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Risk factors of local recurrence after surgery in extraabdominal desmoid-type fibromatosis: A multicenter study in Japan

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Abstract

This study was undertaken to clarify the risk factors, including the mutation status of *CTNNB1*, for the local recurrence after surgery of the rare disease desmoid-type fibromatosis. It was designed as a multiinstitutional joint research project with 7 major centers in Japan participating. The committee members of 7 major medical centers specializing in bone and soft tissue tumors formed this study group to develop clinical care guidelines. Of 196 cases with specimens and medical records collected from the 7 institutions, 88 surgically treated ones were analyzed regarding clinicopathologic prognostic factors including *CTNNB1* mutation status. Excluding R2 cases (n = 3),

5-year local recurrence-free survival (LRFS) was 52.9%. No case had received pre- or postoperative radiotherapy. Univariate analysis revealed that extremity location ($P < .001$) and larger size (8 cm or more, $P = .036$) were significant adverse risk factors for LRFS. Multivariate analysis indicated that extremity location ($P < .001$) was a significantly adverse factor in addition to recurrent tumor ($P = .041$), S45F mutation ($P = .028$), and R1 surgical margin ($P = .039$). Preoperative drug treatment, including nonsteroidal antiinflammatory drugs, did not reduce the incidence of local recurrence ($P = .199$). This is the first study to analyze the factors correlating with outcomes of surgical treatment, including *CTNNB1* mutation status, in a relatively large number of cases from an Asian country. Tumor location was found to be the most influential prognostic factor for local recurrence, similar to the results from Europe and North America. The development of more sensitive method(s) for determination of *CTNNB1* mutation is a priority for future study.

KEYWORDS

CTNNB1, desmoid, local recurrence, prognostic factor, surgery

1 | INTRODUCTION

Desmoid-type fibromatosis (DF) is a rare tumor characterized by monoclonal fibroblastic/myofibroblastic neoplasms arising in muscles, tendons, and ligaments. According to WHO (2013), it belongs to the group of locally aggressive, nonmetastasizing mesenchymal tumors. Overall incidence of DF in the population ranges from 2 to 4 new cases per million persons per year.[1] Extraabdominal DF affects all age groups and accounts for approximately 0.03% of all neoplasms. Desmoid-type fibromatosis occurs mainly between the ages of 15 and 60 years, with a peak incidence at approximately 30 years.[2] The treatment method for DF has shifted from surgery to conservative therapy, including watchful waiting.[3-6] The latest global consensus guideline for DF including Europe, America, and Japan confirmed that "active surveillance" is the first treatment option for many DF patients.[4] However, not a few number of patients still require surgical treatment for DF at some point during the course of their disease.[6,7]

The clinical course of DF cannot be predicted by watchful waiting. Moreover, medical therapy with anticancer agents[8,9] or molecular targeted drugs[10-12] requires a period of several months to obtain the anticipated efficacy. It has been pointed out that, even if efficacy is demonstrated, there is no evidence that guarantees a sustained effect.[13] A considerable number of patients continue to require surgical treatment eventually for reasons such as severe pain and/or exacerbation of joint involvement because they cannot wait for the therapeutic benefit of the drug treatment.

For these reasons, it is vital to identify the factors affecting the outcome of surgery for DF. Recently, there have been reports that the type of *CTNNB1* mutation (β-catenin gene), which many sporadic desmoids harbor, is associated with postoperative recurrence, with particularly S45F mutation cases having a poor outcome.[14-16] But all such reports have been from Europe and North America, with none thus far from Asian ones.

The purpose of this study is to clarify the risk factors for local recurrence after surgery, including the mutation status of *CTNNB1*, and to best identity those patients with DF who could benefit from surgical treatment. Desmoid-type fibromatosis is a rare disease and the number of cases at any single institution is not sufficient to obtain meaningful results. To overcome this, the present study was designed as a multiinstitutional joint research project by 7 major centers in Japan.

