Ann Surg Oncol (2019) 26:4699–4706
https://doi.org/10.1245/s10434-019-07826-6

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – SARCOMA

Outcome of Primary Desmoid Tumors at All Anatomic Locations Initially Managed with Active Surveillance

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ABSTRACT

Background. The behavior of desmoid tumors is unpredictable and varies from spontaneous remission to symptomatic and radiologic progression. This study aimed to evaluate the radiologic and symptomatic course of the disease in patients initially managed with active surveillance.

Methods. Patients with a primary desmoid tumor at any anatomic location diagnosed between 1998 and 2016 were identified in a prospectively maintained database from a single sarcoma reference center in the United Kingdom. Inverse univariate Cox proportional hazard regression analyses were conducted to evaluate the course of the disease and indications for initiating treatment.

Results. The study identified 168 patients with a primary desmoid tumor initially managed with active surveillance. The tumors were located in the abdominal wall (n = 61, 36%), an extremity (n = 51, 30%), chest wall (n = 30, 18%), intra-abdominal site (n = 15, 9%), or elsewhere (n = 11, 6%). Of all the patients, 36% experienced radiologic progressive disease, 36% had stable disease, and 27% regressed. The patients younger than 50 years were more likely to progress (p = 0.046), whereas the patients with chest wall or upper-extremity tumors reported significantly more pain (p = 0.01). Eventually, 46% of the patients proceeded to treatment. The median time to start of treatment after initial surveillance was 31 months, whereas the median follow-up time for the patients not receiving any treatment was 40.5 months. The indications for initiation of treatment were pain (32%), progression (31%), or both (13%).

Conclusions. Patients with desmoid tumors can be managed with initial active surveillance, although almost half of patients may eventually need treatment. Pain, tumor progression, or both are the most common indications for the initiation of treatment.

BACKGROUND

A desmoid tumor, also known as desmoid type fibromatosis, is a rare mesenchymal proliferative disease that lacks metastatic potential but can be locally aggressive. Desmoid tumors are thought to arise from a clonal proliferation of mesenchymal stem cell progenitors.[1,2] They occur at a variety of anatomic locations including extremities, abdominal wall, intra-abdominal locations, head and neck, and chest wall.[3,4] The incidence is approximately three to four cases/million per annum.[5,6]

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First Received: 18 April 2019;
Published Online: 17 September 2019

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Until recently, surgical resection was the standard of care, but local recurrence rates after surgery are about 40%,[7] even when wide margins are taken. Furthermore, a spectrum of behavior exists, and a large proportion of these tumors are stable or regress with no treatment. Consequently, the high recurrence rate after surgery and the unpredictable clinical behavior of this tumor have resulted in a shift toward an initial management approach of pain control and active surveillance. In addition, several effective systemic therapies are available to treat this disease.[8–10] Also, a number of alternative local treatment options are available such as isolated limb perfusion, radiotherapy, local ablative techniques, and high-intensity focused ultrasound (HIFU).[8,9,11]

The outcome for patients managed by an initial approach of active surveillance has been evaluated in a small number of retrospective studies. The study findings indicate that this is a safe approach, both for intra-abdominal desmoid tumors and for extra-abdominal tumors.[12–15] However, no clear prognostic or predictive factors for treatment initiation after an initial surveillance period have been found. Tumor progression is an indication for treatment of malignant soft tissue tumors, but it is questionable whether this is always the case for desmoid tumors because a proportion regress spontaneously. Furthermore, a subset of patients experiences pain or other symptoms and require treatment despite minimal or slow tumor growth.

This retrospective study aimed to examine the course of the disease in terms of disease progression and pain and the most important indications for initiating treatment.

METHODS

Patients and Inclusion Criteria

All patients with a primary desmoid tumor treated at the Royal Marsden Hospital Foundation Trust (RMH) between January 1998 and June 2016 were identified from our prospectively maintained database. All patients were discussed by multidisciplinary sarcoma boards, and their diagnosis was confirmed by specialized sarcoma pathologists. Only sporadic desmoid tumors were included in the analysis. The study was conducted according to good clinical practice and performed in accordance with the Declaration of Helsinki.

