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MAGNETIC RESONANCE

The value of the black fiber sign on T1-weighted images for predicting stability of desmoid fibromatosis managed conservatively

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Abstract

Objectives It is challenging to know at the first which patients with desmoid fibromatosis (DF) are better suited to conservative or aggressive treatment. To investigate whether the low signal intensity bundles on T1- or T2-weighted images (WI), termed the "black fiber sign (BFS)," can predict non-progressive behavior in the conservative approach.

Methods This retrospective study included 59 patients with primary DF managed with wait-and-see approach from 2005 to 2018 and serial MR images were analyzed. Three observers blinded to the patient information verified the presence or absence of BFS on baseline T1 or T2WI. The likelihood of progression-free survival (PFS) after ascertaining the presence or absence of the BFS was estimated using the Kaplan–Meier method and analyzed with the log-rank test.

Results PFS was significantly higher in cases with BFS than without BFS on T1WI ($p < 0.01$), but there was no significant difference in PFS between cases with and without BFS on T2WI. Multivariable Cox proportional hazards analysis revealed that the absence of BFS on T1WI was a high-risk factor for progression (hazard ratio, 14.9; $p < 0.01$). Drastic tumor regression was apparent with significantly increased low-signal area in cases with BFS on T1WI. Intra- and interobserver reliabilities of BFS on T1WI were in almost-perfect agreement ($\kappa > 0.8$).

Conclusion Our retrospective observational data support that presence of BFS in baseline MRI may be a predictor for progression-free survival of DF. BFS on T1WI is easily identifiable and can be utilized clinically in patients with DF.

Key Points

- *We proposed a new imaging marker for prediction of desmoid fibromatosis progression.*
- *The absence of black fiber sign predicted a high risk of disease progression.*

Keywords Desmoid · Magnetic resonance imaging · Prognostic factors · Observation

Abbreviations

BFS	Black fiber sign
CR	Complete response
DF	Desmoid fibromatosis
FAP	Familial adenomatous polyposis
HR	Hazard ratio
MRI	Magnetic resonance images
NSAIDs	Non-steroidal anti-inflammatory drugs
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
ROI	Region of interest
SD	Stable disease
WI	Weighted imaging

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Introduction

Extra-abdominal desmoid fibromatosis (DF) has a locally aggressive infiltrative character, with no metastasis; therefore, DF therapy aims to achieve local control. Historically, complete surgical resection with an aggressive wide margin has been the standard care, but resection of this type often results in significant functional impairment and the need for soft tissue reconstruction. Moreover, DF has a high risk of local recurrence after resection ranging from 42 to 86% [1, 2].

Given this unpredictable biological behavior, including the possibility of spontaneous regression, attention has increasingly been directed toward initial nonsurgical management. An observational approach, known as the wait-and-see policy, has now become the more standard initial approach for DF [3, 4]. Fiore et al reported that the 5-year progression-free survival (PFS) was 49.9% in the wait-and-see group [5].

Castellazzi et al suggested that DF has variable characteristics on MRI and that it is impossible to predict tumor behavior based on MRI [6]. Therefore, it is important to identify predictors of DF progression during aggressive observation in clinical decision-making.

Histologically, DF is monoclonal proliferation of myofibroblasts with variable collagen deposition. In general, DF has histologically active and inactive areas. The transcriptionally inactive region has sparse cells with narrow, darker-staining nuclei and few mitoses with more extensive collagen [7, 8]. The histologically active region is characterized by light-staining oval nuclei, greater cell density, and increased mitotic activity with less collagen deposition. Furthermore, Rhim et al showed that low-signal-intensity bands on T1-weighted images (WI) correlated well with hypocellular and dense collagenous stroma on pathologic specimens [9]. Loss of T1 and T2 signals, suggesting a response to chemotherapy or radiation therapy in soft tissue tumor including DF, was associated with increased collagen deposition and decreased cellularity [10–12].

We therefore hypothesized that the cases with low-signal-intensity bands, called the "black fiber sign" (BFS), which might be associated with inactive DF regions, have a high likelihood of spontaneous regression or stabilization while under wait-and-see care. The objective of this retrospective cohort study was to examine whether tumors with BFS on T1WI and/or T2WI had non-progressive behavior, based on serial MRI evaluations, and to identify whether the BFS could be a reliable prognostic predictor of progression of extra-abdominal DF managed with observation.

Materials and methods

Patients

In total, 107 patients with pathologically confirmed extra-abdominal DF were treated in three institutions between January 2005 and April 2018 (Fig. 1). To preserve homogeneity in the study, we included only primary DF managed by observation over 3 months, as the first-line approach, with or without administration of drugs, including non-steroidal anti-inflammatory drugs, tranilast, and tamoxifen. Patients with recurrent disease or were treated by immediate active intervention, including surgery, radiotherapy, and chemotherapy (methotrexate, vinblastine, and imatinib), as first-line management, and without consecutive MRI studies were excluded. To avoid the effect of responses to active intervention, patients who were switched to active treatment, including surgery, radiotherapy, and chemotherapy during the study period, were analyzed until intervention commencement.