2 | MATERIALS AND METHODS

A committee was formed with the assistance of the Ministry of Health, Labor and Welfare of Japan to develop a clinical guideline to answer 11 clinical questions for treatment of extraabdominal DF (chair, YN) in Japan.[17] The committee members are from 7 major medical centers specializing in bone and soft tissue tumors who participated in the present study. As *CTNNB1* mutation analysis is not routinely undertaken in Japan, tumor samples were collected from the 7 centers and sent to the institution (Nagoya University [NU]) where *CTNNB1* mutation analyses were carried out for more than 100 cases using Sanger methods to proceed with this study. Initially, this study, including DNA analysis, was approved by the Institutional Review Board (IRB) at the main research institution (NU, approval number 2014-0217), and was also approved by the IRBs of the remaining 6 institutions as a basis for its documentation of the main institution (NU). This study was undertaken in accordance with the Helsinki Declaration.

Cases with frozen and/or formalin-fixed, paraffin-embedded (FFPE) tumor samples, which were stored in each of the 7 institutions

and available, were included in the present study. To investigate the correlation between clinicopathologic factors, including *CTNNB1* mutation type and surgical outcomes, we excluded patients who were lost to follow-up or lacked complete clinicopathologic data. Initially, we collected data including cases with macroscopically complete (R0 and R1) and incomplete (R2) resection.

Patient age was defined as the age at surgery for primary or recurrent tumors. Tumor size, defined as the maximum diameter of a tumor, was evaluated by the MRI or computed tomography report prior to the initial surgery. Tumor site was categorized as neck (no cases with head location), trunk (other than abdominal wall), abdominal wall, extremities including girdles (shoulder/axilla and hip/buttock/groin), or retroperitoneal cavity. Intraabdominal cases and familial adenomatous polyposis-related DF were excluded from the present study. Only 2 cases of retroperitoneal DF were included as trunk site. Therefore, en-bloc resection was achieved in almost all cases including DF of trunk site. However, the indication for surgery varied depending on the research institution. Patients were considered as primary when they had no history of surgical intervention, and to have recurrent DF if the tumor showed regrowth at least once after surgical resection.

Microscopic margin status was retrieved from the final pathology report and was considered positive if tumor was identified at the edge of the pathological specimen. Radiation therapy was not given in any case, even if the clinical risk of recurrence was predicted to increase. Imaging studies were usually undertaken once per visit or every 2 visits, generally MRI. Recurrence in R2 cases was defined as the time when it was recognized as a mass by postoperative MRI. However, the analysis was carried out separately with and without the R2 cohort.

To confirm the histological diagnosis of DF, sections of all cases were transmitted to the Pathology Laboratory at Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital for central pathology review (TM). All cases included in the present study were histologically confirmed as DF.

Anonymized medical records were collected from the 7 institutions participating in this study. Frozen or FFPE specimens obtained during biopsy or surgery were also collected, and subjected to DNA isolation and *CTNNB1* mutation analyses by direct sequencing as previously described at the main institution (NU).[18] Clinicopathologic factors correlating with local recurrence were statistically analyzed.

2.1 | Statistical analyses

Local recurrence-free survival was defined as the time from the date of surgery to the date of recurrence or death, or censored at the date of the last follow-up assessment in patients without local recurrence. The survival curves for local recurrence-free survival (LRFS) were estimated using the Kaplan-Meier product limit method. Log-rank test was used to determine whether any differences in survival were present between groups. The effects of potential risk factors on local recurrence were analyzed using multivariate Cox proportional hazards regression models. Hazard ratios (HRs) with 2-sided 95% confidence intervals (CIs) were derived from the stratified Cox proportional hazards model. All the variables were tested, with simultaneous forced entry, in multivariate models. The assumption of proportional hazards was checked in all models and was not violated. Two-sided *P* values below the threshold of 0.05 were considered statistically significant. All analyses were undertaken with SPSS Statistics version 17.0 (IBM).

