Received: 2 December 2022 | Revised: 3 February 2023 | Accepted: 21 February 2023

DOI: 10.1002/ijc.34493

CANCER THERAPY AND PREVENTION

IJC INTERNATIONAL JOURNAL of CANCER

Pain in desmoid-type fibromatosis: Prevalence, determinants and prognosis value

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Funding information
APICIL Foundation; Intersarc; Ligue Nationale Contre le Cancer, Grant/Award Number: PRE2016.LCC/NP; S. Wisnia; SOS Desmoïde; French National Cancer Institute (INCa)

Abstract

The aim of this study is to evaluate the prevalence, determinants and prognostic value of pain at diagnosis in patients with desmoid-type fibromatosis (DF). We selected patients from the ALTITUDES cohort (NCT02867033), managed by surgery, active surveillance or systemic treatments, with pain assessment at diagnosis. Patients were invited to fill QLQ-C30 questionnaire and Hospital Anxiety Depression Scale. Determinants were identified using logistic models. Prognostic value on event-free survival (EFS) was evaluated using the Cox model. Overall, 382 patients were

Abbreviations: CI, confidence interval; Cox2, cyclo-oxygenase 2; *CTTNB1*, catenin beta 1; DF, desmoid-type fibromatosis; EFS, event-free survival; FAP, familial adenomatous polyposis; HADS, Hospital Anxiety Depression Scale; HR, hazard ratio; HR-QoL, health-related quality of life; MD, missing data; MICE, multiple imputation by chained equations; MRI, magnetic resonance imaging; NPRS, numeric pain rating scale; OR, odds ratio; QLQ-C30, EORTC Core Quality of life questionnaire C30; R0, microscopically margin-negative resection; R1, *microscopic residual tumor* resection.

included in the current study (median age: 40.2 years; 117 men). The prevalence of pain was 36%, without significant difference according to first-line treatment ($P = .18$). In the multivariate analysis, pain was significantly associated with tumor size >50 mm ($P = .013$) and tumor site ($P < .001$); pain was more frequent in the neck and shoulder locations (odds ratio: 3.05 [1.27-7.29]). Pain at baseline was significantly associated with poor quality of life ($P < .001$), depression ($P = .02$), lower performance status ($P = .03$) and functional impairment ($P = .001$); we also observed a non-significant association with anxiety ($P = .10$). In the univariate analysis, baseline pain was associated with poor EFS; the 3-year EFS was 54% in patients with pain compared to 72% in those without pain. After adjustment for sex, age, size and line of treatment, pain was still associated with poor EFS (hazard ratio: 1.82 [1.23-2.68], $P = .003$). One third of recently diagnosed patients with DF experienced pain, especially those with larger tumors and neck/shoulder locations. Pain was associated with unfavorable EFS after adjustment for the confounders.

KEYWORDS
depression, Desmoid-type fibromatosis, outcome, pain, quality of life

What's new?

The natural course of desmoid-type fibromatosis (DF) is unpredictable, ranging from spontaneous regression to life-threatening disease progression. Pain, which is a major concern in patients with DF, could be a revealing symptom. This prospective cohort study of newly diagnosed cases is the first study to analyze the frequency of pain in a large number of DF patients, as well as the determinants and consequences of pain. One third of recently diagnosed patients experienced pain, especially those with larger tumors and neck/shoulder locations. Pain severely impacted quality of life and was associated with unfavorable event-free survival after adjustment for confounders.

1 | INTRODUCTION

Desmoid-type fibromatosis (DF) is a rare soft tissue nonmetastatic infiltrative malignancy diagnosed in mainly women aged of approximately 40 years. The most common sites are the abdominal wall, limb and intra-abdominal areas. Approximately 10% of the cases are related to familial adenomatous polyposis (FAP). Excluding those cases related to FAP, most of the sporadic cases of DF are associated with somatic pathogenic variants of catenin beta 1 (*CTTNB1*) gene. The natural course of DF is unpredictable, ranging from spontaneous regression to life-threatening disease progression. Current front-line management is active surveillance followed by treatment in only cases of progressive DF.[1-3]

Pain, which is a common symptom in patients with DF, could be a revealing symptom. This pain could worsen with tumor progression and may contribute to the decision to start a systemic treatment regimen. Nevertheless, pain could occur in spontaneously regressing DF. Finally, in case of regression, spontaneous or following treatment, an evolution towards retractile fibrosis could be observed, which is also a cause of pain.[4,5] This evolution towards retractile fibromatosis is well documented in recent clinical trials (assessing clinical benefit of tyrosine kinase inhibitors), since the patients in these trials were prospectively followed up using sequential magnetic resonance imaging (MRI) to document treatment activity.