Evaluation

MRI was mainly performed using Magnetom series at 1.5 T (Siemens Healthcare), Signa series at 1.5 T (GE Healthcare), or Gyroscan and Ingenia series at 1.5 T (PHILIPS Healthcare) with a fast spin echo sequence. The contrast agent, gadopentetate dimeglumine (Magnevist; Bayer Healthcare), gadodiamide hydrate (Omniscan; Daiichisankyo), or gadoteridol (ProHance, Bracco) were mainly used. Consecutive MRI investigations were obtained over a period ranging from 3 to 12 months. An expert musculoskeletal oncologist (observer 1, Y.M.) with 12 years of experience, and blinded to the clinical information, analyzed the MR images. Tumor size at baseline and in serial images was calculated using the Response Evaluation Criteria in Solid Tumors guidelines, based on T2WI [13]. On the baseline MRI, the blinded observer determined the presence or absence of the BFS. A T1 or T2WI with very low signal intensity (the same as air) known as signal void more than 1 mm in diameter, and that had multiple, well-defined bundles inside the tumor, not at its periphery, was scored as positive for the BFS (Fig. 2a–d). Images with no significant low signal intensity and ill-defined low-signal area borders inside the tumor on T1 or T2WI were scored as negative (Fig. 2c).

Inter- and intraobserver reliabilities for determining of BFS on T1WI were assessed using kappa values. These were interpreted as follows: 0.00–0.20, poor; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and > 0.80, almost-perfect agreement [14]. To ensure interobserver concordance, two blinded observers (M.E., observer 2: musculoskeletal oncologist with 16 years of experience; J.S., observer 3: musculoskeletal oncologist with 8 years of experience) independently evaluated the presence or absence of BFS on T1WI. To assess intraobserver reliability, the observers made a double evaluation, 3 months apart.

PFS was calculated from the date of the first examination to the date of imaging progression, using the Response Evaluation Criteria in Solid Tumors. Time to intervention was defined as the time between the first examination and

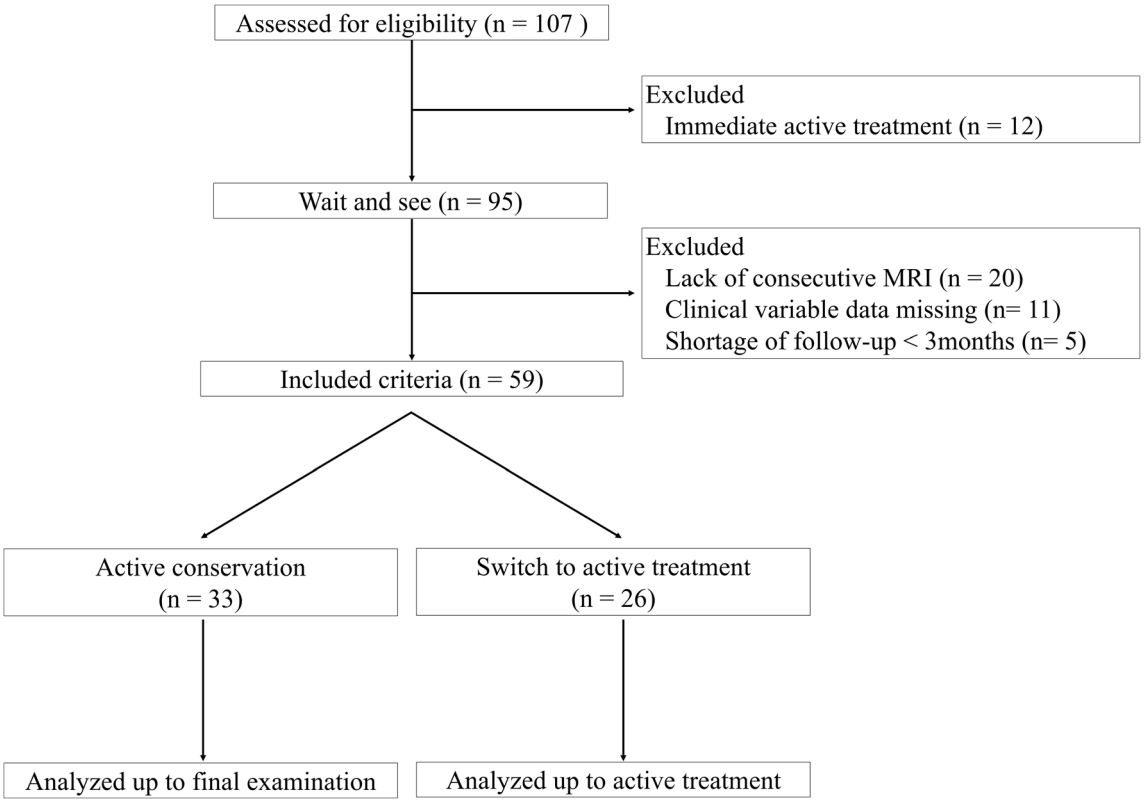

Fig. 1 Flowchart of patient inclusion

the date on which intervention (surgery, radiotherapy, or chemotherapy) was initiated. Furthermore, we examined whether tumor growth was related to fiber size or characterization of fiber borders (sharp or indistinct) on baseline T1WI. We analyzed the ratio of the very-low-signal area to the tumor (as the fiber size ratio) by drawing each region of interest at its greatest cross-sectional diameter using axial images.

