analogue Self Assessment; MDASI, MD Anderson Symptom Inventory; NA, not applicable; NC, non-comparative; NS, not specified; Obs, observational; PC, placebo-controlled; PRO, patient-reported outcome; PRO-CTCAE®, PRO version of the Common Terminology Criteria for Adverse Events; PROMIS, Patient Reported Outcome Measurement Information System; R, recruiting; RA, randomized; SA, single-arm.

population. Some resulting limitations in outcome measurements and current efforts to produce more appropriate measures of PROs are discussed below.

Patient-Relevant Tools in Desmoid Tumor

GODDESS

In order to better capture the patient experience and treatment effects in DT, the GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale (GODDESS©) was developed through a collaboration of the Desmoid Tumor Research Foundation and Memorial Sloan Kettering Cancer Center.[48] The goal was to construct a novel regulatory and clinical trial endpoint uniquely developed for patients with DT to complement existing general PRO measurements, such as the EORTC QLQ-C30.[14] The process began with concept elicitation interviews of patients who were asked to spontaneously identify symptoms and/or impacts that they attributed to DT.[14] Cataloging of de-identified patient summaries provided a list of 33 unique symptoms that were drafted into 4 key symptom domains and 5 impact

domains, resulting in a 35-item draft instrument based on a 24-hour recall for the symptoms and 7-day recall for impacts. In order to probe patient comprehension of instruction, items, and response options, a series of cognitive interviews with a separate cohort of patients with DT was then carried out in 3 phases.

The final version of GODDESS includes an 11-item Desmoid Tumor Symptom Scale (DTSS), which measures signs and symptoms of DT, and a 17-item Desmoid Tumor Impact Scale (DTIS), which examines the impact of DT on physical functioning, emotional functioning, and sleep (Figure 2). All symptom items except for tumor location are evaluated on a 0–10 numerical scale, with 0 being "none" and 10 being "as bad as you can imagine". Impact items use either a 0–10 scale or a 5-point Likert scale, with anchors varying for amount, frequency, satisfaction, and severity. The reliability, construct validity, and responsiveness of GODDESS were assessed using results from DeFi, the global phase 3 trial of nirogacestat (NCT03785964). In addition, meaningful change thresholds (MCTs) for improvement of symptom and impact domain scales were estimated, which potentially may be of use in identifying responders and non-responders in clinical trials.[48]

DeFi is the largest randomized, double-blind, placebo-controlled trial of patients with DT completed to date (Table 1). The trial randomized adults with progressing DT to twice-daily oral nirogacestat or placebo, taken in continuous 28-day cycles.[46] The primary endpoint was PFS; secondary efficacy endpoints included confirmed objective response rate and the change from baseline at cycle 10 in the following PROs: GODDESS DTSS total symptom score and DTIS physical function domain scores; EORTC QLQ-C30 scales for global health status QoL, physical functioning, and role functioning; and Brief Pain Inventory-Short Form (BPI-SF) average worst pain intensity score. All pre-specified PRO endpoints in DeFi were met in a statistically significant and clinically meaningful manner. In the nirogacestat arm, GODDESS DTSS total symptom score ($P < 0.001$) and DTIS physical functioning domain score ($P < 0.001$) were significantly improved relative to placebo; improvements were seen by the first post-treatment assessment (cycle 2) and were sustained throughout the trial. These improvements in DT-specific physical and role functioning as assessed by GODDESS were corroborated by the well-established EORTC QLQ-C30 and BPI-SF questionnaires, which also demonstrated significant improvements with nirogacestat relative to placebo at cycle 10 ($P \leq 0.01$, all).[46]

Validity and reliability analyses for DTSS and DTIS scales using data from DeFi indicated that all scores were valid and reliable measures of DT symptomology and impact, and the recommended reliability thresholds for construct validity were met.[48] Further, GODDESS proved sufficiently responsive regardless of low patient symptomology at baseline. Based on these findings, GODDESS became the first validated DT-specific PRO measure designed to meet FDA regulatory requirements.[14,28]

