ORIGINAL ARTICLE

Clinical features and treatment outcome of desmoid-type fibromatosis: based on a bone and soft tissue tumor registry in Japan

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Abstract

Background Treatment modality of desmoid-type fibromatosis (DF) has changed from surgery with a wide surgical margin to conservative treatment. In this study, tumor characteristics of DF, transition of the treatment modality, and clinical outcome of surgical treatment were analyzed based on data obtained from the bone and soft tissue tumor registry established in Japan.

Methods Data were collected as registration data and follow-up data. Five hundred and thirty registered cases of DF were identified, including 223 cases with follow-up data with or without surgical treatment.

Results The number of registered patients increased gradually. The frequency of surgical treatment was gradually reduced year by year. The 3-year local recurrence free survival (LRFS) was 77.7%, with tumor location and size tending to correlate with LRFS. Interestingly, there was no significant difference in LRFS between wide and marginal margin ($P = 0.34$).

Conclusions The treatment modality has shifted from surgical to conservative treatment, with risk factors for surgical treatment similar to those noted in previous studies. The National registry system is crucial for a rare disease such as DF, and in the future, a population based registry system should be established to better comprehend the actual status of DF.

Keywords Desmoid-type fibromatosis · Registry · Treatment modality · Marginal resection

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Introduction

Desmoid-type fibromatosis (DF), also known as aggressive fibromatosis, is a slow-growing, clonal fibroblastic proliferation. It is defined by the World Health Organization (WHO) as an intermediate soft tissue tumor with a tendency to infiltrate local tissues, but does not metastasize. The incidence of DF is 2–4 per million per year, and it occurs mainly in the age range of 15 and 60 years, most commonly between 25 and 35 years [1, 2].

The standard treatment modality has been surgical resection aiming at a negative surgical margin. However, the published recurrence rates range from 20 to 60% [3–5], being even higher in children and adolescents [6]. This tumor is known for its complex and non-uniform natural history. Some tumors will undergo stabilization or self-regress with extended asymptomatic periods, while others will progress causing significant functional impairment. No definitive markers including clinical and genetic factors have been identified to predict the behavior of DF. The high recurrence rate, morbidity after surgical treatment, and enigmatic behavior of this tumor have led physicians to initiate a "wait and see" approach for it [7, 8]. However, such a "wait and see" stance is not appropriate for patients with severe pain, cosmetic issues, and/or functional impairment due to the disease and its progression.

For patients with this rare and difficult to treat intermediate tumor, it is important to establish optimal treatment guidelines. Several western countries or groups have formulated guidelines for this tumor including the National Comprehensive Cancer Network, the European Society for Medical Oncology [9], and the British Sarcoma Group [10, 11]. Treatment guidelines should be developed according to the country- or regional-specific treatment standards and clinical outcomes including patient-based ones, which may differ to varying extents between individual countries and ethnic groups.

As the first step to providing the optimal treatment modality for patients with DF, we should know the clinical features, treatment modality and outcomes in specific countries. The aims of this study are to clarify in Japan the features of patients with DF, treatment modality of specialized institutions/hospitals, and treatment outcomes of this tumor with surgical treatment based on the data of the Bone and Soft Tissue Tumor Registry in Japan.

Patients and methods

Data source and patient population

Primary data were obtained from the Bone and Soft Tissue Tumor Registry database in Japan. It is a nationwide organ-specific cancer registry for bone and soft tissue tumors that was launched in the 1950s, being organized and funded by the Japanese Orthopaedic Association (JOA) and promoted by the National Cancer Center. All the JOA-certified hospitals ($n = 89$) for musculoskeletal oncology are required to participate in the registry. Therefore, most of cases with DF treated by specialized centers of bone and soft tissue tumors are registered. This registry survey of patients diagnosed from January 1 to December 31 of the previous year are conducted annually in May. The survey includes basic demographic data of the patient. The next survey is conducted 2, 5, and 10 years after the initial registration at prognosis including local recurrence, distant metastasis, and oncological status [12, 13]. Musculoskeletal Tumor Committee. Data of patients with soft tissue sarcoma diagnosed in a given year were collected to the National Cancer Center, Japan, from the orthopaedic oncologists at specialized centers. In 2012, 93 institutions/hospitals registered cases of DF. This database is composed of registration data and follow-up data. Data were collected as registration data (cases registered from 2006 to 2012) and follow-up data (determined in December, 2013, for cases registered from 2006 to 2010). Medical information included patients' age, gender, tumor location, size, treatment modality, surgical margins, and date of recurrence. Five hundred and thirty registered cases of DF were identified. Because cases registered in 2011 and 2012 did not have follow-up data yet, follow-up data could be obtained from cases registered from 2006 to 2010. Among 384 cases registered from 2006 to 2010, we collected 223 cases (58%) of follow-up data with or without surgical treatment.