3 | RESULTS

The medical records and tumor specimens from a total of 196 cases were collected from the 7 institutions. Twenty-five of them with specimens of too poor quality for DNA extraction, 80 cases without surgery, and 3 cases lacking sufficient clinical data were excluded from the present study. For evaluating LRFS, 3 cases with R2 resection were excluded from the analyses. In total, 85 cases composed this study (Figure 1). Thirty tumor samples were provided from 1 of the 7 centers; however, appropriate *CTNNB1* mutation analysis was not possible in 22 of them due to the insufficient quality of DNA extracted from the tumor samples. The remaining 8 samples from this institution were included in the present study.

Of the 88 cases, R0 resection was seen in 41, R1 in 44, and R2 in 3 cases. Thirty-five cases developed recurrence (40.0%). The median follow-up duration (recurrent case, from the date of surgery to

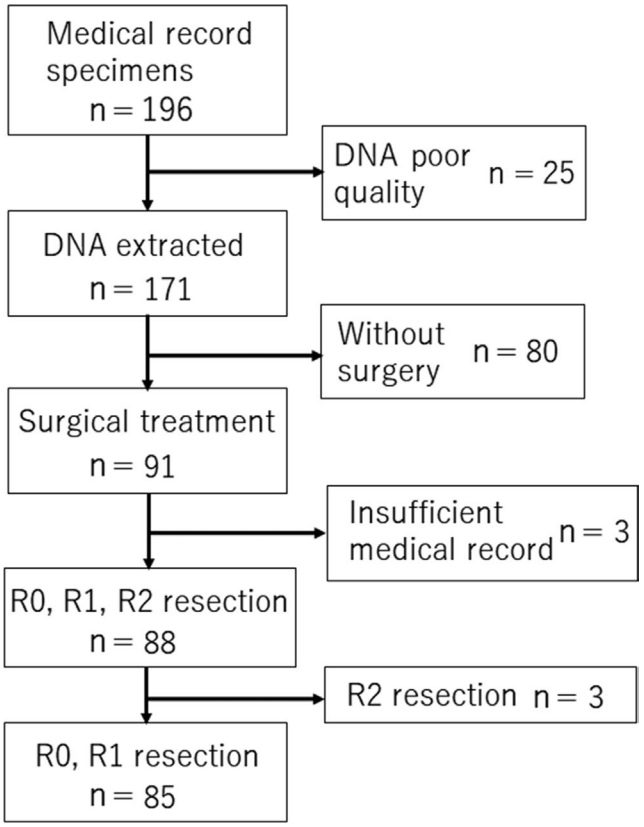

FIGURE 1 Flowchart for the selection of cases of extraabdominal desmoid-type fibromatosis in the present study

date of recurrence; nonrecurrent case, from the date of surgery to the date of last follow-up) was 42 months for nonrecurrent cases (range, 6-151 months) and 10 months for recurrent cases (range, 3-53 months). Excluding the R2 cases (n = 3), the recurrence rate was 37.6%. Demographic data of 85 cases excluding the R2 cases with or without recurrence are shown in Table 1, which was subjected to the final analyses. Mean age was 36 years (median, 35 years), ranging from 4 to 70 years. Mean tumor size (maximum diameter) was 8.1 cm (median, 7.8 cm), ranging from 3 to 18 cm. Based on the mean age and tumor size, we categorized the age and tumor size into 2 groups, with cut-off values of 36 years and 8.0 cm, respectively. Mutation analysis was undertaken in all 85 cases. Hotspot mutation of *CTNNB1* was detected in 53 cases (62%). Of them, T41A mutation was present in 37 cases (44%), S45F mutation in 15 (18%), and S45P mutation in 1. Regarding tumor location, extremity cases had a higher recurrence rate (67%) compared with other locations. The demographic data are presented as Table S1 when the R2 cases were included.

