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ORIGINAL REPORT

Prognostic Factors Influencing Progression-Free Survival Determined From a Series of Sporadic Desmoid Tumors: A Wait-and-See Policy According to Tumor Presentation

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ABSTRACT

Purpose
Desmoid tumors are mesenchymal fibroblastic/myofibroblastic proliferations with locoregional aggressiveness and high ability to recur after initial treatment. We present the results of the largest series of sporadic desmoid tumors ever published to determine the prognostic factors of these rare tumors.

Patients and Methods
Four hundred twenty-six patients with a desmoid tumor at diagnosis were included, and the following parameters were studied: age, sex, delay between first symptoms and diagnosis, tumor size, tumor site, previous history of surgery or trauma in the area of the primary tumor, surgical margins, and context of abdominal wall desmoids in women of child-bearing age during or shortly after pregnancy. We performed univariate and multivariate analysis for progression-free survival (PFS).

Results
In univariate analysis, age, tumor size, tumor site, and surgical margins (R2 *v* R0/R1) had a significant impact on PFS. PFS curves were not significantly different for microscopic assessment of surgical resection quality (R0 *v* R1). In multivariate analysis, age, tumor size, and tumor site had independent values. Three prognostic groups for PFS were defined on the basis of the number of independent unfavorable prognostic factors (0 or 1, 2, and 3).

Conclusion
This study clearly demonstrates that there are different prognostic subgroups of desmoid tumors that could benefit from different therapeutic strategies, including a wait-and-see policy.

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INTRODUCTION

Desmoid tumors (or aggressive fibromatosis) are soft tissue tumors of clonal origin and mesenchymal fibroblastic/myofibroblastic proliferations, with an incidence of two to four new cases per million people per year.[1,2] Tumorigenesis is linked to beta-catenin stabilization involving beta-catenin/WNT/TCF signaling.[3] These benign tumors behave aggressively, deeply infiltrate tissues, and may relapse locoregionally but never metastasize.[4,5] They arise in the abdominal wall, in the abdominal cavity or, more frequently, in the extremities or the trunk.[6] Most desmoid tumors develop sporadically in young adults, although some cases occur in the context of Gardner's syndrome (a variant of familial adenomatous polyposis), and their location is more often intra-abdominal compared with the sporadic form.[7] Abdominal wall desmoids occur most commonly in women of child-bearing age during or shortly following pregnancy.[8]

Complete surgical removal remains the optimal treatment but may be difficult or mutilating according to the tumor location or local extension. Moreover, a significant proportion of patients will relapse locally and/or regionally after initial surgery. Recurrence rates ranging from 30% to 40% have been reported in the major published series.[9] In this case, mutilating surgery and/or radiotherapy are often used with a large risk of functional consequences in the case of musculoskeletal or organ resections. When local treatments are not feasible, systemic therapies, including antiestrogen, nonsteroidal anti-inflammatory drugs, chemotherapy and, more recently, targeted therapy, may induce responses.[10] In addition, some desmoids can spontaneously regress

or present growth arrest, so some patients should benefit from a wait-and-see policy without the use of aggressive therapies. For this reason, the benefit of surgery in curing desmoids has recently been questioned.[4,11-15] The purpose of this study is to investigate the prognostic factors influencing progression-free-survival (PFS) of sporadic desmoids.

PATIENTS AND METHODS

Patient Selection

From February 1, 1965, to March 6, 2008, 426 consecutive patients with sporadic aggressive fibromatosis were diagnosed for their first tumoral event in 24 participating cancer centers and were entered into the European database.[16] Twenty-five patients were excluded from this study because they presented desmoid tumors in the context of Gardner's syndrome. Patients considered as having Gardner's syndrome were those having an association of a desmoid tumor and family history of colorectal polyposis. We excluded this minority population to retain a homogeneous group knowing that PFS in these patients is significantly different from PFS in those with a sporadic desmoid tumor (Appendix Fig A1, online only). The diagnosis of desmoid tumors was confirmed in each case by collegial histologic analysis (mesenchymal fibroblastic/myofibroblastic proliferations).