We analyzed the ratio of the very-low-signal-intensity area (same as air) to the tumor with the presence of the BFS on T1WI. T1WI values were assessed by two methods. First, the oncologist drew the largest electronic region of interest within the boundaries of each tumor at its greatest cross-sectional diameter using the axial images and calculated the tumor size. Second, the size of the very-low-signal-intensity area was calculated. These measurements were repeated at the same location in the tumor on the first and the latest studies. Then, we analyzed the tumor size and the ratio of the very-low-signal area to the tumor at the first and the latest examination.

We finally assessed tumor T2 signal intensity using the modified Choi technique as previously described [15]. Briefly, the largest circular region of interest within the boundaries of each tumor at its greatest cross-sectional diameter and then, another circular region of interest at the adjacent, normally appearing muscle was drawn on the baseline examination. Finally, the ratio between tumor and muscle mean T2 signal intensities was calculated.

Statistical analysis

Data were expressed as the means ± standard deviation using EZR, a graphical user interface for R (The R Foundation for Statistical Computing) [16]. Statistical significance was evaluated using Welch's *t* test for comparison. The difference in the characterization of tumor borders (sharp or indistinct) between partial response (PR) and stable disease (SD) was analyzed using Fisher's exact test. The likelihood of PFS and intervention-free survival after ascertaining the presence or absence of the BFS on the first examination was estimated using the Kaplan–Meier method. Differences between cases with and without the BFS were analyzed with the log-rank test. The Cox proportional hazard model was performed to determine independent predictors of PFS. Univariable and multivariable analyses were used to identify potential predictors of PFS. Variables with a p value < 0.5 on univariable analysis were included in the multivariable analysis [17]. For all statistical analyses, p values < 0.05 were considered significant.

Ethics and registration

This study was carried out in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the Institutional Review Board for Clinical Research at our hospital (reference number