Kaplan-Meier survivorship analysis for 85 cases showed that 5-year LRFS was 52.9% (Figure 2). LRFS including R2 resection, 5-year LRFS was 51.1% (Figure S1). Univariate analysis revealed that extremity location ($P < .001$) and larger size (≥8 cm, $P = .036$) were significant risk factors for local recurrence (Table 2 and Figure 3). S45F mutation had a higher local recurrence rate, but did not predict poor outcome significantly with univariate analysis. Multivariate analysis with simultaneous forced entry method indicated that extremity location ($P < .001$) (HR 5.59; CI, 2.55-12.2), recurrent tumor ($P = .041$) (HR 3.1; CI, 1.05-9.18), S45F mutation ($P = .028$) (HR 2.92; CI, 1.12-7.6), and R1 surgical margin ($P = .039$) (HR 2.39; CI, 1.04-5.46) were significant adverse prognostic factors for local recurrence. Multivariate Cox regression analyses were also undertaken with stepwise, backward elimination, forward selection methods. The results differed slightly depending on the analysis method. Stepwise (slentry [significance level for entering variables] = 0.05; slstay [significance level for removing variables] = 0.05) selection method indicated that only extremity location was a significant predictor of poor outcome ($P < .001$) (HR 4.34; CI, 2.14-8.79) (Table S2). In the present study, final analyses were carried out based on the data of 85 cases. In addition, analyses of 88 cases including the R2 cohort indicated similar results with multivariate analyses; extremity location, S45F mutation, and surgical margin all affected the outcome significantly (Table S3).

Preoperatively, 29 patients received drug treatment with nonsteroidal antiinflammatory drugs (NSAIDs) and/or tranilast, which is an antiallergic agent used traditionally in Japan. The NSAIDs used were celecoxib, meloxicam, and sulindac. Cases with preoperative use of these drugs showed lower LRFS (5-year; 35.1%) compared with those without drug treatment (5-year; 60.6%), although this difference was not significant ($P = .199$) (Figure S2). One case received chemotherapy with low-dose methotrexate (MTX) and vinblastine (VBL).

4 | DISCUSSION

An important clinical issue needing attention when devising clinical guidelines for the rare disease, DF, is whether any factors exist that

TABLE 1 Demographic data of 85 cases of extraabdominal desmoid-type fibromatosis, excluding R2 cases

Variables	Category	Total number	Recurrence +	Recurrence−
Gender	Male	29	10	19
	Female	56	22	34
Age, years	≥36	40	14	26
	>36	45	18	27
Location	Neck	9	1	8
	Trunk	34	11	23
	Abdominal wall	13	1	12
	Extremity	27	18	9
	Retroperitoneum	2	1	1
Primary	Primary	73	26	47
	Recurrence	12	6	6
CTNNB1	T41A	37	13	24
	S45F	15	7	8
	S45P	1	0	1
	WT	32	12	20
Size, cm	≥8	42	21	21
	>8	43	11	32
Margin	R0	41	12	29
	R1	44	20	24

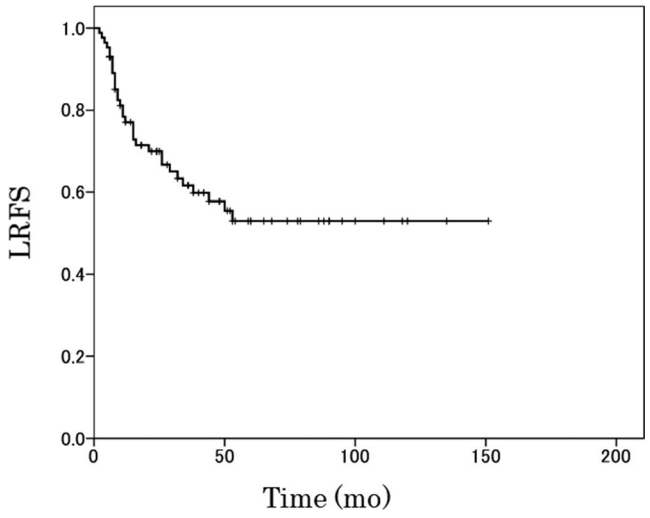

FIGURE 2 Kaplan-Meier survival curve in cases of extraabdominal desmoid-type fibromatosis with surgical treatment (n = 85). R2 cases (n = 3) were excluded. LRFS, local recurrence free survival