Clinical Data

Demographic data as well as patient, tumor, and treatment details were obtained from the database. For all the patients initially managed with active surveillance, further details including tumor behavior and clinical data were retrieved from the patient files. Three events were scored during the follow-up period, namely, progression versus stable disease or regression, pain, and initiation of treatment after initial surveillance.

Active Surveillance of Patients

Active surveillance consisted of 3- to 4-monthly imaging with magnetic resonance imaging (MRI) or ultrasound combined with clinical examination. When the tumors were radiologically stable and the patients were either asymptomatic or attended with stable symptoms, the interval between clinical visits decreased to 6-monthly visits and eventually to yearly visits. Patients were no longer followed when the tumor neither progressed nor caused major symptoms during a period of 2–3 years.

Progression, stable disease, or regression was determined according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1.[16] Pain was determined according to clinical notes in the electronic patient record and categorized as

- No pain: no documentation of pain in the patient files during the follow-up period.
- Pain: pain experienced by the patient when documented in the patient file or when daily usage of analgesics was documented.

Statistical Analysis

Differences between patient groups (active surveillance vs. any form of treatment as first-line management, need for treatment vs. no need for treatment after initial active surveillance only, occurrence of pain vs. no pain, tumor behavior, progressive disease vs. stable disease vs. regressive disease) were analyzed with Chi-square tests. Inverse uni- and multivariate Cox proportional hazard regression analyses were performed to assess factors associated with need for treatment. Multivariate Cox proportional hazard regression analyses of covariates significantly associated with the outcome (at $p < 0.05$) in the univariate analysis was performed.

RESULTS

Patient Characteristics

The study identified 584 patients with a confirmed primary desmoid tumor. Of these patients, 168 initially were managed with active surveillance, whereas 416 received immediate treatment, which initially consisted primarily of

surgery but over time shifted more toward systemic treatment. All patients were discussed in a multidisciplinary meeting before initiation of any treatment or surveillance.

Over time, the percentage of patients initially managed with active surveillance increased, from 10% in 1998 up to 40% in 2016. Surveillance was offered as first-line management when patients had mild symptoms or none, or when the tumor did not grow rapidly and did not potentially affect relevant structures. The decision for active surveillance also could be made based on a patient's request, for whatever reason.

The characteristics of all 168 patients managed with active surveillance are shown in Table 1. All anatomic locations were represented, although only two patients had tumors in the head and neck region.

Tumor Behavior

Of the 168 desmoid tumors initially managed with active surveillance, 36% progressed ($n = 60$), 36% remained stable ($n = 60$), and 27% partially or completely regressed ($n = 45$; Table 2). For three patients (2%), the tumor behavior was unknown. At the end of the follow-up period, 12 patients had no evidence of disease. The tumors in these 12 patients comprised 7 tumors in the abdominal wall, 2 tumors in the lower extremity, 2 tumors located intraabdominally, and 1 tumor in the breast.

The univariate analysis of risk factors for tumor behavior is shown in Table 2. The patients younger than 50 years were more likely to show tumor progression ($p = 0.034$) than the older patients, whereas tumor size and gender did not significantly influence tumor behavior. Of all the anatomic locations, upper-extremity and chest wall desmoid tumors showed the highest percentage of progression (47% vs. 39%, respectively; Fig. 1), although this difference was not significant compared with other locations.

TABLE 1 Patient characteristics

	($n = 168$) *n* (%)
Sex	
Female	118 (70)
Male	50 (30)
Age at diagnosis (years)	
Median	42.2
Range	11–86
Size (cm)	
Median	5.9
Range	1–50
Site of tumor	
Lower extremity	20 (12)
Upper extremity	31 (18)
Abdominal wall	61 (36)
Intra-abdominal/mesenteric	15 (9)
Chest wall	30 (18)
Other	11 (6)

Pain

Of the 168 patients managed with active surveillance, 56 reported pain due to the tumor (33%), whereas 112 patients (67%) had pain symptoms that were not documented. Desmoid tumors located in the chest wall and upper extremity were significantly correlated with a higher incidence of pain when compared to other locations (55% and 47%, respectively; $p = 0.01$; Fig. 1).