Since pain profoundly impacts the daily life of patients with DF, it is a major concern in patients with DF. We conducted a prospective cohort study of newly diagnosed cases of DF; data from 628 patients were collected. Prospective pain assessment as well as health-related quality of life (HR-QoL) and anxiety/depression data were obtained. The objectives of this study were to (i) determine the prevalence of pain at diagnosis, (ii) identify the determinants of pain and the consequences for the patient and (iii) estimate whether pain at diagnosis was associated with higher risk of poor outcome. We also aimed at evaluating the association between poor HR-QoL, anxiety and depression at diagnosis and the outcome.

2 | PATIENTS AND METHODS

2.1 | Study overview

ALTITUDES is a prospective nationwide clinical-biological cohort of newly diagnosed DF cases, diagnosed from January 2016 to February

2021 and confirmed by central pathological review.[1] The inclusion criteria were (i) newly diagnosed case of DF diagnosed in France, (ii) diagnosis confirmed by pathology review in the French Sarcoma Group, (iii) affiliation to National Health Insurance and (iv) signed informed consent (both parents' signature in adolescent patients). The exclusion criteria were (i) deprivation of liberty and (ii) patient not able or unwilling to provide consent. The ALTITUDES study does not include specific therapeutic interventions but provides prospective data (including the self-assessment Hospital Anxiety and Depression Scale [HADS][6] and EORTC QLQ-C30 version 3.0 questionnaire) and biobanking.[7] Pain was assessed by self-assessment at baseline using both a binary question (yes/no) and a numeric pain rating scale (NPRS, from 0 to 10). Pain information was subsequently collected at each visit; however, longitudinal assessment of pain is not part of the present study. The ALTITUDES study is purely descriptive and hypothesis generating; thus, no formal sample size calculation was performed.

2.2 | Patient selection

Patients enrolled within 6 months after diagnosis, treated by initial surgery or systemic treatment or with active surveillance as first approach were included in the study. Patients who were referred to investigating centers 6 months or later after initial diagnosis, as well as patients with no information about pain at diagnosis (participant flow in Figure S1) were excluded.

2.3 | Statistical analysis

We used chi-square and Wilcoxon tests, as appropriate, to evaluate the association between pain and the distribution of patient characteristics, tumor features and the parameters that could be consequences of DF rather than determinants, namely HR-QoL, anxiety and depression, performance status and functional impairment (as defined by the investigator).

Determinants of pain were identified using univariate and multivariate logistic regression. We considered sex, age, tumor size, DF location and *CTNNB1*-mutational status as potential determinants for pain. Multiple imputations by chained equations (MICE method) were used to manage missing values.

The association between pain (as well as quality of life, anxiety and depression) and outcome was analyzed using the event-free survival (EFS) as the endpoint. As previously reported, the events considered were local relapse after complete (R0/R1) resection, disease progression according to the local investigator after R2 resection, during active surveillance and systemic treatments or death from any cause.[8,9] EFS was censored at the date of the last contact when no event was reported in the follow-up and at the date of second-line treatment if treatment was started because of worsening symptoms but without documented progression or relapse. The association between pain and EFS was assessed by Log-rank test in the univariate analysis and by multivariate Cox models to control for possible confounders. We first evaluated the prognostic value of pain considering pain as a binary variable (yes vs no) and subsequently considering the level of pain (NPRS).

We evaluated the association between pain (yes vs no) and EFS according to the type of first-line management (active surveillance, systemic treatment or surgery) by including an interaction term between pain and first-line management in the multivariable model. Results are illustrated by a forest plot. As the study population included both patients with a history of polyposis and sporadic cases, which can be considered as two different entities, we also evaluated whether the association between pain and EFS varied between these two subgroups.

All the estimates are reported with their 95% confidence intervals (95% CIs) and analyses were performed at a two-sided 5% alpha level.

Statistical analyses were conducted using STATA/SE version 15.1 statistical software (StataCorp, LP, College Station, TX).

3 | RESULTS

3.1 | Study population and prevalence of pain at diagnosis

The study population consisted of 382 patients, including 117 men, with a median age of 40.2 years. The patient characteristics are depicted in Table 1; overall and according to the presence of pain at diagnosis or not, pain at diagnosis was confirmed in 137 patients with a prevalence of 36%. Among the 382 eligible patients, baseline NPRS scores were available for 338 patients. The distribution of NPRS was as follows: NPR = 0 (N = 245, 73%), NPR = 1-2 (N = 35, 10%) and NPR ≥3 (N = 58, 17%).

3.2 | Determinants and factors associated with pain at diagnosis

Pain at baseline was significantly associated with the tumor location ($P < .001$) and size ($P = .04$). We did not observe any significant difference between the patients with and without pain at diagnosis based on the patient demographic characteristics, marital status or professional activity (Table 1).