Variables

Age was divided into 4 groups; child (< 15), adolescent and young adult (15–39), adult (40–59), and elderly (60 $\leqq$). Tumor size of the greatest dimension was converted into a categorical variable with groups ≤ 8 cm, > 8 cm, and unknown. Location of the primary tumor was grouped into upper and lower extremity, head and neck, trunk, abdominal wall, and others. Location of shoulder and buttock was grouped into extremity. Location of abdominal wall was excluded from the trunk group because previous studies reported that patients with abdominal wall desmoid have

a more favorable prognosis [14]. Surgical margins were defined as wide, marginal, or intralesional based on the macroscopic findings. Microscopic evaluation of the surgical specimens was not performed because registry data do not include it. Registered year was also analyzed as a possible variable to influence local recurrence.

Clinical outcome after surgical treatment was assessed using follow-up data of the database. Recurrence-free survival was calculated from the date of surgery to the last follow-up or the date of recurrence. Patients who were lost to follow-up were recorded as censored. Patients who died of other disease were also recorded as censored. This retrospective study based on the database of a bone and soft tissue tumor registry was approved by the Ethical Review Board of JOA.

Statistical analysis

Data were presented as frequencies and percentage of the total for categorical variables and means and range for continuous variables. Comparisons between groups were performed using the chi-square test or Fisher's exact test for categorical variables, and student t test or one-way analysis of variance (ANOVA) for the comparison of means (mean age in each fiscal year) between 2 or more groups, respectively. For patients receiving surgical treatment, the endpoint was local recurrent-free survival (LRFS) as time from surgery to date of recurrence. Survival rates were estimated using the Kaplan–Meier method. The influence of clinical variables including surgical margin on LRFS was analyzed using the log rank test for univariate analysis. Multivariate Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Variables of tumor size, location, and surgical margin in addition to age and registered year were subjected to the multivariate analysis. All statistical analyses were performed using SPSS version 20. All P values were two-sided, and $P < 0.05$ was considered as statistically significant.

Results

In total, 530 patients were registered with DF. Mean age was 44 years ranging from 1 to 86 (median; 42 years), and there were 323 females and 207 males. The number of registered patients diagnosed with DF increased gradually, although the ratio of females to males did not differ significantly among years ($P = 0.43$, Fig. 1a). Mean age of DF patients did not differ significantly among registered years ($P = 0.39$, Fig. 1b). Location of the tumor was lower extremity in 135, trunk in 134, abdominal wall in 84, upper extremity in 80, head and neck in 65, others in 26, and unknown in 3. The
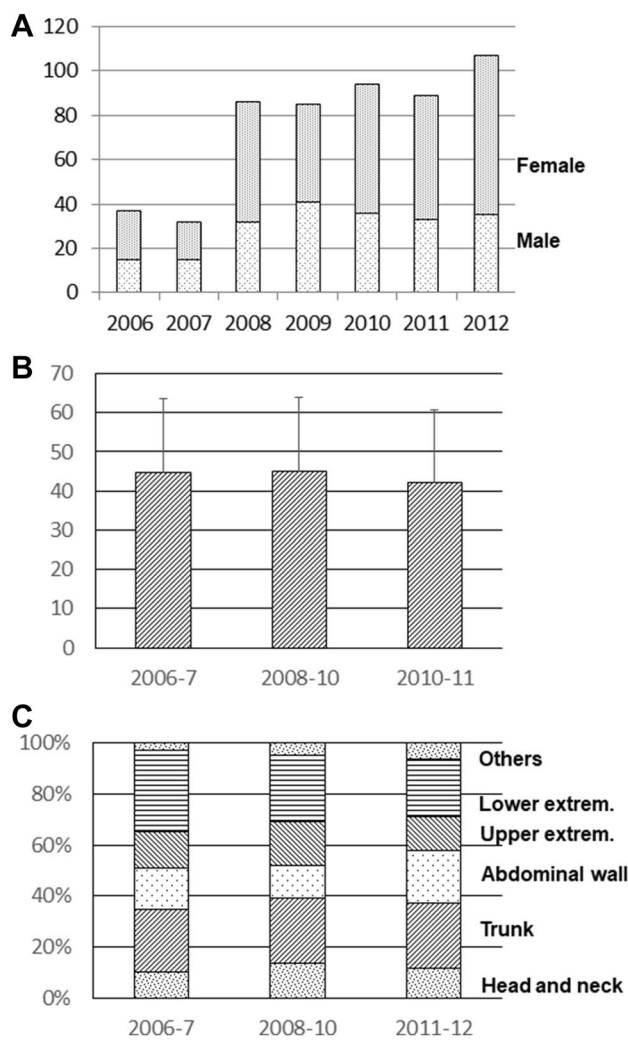