In addition to DeFi, two other DT trials are currently using GODDESS PROs as prespecified outcome measures (Table 1). An ongoing single-arm, phase 2 trial (NCT04195399) investigating nirogacestat in patients <18 years of age with progressing DT utilizes PROs per GODDESS as an exploratory endpoint. RINGSIDE (NCT04871282) is an ongoing global phase 2/3 trial of the gamma secretase inhibitor AL102 recruiting patients ≥12 years of age with progressing DT.[39,49] The primary outcome measure is PFS; changes from baseline in GODDESS DTIS and DTSS scores are among the prespecified secondary outcomes. Promising safety and response data from the non-randomized phase 2 part of the trial have been reported[39] and have led to FDA orphan drug and fast track designation,[50] although no data regarding PROs have been reported.

DTF-QoL

A DT-specific HRQoL questionnaire has been developed in Europe in accordance with EORTC guidelines to be used as a supplement to the widely used EORTC QLQ-C30 questionnaire[45] but has not yet been validated. Initially, focus groups in the United Kingdom and the Netherlands were interviewed, and 124 issues spanning domains that included diagnostic pathways, treatment pathways, daily limitations, and experience with the current healthcare system were identified. These were ranked according to relevance by patients and healthcare providers, after which the 102 most relevant were converted into questions for the Desmoid-Type Fibromatosis Quality of Life (DTF-QoL) questionnaire.

The 96-item DTF-QoL questionnaire includes symptom scales regarding emotional and psychological consequences, physical consequences, and pain and discomfort (Figure 3).[51] Patients are asked to score items on a 4-point Likert scale, (1, not at all; 2, a little; 3, quite a bit; and 4, very much). The developers of DTF-QoL, concerned that the 24-hour

Desmoid Tumor Symptom Scale (DTSS)

11 items assessing key signs and symptoms severity

Total symptom score (items 1-7)

Domains	Item(s)	Item scoring (higher indicates more severe)
Pain domain	1: Pain 2: Dull pain 3: Shooting pain	NRS: 0 → 10[b]
—	4: Fatigue	NRS: 0 → 10[b]
Extra-abdominal domain	5: Swelling 6: Muscle weakness 7: Difficulty moving	NRS: 0 → 10[b]
—	8: Tumor location	N/A
Intra-abdominal Domain[a]	9: Abdominal pain 10: Nausea 11: Fullness	NRS: 0 → 10[b]

Desmoid Tumor Impact Scale (DTIS)

17 items assessing symptoms impact on functioning and daily living

Physical functioning domain (items 1, 2, 6, 7, 8)

Domains	Item(s)	Item scoring (higher indicates more severe)
—	1: Moving	Likert: none → all[c]
—	2: Reaching (frequency)	Likert: none → all[c]
Sleep impact	3: Falling asleep 4: Comfortable in bed 5: Staying asleep	Likert: none → all[c]
—	6: Vigorous activity	Likert: none → all[c]
—	7: Moderate activity	Likert: none → all[c]
—	8: Accomplished less	Likert: none → all[c]
—	9: Avoidance because of appearance	Likert: none → all[c]
—	10: Reaching (difficulty)	NRS: 0 → 10[d]
—	11: Dissatisfied with appearance	NRS: 0 → 10[d]
Emotional impact	12: Fear of tests 13: Fear of growth/recurrence 14: Hopelessness 15: Anger 16: Anxiety 17: Frustration	NRS: 0 → 10[d]

Figure 2 GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale (GODDESS©) PRO Measure.[48] [a]Administered only to those reporting intra-abdominal tumor location in item 8. [b]11-point scale where 0 indicates "none" and 10 indicates "as bad as you can imagine", with a 24-hour recall period. [c]5-point Likert scale ranging from "none of the time" to "all of the time". [d]11-point scale where 0 indicates "none" and 10 indicates "as bad as you can imagine", with a 7-day recall period.
Abbreviations: NA, not applicable; NRS, numeric rating scale.