would reliably predict its postoperative outcomes. Several previous reports identified significant risk factors for surgical outcomes of DF including age, gender, tumor size, location, and surgical margin.[19-23] In the last decade, *CTNNB1* mutational status has also been reported as an important predictor of surgical outcomes.[14-16] In a search of published reports, Timbergen et al documented an association of *CTNNB1* mutation with surgical outcomes, and based on the results of 7 studies, concluded S45F mutation to be associated with a significantly higher risk for local recurrence.[24] These results are consistent, in part, with those of the present study, in which tumor location was noted to be the most crucial risk factor for local recurrence, with S45F mutation as well as surgical margin and primary/recurrent tumor also significant factors. Although the S45F mutation appears to be associated with a high recurrence rate, if included in the nomogram,[20] it would be a weaker factor than tumor location. Joint involvement, which is considered to be one of the indications for surgery, is commonly observed in cases of extremity location. In these cases, even if surgery is carried out, the recurrence rate is predicted to be high.

There is no huge cancer center in Japan like in the United States, and centralization of soft tissue tumor treatment has not yet been realized like in Europe, making it difficult to analyze large volumes of cases of rare tumors such as DF. Such reasons made it necessary for 7 large bone and soft tissue oncology institutions to work together to undertake this multicenter research. Investigation using over 80 cases would be meaningful, particularly in Asian countries, where no previous studies have analyzed the association between *CTNNB1* mutation status and surgical outcomes. In addition, *CTNNB1* mutation analysis is not carried out in most institutions, including even specialized facilities for soft tissue tumors (data obtained from a questionnaire survey showed that only 2 institutions carry out the *CTNNB1* analysis). The present study, for the first time in Asia, revealed similar results, regarding risk factors for surgical outcomes including *CTNNB1*, to those from Europe and North America.[14-16,24] However, ethnic difference in survival rates has been reported in other cancer types. For instance, Fang et al reported that the survival of black and American Indian/Alaskan Native bladder cancer patients is worse than that of other ethnicities. They used a nomogram including "Race" to estimate patient survival.[25] Compared to this, there would be no difference in survival and prognostic factors of DF between European/North American and Asian countries.

TABLE 2 Cox regression analyses for local recurrence-free survival among 85 cases of extraabdominal desmoid-type fibromatosis (n = 85)

			Univariate			Multivariate		
Variable	Category	n	HR	95% CI	*P* value	HR	95% CI	*P* value
Gender	Male	29	1.00			1.00		
	Female	56	1.05	0.49-2.21	.905	1.20	0.55-2.65	.643
Age, years	≥36	44	1.00			1.00		
	>36	41	0.73	0.37-1.48	.387	1.75	0.70-4.37	.234
Location	Others	58	1.00			1.00		
	Extremity	27	4.34	2.14-8.79	<.001	5.59	2.55-12.20	<.001
Primary	Primary	73	1.00			1.00		
	Recurrent	12	1.51	0.62-3.66	.367	3.1	1.05-9.18	.041
CTNNB1	Others	70	1.00			1.00		
	S45F	15	1.48	0.64-3.44	.361	2.92	1.12-7.60	.028
Size, cm	≥8	42	1.00			1.00		
	>8	43	0.46	0.22-0.95	.036	0.48	0.21-1.08	.075
Margin	R0	41	1.00			1.00		
	R1	44	1.53	0.75-3.13	.244	2.39	1.04-5.46	.039

Cases with R2 margin (n = 3) were excluded from the analyses.
CI, confidence interval; HR, hazard ratio.