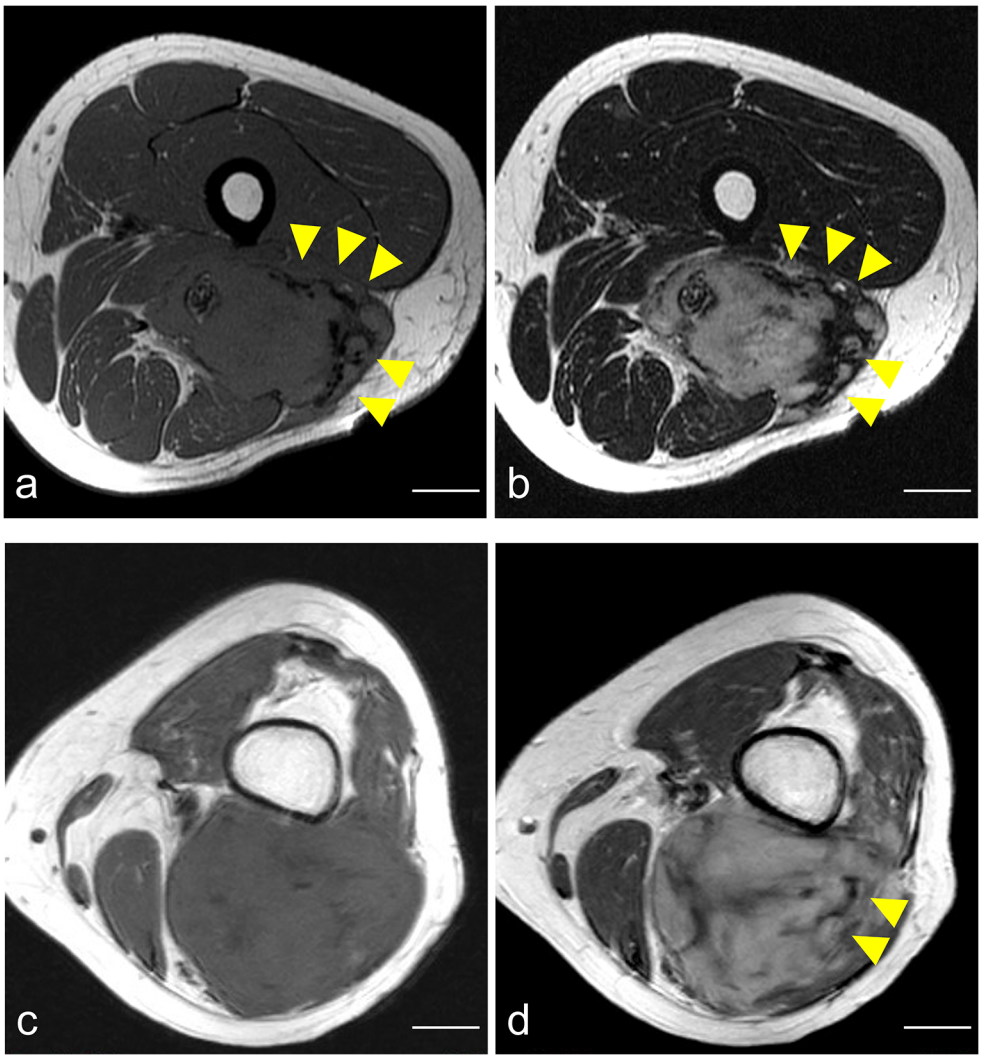

Fig. 2 Black fiber sign on T1- or T2-weighted MRI. **a**, **b** A 15-year-old female with desmoid fibromatosis in the posterior compartment of the left thigh. The black fiber sign is present in the tumor on (**a**) T1 and (**b**) T2-weighted imaging (arrow head). **c**, **d** A 58-year-old female with desmoid fibromatosis in the posterior compartment of the left thigh. The black fiber sign is absent on (**c**) T1-weighted imaging and presents on (**d**) T2-weighted imaging (arrow head). Scale bar, 2 cm

312-2; June 5, 2019). Written informed consent was waived for the patients with DF because of the retrospective nature of this study.

Results

Patient and tumor characteristics

Table 1 shows the demographic characteristics and treatment factors in enrolled patients with DF. The ratio of male to female patients was approximately 1:2.5. The mean age was 46.4 years (range, 15–76 years). The most common location of the tumor was the trunk (66.1%); the mean tumor size was 57 mm. Only one patient had a confirmed diagnosis of familial adenomatous polyposis, and 58 patients had the sporadic disease.

We analyzed the baseline and serial MR images using the Response Evaluation Criteria in Solid Tumors; the rates of complete response, partial response (PR), stable disease

Table 1 Clinical data and MRI features of desmoid fibromatosis

Sex	Male	17(28.8%)
	Female	42 (71.2%)
Age (year) [range]		46.4 [15–76]
Duration of follow-up (months) [range]		29.1 [3–137]
Oral administration	NSAIDS	33 (55.9%)
	Tranilast	36 (61.0%)
	Tamoxifen	2 (3.4%)
Location	Trunk	39 (66.1%)
	Extremity	20 (33.9%)
Size (mm) [range]		57.0 [13–136]
RECIST criteria	CR	0 (0%)
	PR	7 (11.9%)
	SD	30 (50.8%)
	PD	22 (37.3%)

(SD), and progressive disease (PD) were 0, 11.9%, 50.8%, and 37.3%, respectively. Overall, 26 patients (44.1%) dropped out from the wait-and-see policy and switched to active treatment for pain or contracture due to tumor growth (Fig. 1). Eleven patients underwent resection, six patients were treated by radiotherapy, and nine patients received chemotherapy.

Association of the BFS with tumor progression

The BFS was present in 19 cases (32.2%) on T1WI and 43 cases (72.9%) on T2WI. Among the 19 patients with the presence of the BFS on T1WI, five (26.3%) had PR and 13 (68.4%) had SD. A 20% increase in the tumor size, in the long-axis (PD), was observed in only one patient (5.3%) at 5 months after the first examination. Among the 40 patients without the BFS on T1WI, two (5%) demonstrated a PR and 17 (42.5%) had SD. PD was observed in 21 patients (52.5%) at a median of 4 months (range, 2–45) after baseline examination. Among the 43 patients with the presence of the BFS on T2WI, five (11.6%) had PR, 22 (51.2%) had SD, and 16 (37.2%) had PD. Among the 16 patients without the BFS on T2WI, two (12.5%) demonstrated a PR, eight (50%) had SD, and six (37.5%) had PD.

The PFS rate was significantly higher in the presence than in the absence of the BFS on T1WI ($p < 0.001$; Fig. 3a). The intervention-free survival rate was also significantly higher in the presence than in the absence of the BFS on T1WI ($p = 0.008$; Fig. 3b). Four out of 26 patients who switched to active intervention had the BFS on T1WI. There was no statistically significant difference in PFS and intervention-free survival rates between the presence and absence of the BFS on T2WI (Fig. 3c, d). Twenty out of 26 patients who switched to active intervention had the BFS on T2WI. We further examined whether tumor behavior was related to the fiber size or characterization of fiber borders on T1WI. There was no significant difference in the fiber size ratio or characterization of fiber borders between PR and SD in patients with BFS on T1WI (Table 2).

