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ORIGINAL ARTICLE – BONE AND SOFT TISSUE SARCOMAS

Spontaneous Regression of Primary Abdominal Wall Desmoid Tumors: More Common than Previously Thought

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ABSTRACT

Purpose. The relevance of the initial observational approach for desmoid tumors (DTs) remains unclear. We investigated a new conservative management treatment for primary abdominal wall DTs.

Methods. Data were collected from 147 patients between 1993 and 2012. The initial therapeutic approaches were categorized as front-line surgery [surgery group (SG), $n = 41$, 28 %] and initial observation or medical treatment [nonsurgery group (NSG), $n = 106$, 72 %]. The cumulative incidence of the last strategy modification was estimated using competing risk methods with variable censoring times.

Results. Of the 147 patients, 143 were female (97 %). In the SG, 27 patients (66 %) required full-thickness abdominal wall mesh repair. In the NSG, 102 patients (96 %) underwent initial observation and four received medical treatment. In the NSG, the 1- and 3-year incidences of changing to medical treatment (no further changes during the follow-up) were 19 % [95 % confidence interval (CI) 11–28] and 25 % (95 % CI 17–35), respectively, and the 1- and 3-year incidences of a final switch to surgery were 14 % (95 % CI 8–22) and 16 % (95 % CI 9–24), respectively. An initial tumor size of >7 cm was associated with a higher strategy modification risk ($p = 0.004$). Of the 102 patients initially observed, 29 experienced spontaneous regression over a median follow-up period of 32 months. All second-intent resections were macroscopically completed, with R0 resections achieved in 82 % of patients.

Conclusions. This study supports an initial nonsurgical approach to abdominal wall DTs ≤7 cm, followed by surgery based on tumor growth in select cases.

Surgery has historically been the primary treatment for patients with resectable desmoid tumors (DTs).[1,2] Recently, the 2012 Guidelines for soft tissue sarcoma included observation as an option for selected patients with resectable DTs.[3,4] These modifications were made on the basis of recent retrospective analyses, some of them including children.[5–11] However, the criteria for selecting the patients for whom watchful waiting is most beneficial require clarification.[12]

Conflicting results from recent retrospective studies investigating the impact of surgical margins illustrate the heterogeneity of rare disease forms, including tumors causing both indolent and more aggressive disease, requiring different treatment options, as well as the unknown host/tumor factors influencing tumor progression.[1,2,5,13,14]

There is consensus that abdominal wall tumors demonstrate good prognoses and the results of systematic surgery are favorable in terms of local control.[1,7,15–19] However, the postsurgical morbidity associated with abdominal wall full-thickness mesh repair and the impact of parietectomy on subsequent pregnancy are poorly understood.

Surgical recommendations have traditionally been based on comprehensive retrospective studies in which surgery

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was proposed when feasible.[16] Therefore, more conservative treatment approaches were often ignored. Our clinical approach to abdominal wall DTs has evolved, with the majority of our patients placed under initial observation over the past 10 years. The objective of our study was to report the results of this new conservative management approach in patients with DTs, specifically within the abdominal wall.

PATIENTS AND METHODS

Data were collected from 147 consecutive patients with DTs within the abdominal wall who were followed at Institut Gustave Roussy, France, and Fondazione IRCCS Istituto Nazionale dei Tumori, Italy, between 1993 and 2012. Diagnoses were confirmed with biopsy results or specimens obtained by a specialized pathologist at each institution. Abdominal wall DTs in patients presenting with familial adenomatous polyposis were excluded. A common database tracked patient characteristics, including gender, age at diagnosis, initial tumor size, and year of diagnosis.

Patients were divided into two groups on the basis of the therapeutic approach employed: patients undergoing front-line surgery (surgery group, SG) or patients who were initially advised to wait and see or who received nonsurgical medical treatment (nonsurgery group, NSG). Follow-up consisted of performing contrast-enhanced abdominal wall magnetic resonance imaging (MRI) at close intervals, including 1 month after the initial evaluation and every 2–3 months thereafter. After 6 months, the patients were followed every 6 months in cases of stable disease. The resection margins in surgically treated patients were classified according to the International Union Against Cancer (UICC) R classification, and abdominal wall mesh repairs were recorded.[20] The last date on which the treatment strategy was modified, reasons for the change (e.g., tumor growth or symptoms), and tumor size (at that time) were recorded. At the last follow-up visit, the date, patient status, and tumor size were recorded.