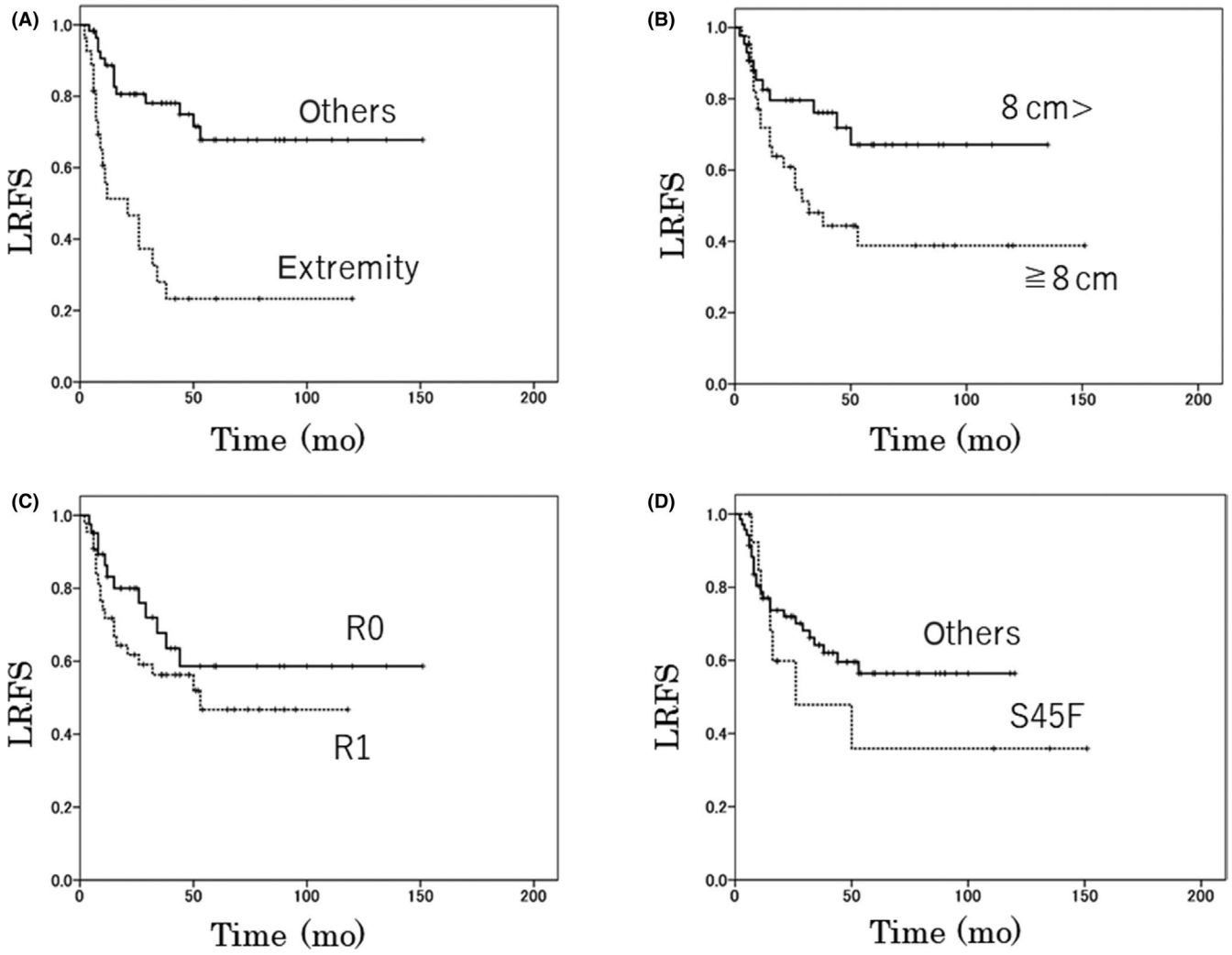

FIGURE 3 Kaplan-Meier survival curves for each variable (n = 85) contributing to risk of local recurrence after surgery in extraabdominal desmoid-type fibromatosis. A, Tumor location. B, Tumor size. C, Surgical margin. D, *CTNNB1* mutation status. LRFS, local recurrence free survival

