

Clinical Outcome of Dermatofibrosarcoma Protuberance. Report From the Bone and Soft Tissue Tumor (BSTT) Registry in Japan

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Abstract. *Background:* Owing to its rarity, dermatofibrosarcoma protuberance (DFSP) is often inappropriately excised. After unplanned excision (UE), additional excision is commonly performed. We aimed to elucidate the effect of additional excision after UE. *Patients and Methods:* We examined 306 patients with primary DFSP. We analyzed surgical outcomes in 291 patients who received planned excision (PE) or additional excision after UE. *Results:* Of 306 patients, 194 received PE and the remaining 112 received UE. Of 112 patients, 97 received additional excision after UE. Additional surgery due to complications was more frequent in patients with UE than in those with PE. The 5-year local recurrence-free rate in patients without additional excision after UE was significantly worse than that in those with additional excision after UE. *Conclusion:* If UE is performed, we recommend additional excision for preventing local recurrence; however, the surgical wound should be carefully observed.

Dermatofibrosarcoma protuberance (DFSP) is a rare, locally aggressive tumor arising in skin tissue. Epidemiology shows 0.8 to 4.2 cases of DFSP per million people per year, which accounts for 2-6% of soft tissue sarcomas (1). DFSP has been confirmed to be a relatively indolent sarcoma, with a disease-specific mortality of less than 2% after 5 years (2, 3). While local recurrence is frequent, metastasis of DFSP is rare. Owing to the rarity, DFSPs will be inappropriately excised by general surgeons without any suspicion of

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malignancy (4, 5). In this situation, it is not uncommon to resect the tumor without magnetic resonance imaging. In such unplanned excisions (UEs), there is no intent to achieve tumor-free margins and the direction of the skin incision is not considered. Inadequate surgical margin increases the risk of local recurrence (1). To reduce the possibility of recurrence, orthopaedic oncologists have performed additional excisions with wide margins. Additional excisions require more extensive surgical margins than conventional wide-margin excisions do because both reactive changes after UEs and inappropriate skin incisions can cause tumor cell contamination of non-tumor regions (6, 7). On the other hand, after UE, some patients will not recur. Therefore, wait and see policy may be performed in some patients. However, the clinical outcome after UE in patients who did not receive additional excision (wait and see policy) was not described.

The Bone and Soft Tissue Tumor (BSTT) registry is a nationwide organ-specific cancer registry for bone and soft tissue tumours in Japan. The aim of this study was to elucidate the clinical outcomes of patients with DFSP using data from the BSTT registry. Furthermore, we also evaluated the impact of the wait and see policy after UE of DFSP on local recurrence and survival.

Patients and Methods

Data source. Launched in 1950's, the BSTT registry is organised and funded by the JOA and promoted by the National Cancer Center. This study was approved by the Institutional Review Board of the Japanese Orthopaedic Association and Mie University hospital. Informed consent was waived because of the nature of the present study. Instead of it, opt-out was performed and the patients had an opportunity of denying of the study participation.

Data extraction. We examined patients with primary DFSP. Data from 2006 to 2016 were obtained from the BSTT registry. Patient age and sex were selected to represent individual clinical variables. Regarding the DFSP lesions, tumor size, location, depth, treatment details were chosen. We also obtained date of diagnosis, oncological events after treatment, and prognosis at the last follow-up. The

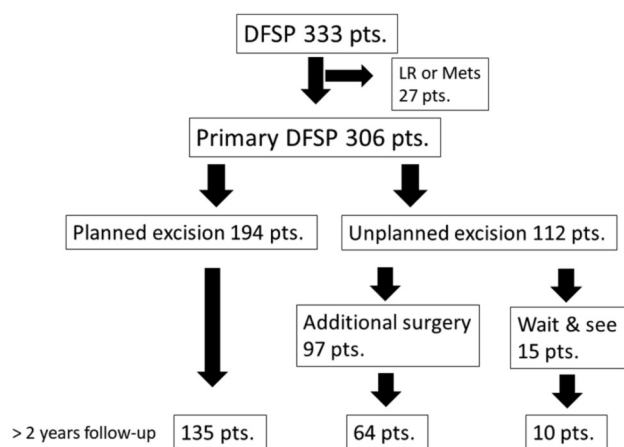


Figure 1. Treatment flow in patients with dermatofibrosarcoma protuberance.

minimum follow-up period was 2 years after initial presentation at the hospital when the patients were registered into the BSTT registry. We excluded the patients with distant metastasis and/or local recurrence when they were registered. We included the patients who received biopsy including excisional biopsy at previous hospital into planned excision (PE) group.

Statistical analyses. Statistical associations between clinicopathological variables were evaluated using the Mann-Whitney *U* and Kruskal-Wallis tests for quantitative data and the Chi-square test for qualitative data. Survival time was measured from the date of diagnosis of the primary tumor to the date of sarcoma-related death or last follow-up. Local recurrence time was measured from the date of diagnosis of the primary tumour to the date of local recurrence. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed using Cox proportional hazards regression models. The factors with *p*-value <0.2 were included as variables in the multivariate analysis. All statistical analyses were conducted using StatView for Windows, version 5.0 (SAS Institute Inc., Cary, NC, USA). *p*-Values <0.05 were considered significant.

