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ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Desmoid-Type Fibromatosis: A Front-Line Conservative Approach to Select Patients for Surgical Treatment

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ABSTRACT

Purpose. Surgery is still the standard treatment for desmoid-type fibromatosis (DF). Recently, the Institut Gustave Roussy (IGR), Villejuif, France, reported a series of patients treated with a front-line conservative approach (no surgery and no radiotherapy). The disease remained stable in more than half of patients. This study was designed to evaluate this approach on the natural history of the disease in a larger series of patients.

Methods. A total of 142 patients presenting to the IGR or Istituto Nazionale Tumori (INT), Milan, Italy, were initially treated using a front-line deliberately conservative policy. Their progression-free survival (PFS) was observed and a multivariate analysis was performed for major clinical variables.

Results. Seventy-four patients presented with primary tumor, 68 with recurrence. Eighty-three patients received a "wait & see" policy (W&S), whereas 59 were initially offered medical therapy (MT), mainly hormonal therapy and chemotherapy. A family history of sporadic colorectal cancer was present in 8% of patients. The 5-year PFS was 49.9% for the W&S group and 58.6% for the medically treated patients ($P = 0.3196$). Similar results emerged for primary and recurrent DF. Multivariate analysis identified no clinical variables as independent predictors of PFS. In the event of progression, all patients were subsequently managed safely.

Conclusions. A conservative policy could be a safe approach to primary and recurrent DF, which could avoid unnecessary morbidity from surgery and/or radiation therapy. Half of patients had medium-term stable disease after W&S or MT. A multidisciplinary, stepwise approach should be prospectively tested in DF.

Desmoid-type fibromatosis (DF) is a clonal fibroblastic proliferation marked by an infiltrative growth and an inability to metastasize.[1,2] For decades, standard treatment has been complete macroscopic surgical resection. However, sizable rates of local recurrences have been reported (range 20–60% at 5 years in major retrospective studies).[3–6] Given the unpredictable outcome of the disease and the lack of metastatic potential, the aggressiveness of surgery has evolved over time. Currently, it differs from that of soft tissue sarcomas.[4–8] In fact, until 1998 the standard treatment for DF consisted of primary resection with wide margins, possibly with radiotherapy when negative margins could not be achieved or surgery would have resulted in major functional or cosmetic defects.[9] Later, function-preserving surgery was advocated for DF, with particular emphasis on limiting unnecessary morbidity.[4–6] A "wait & see" (W&S) policy alone was first proposed for recurrent but stable lesions.[10] An initial period of observation also was considered for unresectable primary tumors.[11] Furthermore, DF may respond to chemotherapy or other systemic treatments

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(including molecular targeted therapy).[12,13] Finally, a recent paper addressed the question of whether aggressive treatments (surgery and/or radiotherapy) should be considered systematically in all patients: a subset of patients with extraabdominal primary disease were managed adopting a front-line conservative approach, and growth arrest was observed in two-thirds of the nonoperated patients.[14] This study was designed to further investigate the role of a conservative policy in the initial management of DF in a larger multi-institutional series.

PATIENTS AND METHODS

All patients with DF presenting between January 1995 and July 2008 at the Institut Gustave Roussy in Villejuif, France (IGR) and between January 1985 and July 2008 at the Istituto Nazionale Tumori in Milan, Italy (INT) who were not treated according to a front-line aggressive strategy (surgery and/or radiotherapy) were identified using the local prospective databases. All patients younger than aged 15 years were excluded from the present study. The histology was confirmed for all patients by an experienced pathologist, either as part of the initial evaluation on core-needle biopsy samples or by reviewing the original slides in the event of recurrent disease previously resected elsewhere. The data retrieved included sex, age at presentation, tumor site, phase (primary vs. recurrent), tumor size, initial treatment, date of disease progression, tumor size at progression, treatment at progression, and latest follow-up.

The tumor site was classified as extremities (including the girdles), abdominal wall, thoracic wall, trunk (e.g., paraspinal disease), head and neck, or intra-abdominal. Progressive disease was defined as tumor growth documented radiologically (by MRI/CT scan) by Response Evaluation Criteria in Solid Tumors (RECIST).[15] Other conservative approaches consisted of medical therapy (MT), including hormonal therapy (e.g., tamoxifen), low-dose chemotherapy (e.g., methotrexate and vinorelbine/vinblastine), NSAIDs (e.g., celecoxib), and imatinib mesylate, at the discretion of each institution's Sarcoma Committee or as part of clinical trials.