We undertook a subgroup analysis with and without preoperative drug treatment in the present study, along with standard prognostic predictors such as tumor location and *CTNNB1* mutation status. Although the difference was not statistically significant, the cohort with preoperative treatment showed a higher local recurrence rate than that without. This could be attributable to the fact that patients with more apparently aggressive disease might preferentially receive drug treatment; another explanation could be that NSAIDs and tranilast do not have sufficient power to actively alter the assumed "natural course" of DF.[5] Actually, a recent review paper by The Desmoid Tumor Working Group found no documented evidence to support the use of antihormonal therapies or NSAIDs in patients with DF.[4] Regarding tranilast, which has long been considered effective in DF in Japan, it was not taken up in the aforementioned review paper because no case series have been reported, and only 2 cases were previously reported in PubMed.[26,27] If the drug can indeed change the "natural course" of DF preoperatively, it would make sense to carry out surgery in the stable or regression phase, thereby reducing the recurrence rate. In the present study, only 1 patient who remained recurrence-free after surgery had received low-dose MTX + VBL therapy. Future studies on the usefulness of preoperative use of effective drugs against DF should be carried out.

None of the present patients had received radiation therapy. In Japan, radiation therapy has not become standard treatment because DF is not malignant, and physicians and patients alike worry about the development of secondary malignant tumors. In addition, the rate of radiotherapy even for malignant tumors in Japan is lower than that in Europe and the United States. This background has itself eliminated any bias associated with radiotherapy, a factor associated with recurrence, in the present study.

There are several limitations in this multicenter study. Due to poor DNA extraction, 25 cases had to be excluded from the study. One factor could be that the formalin fixation time was too long at some facilities, which might be related not only to the failure to extract DNA but also to the low *CTNNB1* detection rate in the present study. In addition, WT was noted in as many as 34 cases

(40%), and its low sensitivity by Sanger sequencing was considered to be a problem due to the low frequency of mutant alleles. With use of next-generation sequencing, the WT evaluated by the Sanger method has been reported to have in fact a mutation in the hot spot of *CTNNB1*.[28,29] In a project that we have already started, it will be necessary to analyze the factors involved in LRFS, including the data of *CTNNB1* mutation type based on whole-exome sequencing. Among 88 cases with surgery in the present study, information was obtained on the first visit date and surgery date for 66 cases, of which 53 cases (80%) received surgery within 3 months after the first visit. In other words, according to the current treatment method for DF, nearly 80% of cases in the present cohort could have been treated with an initial active surveillance policy, avoiding surgical treatment. A recent study[30] reported the clinical outcomes of 168 cases with active surveillance. Results showed that the only significant risk factor for tumor progression with active surveillance was younger age ($P = .034$), and there was no association with tumor size or location. Therefore, it seems that the extremity location and large tumor size might be also detected as risk factors for surgical treatment in cases with tumor progression after active surveillance policy. However, when the tumors grow during active surveillance, these should be treated with an effective drug with evidence rather than surgical treatment.

Surgical margin is a factor that contributes to the outcome of surgery, but the existence of any difference between R0 and R1 is controversial and could not be completely resolved in the present study either. No significant difference could be identified between R0 and R1 with univariate analysis with Cox regression analysis ($P = .244$). Although multivariate analysis with simultaneous forced entry method detected significance between R0 and R1 ($P = .039$), the significance disappeared with the stepwise method (Table S2). A considerable number of previous studies did not detect significant differences in the results of surgery between R0 and R1 either.[20,23,31-33] Considering these previous and present results together, surgical margin is considered to be only a weak factor in the surgical prognosis, and so R1 resection may be appropriate in selected cases depending on the location and/or *CTNNB1* mutation type, thereby avoiding surgery that reduces function.[34]

In conclusion, this multicenter study suggested that several factors including extremity location, S45F mutation status, surgical margin, and recurrent tumor, are helpful criteria when determining the desirability of surgical treatment in patients with extraabdominal DF. Determination of *CTNNB1* mutation type with more sensitive methods warrants future study in order to establish a more accurate nomogram for surgical treatment in DF patients.

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CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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