Pathology Review

Histologic slides of all patients entered in this study were reviewed by the pathology subcommittee of the French Sarcoma Group (GSF). The subcommittee included 20 pathologists, and a monthly slide review session was performed. For each tumor, one to eight slides were collegially reviewed. Histologic typing was based on the WHO histologic typing of soft tissue tumors.[17]

Data Collection

Data regarding patients' characteristics, tumor description, treatment modalities and their results, and outcome were obtained from a retrospective review of medical records. These records and histologic data were entered into a centralized computerized database.[16] The following eight variables were analyzed for their potential prognostic value: age at presentation, sex, delay between first symptoms and diagnosis, tumor size, tumor site, previous history of surgery or trauma in the area of the primary tumor, surgical margins (macroscopic incomplete resection as R2 resection; microscopic incomplete

Table 1. Patient and Disease Characteristics at Baseline

Characteristic	Overall Patients (N = 426) No.	%
Age at diagnosis, years		
Median	37	
Range	0.3-83	
Sex		
Male	142	33.3
Female	284	66.7
Tumor localization		
Abdominal wall	74	17.4
Abdominal cavity	46	10.8
Extra-abdominal	296	69.5
Multifocal	10	2.3
Tumor size, cm		
Median	7	
Range	0.8-30	
Delay between first symptoms and diagnosis, months		
Median	4.74	
Range	0.1-142	
Extra-abdominal localization		
Trunk	119	40.2
Upper and lower limbs	109	36.8
Head and neck	27	9.1
Buttocks	22	7.4
Unknown	19	6.5
Limb localization		
Proximal	52	47.7
Distal	57	52.3
Context of abdominal wall desmoids in women of child-bearing age during or shortly after pregnancy		
Yes	33	7.7
Previous history of surgery in area of primary tumor		
Yes	36	8.4
Previous history of trauma in area of primary tumor		
Yes	17	3.9

Table 2. Treatment Characteristics and Outcome

Characteristic	Overall Patients (N = 426) No.	%	95% CI
Surgery			
Yes	370	86.9	
No	56	13.1	
Wait-and-see policy			
Yes	27	6.3	
No	399	93.7	
Surgical margins			
Microscopically complete tumor resection (R0)	111	30	
Microscopically incomplete tumor resection (R1)	110	29.7	
Macroscopically incomplete resection (R2)	37	8.6	
Unknown	112	30.3	
Radiotherapy			
No radiotherapy	376	88.3	
Radiotherapy	43	10.1	
Unknown	7	1.6	
Medical treatment			
None	363	85.1	
Preoperative	6	1.5	
Postoperative	29	6.8	
Exclusive	23	5.4	
Unknown	5	1.2	
Median follow-up, months	52		43 to 60
Outcome			
Spontaneous remission after wait-and-see policy	5	1.2	
Stable disease after wait-and-see policy	16	3.8	
Progression after wait-and-see policy	6	1.4	
Progression during treatment	9	1.9	
Absence of residual tumor after treatment	323	75.8	
Residual tumor after treatment	63	14.7	
Currently under treatment	1	0.02	
Status unknown	4	1	
Median progression-free survival, months	41		29 to 53
Local recurrence for patients with absence of residual tumor after treatment	143	44.3	
Progression for patients with residual tumor after treatment	42	66.6	
Death from desmoid tumor	0		
Death	15	3.5	

resection as R1 resection; microscopic complete resection as R0 resection), and context of abdominal wall desmoids in women of child-bearing age during or shortly after pregnancy. The status of resection margins in surgically treated patients was classified according to the International Union Against Cancer (UICC) R classification.[18] Absence of residual tumor after local treatment meant that the patients had no disease visible on imaging after surgery and/or radiotherapy.