Patients were followed up closely with clinical and radiological examinations (MRI and/or CT scan), with a first check-up at 3 months, then again 3 months later, and then 6-monthly (IGR), or every 3 months until the second year and twice yearly thereafter (INT). All study patients remain in active follow-up, with the latest update as of October 2008.

Statistical Methods

Standard descriptive statistics were calculated for continuous variables (mean or median, minimum, maximum, interquartile range) and categorical variables (absolute frequency and percentage), as appropriate. To summarize the time to disease progression in the series as a whole or in separate subgroups, progression-free survival (PFS) curves were plotted using the Kaplan–Meier method. The statistical analysis of this study end point was performed using a multivariable Cox's regression model. Factors of prognostic interest were categorized and entered into the model by means of indicator (0–1) variable. Results are shown in terms of hazard ratio estimates, corresponding 95% confidence intervals, and P values at the Wald's test.

RESULTS

Patient Characteristics

In all, 142 patients were identified by the two institutions. At IGR before the year 2001, six patients were primarily treated by a front-line conservative approach. At INT before the year 2003, they were 34 (the remaining 171 patients who presented during the same period received surgery and/or radiation therapy). Since 2001 (at the IGR) and 2003 (at the INT), a front-line conservative approach has routinely been recommended by the local Sarcoma Committees for all cases who presented at the two institutions with primary and recurrent DF. The clinical characteristics of the entire study population are listed in Table 1.

Seventy-four patients presented with primary disease, without having been previously treated by any therapy, whereas 68 had a recurrent tumor, after one or more surgical resections (in some cases associated even to radiation therapy).

The median age at the time of referral was 33 (IQ range, 26–44) years. The female to male ratio was 2.3:1. The median tumor size was 60 (IQ range, 42–90) mm. The tumor was extra-abdominal in 127 patients and intra-abdominal in 15. The most frequent tumor site was extremity/girdle (46%), followed by abdominal wall (23%), intra-abdominal sites (11%), thoracic wall (9%), trunk (6%), and head and neck (5%).

Roughly two-thirds of the female patients in the group as a whole had a recent history of pregnancy (within the previous 2 years), whereas the prevalence of recent pregnancy was 51.6% among those with an abdominal wall DF. When divided according to treatment strategy, recent pregnancy was significantly more frequent in the W&S subgroup (36.1% vs. 2.6%, $P < 0.0001$).

Four percent of the patients had Gardner's syndrome (FAP). Eight percent (6/77) of patients with DF with no related FAP presenting to the IGR had cases of "sporadic" colorectal cancer (not hereditary nonpolyposis colorectal

TABLE 1 Main patient and disease characteristics, by presentation and treatment

	Overall (142 patients)		Primary (74 patients)		Recurrent (68 patients)		Wait & see (83 patients)		Any Tx (59 patients)		*P*
Center											<0.0001
IGR	68	47.9	39	52.7	29	42.6	56	67.5	12	20.3	
INT	74	52.1	35	47.3	39	57.4	27	32.5	47	79.7	
Presentation											0.0002
Primary							54	65.1	20	33.9	
Recurrent							29	34.9	39	66.1	
Age (yr)											0.0031
≤25	35	24.6	10	13.5	25	36.8	13	15.7	22	37.3	
26–45	75	52.1	49	66.2	26	38.2	53	63.9	22	37.3	
>45	32	22.5	15	20.3	17	25	17	20.5	15	25.4	
Sex											0.2455
Female	99	69.7	58	78.4	41	60.3	61	73.5	38	64.4	
Male	43	30.3	16	21.6	27	39.7	22	26.5	21	35.6	
Site											<0.0001
Extremities	65	45.8	20	27.0	45	66.2	27	32.4	38	64.4	
Trunk	9	6.3	4	5.4	5	7.4	5	6.0	4	6.8	
Head and neck	7	4.9	3	40.1	4	5.9	3	3.6	4	6.8	
Abdominal Wall	33	23.2	28	37.8	5	7.4	33	39.8	0	0	
Thoracic wall	13	9.2	9	12.2	4	5.9	9	10.8	4	6.8	
Intra-abdominal	15	10.6	10	13.5	5	7.4	6	7.2	9	15.3	
Size (mm)											<0.0001
≤50	54	41.5	32	45.7	22	36.7	43	55.1	11	21.2	
51–100	55	42.3	28	40.0	27	45.0	32	41	23	44.2	
>100	21	16.2	10	14.3	11	18.3	3	3.8	18	34.6	
NA	12	–	4	–	8	–	5	–	7	–	
Recent pregnancy (women only)											0.079
Yes	23	34.3	17	37.8	6	27.3	22	38.6	1	10	
No	44	65.7	28	62.2	16	72.7	35	61.4	9	90	
NA	32	–	13	–	19	–	4	–	28	–	
Initial treatment											
Wait & see	83	58.5	54	73.0	29	42.7					
Anti-estrogens	20	14.1	10	13.5	10	14.7					
NSAIDs	2	1.4	1	1.4	1	1.5					
Imatinib	1	0.7	0	–	1	1.5					
Low-dose CT	28	19.7	7	9.5	21	30.9					
ILP	3	2.1	1	1.4	2	2.9					
Multiple	5	3.5	1	1.4	4	5.9					