The patients' initial characteristics were presented as percentages or medians and ranges, and subgroup comparisons were performed by the Chi squared and Wilcoxon tests.[21] The cumulative incidence of final strategy modifications and the cumulative incidence of each change, together with the confidence intervals (CIs), were computed using competing risk methods and by considering the variable censoring times.[22] Patients with <1 year of follow-up ($n = 18$), 1–2 years of follow-up ($n = 9$), and 2–3 years of follow-up ($n = 14$) were excluded from the 1- and 3-year incidence estimations of last strategy modification. Only the last change was recorded in the database; therefore, these curves may reflect patients who switched to surgery after initially waiting and who previously switched to medical treatment. The factors associated with strategy modification were investigated by a Cox model, with the results expressed as hazard ratios (HRs) of modification and 95 % CIs. SAS software version 9.2 was used for the statistical analyses (SAS, Cary, NC). The data collection and the statistical analyses were approved by the institutional review boards of both institutions.

RESULTS

Patient Characteristics

A total of 143 female and 4 male subjects were included in the study (ratio 36/1). The median patient age at the initial diagnosis was 34 years (range 14–74 years). A family history was observed in 30 % of the subset of French patients analyzed for sporadic intestinal cancer or polyps. The median primary DT size was 50 mm (range 10–156 mm). Of the female subjects, 25 % had a history of pregnancy over the 18 months preceding the diagnosis (Table 1).

Initial Strategies

Forty-one patients (28 %) underwent front-line surgical resection (SG), with negative margins reported in 23 cases (56 %). Full-thickness abdominal wall mesh repair was required in 27 patients undergoing surgery (66 %), and 106 patients (72 %) were initially not operated on (NSG). In these patients, the diagnosis was obtained by percutaneous core-needle biopsy and confirmed by a specialized pathologist (NSG) (Table 1).

In the NSG, according to our sarcoma boards strategy, 102 patients (96 %) underwent clinicoradiological surveillance and four patients (median tumor size, 11.2 cm) received medical treatment as first-line therapy [antihormone therapy ($n = 3$), with vinorelbine therapy in one case].[16] The SG and NSG were well balanced with respect to gender ($p > 0.90$), age ($p = 0.40$), pregnancy history ($p = 0.37$), and tumor size ($p = 0.53$). No patients received radiotherapy.

Follow-Up

The median follow-up period for all patients was 36 months (range 1–226 months). Final reports were obtained in 2011 or later for 89 % of the patients. For the front-line SG, the median year of diagnosis was 2004 and the median follow-up period was 97 months (range 9–226 months) (Table 1). Only 1 male patient with front-line R1 surgery exhibited recurrence. In the NSG, 2009 was the median diagnosis year and the median follow-up period

TABLE 1 Patients characteristics and follow-up

Characteristic	Overall	W&S ($n = 102$) and MT ($n = 4$)	Surgery
No. of patients	147	106	41
Sex			
Male	4 (3 %)	3 (3 %)	1 (2 %)
Female	143 (97 %)	103 (97 %)	40 (98 %)
Age at diagnosis (years)			
Median (range)	34 (14–74)	34.5 (14–66)	34 (18–74)
Pregnancy during last 18 months			
Yes	36 (25 %)[a]	28 (27 %)[a]	8 (20 %)[a]
Initial tumor size (mm)			
Median (range)	50 (10–156)	50 (10–156)	50 (17–150)
≤50 mm	80 (54 %)	57 (54 %)	23 (56 %)
51–100 mm	53 (36 %)	42 (40 %)	11 (27 %)
>100 mm	14 (10 %)	7 (7 %)	7 (17 %)
Year of diagnosis			
Median (range)	2009 (1993–2012)	2009 (2001–2012)	2004 (1993–2012)
Vital status			
Death	0	0	0
Follow-up (month)			
Median (range)	36 (1–226)	30.5 (1–136)	97 (9–226)
Quality of follow-up, year of last news			
Median (range)	2012 (2002–2012)	2012 (2002–2012)	2012 (2002–2012)
2002–2010	16 (11 %)	2 (2 %)	14 (34 %)
≥2011	131 (89 %)	104 (98 %)	27 (66 %)

W&S wait and see, *MT* medical treatment

[a] Only in female population

was 31 months (range 1–136 months). No patients died during the follow-up.