Treatment After Active Surveillance

Of the 168 patients initially managed with surveillance only, 78 (46%) needed some form of treatment in the course of the follow-up period (Fig. 1). The medium time to the initiation of any treatment was 6.5 months after the initial surveillance. The remaining 54% of the patients continued with surveillance until discharge, with a median follow-up time of 40.5 months.

The first treatment after surveillance consisted of surgery for 40 patients (51%), systemic therapy for 36 patients (46%), and radiotherapy for 2 patients (3%). In the last years of this study, only about 20% of the patients underwent surgery after failure of the active surveillance (mostly patients with abdominal wall and symptomatic abdominal desmoids requiring emergency interventions), whereas in the first years of the study, all the patients underwent surgery when active surveillance failed.

Of all the patients undergoing surgery, 10 (25%) experienced a recurrence during the follow-up period. Systemic treatment consisted mostly of tamoxifen with a nonsteroidal anti-inflammatory drug, pazopanib, or pegylated liposomal doxorubicin. Tumors larger than 7 cm was significantly associated with a higher risk of initiation of treatment (hazard ratio [HR], 2.04; 95% confidence interval [CI], 1.29–3.21; $p = 0.002$). No significant correlations were found for age, gender, or tumor site in the uni- and multivariate analyses (Table 3), although a relatively high number of desmoid tumors in the chest wall and upper extremities were treated after an initial wait-and-see policy (57% and 58%, respectively; Fig. 1).

The main indication for treatment was pain (32%), radiologic progression (31%), or both (13%). The indications for treatment also included functional symptoms or

TABLE 2 Univariate analysis of factors correlating with desmoid tumor behavior

	Progression (n = 60, 36%) n (%)	Stable disease (n = 60, 36%) n (%)	Regression (n = 45, 27%) n (%)	p value
Sex				0.83
Male	21 (40)	18 (34)	14 (26)	
Female	39 (35)	42 (38)	31 (28)	
Age at diagnosis (years)				0.034[a]
< 50	49 (41)	37 (31)	35 (29)	
≥ 50	11 (25)	23 (52)	10 (23)	
Size (cm)				0.21
< 7	28 (31)	37 (41)	26 (29)	
≥ 7	31 (44)	22 (31)	17 (24)	
Site of tumor				0.34
Lower extremity	4 (31)	8 (62)	1 (8)	
Upper extremity	12 (39)	12 (39)	7 (23)	
Abdominal wall	20 (36)	16 (29)	20 (36)	
Intraabdominal/mesenteric	3 (20)	6 (40)	6 (40)	
Chest wall	14 (47)	11 (37)	5 (17)	
Other	7 (35)	7 (35)	6 (30)	