cancer [HNPCC]) in the family. The family history of colorectal cancer was not available retrospectively for the INT patients.

Therapeutic Strategy

Eighty-three patients were initially only monitored (W&S), whereas 59 were treated with any of the above-mentioned medical treatments (MT). In the W&S group, 54 patients (65%) had a primary tumor. The characteristics of the patients in this subgroup were different from those of the MT group, i.e., there was a greater female predominance, (4.4:1), patients were younger, the abdominal wall was the site most often affected, and the tumors were smaller and not symptomatic.

In the group of patients initially given MT, 28 patients (47.4%) received chemotherapy (mainly low-dose methotrexate and vinblastine/vinorelbine), 20 (33.9%) received

hormonal therapy (mainly tamoxifen), 11 (18.7%) other treatments (nonsteroid anti-inflammatory drugs, a combination of hormonal and anti-inflammatory nonsteroid drugs, imatinib, isolated limb perfusion).

In this group of MT patients, 20 (34%) had a primary tumor. The most common site was an extremity/girdle (64%). Roughly one-third of the treated patients had a tumor larger than 100 mm in size, and in most cases it was accompanied by pain or functional impairment, or both. Notably, none of the patients with abdominal wall DF were in this group.

Given the retrospective nature of our study, it was not always possible to identify the clinical reasons to choose one treatment or another. Nevertheless, the differences among the two major subgroups (W&S and MT) mainly reflect that better tumors (smaller in size, asymptomatic, and located at sites where an increase in size would not affect surgery) were more likely to be initially just observed, whereas those being large, symptomatic, and/or located at difficult sites were more likely to receive at least one of the available medical therapies.

Considering disease presentation at the time of referral, a W&S policy was initially offered to up to 73% of patients with primary tumors and only 43% of those with recurrent tumors, who more often tended to be treated initially with one of the available MT.

Patient Outcome

The median follow-up was 33 (IQ range, 13–73) months, and the vast majority of patients (87%) experienced tumor progression or were followed up for at least 5 years, until the year 2008. The estimated 3- and 5-year PFS rates for the group as a whole were 63.8% (SE, 4.6%) and 53.4% (SE, 5.3%), respectively (Fig. 1).

Twenty-eight events were recorded in the W&S subgroup, 26 among MT patients, and the 5-year PFS was 49.9% (SE, 7.7%) for the former and 58.6% (SE, 7.3%) for the latter ($P = 0.3196$). The estimated 5-year PFS rates for W&S and MT patients with primary tumors were 47% (SE, 10.3%) and 53.6% (SE, 13.3%), respectively ($P = 0.7018$; Fig. 2a). The corresponding figures for W&S and MT patients with recurrent tumors were 54% (SE, 11.6%) for the former and 61.1% (SE, 8.7%) for the latter ($P = 0.4832$; Fig. 2b).

For patients who progressed, the time to progression (TTP) ranged between 1 and 124 (median, 14) months. The TTP was more than 60 months in only 9% of cases.

Table 2 shows the results of Cox multiple regression model for the whole series. Only tumor site and size revealed a borderline significance. Tumors located in the trunk or thoracic wall and/or larger than 10 cm had the worst local outcome.