The results of Cox proportional hazards analysis of progressive disease are summarized in Table 3. In univariable analyses, the BFS on T1WI showed a statistical significance ($p = 0.008$). We used a composite of five factors with a p value < 0.5 (age, size, BFS on T1WI, and drug administration including non-steroidal anti-inflammatory drugs and tamoxifen) in multivariable analysis. The absence of BFS on T1WI predicted a high risk of PD ($p = 0.009$) in multivariable analysis, with a hazard ratio of 14.89.

To clarify the change in the size of the low-signal-intensity area in the tumor, we calculated this size on T1WI obtained at the first and the latest examinations. Representative T1-weighted MR images demonstrate tumor regression with an increasing low-signal area after 72 months (Fig. 4a, b). In quantitative outcome data, the size of the tumor was decreased significantly, and the ratio of the low-signal area to the tumor was statistically significantly increased at the latest examination (Fig. 4c).

A previous study has shown that the T2 signal ratio was associated with DF growth behavior [15]; thus, we evaluated the association of the T2 signal ratio with tumor growth in the current study. The group with a T2 ratio < 1 tended to have higher PFS and intervention-free survival rates than the group with a T2 ratio ≥ 1, but there was no statistically significant difference (Fig. 5a, b). Furthermore, we examined the value of the T2 ratio in the cases with or without BFS on T1WI. BFS-positive cases had a significantly lower T2 ratio than BFS-negative cases (Fig. 5c). Low-signal-intensity area (signal void) on T1WI was very low (signal void) in most cases even on the T2WI, and showed no enhancement on T1WI after administration of gadolinium-based contrast material. In contrast, low-signal-intensity area (signal void) on T2WI had a heterogeneous, low- to isointense to muscle on T1WI.

Inter- and intraobserver variability in the identification of the BFS

Observers 2 and 3 independently analyzed the T1WI of all eligible tumors and found 16 (27.1%) and 17 cases (28.8%) with the BFS, respectively. The interobserver variability between the three readers was excellent (Table 4). Intraobserver reproducibility for MRI detection of the BFS was in almost-perfect agreement ($\kappa = 0.920$; 95% CI, 0.811–1.029).

Discussion

We proposed a new marker for prediction of desmoid fibromatosis progression based on the low-signal intensity bundle, known as the black fiber sign, on T1-weighted images. The black fiber sign on T1-weighted images was significantly associated with the risk of progression and a switch from the wait-and-see approach to active intervention. Multivariable Cox proportional hazards analysis revealed that the absence of the black fiber sign on T1-weighted images was a high-risk factor for progression in patients treated with the wait-and-see policy. Furthermore, intra- and interobserver reliabilities in this study were almost perfect.

Most studies only reported the prognostic factors for local recurrence and few assessed tumor behaviors in the conservative approach [18–22]. In previous studies, the age, location, size, and surgical margin were independent prognostic factors for local recurrence [19, 20]. In some studies on the natural history of the disease with the wait-and-see policy, multivariable analysis identified no clinical variables or MRI characteristics as independent predictors of PFS [5, 6]. In the current study, there was also no statistically significant association between progression and age, sex, and tumor location, or size,