[a]$p < 0.05$ was considered significant

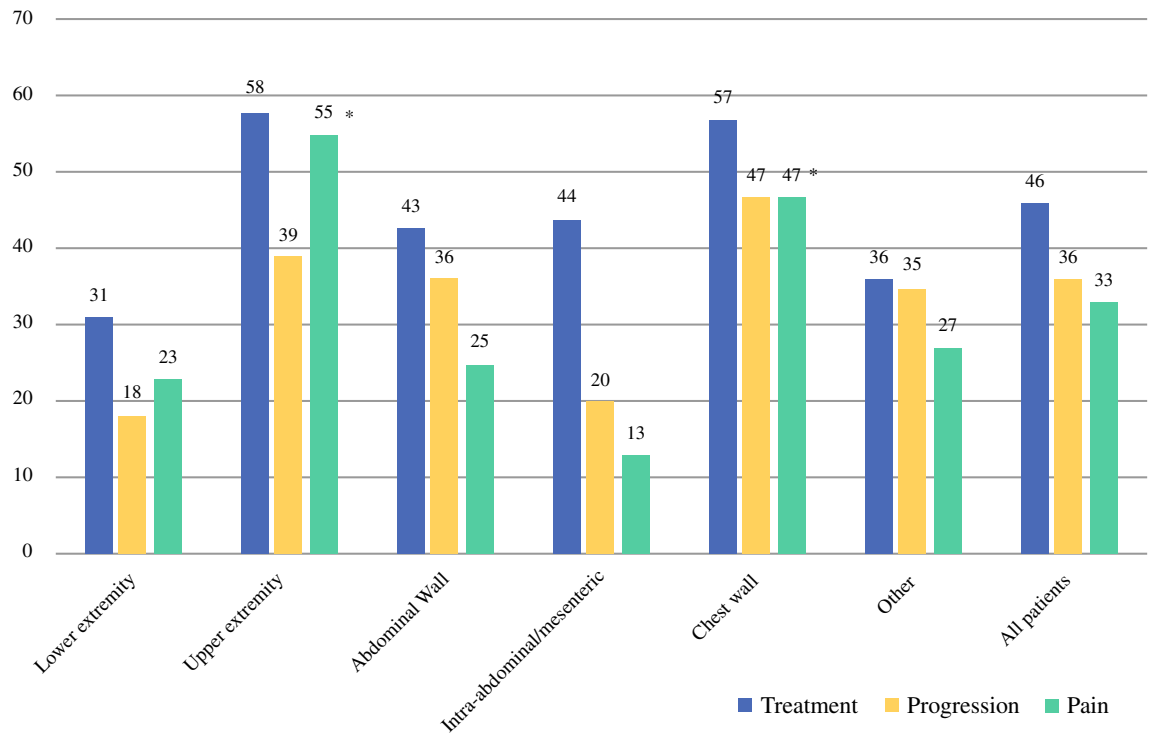

FIG. 1 Percentage of events per anatomic location after initial surveillance: treatment initiation after initial surveillance (blue), progression during surveillance (yellow), occurrence of pain during surveillance (green). *$p < 0.05$

patients requesting removal of the tumor. Initiation of treatment was more likely for the patients with progressive disease (HR 12.36; 95% CI 4.86–31.42) or stable disease (HR 4.75; 95% CI 1.79–12.59; $p < 0.0001$) than for those showing disease regression. In addition, initiation of treatment was more likely for those experiencing pain (HR

TABLE 3 Uni- and multivariate analyses of factors correlating with treatment after initial surveillance

	No treatment (n = 90) n (%)	Treatment (n = 78) n (%)	p value	Univariate HR (95% CI)	Multivariate HR (95% CI)
Sex			0.84		NA
Male	61 (53)	54 (47)		Ref	
Female	29 (55)	24 (45)		0.99 (0.6–1.6)	
Age at diagnosis (years)			0.13		NA
< 50	61 (50)	61 (50)		Ref	
≥ 50	29 (63)	17 (37)		0.7 (0.4–1.2)	
Size (cm)			< 0.01		
< 7	61 (66)	32 (34)		Ref	Ref
≥ 7	26 (37)	45 (63)		2.0 (1.2–3.2)[a]	1.8 (1.1–2.8)[b]
Site of tumor			0.36		NA
Lower extremity	9 (69)	4 (31)		Ref	
Upper extremity	13 (42)	18 (58)		1.8 (0.6–5.2)	
Abdominal wall	32 (57)	24 (43)		1.4 (0.5–4.0)	
Intraabdominal/mesenteric	9 (56)	7 (44)		1.4 (0.4–4.8)	
Chest wall	13 (43)	17 (57)		2.1 (0.7–6.2)	
Other	14 (64)	8 (36)		1.1 (0.3–3.6)	
Pain			< 0.001		
No	73 (65)	39 (35)		Ref	Ref
Yes	17 (30)	39 (70)		2.6 (1.6–4.0)[a]	2.1 (1.3–3.3)[a]
Tumor behavior			< 0.001		
Regression	40 (89)	5 (11)		Ref	Ref
Stable	38 (63)	22 (37)		4.8 (1.8–12.7)[a]	4.9 (1.8–13.0)[a]
Progression	11 (18)	49 (82)		12.4 (4.9–31.4)[a]	10.5 (4.1–26.7)[a]

HR hazard ratio, *CI* confidence interval, *NA* not applicable (univariate none significant), *Ref* reference category