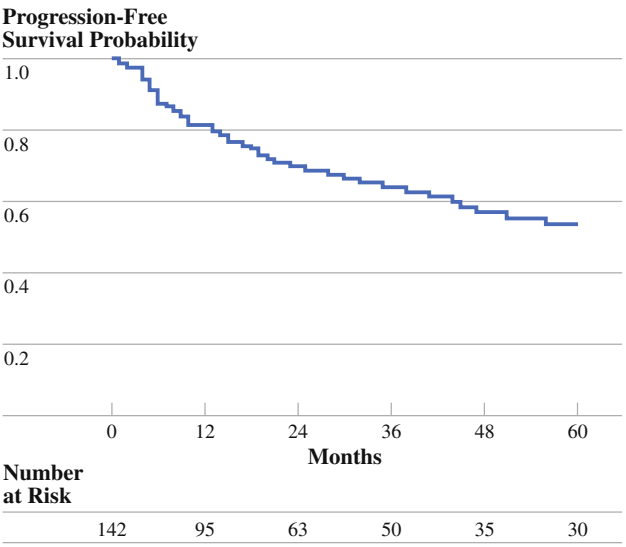

FIG. 1 Progression-free survival in the whole series

W&S Group A spontaneous regression in tumor size was documented in three primary cases after 3, 4, and 6 months, and persisted afterwards for a median of 12 months. No spontaneous regressions occurred in recurrent cases.

As for site, in primary cases, the 5-year PFS was 53.9% (SE, 16.2%) for trunk or thoracic wall tumors, 52.5% (SE, 14.3%) for the abdominal wall ones, and not estimable for the extremity ones due to the limited numbers. The corresponding figures for recurrent cases were not estimable for trunk or thoracic wall tumors and abdominal wall tumors due to the limited numbers, and 74% (SE 13%) for the extremity ones.

As concerns size, in primary cases 5-year PFS was 43.8% (SE 15.9%) for tumors $\leq$50 mm, 60% (SE 13.3%) for tumors 50 to 100 mm in size, and not estimable for tumors $\geq$100 mm due to the limited numbers. The corresponding figures for recurrent cases were 59.1% (SE 17%) for tumors $\leq$50 mm, 42.9% (SE 17.4%) for tumors 50 to 100 mm in size, and not estimable for tumors $\geq$100 mm due to the limited numbers.

MT Group As for site, in primary cases, the 5-year PFS was 50% (SE, 14.4%) for trunk or thoracic wall tumors, not estimable for the abdominal wall ones due to the limited numbers, and 65.6% (SE 20.9%) for the extremity ones. The corresponding figures for recurrent cases were 85.7% (SE, 13.2%) for trunk or thoracic wall tumors, not estimable for the abdominal wall ones due to the limited numbers, and 54.8% (SE 10%) for the extremity ones.

As concerns size, in primary cases 5-year PFS was not estimable for tumors $\leq$50 mm due to the limited numbers, 57.1% (SE 24.9%) for those 50 to 100 mm in size, and

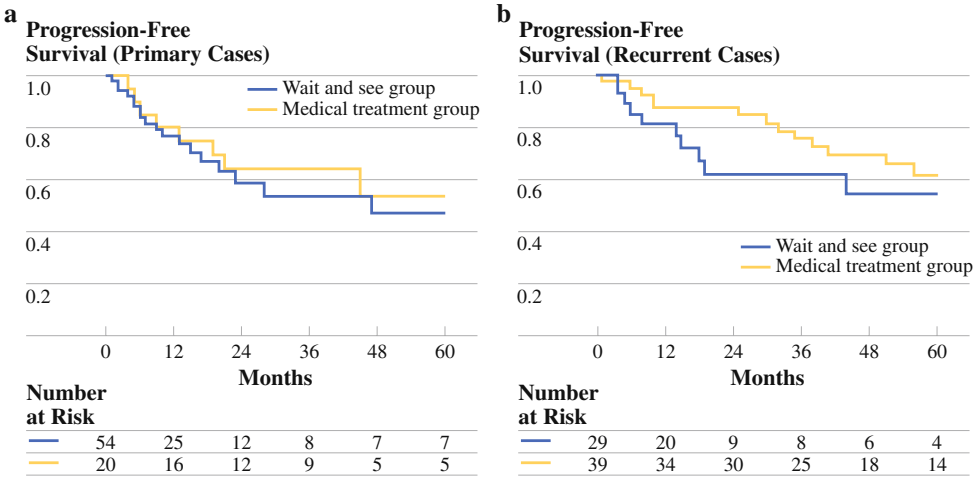

FIG. 2 Progression-free survival in primary (**a**) and recurrent (**b**) cases, according to initial approach (wait & see group, *continuous line*; medical treatment group, *dashed line*)