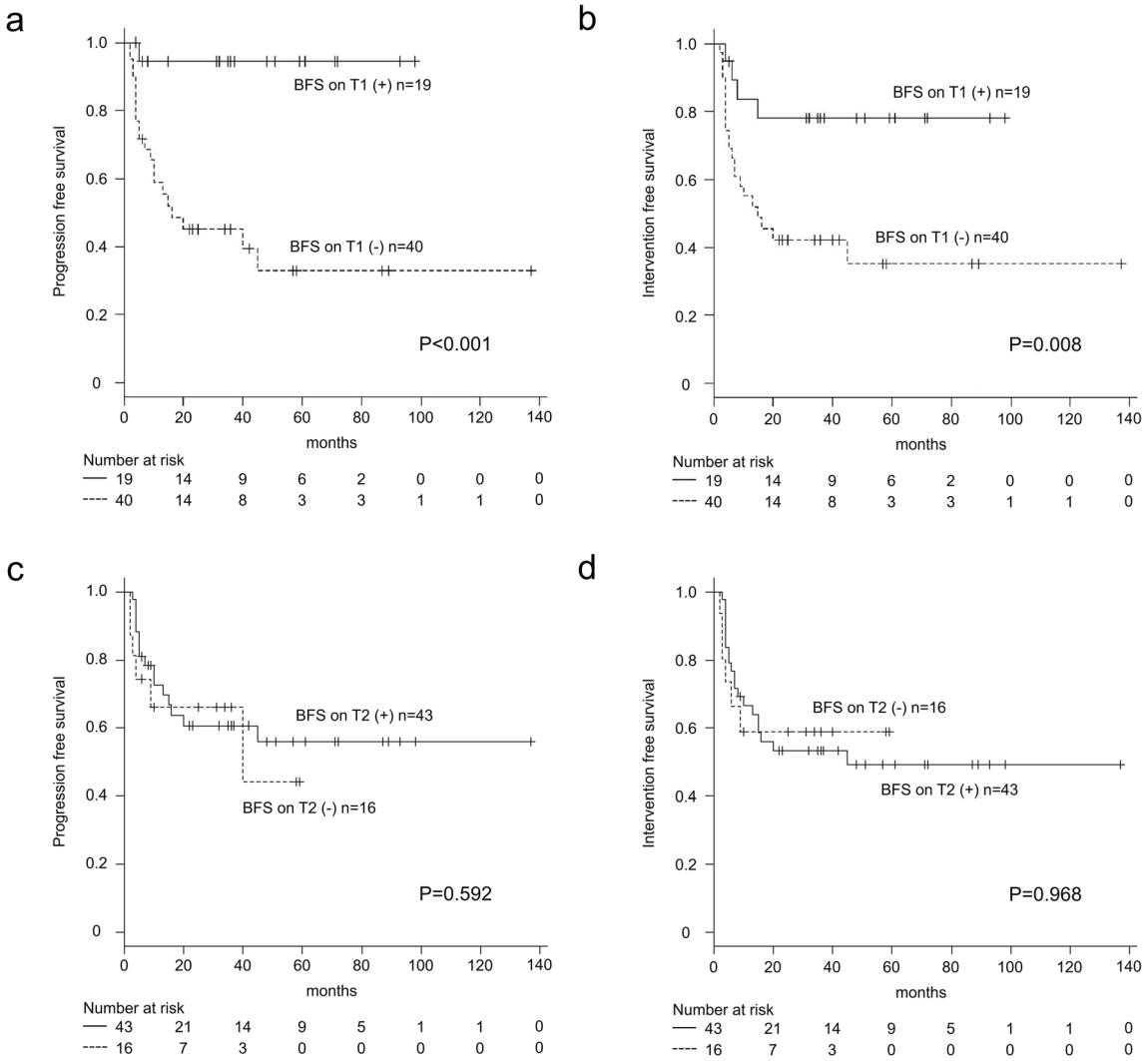

Fig. 3 Kaplan–Meier curves for (**a**, **c**) the progression-free survival and (**b**, **d**) intervention-free survival, stratified by the presence of the black fiber sign on (**a**, **b**) T1-weighted image and (**c**, **d**) T2-weighted image

according to univariable and multivariable Cox proportional hazards analysis. In contrast, Salas et al demonstrated that age, tumor localization, tumor size, and surgical margin influenced PFS in 426 cases of DF treated with different therapeutic strategies, including surgery, radiotherapy, medical treatment, and the conservative approach [21].

MRI may reveal changes associated with increased collagen deposition and decreased cellularity, such as a loss of T2 signal, which suggests either a response to treatment or a spontaneous regression in disease activity [9, 10, 23–26]. Rhim et al showed that the low-signal-intensity bands in T1WI of DF in the head and neck correlated with dense collagenous stroma within the mass [9]. Histologically, more collagen deposition is evident in regions in which cells have narrow, darker-staining nuclei and few mitoses, and appear transcriptionally inactive [7, 27]. Typically, the areas with more "transcriptionally inactive" cells are often separated by extensive collagen. Consecutive MR images typically show tumor shrinkage and reduction in T1- and T2-signal intensity in response to active intervention including chemotherapy and

Table 2 Relationship between tumor behavior and fiber characteristics

		PR	SD	*p* value
Fiber size ratio (%) [range]		3.35 [0.69–9.84]	8.24 [0.17–19.01]	0.277
Fiber border (cases)	Sharp	2	3	0.583
	Indistinct	3	10	

Table 3 Cox proportional hazards analysis for time to progression in 59 patients with desmoid fibromatosis

	Univariate analysis		Multivariate analysis	
	HR (95% CI) for progression free	*p* value	HR (95% CI) for progression free	*p* value
Sex (female vs. male)	0.77 (0.30,1.98)	0.593		
Age (< 60 years old vs. ≥ 60 years old)	0.58 (0.21, 1.57)	0.281	0.63 (0.23, 1,74)	0.375
Tumor location (trunk vs. extremity)	0.82 (0.33, 2.01)	0.662		
Depth (superficial vs. deep)	0.85 (0.33, 2.16)	0.726		
Black fiber sign on TIWI (absence) vs. presence	15.02 (2.01, 112.20)	*0.008**	14.89 (1.95, 1133.90)	*0.009**
Therapy NSAIDS (no. vs. yes)	1.71 (0.70, 4.20)	0.241	1.12 (0.45, 2.80)	0.815
Tranilast (no. vs. yes)	1.19 (0.48, 2.93)	0.705		
Tamoxifen (no. vs. yes)	2.72 (0.35, 21.16)	0.338	2.29 (0.26,19.80)	0.452