[a] $p < 0.01$

[b] $p < 0.05$

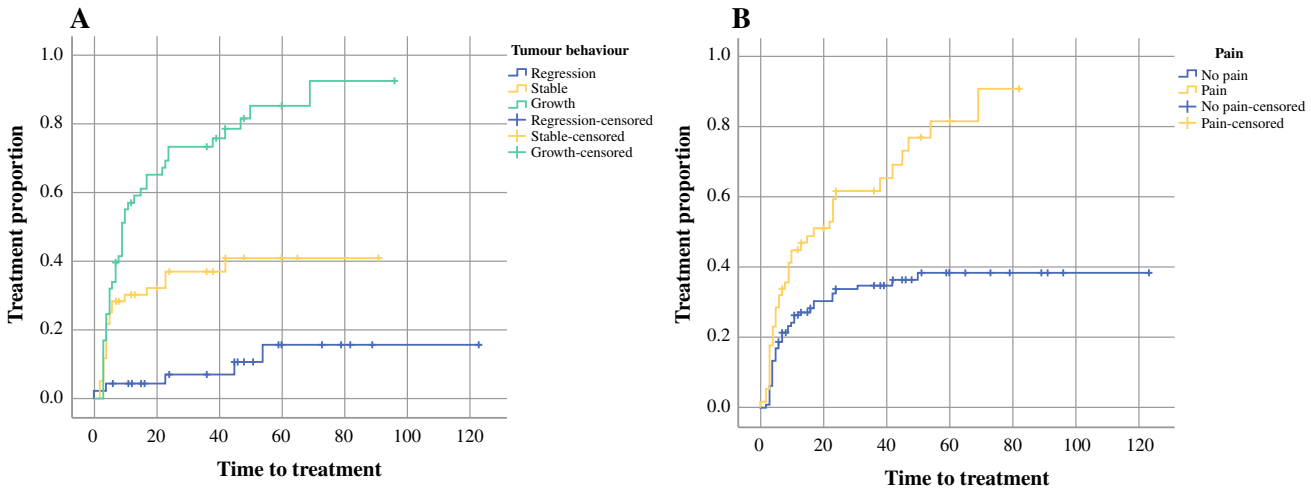

FIG. 2 **a**, **b** Kaplan–Maier curves showing treatment rate in relation to tumor behavior (progression vs. stable disease vs. regression) and pain (pain vs. no pain)

2.55; 95% CI 1.63–3.99; $p < 0.0001$; Table 3; Fig. 2a, b). Notably, in the group of 25 patients undergoing treatment for pain as the main indication for treatment, only 12 of 25 tumors were progressive.

DISCUSSION

This study retrospectively analyzed the outcome of all primary desmoid patients managed with active surveillance between 1998 and 2016 in one tertiary referral center. Initial surveillance was not routinely used in 1998 but became more frequently used over time. In the given period, 168 patients were identified, making this cohort, to the best of our knowledge, the largest retrospective cohort describing outcomes of primary desmoid tumors after an initial period of active surveillance at all anatomic locations.

In this study, almost half of the patients needed some form of treatment after an initial surveillance period (46%). This is in congruence with the 40–55% of patients needing treatment in other retrospective studies reported in the literature.[13,14,17]

With regard to tumor behavior, we found that only 36% of all tumors were progressive, which is comparable with another retrospective study of different anatomic locations, which found 19 (35%) of 54 tumors to be progressive.[12] In our study, all anatomic locations were represented, including intra-abdominal/mesenteric, extremity, and trunk desmoid tumors, but the number of head and neck patients was relatively low (1%, 2/168 patients). When comparing the different anatomic locations, this study showed that upper-extremity and chest wall desmoid tumors cause significantly more pain, possibly leading to a higher treatment rate. This is consistent with a French study, in which chest wall, upper-extremity, and head and neck tumors were significantly worse in terms of progression or need for treatment after initial surveillance.[18]

For sporadic intra-abdominal and abdominal wall desmoids, one Canadian study[14] reported that initial surveillance is safe and associated with a relatively good outcome, with 50 (46%) of 109 patients undergoing some form of treatment after initial surveillance. This is very similar to our study in which 43% of all abdominal wall and 44% of all intra-abdominal desmoid tumors needed treatment after initial surveillance.