In the multivariate model (Table 2), the two determinants of pain were the tumor size and DF location. Pain was more frequent in tumors larger than 50 mm (adjusted odds ratio: 1.76; 95% CI: 1.12-2.76). Pain was more frequent in DF located in the neck and shoulder (OR: 3.04; 95% CI: 1.27-7.27) and less frequent in DF located in the abdominal wall (OR: 0.52; 95% CI: 0.31-0.87) or in intra-abdominal DF (OR: 0.42; 95% CI: 0.19-0.92).

The presence of pain was associated with lower performance status ($P = .024$) and functional impairment ($P = .001$). As illustrated in Figure S2 for the QLQ-C30, we observed a significantly lower score for the global health status ($P < .001$), as well as for the five functioning scales (physical functioning: $P < .001$, role functioning: $P < .001$,

TABLE 1 Patients characteristics, determinants and factors associated with pain at diagnosis in patients with desmoid-type fibromatosis.

Characteristics	Pain				Total (N = 382)		*P*-value
	No (N = 245)		Yes (N = 137)				
Sex							.49
Male	78	31.8%	39	28.5%	117	30.6%	
Female	167	68.2%	98	71.5%	265	69.4%	
Age at diagnosis (years)							.76
Median (min-max)	39.7	(0.1-78.4)	40.5	(10.8-76.9)	40.2	(0.1–78.4)	
Marital status (MD = 135)							.73
Bachelor	39	26.7%	28	27.7%	67	27.1%	
Married	86	58.9%	62	61.4%	148	59.9%	
Divorced	16	11.0%	10	9.9%	26	10.5%	
Widower	5	3.4%	1	1.0%	6	2.4%	
Professional activity (MD = 129)							.27
Yes	50	33.6%	42	40.4%	92	36.4%	
No	99	66.4%	62	59.6%	161	63.6%	
Preventive colectomy (MD = 6)							.34
Yes	10	4.1	3	2.2	13	3.5	
No	232	95.9	131	97.8	363	96.5	
History of polyposis (MD = 5)							.23
Yes[a]	21	8.6	7	5.2	28	7.4	
No	222	91.4	127	94.8	349	92.6	
Tumor sampling							.08
Core-needle biopsy	173	70.6	105	76.6	278	72.8	
Open surgical biopsy	28	11.4	19	13.9	47	12.3	
Surgical specimen	44	18.0	13	9.5	57	14.9	
Tumor location (MD = 2)							<.001
Abdominal wall	94	38.5	36	26.5	130	34.2	
Neck or shoulder	9	3.7	18	13.2	27	7.1	
Intra-abdominal or pelvic soft tissue	34	13.9	10	7.4	44	11.6	
Another site[b]	107	43.9	72	52.9	179	47.1	
Multifocal tumor							**.68**
Yes	15	6.1	7	5.1	22	5.8	
No	230	93.9	130	94.9	360	94.2	
Tumor size (mm) (MD = 3)							.04
Median (min-max)	50	(4-500)	60	(10-530)	50	(4-530)	
CTNNB1 mutational status (MD = 42)							.06
p.S45F mutation	23	10.6	22	17.7	45	13.2	
Other mutation/no mutation[c]	193	89.4	102	82.3	295	86.8	
ECOG performance status (MD = 39)							.024[d]
0	206	92.0	100	84.0	306	89.2	
1	15	6.7	16	13.4	31	9.0	
2	3	1.3	3	2.5	6	1.7	
Functional impairment (MD = 17)							.001
No	228	96.2	111	86.7	339	92.9	
Yes	9	3.8	17	13.3	26	7.1	
QLQ-C30 Global health status (%) (MD = 32)[e]							<.001
Median (min-max)	83.3	(0.0-100)	66.7	(16.7-100)	75.0	(0.0–100)	

TABLE 1 (Continued)

Characteristics	Pain				Total (N = 382)		*P*-value
	No (N = 245)		Yes (N = 137)				
Depression HADS (score)							.063
Median (min-max)	2.0	(0.0-15.0)	2.0	(0.0-13.0)	2.0	(0.0-15.0)	
Anxiety HADS (score)							.096
Median (min-max)	6.0	(0.0-20.0)	7.0	(0.0-18.0)	6.0	(0.0–20.0)	
First-line management							.18
Surgery	48	19.6	17	12.4	65	17.0	
Active surveillance	169	69.0	105	76.6	274	71.7	
Systemic treatments	28	11.4	15	10.9	43	11.3	