Fig. 1 Registry data of desmoid-type fibromatosis by year from 2006 to 2012. **a** Registered numbers of patients separated by gender are graphed. **b** A graph shows mean age of registered patients in years (2006–2007, 2008–2010, 2011–2012). Bars indicate the standard deviation. **c** Registered number of patients are graphed by locations in years (2006–2007, 2008–2010, 2011–2012)

distribution of occurrence sites did not show significant differences among years ($P = 0.40$, Fig. 1c).

The frequency of surgical treatment was gradually reduced year by year. Almost equal numbers of cases were treated with ($n = 17$) or without surgery ($n = 18$) in 2006, whereas one third and two thirds of cases were treated with ($n = 34$) or without surgical treatment ($n = 73$) in 2012, respectively. There was a statistically significant difference in treatment modality (surgical vs conservative treatment) between the years ($P = 0.019$, Fig. 2). Follow-up data were available in 223 cases registered from 2006 to 2010. Of these, 109 cases received surgical treatment. Six cases underwent palliative surgery, such as mass reduction for pain relief. Excluding these 6 cases, 103 cases were subjected to
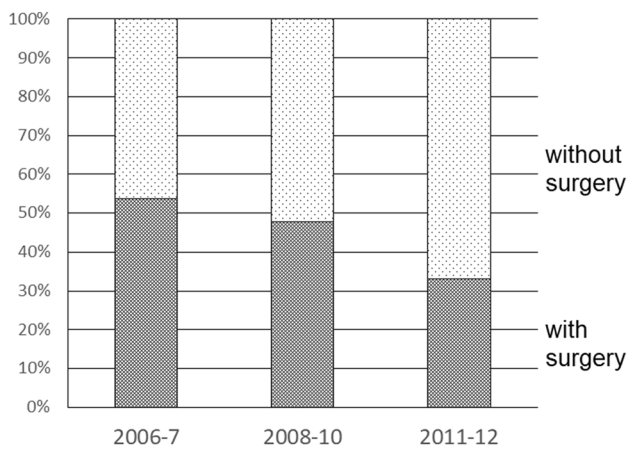
Fig. 2 Transition of treatment modality in each year. Proportions (%) of treatment modality (with surgery or without surgery) were graphed

the analyses of LRFS using Kaplan–Meier method with log rank test.

Three-year LRFS was 77.7% (Fig. 3a). There were no significant differences in LRFS with respect to age (P = 0.68, Fig. 3b), gender (P = 0.762, Fig. 3c), tumor