Statistical Analysis

PFS is defined as time from the date of initial diagnosis to the date of progression or recurrence or last follow-up. Follow-up times were described as medians by using the inverse Kaplan-Meier estimator.[19] Continuous variables were expressed as medians and range, and categorical variables were expressed as percentage. Survival curves were obtained by using the Kaplan-Meier method and were compared with the log-rank test. The Cox proportional hazards model was used to calculate adjusted hazard ratios (HRs) and their 95% CIs. All statistical tests were two-sided, and the threshold for statistical significance was $P = .05$. Variables with a P value of less than .05 in univariate analyses were tested in the multivariate analysis. Analyses were performed with SPSS software, version 17.0 (SPSS, Chicago, IL).

RESULTS

Patient and Disease Characteristics

Patient characteristics are listed in Table 1. The median age was 37 years (range, 0.3 to 83 years). Fifty-six patients (13%) were younger than age 18 years. Two thirds of the 426 patients were female. Tumor locations were as follows: abdominal wall, 74 (17.4%); abdominal cavity, 46 (10.8%); and extra-abdominal 296 (69.5%). Ten tumors (2.3%) were multifocal (lesions affecting more than one primary site). Among patients with an extra-abdominal tumor, 119 (40.2%) had fibromatosis arising in the trunk, 109 (36.8%) in the upper and lower limbs, 27 (9.1%) in the head and neck region, and 22 (7.4%) in the buttocks. Among patients with limb tumors, 57 (52.3%) had distal limb tumors and 52 (47.7%) had proximal limb tumors. Tumor size was known in 329 patients (77.2%), and the median largest diameter was 7.0 cm. Median time between first symptoms and diagnosis was 4.74 months (range, 0.1 to 142 months). Thirty-six patients (8.4%) had a previous history of surgery in the area of the primary tumor, and 17 (3.9%) had a previous history of trauma in the area of the primary tumor. Thirty-three (7.7%) abdominal wall desmoids occurred in women of childbearing age during or shortly after pregnancy.

Local Treatment

Patients' treatment characteristics and outcomes are described in Table 2. Three hundred seventy patients (86.9%) had an initial surgical resection. Histologic evaluation of surgical margins was available in 258 patients (70%). One hundred eleven patients (30%) had R0 resection, 110 (29.7%) had R1 resection, and 37 (8.6%) had R2 resection. Radiotherapy generally included photons or electrons with a median dose of 50 Gy. Forty-three patients received radiotherapy. Surgery was followed by radiotherapy in 37 patients. Among these patients, one had R0 resection, 24 had R1 resection, five had R2 resection, and seven had unknown margins. Six patients received radiotherapy as the only treatment for their disease.

Medical Treatment

Only 23 patients (5.4%) received medical treatment exclusively as first-line treatment. Ten patients received chemotherapy: six patients were treated with chemotherapy only, three patients were treated with chemotherapy and tamoxifen or toremifene, and one patient was treated with chemotherapy and a nonsteroidal anti-inflammatory drug. Twelve patients were treated with tamoxifen or toremifene and/or a nonsteroidal anti-inflammatory drug. One patient was treated with imatinib. Medical treatment was given as adjuvant treatment in 29 patients (6.8%) and as neoadjuvant treatment in six patients (1.5%). Twenty patients who received chemotherapy were treated with an anthracycline or with a methotrexate-vinblastine–containing regimen. Thirty-three patients were treated with tamoxifen or toremifene, 22 with a nonsteroidal anti-inflammatory drug, and one with imatinib. Association of different medical treatments was possible.

Wait-and-See Policy

A nonaggressive approach was adopted in a subgroup of patients in an attempt to avoid surgery. Twenty-seven patients (6.3%) were thus placed under initial attentive medical surveillance. A wait-and-see policy