Abbreviations: HADS, Hospital Anxiety and Depression Scale; MD, number of missing values.
[a]Personal or familial history of familial adenomatous polyposis.
[b]Other locations: chest wall (n = 63), lower limb (n = 33), breast (n = 20), digestive tract (n = 19), upper limb (n = 13), intra-thoracic (n = 12), head (n = 10), gynecologic organ (n = 2), paratesticular (n = 1), not specified (n = 6, including four soft tissue lesions, not other specified and two visceral lesions, not otherwise specified).
[c]Among the 340 patients with informative *CTNNB1* mutational status, the distribution is as follows: p.S45F mutation (n = 45), p.41A mutation (n = 177), p.S45P mutation (n = 60), other mutation (n = 9: p.T41I, p.S33V, 4 p.H36P, p.(THR41_PRO52DELINSARG), p.HIS36DEL, p.(ALA39_GLY48DEL)), no mutation (n = 49).
[d]Comparison between Eastern Cooperative Oncology Group score 0 vs 1-2.
[e]The "Global Health" dimension of quality of life is based on questions 9 and 19 of the QLQ-C30 questionnaire. The distribution of QLQ-C30 scores for the different dimensions is illustrated in Figure S2.

TABLE 2 Determinants of pain at diagnosis in patients with desmoid-type fibromatosis.

Characteristics	Patients with pain/N	Univariate analysis			Multivariate analysis[a]		
		OR	95% CI	*P*-value	OR	95% CI	*P*-value
Sex				.49			.07
Male	39/117	0.85	(0.54-1.35)		0.63	(0.38-1.05)	
Female	98/265	1			1		
Tumor site (MD = 2)				<.001			<.001
Abdominal wall	36/130	0.57	(0.35-0.93)		0.52	(0.31-0.86)	
Neck or shoulder	18/27	2.97	(1.27-6.98)		3.05	(1.27–7.29)	
Intra-abdominal or pelvic soft tissue	10/44	0.44	(0.20-0.94)		0.42	(0.19-0.93)	
Another site	72/179	1			1		
Tumor size (mm) (MD = 3)				.034			.013
≤50	59/192	1			1		
>50	77/187	1.57	(1.03-2.40)		1.77	(1.13-2.77)	
CTNNB1 mutational status (MD = 42)				.07			.13
p.S45F mutation	22/45	1.81	(0.96-3.40)		1.69	(0.86-3.32)	
Other mutation/no mutation	102/295	1			1		

Note: The MICE method (Multiple Imputation by Chained Equations) was used to manage missing variables.
Abbreviations: MD, number of missing values; OR, odds ratio; 95% CI, 95% confidence interval.
[a]Multivariable logistic model including sex, age at diagnosis, tumor site, tumor size and mutational status. We considered sex as a potential predictor, based on background knowledge, regardless of the *P*-value in the univariate analysis. The other variables were selected based on the univariate analysis as the *P*-value was <0.20.[26,27]

emotional functioning: $P = .04$, cognitive functioning: $P = .03$ and social functioning: $P < .001$). Considering the symptoms scales evaluated by the QLQ-C30, we observed a significant association with fatigue ($P = .004$) and insomnia ($P < .001$), but not with the symptoms supposedly unrelated to pain (nausea and vomiting: $P = .63$, dyspnea: $P = .64$, appetite loss: $P = .46$, constipation: $P = .22$ and diarrhea: $P = .56$). Considering the HADS scores, we observed a nonsignificant trend for higher depression ($P = .063$) and anxiety ($P = .096$) scores in patients with pain.

The distribution of pain did not differ according to the first-line management (active surveillance, surgery and systemic treatment, $P = .18$).

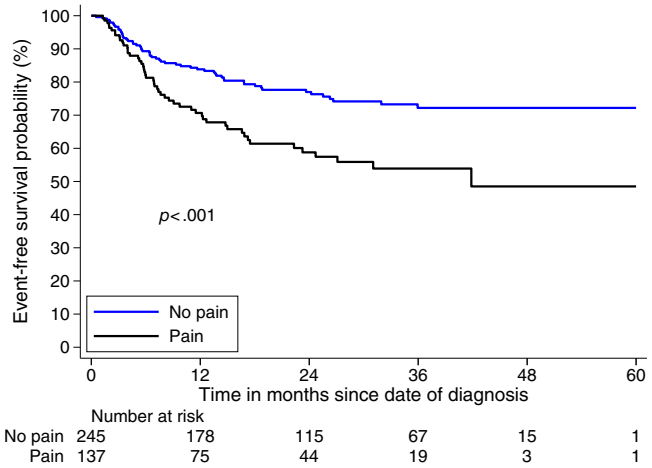


FIGURE 1 Event-free survival in desmoid-type fibromatosis according to the presence of pain.