location (P > 0.05; any variables compared, Fig. 3d), or registered year (P > 0.05; any years compared). Interestingly, local recurrence tended to worse in patients registered in 2006 as compared with that in 2010 (P = 0.051). Extremity location tended to have a higher recurrence rate compared to that of abdominal wall location (P = 0.11). Tumors of more than 8 cm in greatest dimension showed a trend to a higher recurrence rate compared with those of less than 8 cm (P = 0.091, Fig. 4a). With regard to the surgical margin, the definitions of wide, marginal, and intralesional were based on the macroscopic evaluation in this registry system [15], while resection with marginal margin may contain R0 or R1 resection microscopically. Resection with intralesional margin may include piece-meal removal. Intralesional margin had a significantly inferior outcome of LRFS compared with those of wide (P < 0.001) or marginal margin (P = 0.014). Interestingly, no significant difference was noted between wide and marginal margin (P = 0.34, Fig. 4b). As a prerequisite for use of Cox proportional model, we confirmed that proportional hazard were maintained for all period. Double-logarithmic plot was drawn to see proportional hazards, and confirmed that double log plot was almost parallel, and performed a
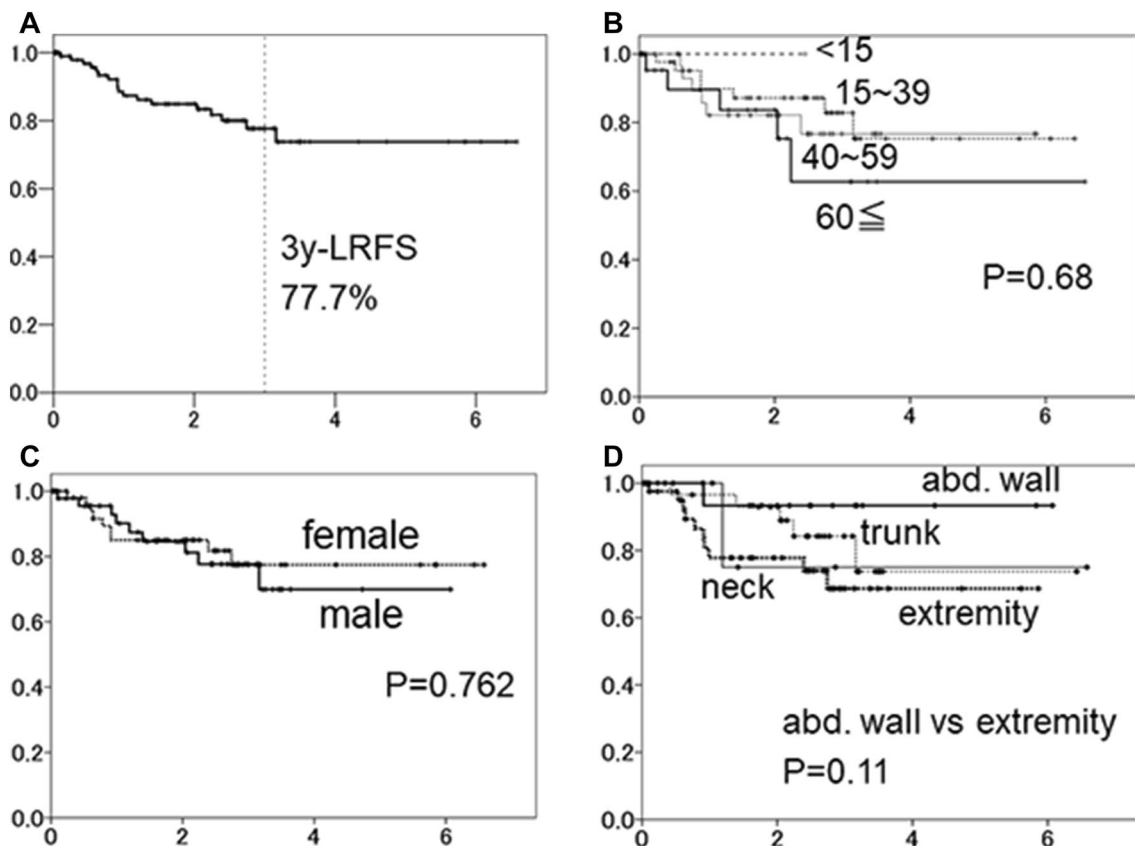