Results

Clinicopathological characteristics. A total of 306 patients with primary DFSP were studied including 203 males and 103 females (Figure 1). The average age was 44 (range=8-87) years. Primary tumor sites were trunk (n=218; 71%), lower leg (n=43; 14%), forearm (n=29; 9.4%), and head and neck (n=27; 8.8%). The tumors were histologically classified as DFSP in all patients. Of the 306 patients, DFSP with a fibrosarcomatous component was present in 15 patients. The average tumor size at diagnosis was 4.8 (range=0.5-20) cm. Tumor size data were missing for 56 patients. PE was performed in 194 patients (64%), while UE in 112 patients (36%). When we compared patient backgrounds between the PE and UE groups, the tumor size was found to be significantly different (Table I).

Table I. The background of the patients who received surgical excision.

Variables	Planned excision (n=194; 63%)	Unplanned excision (n=112; 37%)	<i>p</i> -Value
Age			
Average	44	43	0.43
Gender			
Male	130	73	0.74
Female	64	39	
Size			
Average	5.2	4.2	0.01
Site			
Trunk	143	75	0.21
Lower extremities	24	29	
Upper extremities	20	9	
Head and neck	7	9	
Margin status*			
Negative		24	
Microscopic posi.		59	
Macroscopic posi.		22	
Unknown		7	
Margin status**			
Wide	185	90	
Marginal	4	5	
Intralesional	4	1	
Unknown	1	1	
Surgical complication			
Yes	8	12	0.009
No	186	85	

Posi: Positive, *margin status at unplanned excision, **margin status at additional excision.

Of 15 patients who did not receive additional excision after UE, adjuvant radiotherapy and chemotherapy were not performed in all patients.

Surgical outcomes. Of the 306 patients, 291 patients received PE or additional excision after UE. There were 195 men and 96 women, with a mean age of 44 years. According to the Kawaguchi margin status (8), wide margins were achieved in 275 patients, whereas marginal or intralesional margins were made in 14 patients. Adjuvant chemotherapy and radiotherapy were not performed in all patients. One hundred and fifty-nine patients (55%) required plastic reconstructions. In detail the reconstructions were pedicled myocutaneous flaps (n=61), skin grafts (n=57), pedicled myocutaneous flaps plus skin graft (n=18), free myocutaneous flaps (n=15), and other procedures (n=8). Twenty patients required additional surgery because of the problem with wound healing (n=19) and surgical site infection (n=1). Additional surgery due to complications was more frequent in patients with UE than in those with PE (*p*=0.009).

Clinical outcomes. Finally, we analyzed 209 patients with a minimum follow-up period of 2 years. The average follow-

Table II. Cox proportional hazard model for predicting local recurrence.

Variables		HR	95% CI	p-Value
Age	Years	1.045	0.986-1.108	0.14
Gender	Male	1		0.7
	Female	1.417	0.235-8.53	
Size	cm	0.952	0.676-1.34	0.78
Planned excision	No	1		0.28
	Yes	0.375	0.063-2.245	

HR: Hazard risk, 95% CI: 95% confidential interval.

Table III. The treatment strategy after unplanned excision.

Unplanned excision/additional treatment	Additional excision (n)	Wait & see (n)
Margin status		
Margin negative	10	9 [2]
Microscopic positive	37 [1]	1
Macroscopic positive	16	0
Unknown	1	0

[]: Number of patients with local recurrence.

up duration was 49 months. At the last follow-up, one patient had died of disease. Four patients developed distant metastasis. Three patients had DFSP with fibrosarcomatous components. The 5-year disease-specific survival (DSS) rate was 99% [95% confidence interval (CI)=97.1-100]. Local recurrence occurred in 5 patients, and the 5-year local recurrence-free rate was 97.2% (95% CI=94.7-99.7). Univariate analysis using a Cox proportional hazards model revealed no prognostic factor for predicting local control (Table II). Of the 209 patients, 79 received UE. Additional excision was performed in 69 patients, while observation was performed in 10 patients (Table III). In these 10 patients, complete resection was observed in 9 patients, and microscopic resection, in one patient after UE. Additional excision was a positive prognostic factor for local control ($p=0.003$). The 5-year local recurrence-free survival was significantly worse in patients without additional excision after UE (67.5%, 95% CI=26.8%-100%) than in those with additional excision (98.4%, 95% CI=95.4%-100%) (Figure 2). There was no difference in the 5-year local recurrence-free survival between the patients with PE (98.5%, 95% CI=96.5%-100%) and additional excision after UE.