DTF-QoL Symptom Scales

Factor	Item	No. Qn.s	Period
W1	Emotional and psychological consequences	8	Past week
W2	Physical consequences	5	
W3	Pain and discomfort	3	

DTF-QoL Impact Scales

Factor	Item	No. Qn.s	Period
1	Concerns about condition	8	Since DX
2	Job and education	5	
3	Doctor-patient relationship, communication, and information	6	
4	Effect of DTF on relationships	13	
5	Physical limitations and consequences	8	
6	Diagnostic and treatment trajectory of DTF	7	
7	Parents and fertility	5	
8	Body image and sensations	4	
9	Supportive care	3	
10	Concerns around treatment and its consequences	4	
11	Unpredictable course and nature of DTF	11	

DTF-QoL Single Items

Item	No. Qn.s	Period
Decreased libido	1	4 weeks
Hair loss	1	Since DX
Changed life in negative way	1	
Hair color	1	
Wasting time of cancer specialists	1	
Rash treatment	1	

Figure 3 Desmoid Tumor Fibromatosis Quality of Life (DTF-QoL) questionnaire.[51] Patients are asked to score items on a Likert scale ranging from 1 (not at all) to 4 (very much).
Abbreviations: DTF, desmoid-type fibromatosis; DX, diagnosis; Qn, question.

symptom recall period of GODDESS could result in bias due to momentary factors,[45] employed a longer (1-week) recall period for the 16 symptom items and a 4-week recall period for the question on reduced libido.[51] For the 74 impact scale items and 5 of the single items, a still longer recall period "since diagnosis" is used. Although DTF-QoL might be applied less frequently than GODDESS due to these much longer recall periods, study authors have noted that completing its many items may be exhausting to patients and suggested that in the future, computer adaptive testing may help evaluate HRQoL more precisely with fewer items.[51]

The psychometric properties of DTF-QoL were pre-tested for use in conjunction with the EORTC QLQ-C30 questionnaire in adults with sporadic DT in QUALIFIED (NCT04289077), a multicenter, observational cohort study conducted in the United Kingdom and the Netherlands.[51,52] In this study, DTF-QoL, EORTC QLQ-C30, and EQ-5D-5L (a generic instrument for describing and evaluating health)[53] were co-primary outcome measures. Item-scale reliability and convergent validity for DTF-QoL proved satisfactory for some scales (W1, W2, and Factors 4, 5, 8, and 11 [Figure 3]) but were suboptimal for others, possibly reflecting common themes.[51] In a separate analysis of QUALIFIED, DTF-QoL was used to identify symptom burden clusters and their associations with healthcare utilization, but the lack of clinical validation for this DT-specific questionnaire must be kept in mind.[16]

Conclusions

The DT patient journey frequently begins with a long diagnostic trajectory characterized by uncertainty and frustration.[18] Misdiagnosis as "cancer" or "malignant sarcoma" may cause emotional distress, which is not entirely alleviated by the eventual correct diagnosis of DT.[20] The long course of a patient's journey with DT may involve potential reliance on painkillers, a sizable financial burden, serious functional limitations, unfavorable employment status change, negative body image, loss of libido, and social isolation.[18] Few people, even among medical professionals, have any understanding of the disease, which is a source of frustration to patients.[18] Additionally, the burden of DT is disproportionately borne by women of childbearing and working age, and because it is associated with low mortality and a relatively young patient population, it typically continues for decades.

Understandably, from the point of view of these patients, the clinician-assessed time-to-event endpoints traditionally used in cancer trials alone are inadequate as sole measures of efficacy. Treatment effects on many of the outcomes affecting the daily lives of patients with DT can only be assessed by the patients themselves. Thus, validated, DT-specific PRO measures are critical in evaluating outcomes and need to be included among prespecified endpoints in DT clinical trials.

Until recently, only non–DT-specific PRO questionnaires existed. GODDESS is the first and only validated DT-specific PRO measure designed to meet FDA regulatory requirements[14]; the non-validated DTF-QoL was also designed specifically for use in patients with DT.[45] As new therapies continue to be developed for patients with this rare and heterogeneous disease, evaluating them in comparative trials against existing DT treatments, such as the recently approved gamma secretase inhibitor nirogacestat,[37,46,47] will become increasingly important. Incorporating DT-specific, non-redundant PRO measures that do not require excessive time or effort for patients to complete into such trials is key to assessing their real effects on patients with DT and paving the way to better outcomes in this unique patient population.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, analysis, interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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