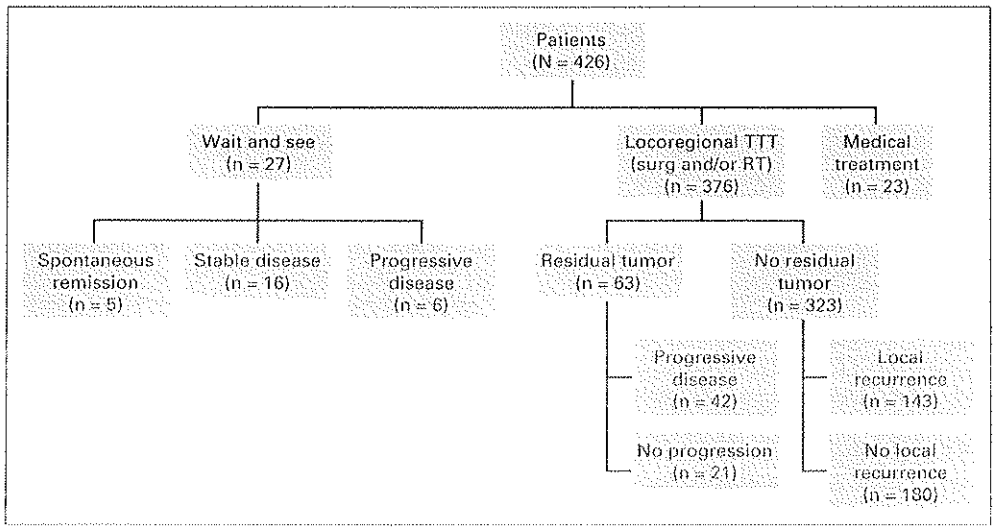

Fig 1. Diagram of patient outcomes. RT, radiotherapy; surg, surgery; TTT, treatment.

was chosen mostly according to the site of progression, which could not be life-threatening or at risk for mutilation (adjacent nerves or vessels).

Outcome in Patients With the Wait-and-See Policy

Patients' outcomes are shown in Figure 1. Median follow-up was 52 months (95% CI, 43.6 to 61.6 months). Among 27 patients with the wait-and-see policy, six presented with progression during follow-up. Median delay to progression was 19.7 months (range, 7.8 to 46.2 months). Sixteen patients had stable disease. Spontaneous tumor regressions occurred in five patients. None of these patients presented with progression at the end of the follow-up.

Response

Absence of residual tumor after local treatment (surgery and/or radiotherapy) was observed in 323 patients (75.8%). Among patients treated with chemotherapy, partial responses were reported in six patients, stable disease in three patients, and progression in one patient. At the time of data analysis, local recurrences had been observed in 143 (44.3%) of 323 patients with no residual tumor after first-line treatment.

Survival Analysis

Overall survival is shown in Appendix Figure A4 (online only) and PFS is shown in Appendix Figure A5 (online only). PFS rates at 5 and 10 years were 35% and 22.8%, respectively. Two hundred forty-eight patients were alive without disease at the end of the follow-up. The mean number of recurrences was two (range, one to 20). No patient died of the disease. Fifteen patients died of other causes. Median PFS was 41 months (range, 29 to 53 months).

Table 3. Univariate Analysis for Prognostic Factors in Progression-Free Survival

Factor	No. of Patients	Progression-Free Survival Rate			Log-Rank *P*
		2-Year	5-Year	10-Year	
Age, years					
≤ 37	199	57.4	36.3	28.7	.005
> 37	205	70.9	49.5	42.1	
Sex					
Male	130	63.1	41.3	23	.35
Female	276	64.4	43.3	39.9	
Context of abdominal wall desmoids in women of child-bearing age during or shortly after pregnancy					
No	374	63.1	41.2	32.9	.06
Yes	32	75	62.3	62.3	
Previous history of surgery in area of primary tumor					
No	371	63.3	41.4	34	.264
Yes	35	70.6	54.5	48.5	
Previous history of trauma in area of primary tumor					
No	389	64.3	42.9	35	.456
Yes	17	55.1	44.1	—	
Tumor localization					
Abdominal wall	91	78.2	61.7	57.2	< .001
Abdominal cavity	43	70	50.2	50.2	
Extra-abdominal	267	59.2	36.5	26.9	
Extra-abdominal localization					
Trunk	93	65.5	53.9	42.6	< .001
Upper and lower limbs	105	50.3	23.9	21.7	
Head and neck	28	71.9	60.4	—	
Buttocks	20	62.3	16.6	—	
Limb localization					
Proximal	52	68.8	54.5	49.5	.006
Distal	59	54.4	22.8	18.3	
Delay between first symptoms and diagnosis, months					
≤ 4.74	114	69.3	54.9	47.8	.942
> 4.74	114	71.9	52.7	46.2	
Tumor size, cm					
≤ 7	181	75.1	57.4	47	.004
> 7	136	58.3	40.6	32.8	
Surgical margins (R0 *v* R1 *v* R2)					
R0	110	76.5	62.5	47.5	< .001
R1	107	73.7	60.5	48.1	
R2	35	43.4	22	16.5	
Surgical margins (R0 *v* R1)					
R0	110	76.5	62.5	47.5	.867
R1	107	73.7	60.5	48.1	