3.3 | Pain and EFS

The median follow-up of patients was 30.2 months (95% CI, 28.4-32.8 months), varying from 0.4 to 67.3 months. Overall, an event (relapse, progression or death) was reported in 107 patients, including 101 relapses or disease progressions, 4 deaths related to disease progression and 2 deaths cause by another cause (1 death related to liposarcoma and 1 death related to ischemic stroke). Overall, the EFS probability at 2 and 3 years was 70.8% (95% CI, 65.5-75.5) and 65.9% (95% CI, 60.1-71.2), respectively. The presence of pain at baseline was associated with a worse outcome ($P < .001$; Figure 1).

The 3-year EFS probability was 72.2% (95% CI, 65.1-78.1) in the absence vs 53.9% (95% CI, 43.3-63.4) in the presence of baseline pain. In the multivariate analysis, after adjustment for confounding variables, the presence of baseline pain remained significantly associated with poor EFS (hazard ratio [HR] = 1.82, 95% CI: 1.23-2.68, $P = .003$). Other factors significantly associated with unfavorable EFS in the multivariate analysis were male sex (HR = 1.74, 95% CI: 1.16-2.61, $P = .008$), age ≤40 years (HR = 1.51, 95% CI: 1.01-2.25, $P = .04$) and type of first-line management ($P = .01$; Table 3). The association between tumor size and EFS was not statistically

TABLE 3 Factors associated with event-free survival.

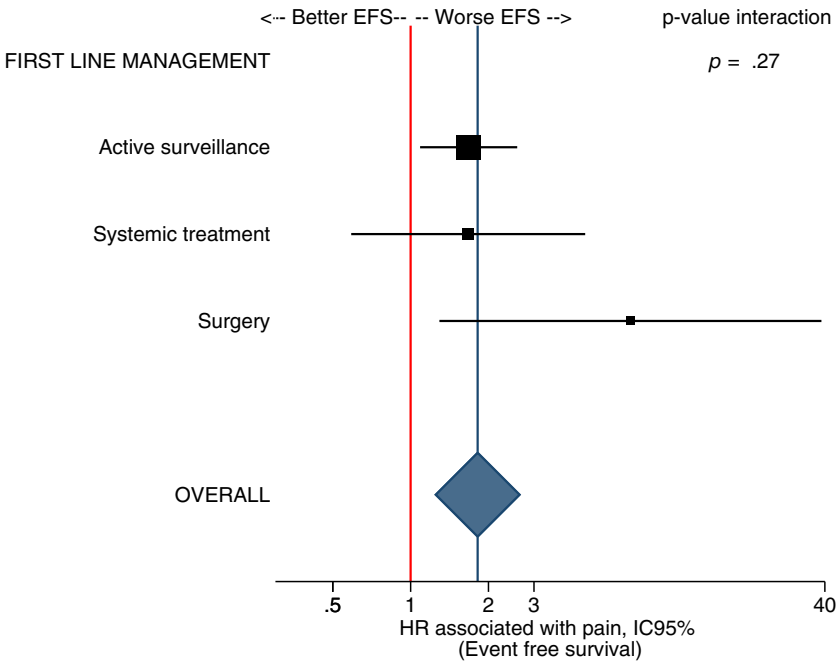
		Univariate analysis			Multivariate analysis[a]		
Characteristics	**Nb events**	**HR**	**95% CI**	***P*-value**	**HR**	**95%CI**	***P*-value**
Pain at diagnosis				.001			.003
No	56/245	1			1		
Yes	51/137	1.95	(1.33-2.85)		1.82	(1.23–2.68)	
Sex				.007			.008
Male	44/117	1.70	(1.16-2.50)		1.74	(1.16-2.61)	
Female	63/265	1			1		
Age at diagnosis				.10			.04
≤40 years	60/188	1.38	(0.94-2.02)		1.51	(1.01–2.25)	
>40 years	47/194	1			1		
History of polyposis (MD = 5)				.25			
Yes	11/28	1.45	(0.77-2.70)				
No	94/349	1					
Tumor site (MD = 2)				.89	-		
Abdominal wall	36/130	0.97	(0.64-1.49)				
Neck or shoulder	8/27	1.14	(0.55-2.42)				
Intra-abdominal or pelvic soft tissue	11/44	0.81	(0.42-1.56)				
Other site	52/179	1					
First-line management				.002			.01
Active surveillance	86/274	1			1		
Systemic treatment	15/43	1.14	(0.66-1.98)		1.04	(0.59-1.82)	
Surgery	6/65	0.23	(0.10-0.53)		0.28	(0.12-0.64)	
Tumor size (mm) (MD = 3)				.007			.09
≤50	42/192	1			1		
>50	64/187	1.72	(1.16-2.53)		1.42	(0.95–2.14)	