Other prognostic factors were explored in our study, but the only significant prognostic factor for a higher progression rate was age younger than 50 years, whereas size larger than 7 cm was significantly correlated with a higher treatment rate. Younger patients, particularly women, possibly have a less favorable outcome because of a possible association between higher estrogen and progesterone levels and progression in desmoid tumors.[19]

Another potential prognostic factor for tumor behavior, not assessed in our study, could be the type of *CTNNB1* mutation. Approximately 70–80% of patients have a *CTNNB1* mutation, and there are suggestions in literature that especially the S45F mutation is correlated with a higher recurrence rate after surgery.[20–22] However, it currently is not known whether this mutation also is correlated with a higher progression rate after surveillance only.

When the decision for treatment was made after an initial surveillance period, the choice of treatment varied over time and still varies widely among institutions and countries. Whereas surgery used to be the treatment of first choice, systemic treatment is increasingly replacing surgery as the first-line treatment of choice. In our cohort, many patients still underwent surgery after initial active surveillance, especially in the first years of the study period, reflecting the period covered by our study, from 1998 when surgery was generally considered the standard of care.

Notably, surgery still can be considered as a good first-line treatment option for some anatomic locations, including the abdominal wall, easily resectable mesenteric tumors, and smaller subcutaneous tumors. However, for most other tumors, systemic therapy is considered to be more appropriate as first-line treatment, as stated in the recently published European Consensus Approach.[8,15] These documents contain an excellent flow diagram for the management of desmoid patients as well as more insight into the different treatment options that can be used in everyday clinical practice as a guideline for the management of desmoid tumors.

A major limitation of our study was the selection bias in offering active surveillance because only 168 of 584 patients had been offered active surveillance as initial treatment. Although the percentage of patients initially managed with active surveillance increased over time, even in later years only around half of all patients was offered active surveillance. This could be explained by the fact that the Royal Marsden is a tertiary referral center with a relatively high number of patients with large progressive and symptomatic desmoid tumors. Nevertheless, this bias might have influenced the results presented in this report.

Another major limitation of this study was its retrospective nature. Scoring pain in a retrospective study is difficult and biased by the potentially inconsistent documentation by different physicians. Pain likely was underestimated in this study due to this limitation.

For further exploration of the outcome after initial surveillance only, several prospective registration studies are being conducted in different countries, and the results are expected within a few years. The secondary endpoints

in these studies will be health-related quality of life because desmoid tumors can be chronic, with a significant and long impact on the lives of patients.[23,24]

The primary indication for treatment in our study was equally divided between pain and tumor progression. Several patients with stable disease and even some patients with regressive disease still received treatment because of mild to severe pain. This highlights the fact that a large subgroup of desmoid tumors can be painful[25] and might need treatment for symptomatic reasons only. Therefore, unless the tumors are located in potential life-threatening or function-limiting locations, the most meaningful endpoint for evaluating effectiveness of treatment strategies for desmoid tumors may be pain- or symptom-free survival rather than radiologic progression-free survival. In any future trial or observational study, it is recommended that symptom- or pain-free survival would be used as an important secondary endpoint or even as a primary endpoint, although developing a validated and reproducible quality-of-life tool specifically for desmoid patients could be challenging. But for many desmoid tumors, slow or limited radiologic progression alone is not necessarily problematic, whereas impaired health-related quality of life can be very limiting for an important subset of patients.[23,24,26] Therefore, any effective method offering symptom relief to desmoid patients might prevent more aggressive treatment in any form, highlighting the need to find better strategies for symptom control during active surveillance. Appropriate patient education and counseling, accompanied by shared decision making with both the patient and an expert clinician, might further improve the care for this group of patients.

In summary, this study showed that active surveillance is safe. Only about one third of all the patients were radiologically progressive, and only about half of all the patients were given some form of treatment. Chest wall and upper extremity desmoids are more likely to have a worse outcome. Further investigations evaluating the right indications for treatment, the impact of this chronic disease on quality of life and the appropriate choice of trial endpoints are required.

DISCLOSURE There are no conflicts of interest.

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