Prognostic Factors for PFS

In univariate analysis (Table 3), poor prognostic factors were age younger than 37 years (median of the whole cohort; $P = .005$; Appendix Fig A6, online only), size more than 7 cm (median of the whole cohort; $P = .004$; Appendix Fig A7, online only), extra-abdominal localization ($P < .001$; Appendix Fig A8, online only), and macroscopic residual disease after surgery (R0/R1 *v* R2; $P < .001$; Appendix Fig A9, online only). Among extra-abdominal tumors, the worst outcome was observed in limb and buttocks tumors. Among limb tumors, distal tumors were those with the worst prognosis. PFS curves were not significantly different for the microscopic assessment of surgical margin (R0 *v* R1). In multivariate analysis, age (HR, 1.97; 95% CI, 1.36 to 2.84; $P = .010$), tumor size (HR, 1.64; 95% CI, 1.13 to 2.36; $P = .008$), and tumor site (extra-abdominal tumor; HR, 2.55; 95% CI, 1.48 to 4.4; $P < .001$) remained significant prognostic variables (Table 4). Three prognostic groups for PFS were defined on the basis of the number of unfavorable prognostic factors. Since only 26 patients had zero poor prognostic factors, we grouped patients with zero or one poor prognostic factors together to constitute three prognostic groups: good prognosis, fair prognosis, and poor prognosis.

Figure 2 shows the PFS curves in patients with zero or one, two, and three unfavorable prognostic factors, respectively. Patients with zero or one prognostic factor were mainly treated with surgery alone (data not shown).

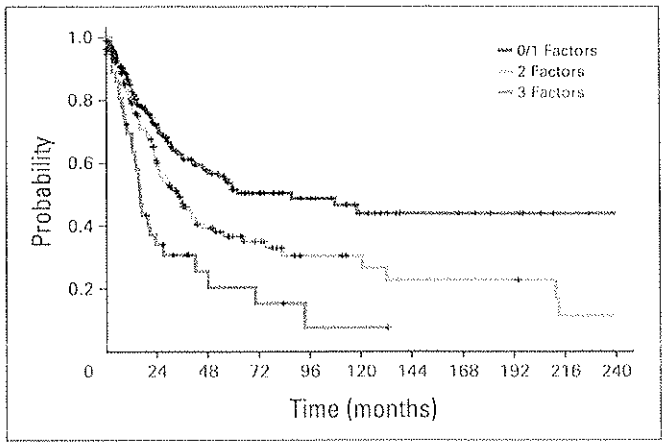

Fig 2. Probability of survival of patients with zero, one, two, or three factors.

DISCUSSION

We present here the results of the largest series of sporadic desmoid tumors ever published to determine the prognostic factors of these rare tumors. One of the main problems in managing desmoids tumor is their locoregional aggressiveness and their high ability to recur after initial treatment. In this study, no patients died of their disease probably because we excluded desmoid tumors in the context of Gardner's syndrome. Seventy-five percent of patients were in complete remission after initial management but nearly 50% did relapse. This explains the choice of PFS and not overall survival in this study to search for prognostic factors. Surgical resection is often responsible for severe functional and esthetic consequences. Moreover, the observation of spontaneous regression in some rare cases of desmoid tumor led us to conduct this study to search for factors of progression and thus identify subgroups of patients eligible for individualized management, including a wait-and-see policy, early surgery, and neoadjuvant or adjuvant treatments.[20-22] In this cohort of patients under the wait-and-see policy, nearly 20% spontaneously regressed and 60% had stable disease, and only 20% had tumor progression. However, this retrospective study cannot provide conclusions regarding the outcome of these patients since the sample was small and the patients were selected.