*p values < 0.05 are marked in italics

radiotherapy [10, 11]. If the collagen deposition represents the very-low-signal-intensity bands on T1WI, the BFS may have a histologically inactive area. Reduction in the contrast effect following systemic therapy is related to clinical response and tumor volume, and contrast enhancement of the tumor may be related to tumor activity [12, 25, 28]. In this study, the BFS on T1WI had almost no contrast enhancement, which suggests that the BFS on T1WI may be the area of low activity. In DF with the BFS on T1WI, tumor size decreased with an increase in the ratio of the low-signal area to the tumor. The BFS on

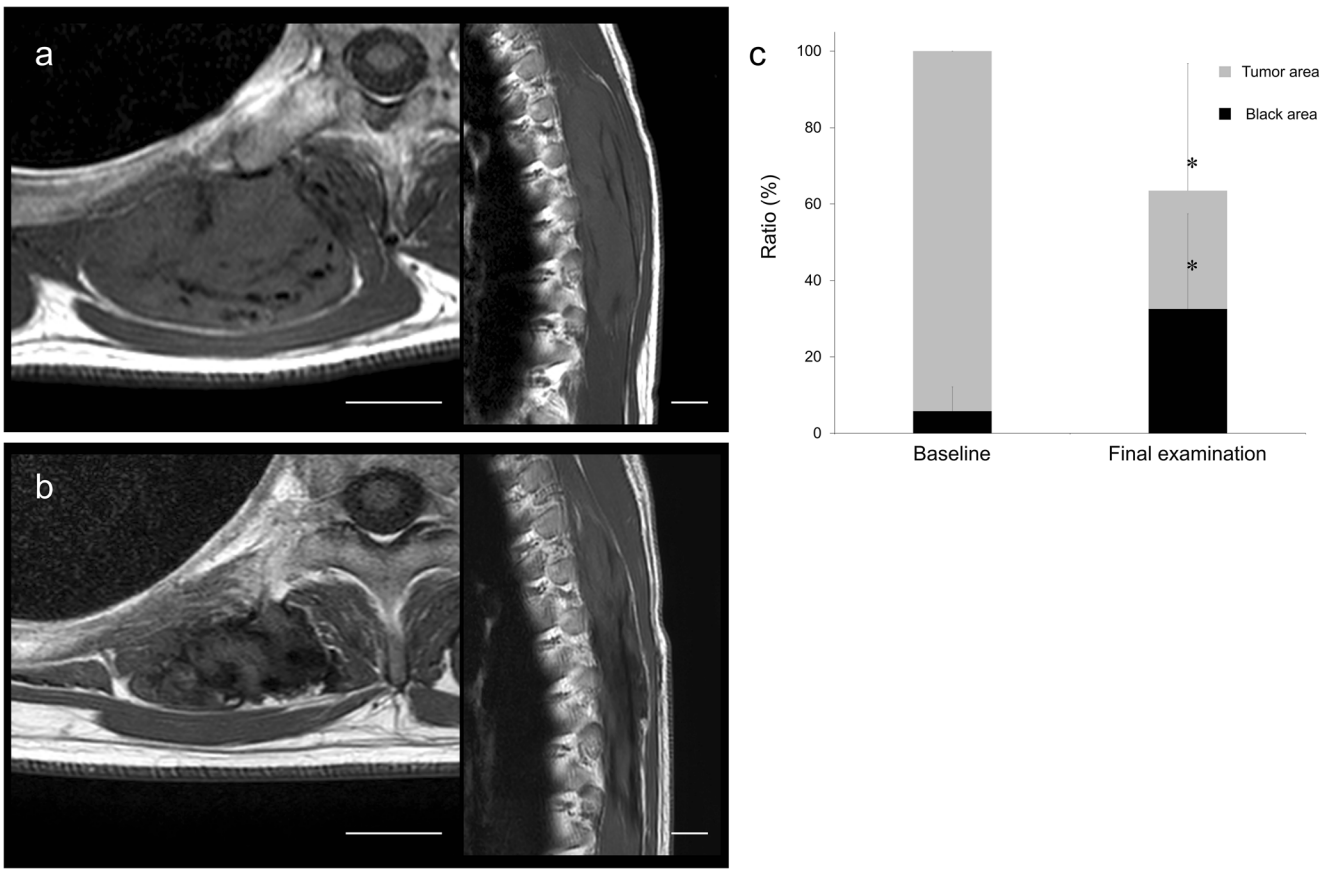

Fig. 4 Increase in low-signal-intensity area in T1-weighted MRI. T1-weighted MRI of the back, depicting desmoid fibromatosis, with a low signal intensity at baseline (first examination); (**a**) and after 72 months (**b**) under the wait-and-see policy. Scale bar, 2 cm. **c** Changes in the total tumor size and the ratio of the low-signal-intensity area to the tumor. Data are expressed as mean ± standard deviation. *$p < 0.001$ between baseline and the latest examination by Welch's t test