Change in Treatment Strategy

The treatment strategy evolution is summarized in Fig. 1. Patients in the NSG were asymptomatic with the exception of their palpable mass. In this group, 39 patients experienced treatment strategy modifications. The reasons for modification were progression in 32 of 39 patients [82 %, switch to MT ($n = 17$) and switch to surgery ($n = 15$)] and symptom changes (increasing pain) in 7 of 39 patients [18 %, switch to MT ($n = 5$), switch to surgery ($n = 2$)]. Overall, a switch to another treatment approach at 1 and 3 years occurred in 33 % (95 % CI 24–43) and 41 % (95 % CI 31–52) of patients, respectively (Fig. 2). The switch to medical treatment after 1 and 3 years, with no further switch during follow-up, occurred in 19 % (95 % CI 11–28) and 25 % (95 % CI 17–35) of patients, respectively, and the final switch to surgery after 1 and 3 years occurred in 14 % (95 % CI 8–22) and 16 % (95 % CI 9–24) of patients, respectively. No patients received radiotherapy.

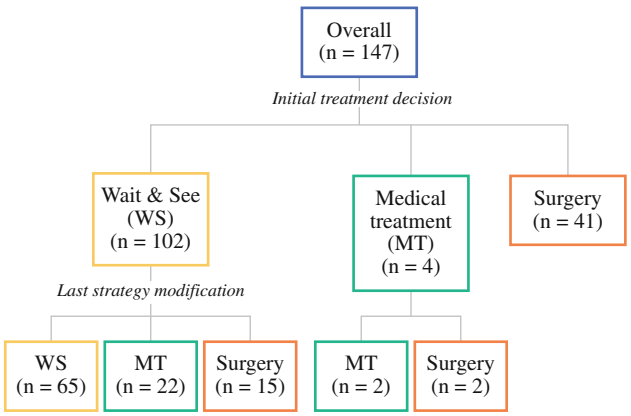

FIG. 1 Evolution of therapeutic strategies

In the 106 NSG patients, the initial characteristics associated with subsequent changes in treatment strategy (39 patients) were investigated. Neither age (continuous, $p = 0.27$) nor pregnancy before the development of DTs ($p = 0.27$) was associated with a change in the treatment strategy. Conversely, a large initial tumor size was associated with a higher risk of strategy change [$p = 0.004$, HR of modification in the different initial size distribution

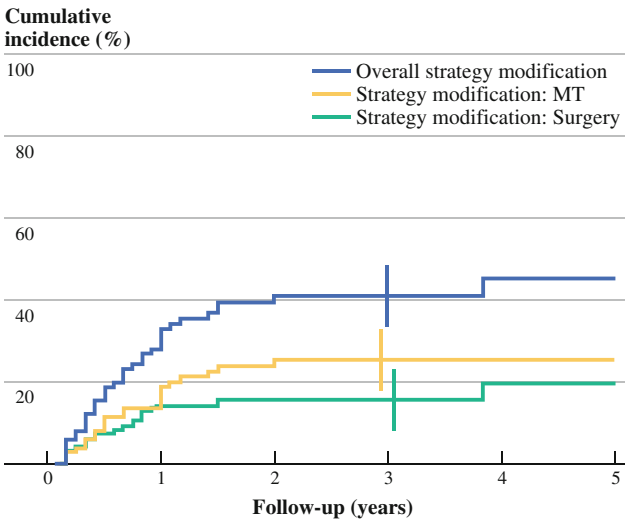

FIG. 2 Cumulative incidence of overall strategy modification, switch to medical treatment with no further switch, and final switch to surgery

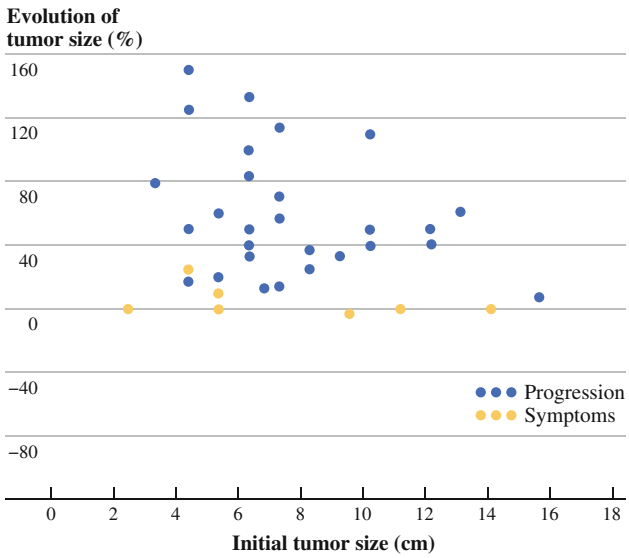

FIG. 3 Change in tumor size for patients with modification strategy (each *point* represents a patient)