TABLE 3 (Continued)

Characteristics	Nb events	Univariate analysis			Multivariate analysis[a]		
		HR	95% CI	*P*-value	HR	95%CI	*P*-value
CTNNB1 mutational status (MD = 42)							
p.S45F mutation	15/45	1.07	(0.62-1.86)	.80			
Other mutation/no mutation	84/295	1					
QLQ-C30 (MD = 32)				.96			
Global health status (%)							
≤50%	24/88	1					
[50%-75%]	28/106	0.89	(0.52-1.54)				
[75%-83.3%]	22/80	0.86	(0.48-1.54)				
>83.3%	21/76	0.96	(0.53-1.73)				
Depression HADS				.81			
Normal	91/316	1					
Borderline/abnormal	16/66	0.94	(0.55-1.59)				
Anxiety HADS				.59			
Normal	68/230	1					
Borderline/abnormal	39/152	0.89	(0.61-1.33)				

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; MD, number of missing values; 95% CI, 95% confidence interval.
[a]Multivariable Cox model including pain (yes vs no), sex, age at diagnosis, tumor size and first-line management. The variables included in the multivariable model in addition to pain were the potential prognostic factors selected based on the univariate analysis (*P*-value <.20).

FIGURE 2 Forest plot of the risk of event associated with pain according to the first-line management. The hazard ratios of event associated with pain in the different subgroups are estimated in a multivariable Cox model including pain (yes vs no), sex, age at diagnosis, tumor size, first-line management and an interaction term between pain and first-line management.



significant (tumor size >50 mm: HR = 1.42, 95% CI: 0.95-2.14, *P* = .09). When considering the pain level evaluated by the NPRS, we confirmed the association between pain level and EFS: patients with a higher level of pain appear to be associated with an increased risk of event, with a HR of 1.21 for a 1-point difference in NPR at baseline (95% CI: 1.11-1.31, *P* < .001 in multivariate analysis; detailed results in Table S1).

We conducted a sub-group analysis in patients with active surveillance as first-line management (N = 274). The median follow-up of the patients was 29.8 months (95% CI, 27.3-32.4 months), varying from 0.4 to 67.3 months. The EFS probability at 2 and 3 years was 66.7% (95% CI, 60.2-72.5) and 62.1% (95% CI, 54.9-68.4), respectively. The 3-year EFS probability was 67.8% (95% CI, 58.8-75.3) in the absence vs 51.8% (95% CI, 39.6-62.6) in the presence of baseline

pain (Figure S3). When exploring the heterogeneity in the association between pain and EFS according to the first-line management in multivariable analysis, we did not observe any significant interaction between the three groups. As illustrated by Figure 2, the HR associated with pain in multivariable analysis was 1.68 (95% CI, 1.09-2.58) in the 274 patients with active surveillance, 1.67 (0.59-4.73) in the 43 patients receiving systemic treatment and 7.08 (1.29-38.8) in the 65 patients who underwent surgery as first-line approach; with a *P*-value of the interaction test is .27. We also did not observe any significant heterogeneity between the strata of patients with history of polyposis and the strata of sporadic DF (HR = 1.34, 95% CI: 0.35-5.16 and HR = 1.92, 95% CI: 1.27-2.91, respectively, with an interaction test *P*-value = .62).

3.4 | Quality of life, anxiety, depression at diagnosis and EFS

When considering the "Global Health" dimension of quality-of-life evaluation (questions 9 and 19 of the QLQ-C30 questionnaire) at diagnosis, we did not observe any association with the EFS ($P = .96$). The patients with borderline or abnormal HADS scores did not have worse EFS compared to those with normal scores (depression, $P = .81$; anxiety, $P = .59$).

4 | DISCUSSION

We found that pain was present in one third of the patients with DF, including pain with NPR ≥3 in 17% of cases. The factors associated with pain were location (neck and shoulder) and tumor size. The presence of pain severely impacted the quality of life in most dimensions. Furthermore, pain was associated with poor EFS.