Fig. 3 Local recurrence free survival. **a** Local recurrence free survival (LRFS) of all patients treated by surgery (103 patients). **b** LRFS by age subgroups. Child (< 15), adolescent and young adult (15–39), adult (40–59), and elderly (60≦). **c** LRFS by gender. **d** LRFS by tumor location
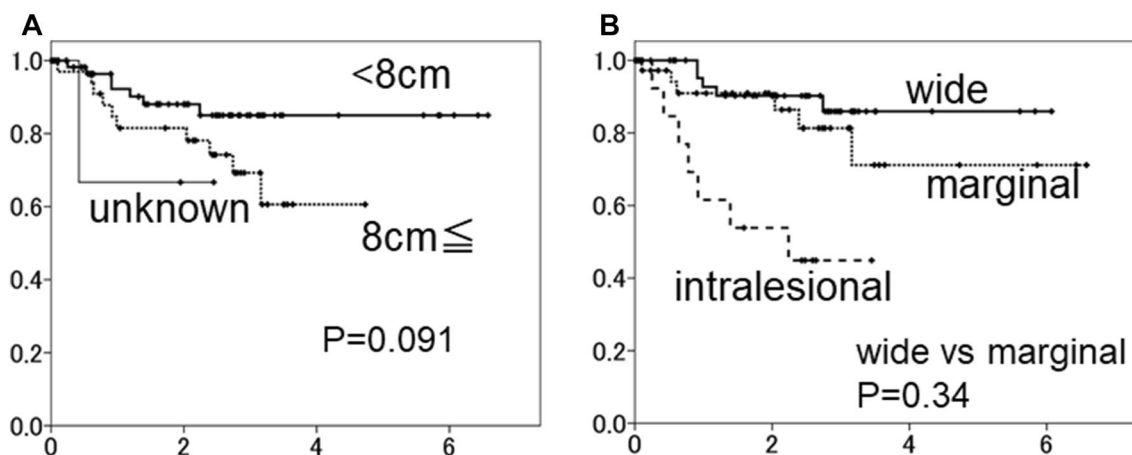
Fig. 4 Local recurrence free survival. **a** LRFS by tumor size. **b** LRFS by surgical margin

Table 1 Multivariate Cox regression analyses for risk factors of LRFS

	Hazard ratio	95% CI	*P* value
Tumor size	3.193	0.990–10.30	0.052
Location	2.970	0.940–9.381	0.064
Surgical margin			
Intralesional	5.102	1.277–20.37	0.021
Marginal	1.561	0.396–6.164	0.525
Age			
≧ 60	4.098	0.996–16.87	0.051
40–59	1.214	0.348–4.232	0.761
Registered year			
2010	0.234	0.046–1.185	0.079
2009	0.369	0.068–2.004	0.248
2008	0.352	0.055–2.271	0.273
2007	0.401	0.051–3.154	0.386

Tumor size ≧ 8 cm vs < 8 cm, Location: extremity vs others

Surgical margin: intralesional, marginal vs wide

Age: ≧ 60, 40–59 vs < 40

Registered year: 2007, 2008, 2009, 2010 vs 2006

test for proportional hazards based on Schoenfeld residuals, and none of the variables are significant.

Multivariate Cox regression analyses revealed that no covariates except surgical margin were statistically significant (Table 1), indicating intralesional margin had worse outcome. However, no significant difference between marginal and wide margin ($P = 0.525$). Tumor size of ≧ 8 cm (vs < 8 cm, $P = 0.052$), location of extremity (vs others, $P = 0.064$), age ≧ 60 (vs < 40, $P = 0.051$), tended to have high recurrence. Whereas registered year of 2010 had better outcome (vs 2006, $P = 0.079$).

Discussion

The past decade has seen dramatic changes in the treatment modality for patients with DF from surgical treatment with wide surgical margin to conservative therapy including watchful waiting [16, 17]. Paying attention to accurate epidemiological data, the transition occurring in the treatment strategy and treatment outcome in recent years are critical for the determination of future treatment algorithms for this rare and enigmatic disease. Meanwhile the increase that has been documented in the registered number of patients from 2006 to 2012 highlights the gradual improvement achieved in this registration system in Japan. Actually, the number of facilities, which registered DF patient in this system, increased year by year (10 in 2006, 13 in 2007, 32 in 2008, 34 in 2009, 42 in 2010, 37 in 2011, 45 in 2012).

The results of the present study exhibited that various demographic features of DF including mean age, ratio of female to male, and occurrence site were not much different from those identified in the report of Penel et al. [18]. Their study focused on patients diagnosed from 2010 to 2016. The female ratio (72.4%) was slightly higher than that in the present study (61%). Median age was similar (Penels' study: 39; present study: 42). A difference was noted in tumor site, with extremity location (41%) being similar to that of trunk including abdominal wall (41%) in the present study, in contrast to Penels' study in which extremity site (15%) was less than that of trunk (61%). A difference was present in the study cohorts in that their study included patients with intra-abdominal location (18%), whereas the Japanese registry data do not include mesentery DF, because the registry has been maintained by JOA whose members are all orthopaedic surgeons.