TABLE 2 Hazard ratio estimates with 95% confidence intervals and *P* value from the Cox proportional hazards model on progression-free survival in the overall series

Category (reference)	Hazard ratio	95% CI	Wald's *P* value
Treatment			
MT (W&S)	0.744	0.374–1.479	0.3992
Sex			
Male (Female)	1.536	0.828–2.848	0.1737
Age			
26–45 (≤25)	0.909	0.448–1.842	0.7907
>45 (≤25)	0.793	0.364-1.730	0.5603
Presentation			
Recurrent (primary)	0.860	0.473-1.562	0.6199
Site			
Trunk-thoracic (extremity)	2.091	0.972-4.502	0.0593
Head and neck (extremity)	0.997	0.223-4.456	0.9973
Abdominal wall (extremity)	1.616	0.646-4.042	0.3047
Intra-abdominal (extremity)	0.692	0.235-2.040	0.5045
Size (mm)			
51–100 (≤50)	0.931	0.488-1.777	0.8286
>100 (≤50)	2.101	0.948-4.658	0.0676

50% (SE 17.7%) for those ≥100 mm. The corresponding figures for recurrent cases were 60% (SE 18.2%) for tumors ≤50 mm, 62.9% (SE 16.6%) for those 50 to 100 mm in size, and 50% (SE 15.8%) for those ≥100 mm.

A detailed outcome according to the different medical approaches is beyond the scope of the present analysis.

Treatment at the Time of Progression

In the subgroup of primary tumors that were initially not treated (W&S), there were 19 cases of progression (Fig. 3). In 89% of cases, these tumors progressed within the first 2 years after referral. The tumors did not usually increase more than twice their initial size, but in two cases the size increased fivefold after 9 and 47 months, respectively.

Six patients were eventually treated with surgery as first choice (3 patients) or after a period of hormonal therapy (2 patients) or hormonal and chemotherapy (1 patient). The tumor site was the abdominal wall in four of these cases, the extremity in one, and the thoracic wall in one (this patient also was offered postoperative radiation therapy after R0 resection of a 150-mm tumor). The median tumor size in this subgroup was 105 mm, and the median TTP was 5.3 months. All six operated patients were alive and disease-free at the latest follow-up.

Ten patients were offered nonsurgical treatment at the time of tumor progression, i.e., hormonal therapy in seven cases, chemotherapy in two, and imatinib mesylate in one. The median tumor size in this subgroup was 66 mm, and the median TTP 11.1 months. Two of these ten patients

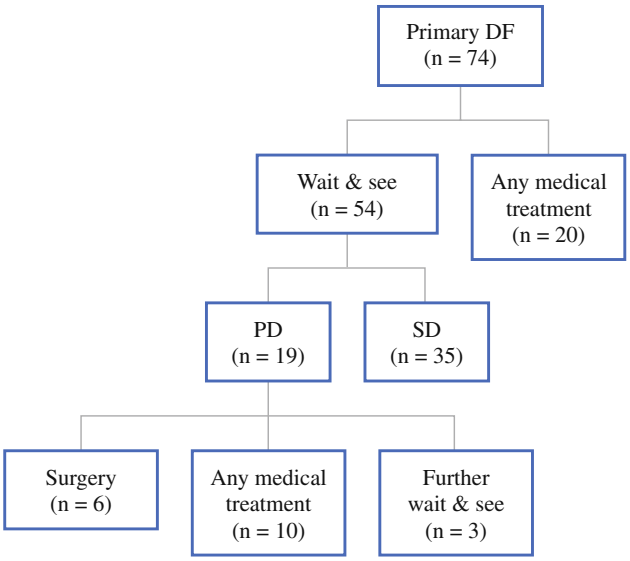

FIG. 3 Flow-chart for primary patients

experienced further tumor progression and were given other medical treatments (no surgery or radiotherapy was considered).

Finally, three patients revealed only a minimal tumor growth, therefore, the W&S approach was maintained; all three had an abdominal wall tumor, and one patient was pregnant at the time of its diagnosis.

In the other subgroups, there were 36 cases of progression: 9 among patients with primary tumors given MT, 10 among those with recurrent tumors in the W&S subgroup, and 17 of those with recurrent tumors given MT. These patients were treated in various ways (second-line medical treatment, surgery, radiotherapy, or combinations of these) not detailed herein, but nobody seemed to be harmed by the front-line nonsurgical approach, although given the retrospective nature of the present analysis a formal evaluation of this issue could not be performed.