It is well known that desmoid tumors can be painful. Nevertheless, the mechanisms of pain in DF are definitely complex and not well understood. Upon uncontrolled monomorphic fibroblastic proliferation, DF could infiltrate the muscles, nerves, tendons and aponeuroses, which could cause pain. Profound DF can be compressive and cause pain by compression of the urinary or digestive tract. Certain DFs are associated with local inflammation, overexpression of COX-2 and presence of tumor-infiltrating lymphocytes or macrophages.[10-14] Last, spontaneously or following treatment, as shown by changes in density on MRI, DF can become highly fibrotic and result in retraction of healthy tissue, which could also be a source of pain.[5]

The frequency of pain widely varies according to the nature of the study (prospective vs retrospective), tool used for assessing the presence of pain and the included population (all comers vs progressive/heavily pretreated patients). In a retrospective study conducted in 42 children or adolescents with treated DF, 2 patients (4%) experienced pain.[15] In the randomized trial assessing activity of sorafenib over placebo, pain at baseline (Brief Pain Inventory>2) was present in 56/87 patients (64%).[16] In a series of 37 patients with advanced DF treated by cryoablation, 20 patients with DF experienced pain with a visual analog scale score ≥5 (54%).[17] In the survey conducted among the active members of the French patient advocacy group (SOS Desmoïde), pain was present in 63% of the cases.[18] The direct comparison of these figures is irrelevant.

Our study is an original analysis attempting to identify the factors associated with pain caused by desmoid tumors. The association between tumor size and pain was expected. We also found a significant association between tumor site and pain with lesions more frequently painful when located at the neck and shoulders compared to other sites. This is in line with numerous case reports.[19-21] Those locations are quite rare (27/382 in our series, 7%). Nevertheless, these rare locations represent 9/34 (26%) of the patients treated with cryoablation in the study by Bouhamama et al. It would be interesting to study this link between pain and DF location based other recently published series (eg, study from Fondazione IRCCS Istituto 279 Nazionale dei Tumori [NCT02547831] and the study from the Netherlands [NTR4714]).

We found that pain at diagnosis was significantly associated with a poor general condition, functional impairment and poor HR-QoL (global score and all functional domains, using the EORTC QLQ-C30 questionnaire). For example, in the present study, pain was associated with alteration of cognitive function, which could be due to pain itself or the use of painkillers (opioids included). Nevertheless, an association of anxiety and depression using the HADS was not observed. Other studies have stressed the impact of pain in patients with DF. In a focus group with 27 patients with DF, patients expressed that pain was the most debilitating symptom and dependency on painkillers was a major concern.[22] In the French advocacy group (SOS Desmoide) survey, pain in 65 of 102 patients (63%) with a median pain intensity was 1 (0-8). Patients mentioned pain resulting in sleep disturbance, permanent work stoppage, part-time job employment, irritability and anxiety in 73% (48/65), 26% (17/65), 10% (7/65), 46% (30/65) and 15% (10/65) of the cases, respectively. HR-QoL research stressed that specific and validated questionnaires are needed for the particular disease.[23] Two specific questionnaires have been developed: the DTF-QoL and the "Gounder/DTRF Desmoid Symptom/Impact Scale" (GODDESS)[24] The GODDESS has already been used in several trials, including two pivotal randomized Phase 3 trials assessing the efficacy of gama-secretase inhibitors (NCT04871282; NCT03785964). The GODDESS questionnaire integrates the pain as assessed by the patient. The data of the DEFI trial (placebo-controlled randomized trial assessing the activity of Nirogacestat) have been recently presented. Severe pain was present in 41% of the patients with DF (58/142, "Worst Pain in the 24 past hours >4). Nirogacestat was associated with a significant decrease in DF size according to RECIST 1.1 and with a significant improvement of pain and HR-QoL as measured by the GODDESS questionnaire. Data regarding the EORTC-QLQ-30 questionnaires and other PROs have not been presented yet.[25] All the recent data support the importance of better exploring the patients' symptoms and integrating PROs into clinical trials.

The most striking result of the present study is the association between pain and EFS. Nevertheless, pain was associated with the DF size. These patients should be followed up with careful attention,

since they are likely to be actively treated more often and earlier. Until now, no validated and reliable biomarker exists that can predict the outcome of DF. Data about the prognostic value of the nature of somatic *CTNNB1* pathogenic variant are questionable; in prior publication from the ALTITUDES study, we did not find an association between the *CTTNB1* mutational status and outcome.[8] Excluding *CTNNB1*, there is no other putative biomarker that could predict the outcome. Pain is possibly an easily obtainable bedside biomarker that could identify DF associated with high risk of relapse of progression. We hypothesized that pain could reflect the infiltrative pattern of certain DFs or pain could be associated with a local inflammatory process. Moreover, it would be interesting to study the association between pain and EFS in other studies.