quartiles, 3.7 (95 % CI 1.0–14) for tumor sizes of 3.5–5 cm; 4.0 (95 % CI 1.1–15) for sizes of 5–7 cm, and 8.2 (95 % CI 2.4–28) for sizes of 7–15.6 cm] compared with the risk associated with tumor sizes of 1–3.5 cm (Figs. 3, 4).

In total, 22 NSG patients were switched to medical treatment. At the time of treatment change, the median increase in tumor size was 29 % (range −3, +110 mm). Seventeen of 106 patients underwent surgery after a waiting period ($n = 15$) or after receiving front-line medical treatment ($n = 2$). The initial median size of the DTs in these patients was 60 mm (range 20–140 mm), and the median increase in tumor size at the time of surgery was 60 %. All resections were macroscopically completed. The quality of the surgery performed at the second intention was R0 in 14 patients (82 %) and R1 in three patients (18 %). A mesh was used in all 17 (100 %) patients. As shown in Fig. 4, of the 67 patients in the NSG who did not require a change in treatment, 26 were stable, 29 exhibited decreased tumor sizes (median size decrease of 66 %, including 12 cases with no tumor detectable and a 100 % decrease), and 12 demonstrated slow progression that eventually ceased. Therefore, 29 of the 102 (28 %) patients who were initially observed experienced spontaneous regression.

Medical Treatments for Second Intent

Of the 22 patients who received medical treatment after the initial wait-and-see period, 19 received antihormone treatment, two were treated with vinorelbine, and one was treated with imatinib alone.

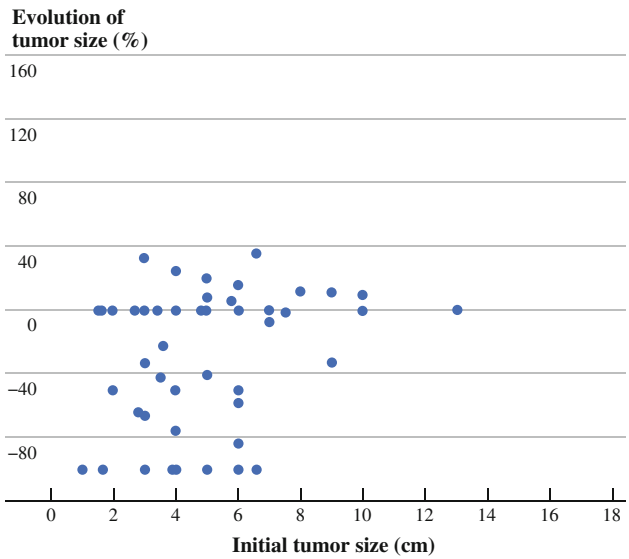

FIG. 4 Change in tumor size for patients without modification strategy (each *point* represents a patient)

DISCUSSION

This study was the first to evaluate both front-line surgical treatment and front-line nonsurgical treatment in patients with abdominal wall DTs, a large majority of whom underwent the initial wait-and-see strategy. One feature was the large predominance of young female patients (97 %) compared with previous case series that included various locations and reported a 2:1 gender ratio.[16] Treatment options must consider these features because surgery can affect subsequent pregnancies, and the

hormonal environment may be a treatment target before performing potentially mutilating surgery.

To date, only three published series assessing 28 consecutive patients affected by DTs of the abdominal wall have been reported.[17–19] In the largest, no local recurrence was reported.[17] Our study confirmed that surgery alone achieved good local control, superior to that reported in other locations.[23] However, because of the initial sizes of the abdominal wall DTs and their infiltrative growth, early and late morbidity related to surgery can be an issue, including hernia, mesh bulging, reoperation, and difficulties associated with pregnancy and delivery.[17,24,25]

Therefore, the main objective should not be to compare local control between these two strategies. In the current study, we found that the initial nonsurgical approach represents a good pragmatic method for selecting patients who could be spared a potentially mutilating surgery. Indeed, patients maintained under surveillance were asymptomatic; changes in treatment strategy were based on tumor growth or symptom development. Thus, this latency should be considered in light of the functional consequences of a mesh.