Comparison Between Institutions

No significant differences in terms of outcome and patient characteristics emerged between the two institutions from an interseries analysis (data not shown).

DISCUSSION

In 142 DF patients first observed at two major reference centers for sarcomas, a front-line W&S or MT approach was selected, even if the tumor was surgically resectable. At 5 years, 50% of these patients were free of progression. This compares favorably with series of patients primarily treated with surgery.[4–6,10,11,17–19] Eventually, approximately two-thirds of our primary patients were able to avoid any surgical resection, and half of them were able to avoid any treatment at all and are still being followed (Fig. 3). In addition, we observed three spontaneous regressions, all in cases of primary tumor. All patients whose tumors progressed could subsequently be managed by surgery, medical treatments, or radiotherapy. This series enlarges the results preliminarily reported by the Villejuif group alone.[14] (Fig. 1).

A conservative policy has been advocated by some authors for recurrent and locally advanced DF.[10,11,14,16] In this series, this strategy was adopted as a front-line approach for primary disease (in addition to recurrent disease). Patient characteristics at presentation suggest that, had a standard first-line R0 surgical approach been adopted, these patients would have experienced a relatively high rate of functional impairment. Radiation therapy was avoided as well, in a proportion of patients. Even if radiation-related complications were lower with doses <56 Gy, they are still clinically relevant, including fibrosis, joint stiffness, and second malignancies.[17–19] This encourages a conservative approach to primary disease, as a means to select those patients who can be spared the impairments deriving from surgery or radiation therapy, in a disease whose anatomic location may be a challenging factor.

No significant clinical variables emerged as independent predictors of outcome, although there was a trend toward a worse course for tumors located in the trunk and those >100 mm (Table 2). These results should be looked with caution given the heterogeneity of the disease and the limited numbers in many of the subgroups identified. The vast majority of progressions (89%) occurred within the first 2 years of observation, and almost all of them within the first 5 years. Patients who remained stable for the first 2 years were much less likely to experience a progression later on. Apart from two cases, none of the tumors increased to more than twice their original size. An initial conservative approach should therefore entail close monitoring until the end of the second year. Decision on when to operate on progressing patients may be difficult because it needs to take into account the expected surgical morbidity: waiting a formal RECIST progression may not be wise in some patients, whereas in others despite a RECIST progression surgery could still be postponed. Different policies may then apply to different patients. A very careful and close follow-up should be scheduled for tumors in anatomic locations close to critical structures, where any increase in their size would imply a more aggressive surgical approach.

Overall long-term disease control proved the same for patients presenting with primary disease and those presenting with locally recurrent tumors (after excision elsewhere) (Fig. 2). Moreover, the fact that some tumors recurred after surgery and then remained stable without

treatment (as in 19 of 29 patients in this series) could have to do with the constitutional host environment and growth factors released after surgery in tumors that, without surgery, might have been indolent from the beginning. This has been suggested by some authors.[20–22] On the other hand, tumor progression after initial W&S may reflect unknown biological factors. In this perspective, it has been claimed recently that the molecular profile of the beta-catenin gene could predict the outcome of DF.[23] It might be possible that patients with a poor outcome could be selected in the future through molecular analysis.

In this series, some patients were selected for a W&S policy and others for MT. Both strategies are conservative, given the kind of medical therapy available for DF (including hormonal therapy and low-dose chemotherapy). In this retrospective analysis, the two subgroups were selected as a physician's choice. Their outcome was essentially superimposable, although the MT group was probably made up of more advanced and/or critical cases. A formal comparison among the two subgroups cannot be made. It is therefore impossible from this retrospective series to understand whether some patients are better approached with conservative MT from the beginning, despite a true W&S policy.

In brief, this retrospective analysis suggests that 50% patients with AF benefit from a front-line nonaggressive policy, because growth arrest is not an uncommon feature of this disease. This strategy could avoid surgical function loss and late radiation-associated complications; the aggressive therapy being selected only for those who really need it. Indeed, a surgical policy for all patients might overtreat 50% of them. For the future, a stepwise strategy may be tested, encompassing an initial W&S approach, then MT if needed, and then surgery and/or radiation therapy. Otherwise, some prognostic factors could be picked up as criteria for the treatment choice, promptly selecting some patients for surgery or for MT from the beginning. These factors may include the molecular profile as long as new insights into this rare disease are collected and validated in the clinic.

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