As already reported in previous studies on the ALTITUDES cohort, we acknowledge certain limitations. The first-line approaches were heterogeneous and the reason to choose one first-line approach over the others was not documented. This heterogeneity in patient management reflects how DF is a hard-to-treat tumor, but is a study limitation. As previously published,[8,9] we have used a complex composite endpoint (EFS) that could be debated, we strongly think that this EFS definition catch the different scenarios of DF worsening. However, the results of our current study were very stable when focusing on patients with active surveillance as first approach, with no significant heterogeneity in terms of the prognostic value associated with pain according to first-line management (interaction test, $P = .27$). The study population includes both patients with a history of polyposis and sporadic DF, which are two distinct entities; however, we observed no significant association between a history of polyposis and pain ($P = .23$), the EFS did not significantly differ between these two entities ($P = .25$); and the prognostic value of pain on EFS appeared rather homogeneous across these two subgroups (interaction test, $P = .62$). Another limitation of the current study is the relatively high number of patients with no pain evaluation reported at diagnosis or with a limited information about pain, in particular with no quantitative evaluation using the NPRS. More precisely, pain was available as a binary variable in 382 patients and as a continuous data (NPR) in 338 patients. Furthermore, data on painkillers were not prospectively collected. The tools for assessing pain and HR-QoL are not ideal (NPRS, HADS and the EORTC QLQ-C30 version 3.0). Although, we designed the study protocol in 2015, no specific validated questionnaire was devised. We wanted to emphasize that the present study included a large sample size of all newly diagnosed cases. Last, longitudinal data about pain during follow-up and treatment were not presented in this study. Finally, the association between CTNNB1 mutation status and pain that we report in the current analysis appears less strong than in the first publication.[8] However, we do not conclude that there is no association.

In conclusion, this study highlights the importance of studying pain in patients with DF and the major impact of pain on the quality of life, which is associated with the aggressiveness of the disease. It seems necessary to have data from other cohorts to validate the prognostic value of pain at baseline before evaluating it as a stratification factor to guide treatment decision.

AUTHOR CONTRIBUTIONS

Nicolas Penel: Conceptualization, validation, investigation, writing-original draft preparation, funding acquisition. **Sylvie Bonvlot:** Validation, investigation, writing-reviewing and editing. **Marie-Cécile Le Deley:** Conceptualization, methodology, software, validation, formal analysis, writing-reviewing and editing. **Antoine Italiano:** Investigation, writing-reviewing and editing. **Camille Tlemsani:** Investigation, writing-reviewing and editing. **Diane Pannier:** Investigation, writing-reviewing and editing. **Clémence Leguillette:** Methodology, software, validation, formal analysis, writing-reviewing and editing. **Jean-Emmanuel Kurtz:** Investigation, writing-reviewing and editing. **Maud Toulmonde:** Investigation, writing-reviewing and editing. **Julien Thery:** Investigation, data curation, writing-reviewing and editing, project administration. **Daniel Orbach:** Validation, writing-reviewing and editing. **Pascale Dubray-Longeras:** Investigation, writing-reviewing and editing. **Benjamin Verret:** Investigation, writing-reviewing and editing. **François Bertucci:** Investigation, writing-reviewing and editing. **Cecile Guillemet:** Investigation, writing-reviewing and editing. **Lucie Laroche:** Software, data curation. **Armelle Dufresne:** Investigation, writing-reviewing and editing. **Jean-Yves Blay:** Validation, investigation, writing-reviewing and editing. **Axel Le Cesne:** Validation, investigation, writing-reviewing and editing. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

ACKNOWLEDGEMENTS

The authors would like to thank the patients and families for their participation in this study, the staff members involved in the trial management and data analysis, in particular Emilie Decoupigny André Michel Bimbaï and Marie Vanseymortier from the sponsorship unit at Centre Oscar Lambret, Lille, all the investigators and their teams who participated in the trial, the patient advocacy group "SOS Desmoïde," Françoise Bonichon for her help in literature research and the data managers from Centre de Traitement des Données du Cancéropôle Nord-Ouest (CTD-CNO), who oversaw the trial data management; the CTD-CNO clinical research platform was funded by the French National Cancer Institute (INCa) and "La Ligue Nationale Contre le Cancer".

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The findings of this study are available from the corresponding author upon reasonable request

FUNDING STATEMENT

This work was supported by a personal grant from a donor (S. Wisnia), the Ligue Nationale Contre le Cancer (PRE2016.LCC/NP), Intersarc (funded by the French National Cancer Institute, INCA), APICIL Foundation and SOS Desmoïde. These funders had no role in the design, conduct or reporting of this work.

ETHICS STATEMENT

This trial was approved by the ethics committee (Approval by the ethics committee on December 21, 2015 [CPP Nord-Ouest I] and by the French Drug Agency on November 20, 2015 [ANSM]). Clinical Trial registration number: NCT02867033. Written informed consent was obtained from each patient.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Penel N, Bonvalot S, Le Deley M-C, et al. Pain in desmoid-type fibromatosis: Prevalence, determinants and prognosis value. *Int J Cancer*. 2023;153(2):407-416. doi:10.1002/ijc.34493