We demonstrated the new finding that approximately one-third of patients remained stable and one-third exhibited spontaneous regression after the initial wait-and-see period, which indicates that surgery can be avoided in these favorable situations. In previous studies, regressions were calculated in various cases, including recurrent DT cases, from any anatomical site; therefore, it is not surprising that this rate was underestimated.[16] Additionally, a hypothesis is that the cell stroma could decrease in size under the influence of hormonal changes, specifically in women.

We have previously reported that the vast majority of progressions (89 %) occur within the first 2 years after diagnosis.[6] Therefore, patients with <3 years of follow-up were excluded from the estimated 1- and 3-year incidence rates for final strategy modifications. The incidence of switching to medical treatment within 3 years, with no further change during follow-up, was 25 %. The median increase in tumor size was 29 %, which is similar to that referenced in the definition of progression according to the response evaluation criteria in solid tumors (RECIST).[26] Size tolerance increases depend on the initial tumor size, the tumor location relative to the inguinal ligament, and the patient's symptoms.

In cases of progression, medical treatment was generally initiated and effectively halted tumor growth in two-thirds of patients. Considering the particular epidemiology of DTs in the abdominal wall, antihormone treatment was our first choice and was administered for 6–12 months.[16,27,28] In a recent retrospective study, antiestrogens and anthracycline-containing regimens appeared to be associated with a higher radiological response rate compared with other agents, although there is no randomized study that has definitely validated their use, and alternative systemic chemotherapy are being evaluated.[29–31] We believe that the known side effects of antiestrogens were temporary and less severe than those of chemotherapy, whereas those of surgery are definitive. No patient received radiotherapy; it was not advisable to irradiate mesh and skin given the intrinsic digestive risks of irradiation at this location.[32]

In cases of further progression despite medical treatment, patients were selected to undergo surgery as a secondary treatment. The incidence of a final switch to surgery within 3 years based on tumor growth or changing symptoms was low (16 %). All patients who required operations as a secondary treatment demonstrated complete surgical results macroscopically.

We found that worse evolution was not predicted by age, as in other studies, although the results are contradictory.[7,33–35] Conversely, medical treatment can be predicted when the initial tumor size is >7 cm, with an early switch to surgery in cases of nonresponse, as patients who require treatment strategy changes after the initial wait-and-see period presented with significantly larger tumor sizes (>7 cm) (HR, 8.2). This size limit was also reported by the French Sarcoma Group study, and both results suggest treating DTs >7 cm in size from the onset.[7] After the decision for surgery was made, our intent was to achieve negative margins, and this goal was met in 82 % of patients.

One of the limitations of this strategy is clearly the difficulty in rapidly classifying patients into an indolent or aggressive group and in identifying the right time to switch the treatment strategy to surgery. In the absence of a routine reproducible biological marker for predicting tumor evolution, an initial wait-and-see approach justifies the adoption of a close follow-up period with good patient compliance to avoid missing significant progression. In particular, some patients may experience a more extensive surgery than initially planned. It will be necessary to evaluate whether this risk is balanced by the one-third chance of spontaneous regression and whether the disadvantage is linked to the endorsement of a mesh per se or to the use of a larger mesh size. Another question is the risk of DT progression associated with subsequent pregnancy, recently evaluated as 42 % in a multi-institutional United States–Europe study), although this eventuality has been safely managed.[36] Another limitation is that the estimated incidence of changes in treatment strategy concerned only the last treatment switch observed, implying that with a longer follow-up, a switch in medical treatment may evolve into a switch to surgical treatment.

To minimize these limitations, our current policy is to repeat MRI at 1 and 2 months after baseline and then perform these analyses intermittently during the follow-up.

Previous studies have reported that VEGF overexpression and that 45F CTNNB1 mutation are associated with poorer 5-year recurrence-free survival rates.[37,38] However, these parameters are presently not routinely used in treatment decision making and require prospective validation; this topic is currently under investigation in a prospective trial (ClinicalTrials.gov identifier NCT01801176).

This study supports an initial nonsurgical approach to abdominal wall DTs measuring up to 7 cm in size, followed by patient selection for surgery based on significant tumor growth. This strategy requires careful management and needs to be confirmed by further studies.

DISCLOSURE The authors declare no conflict of interest.

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