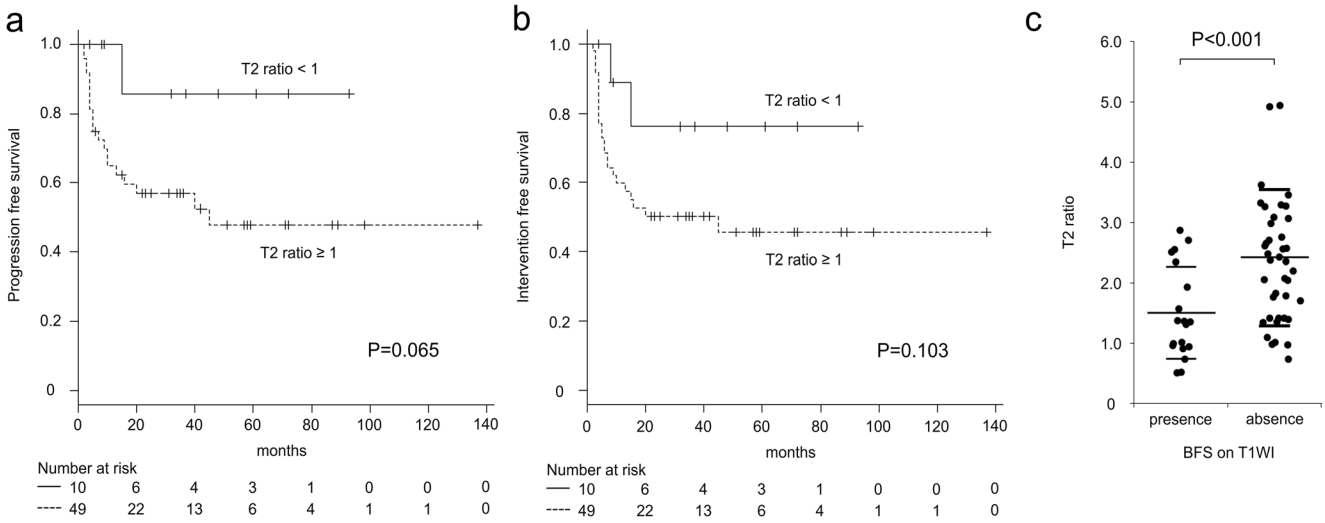

Fig. 5 Kaplan–Meier curves for (**a**) the progression-free survival and (**b**) intervention-free survival, stratified by the T2 ratio. **c** Dot plot of T2 ratio in desmoid fibromatosis with and without black fiber sign on T1-weighted image

initial T1WI may reflect the area that will later change to the collagen deposition area, appearing transcriptionally inactive. Meanwhile, the relationship between fiber characteristics (size and border) and tumor behavior has not been clarified. There was no significant difference in PFS and intervention-free survival between the cases with and without BFS on T2WI; thus, the BFS on T2WI did not serve as a prognostic indicator. The BFS on T2WI had a heterogeneous, low- to isointense to muscle on T1WI, and might contain some area without collagen deposition which appear transcriptionally inactive.

Various reports underscore the importance of T2 signal assessment in DF growth behavior [15, 25, 26, 29]. Gondim Teixeira et al showed that DF growth behavior was significantly related to hyperintense signal on T2WI and established a threshold of T2 value which predicts tumor growth [15]. In the current study, DF with T2 ratio < 1 tended to have higher PFS and intervention-free survival than that with ratio ≥ 1, but there was no statistically significant difference. This may be due to the small sample size in our study and differences in methods of DF behavior assessment between both studies. The tumors with BFS on T1WI had significantly lower signal on T2WI than those without BFS; thus, the BFS on T1WI may be related to T2 values of the whole tumor. However, some cases with BFS on T1WI had high T2 signal values, and some cases with BFS on T1WI had low T2 signal values. In the current study, the BFS appears to be more involved in the DF growth behavior than the T2 signal.

However, the study had some limitations, including the small sample size and relatively short follow-up period. To validate our results, further prospective studies are warranted. To preserve homogeneity, patients with recurrence after resection were excluded in the current study. In the future, it should be investigated whether the BFS is associated with tumor behavior in recurrent DF. Furthermore, MRIs were performed only with a fast spin echo sequence, and results of the BFS with other sequences such as the gradient echo sequence are unclear.

In conclusion, we demonstrated that the absence of the black fiber sign on T1-weighted images is a significant risk factor for the progression of desmoid fibromatosis managed with the wait-and-see policy. The black fiber sign could be easily ascertained in clinical settings, and, therefore, may be a factor in choosing the treatment.

Table 4 | Interobserver agreement of three observers according to the kappa statistics for all 59 cases

Observer	1	2	3
1		$\kappa = 0.879$	$\kappa = 0.920$
2			$\kappa = 0.874$
3			

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Toshihiko Yamashita.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry Hirofumi Ohnishi kindly provided statistical advice for this manuscript.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- prognostic study
- multicenter study

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