Discussion

Using the BSTT registry, the present study analysed 306 patients with primary DFSP. The most frequent presenting location was the trunk (71%). This is in line with previous reports (42%-72%) (1, 2, 9, 10). DFSP is diagnosed

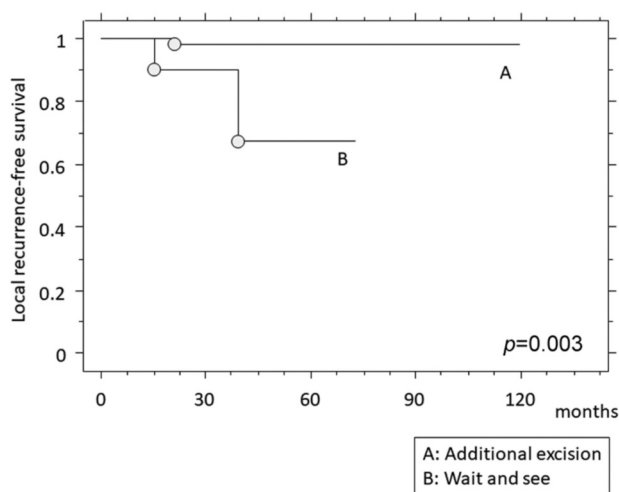


Figure 2. Kaplan-Meier curve showing the local recurrence-free survival. Patients who received additional excision after unplanned excision had better local recurrence-free survival than those who followed wait-and-see strategy.

predominantly in individuals aged 20 to 59 years (11), which was also consistent with the present study. Diagnostic delay is common, with a median delay of 3 to 5 years (12, 13). Unplanned excision is common in previous studies of DFSP patients (2, 14, 15). In the present study, a total of 36% of patients referred came to tumour-specific hospitals after UE. Tumour size in patients with UE was smaller than that in patients with PE. DFSP can be easily misdiagnosed in its early stage (4). Most tumors had been regarded as keloid or benign tumors such as fibroma, neurofibroma, epidermal cyst, and dermatofibroma (4, 5). If UE was performed, additional excision should be considered (16, 17). Standard treatment of DFSP is wide excision, with an expected local recurrence rate of less than 10% (2, 3, 18-20). In Japan, orthopaedic oncologists also aim to resect DFSP with wide margins (8). In the present study, wide margins were achieved in 94.5% of patients. Even if unplanned excision is performed, local control can be acquired by additional wide excision. Our analyses identified that the local recurrence-free survival in patients with additional excision after UE was consistent with that in patients with PE. Additionally, the local recurrence rate in patients without additional excision after UE was poorer than that with additional excision after UE. Generally, disease-specific survival was excellent in patients with DFSP. Recently, Decanter G *et al.* reported that watch and wait approach for re-excision after UE with macroscopically positive margin did not affect metastatic risk or amputation rate in soft tissue sarcoma (21). However, recurrent DFSP has an increased risk of metastatic disease. High-grade DFSP has

a higher incidence of metastasis than primary DFSP, and is more common after several local recurrences (22). The role of radiotherapy is not well established, although the effect of radiotherapy was reported in 1990's (23, 24). Therefore, we recommend additional excision after UE for preventing local recurrences and their metastatic potential (1).

In the present study, additional surgical procedures due to surgical complications may be frequently necessary in patients with additional excision after UE. Morattel *et al.* reported that patients who undergo UE need significantly more procedures, with an average of two more surgical interventions in patients with soft tissue sarcoma (25). This may be because a tumour bed excision in this situation may involve a large skin and soft tissue excision, requiring secondary graft, suture, or flap coverage (6, 7, 25). In soft tissue sarcomas, the tumor size was reported to be an independent prognostic factor for local control (26-28). However, for what DFSP is concerned, tumor size does not appear to have a significant influence on the incidence of local recurrence (1, 8, 29). In the present study, tumor size was not a significant factor for predicting local recurrence.

In the present study, 4 of 209 patients developed metastasis. While local recurrence is frequent, metastasis of DFSP is rare (30-32). It should be interesting to investigate the survival after metastasis in patients with DFSP, although we cannot analyze it because of the small number of the patients.

There are certain limitations to the present study. It did not control for several clinical parameters that may have affected the outcome. For example, tumor size data were missing for 56 patients. functional outcome was not evaluated because due to the lack of information. The small number of local recurrences in the present study prevented us from performing reliable multivariate analyses of prognostic factors. Retrospective study is also a limitation in the study. Despite these limitations, we believe that the present study is valuable because this is the largest study of clinical outcomes in patients with DFSP in Japan.

In conclusion, if UE is performed, we recommend additional excision for preventing local recurrence; however, the surgical wound should be carefully observed.

Conflicts of Interest

There were no conflicts of interest in the present study.

Authors' Contributions

Tomoki Nakamura conceived the study, collected and analyzed the data and wrote the manuscript. Kunihiro Asanuma and Tomohito Hagi analyzed and interpreted the clinical data. Akihiro Sudo and Akira Kawai interpreted the clinical data, and reviewed the manuscript.

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