The treatment strategy has been changing gradually from operative to conservative treatment, similar to the trend also reported recently from western countries [16, 19, 20],

because of the high recurrence rate after resection despite attainment of an adequate surgical margin [17, 21, 22]. As the next step, clinical outcomes of conservative therapy including NSAID [23, 24] with or without tamoxifen [25, 26], methotrexate and vinblastine low-dose chemotherapy [27–29], and watchful waiting [18, 20], will need be clarified to establish a novel treatment algorithm for patients with DF. Given that the incidence of DF is very low, collection of sufficient data regarding conservative treatment from a single institution is unlikely, making a prospective multi-center clinical trial of conservative treatment necessary to obtain definitive evidence to establish practice guidelines for DF.

Several prognostic factors of the clinical outcome of surgical treatment for DF have been reported previously. Principal prognostic factors described are age [14, 30, 31], tumor size [3, 14, 30], location [3, 14, 18, 30, 31], surgical margin (R0 vs R1) [31, 32], and recently CTNNB1 mutational status [33–35].

As a prognostic factor for recurrence after surgical treatment, surgical margin has been discussed but remains controversial. Several studies demonstrated the importance of surgical margin status [31, 36], whereas not a few others documented no significant relationship between the surgical margin and recurrence rate [3, 5, 14, 22, 30]. Considering that surgical margin has generally been found to be a powerful prognostic factor in malignant neoplasms, the results of these studies demonstrating no relationship between the quality of surgery and local recurrence rate cast doubt on the role of surgical treatment as a mainstay of treatment for DF.

CTNNB1 mutation status should be determined in all patients suspected of having DF. To make the diagnosis more confident, hot spot mutation analysis of CTNNB1 is critical. A recent study reported that CTNNB1 mutations were highly detected in 88% of sporadic DF, whereas no hot spot CTNNB1 mutations were found in any of the spindle cell tumors or desmoid mimics [37]. However, mutation analysis of CTNNB1 hot spot for DF (codon 41 and 45) has not been standardized in the clinical context. Moreover, the mutation status of CTNNB1 provides useful information to patients and physicians regarding the predicted clinical outcome of both surgical treatment [33–35, 38] and conservative treatment [39]. In the near future more data will be accumulated regarding the relationship between various treatment modalities including watchful waiting and CTNNB1 mutation status, which will be of benefit to patients.

There are several limitations in the present study. First, this registry system is not a population-based, but an institution-based one. Not all the patients with DF were registered. The institutions/hospitals in this registry system had specialists for the treatment of bone and soft tissue tumors, particularly orthopaedic oncologists. Patients treated by general surgeons, plastic surgeons, or other physicians, were not included in this registry. A critical issue to be resolved for DF, a rare disease that is treated by physicians of many specialties, is to establish a rare-disease specific registry system, and to educate both physicians and patients about adequate treatment modalities. Second, due to the fact that this registry system is maintained by orthopaedic oncologists, intra- and retro-peritoneal DF was generally not included in this database. Thus the results of the present study reflect the features and outcomes of only patients with extra-peritoneal DF. Third, a centralized pathological diagnosis system for DF is not yet available. The pathological diagnosis was determined by the specialized pathologists in each institution/hospital. Also, very few institutions are yet capable of determining the CTNNB1 mutation status. Another limitation is that there were fewer follow-up data than prognostic ones, thereby biasing the results of clinical outcomes. A possible explanation of the good clinical outcome found for surgical treatment might be that patients with a poor prognosis were not reported.

Conclusions

In conclusion, the present study based on the data of the Japanese bone and soft tissue tumor registry in Japan revealed that the number of DF patients registered is increasing, the treatment modality has shifted to a conservative one, and risk factors for surgical treatment are identical to those identified in previous reports. Interestingly, LRFS between the wide surgical margin and marginal groups did not differ significantly. A broader registry system may be required for this very rare disease, DF, because physicians with various specialties have the opportunity to provide treatment.

Compliance with ethical standards

Conflict of interest Yoshihiro Nishida has no conflict of interest regarding this study, Akira Kawai has no conflict of interest regarding this study, Junya Toguchida has no conflict of interest regarding this study, Akira Ogose has no conflict of interest regarding this study, Keisuke Ae has no conflict of interest regarding this study, Toshiyuki Kunisada has no conflict of interest regarding this study, Yoshihiro Matsumoto has no conflict of interest regarding this study, Tomoya Matsunobu has no conflict of interest regarding this study, Kunihiko Takahashi has no conflict of interest regarding this study, Kazuki Nishida has no conflict of interest regarding this study, Toshifumi Ozaki has no conflict of interest regarding this study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was waived because of the study based on the national registry data.

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