Table 4. Multivariate Progression-Free Survival Analysis

Variable	Crude HR	95% CI	*P*
Median age	1.97	1.36 to 2.84	< .001
Median size	1.64	1.13 to 2.36	.008
Tumor site			
Abdominal wall			
Intra-abdominal tumor	1.96	0.92 to 4.15	.084*
Extra-abdominal tumor	2.55	1.48 to 4.4	< .001

Abbreviation: HR, hazard ratio.
*Not significant.

In contrast with other studies, prognosis was not significantly different for microscopic assessment of surgical margins (R0 *v* R1).[9,13,23-26] In other studies, however, the presence of microscopic disease did not necessarily affect long-term disease-free survival.[5,14] These results are probably due to the fact that desmoid tumors are extremely infiltrative locally, making it difficult to assess microscopic resection margins. Thus, function-sparing surgery should be preferred to aggressive surgery seeking negative margins.[14]

Our results show that age (older than 37 years) is statistically associated with longer PFS. Age as a prognostic factor for local recurrence of desmoids has already been studied in several publications. In one series, age (older than 30 years) was a negative prognostic factor,[27] in two series it was a positive factor (age younger than 18 years in the study by Spear et al[28]; age younger than 32 years in the study by Sorensen et al[25]), and in most of the other series, it had no prognostic value.[5,9,13,24,29] Recently, the identification of biologic pathways involved in the tumorigenesis of desmoids emphasized these age differences, genomic alterations being more common in older patients. This could explain the prognostic role of age.[3]

Tumor location as a prognostic factor has already been demonstrated, with tumors of the extremities having the worst prognosis.[9,13,25,27,30] In our study, among extra-abdominal tumors, the worst outcomes were observed in limb tumors, especially in distal locations. A subset of patients with extra-abdominal fibromatosis could be managed with a different policy: head and neck and trunk tumors have a better prognosis. Thus, location is an important factor in the assessment of patients at diagnosis and for stratifying patients taking part in randomized trials. It is unclear, however, whether these differences are related to biologic or to surgical management differences.

These findings therefore point to three prognostic factors of PFS (age, tumor size, and tumor site) based on the results of the largest series ever published. The natural history of these tumors is unique. Although considered nonmalignant because of their inability to metastasize, their locoregional aggressiveness and recurrence rate after resection are particularly high. With nearly 50% of recurrences and the likelihood of accelerating the evolution of the disease, the value of surgery (ie, the mainstay in initial management) is under debate.

Several physicians now adopt a wait-and-see policy as initial strategy for some selected patients.

This study clearly demonstrates that there are different prognostic subgroups of desmoid tumors that could benefit from different therapeutic strategies. The main question raised by our findings is how patients should be managed. Should we consider that patients with good prognostic factors (older than 37 years, tumor size < 7 cm, and tumor located in the abdominal wall or intra-abdominally) have less risk of recurrence after surgery and should they thus undergo surgery straightaway in a curative intent? Or that such patients must have indolent tumors that could benefit from a wait-and-see policy? It would be interesting to take subjective morbidity into account as well as the morbidity associated with treatment, which could have an impact on therapeutic management.

This study could be the starting point for prospective studies, the only way to answer these questions and optimize the management (surgery versus wait-and-see policy) of desmoid tumors. While awaiting such results, it seems logical to carefully watch the evolution of a desmoid tumor after its diagnosis and propose local treatment only in the case of progressive and/or symptomatic disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Manuscript writing: All authors
Final approval of manuscript: All authors

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