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Trends in diagnostic and therapeutic strategies for extra-abdominal desmoid-type fibromatosis: Japanese musculoskeletal oncology group questionnaire survey

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Abstract

Objective: The mainstay of treatment modality for extra-abdominal desmoid-type fibromatosis (DF) has shifted from surgery, which often impairs ADL/QOL, to conservative treatment including active surveillance. In the present study, we conducted a longitudinal survey on the diagnosis and treatment of DF at facilities belonging to the Japanese Musculoskeletal Oncology Group, which is a research group of facilities specializing in the treatment of bone and soft tissue tumors in Japan to clarify the transition of medical care for extra-abdominal DF.

Methods: The same questionnaire was administered in 2015 and 2018, and responses were obtained from 46 (69%) of 67 facilities and 42 (53%) of 80 facilities in 2015 and 2018, respectively.

Results: Although immunostaining for β-catenin was often used for the pathological diagnosis in both 2015 and 2018, CTNNB1 mutation analysis was not performed either in 2015 or in 2018. As for the treatment strategy for resectable cases, surgical treatment including wide resection was selected at 11 facilities (24% of respondents) in 2015, and further decreased to 5 facilities (12%) in 2018. Conservative treatment with active surveillance or medical treatment was the most common treatment for both resectable and difficult-to-resect cases. COX-2 inhibitors and tranilast were often used in the drug treatment of both resectable and difficult-to-resect cases. Few facilities provided radiotherapy, methotrexate and vinblastine, or DOX-based chemotherapy for refractory cases in both 2015 and 2018.

Conclusions: A good trend was found in the questionnaire survey. It will be further necessary to disseminate clinical practice guidelines to physicians more widely, and to have them understand and implement the most up-to-date medical practice strategies for this rare disease.

Key words: desmoid-type fibromatosis, beta-catenin, CTNNB1, treatment modality, medical care guideline

Introduction

Desmoid-type fibromatosis (DF) is a soft tissue tumor of fibroblastic/myofibroblastic origin, classified as intermediate, locally aggressive and non-metastasizing in the 2020 WHO classification. It is a rare disease with 3–4 cases per million persons (1). There is a significant difference in prognosis between intra- and extra-abdominal development, and extra-abdominal development is known to be rarely life-threatening (2–5). However, in some cases ADL/QOL are reduced, for example due to limited range of motion of the involved joints and severe pain (6). Therefore, proper implementation of diagnostic and therapeutic procedures is important to maintain and improve patients' ADL/QOL. In the diagnosis of DF, because most sporadic DF is thought to be caused by nuclear hyperaccumulation of β-catenin due to hot spot mutations in the β-catenin gene CTNNB1, nuclear dark staining by immunostaining for β-catenin is widely used in the pathological diagnosis (7,8), including in Japan. However, there seem to be few facilities where mutation analysis of CTNNB1 has been performed in Japan. Regarding the treatment modality, due to the high postoperative recurrence rate of 24–77% (2,9–11), non-surgical treatment including active surveillance, medical treatment and radiotherapy are now being selected (12–14). In terms of medical treatment, there are no drugs covered by insurance for the purpose of controlling DF in Japan. However, a variety of drugs with low toxicity are used in clinical practice. Insurance systems are different in Europe and the USA. It seems that the use of molecular-targeted drugs pazopanib and methotrexate (MTX) + vinblastine (VBL), doxorubicin (DOX)-based anticancer drug treatments has been approved.

In 2014, the Ministry of Health, Labour and Welfare (MHLW) began activities to elucidate the actual status of DF treatment and to formulate treatment guidelines in its policy research on intractable diseases. Through these activities, clinical practice guideline for extra-abdominal DF was published in August 2019 (https://minds.jcqhc.or.jp/docs/gl_pdf/G0001130/4/desmoid.pdf). During the period when the guideline was being prepared, awareness-raising activities were carried out through academic conferences for medical professionals involved in DF treatment, especially in bone and soft tissue tumor treatment.

The purpose of the present study was to clarify the transition of medical care for extra-abdominal DF in Japan by conducting a longitudinal questionnaire survey on desmoid medical care for participating facilities of the Japanese Musculoskeletal Oncology Group (JMOG).

Methods

We started the activities of the DF Research Group of the Ministry of Health, Labour and Welfare (MHLW) in 2014, conducting educational activities on medical treatment policies through the Japanese Orthopaedic Association (JOA) scientific meetings, and other venues. In 2017, we completed a medical treatment algorithm for DF, and published it on the website of the JOA (https://www.joa.or.jp/public/bone/algorithm.html) and in the Public Relations Office News of the JOA (JOA News No. 109). At that time, it was strongly recommended to use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system as an approach to the evaluation of evidence and the preparation of recommendations in the development of clinical practice guidelines. According to this, a new clinical question was set up, a guideline was formulated in line with GRADE, and it was published in 2019 (https://www.joa.or.jp/public/bone/pdf/desmoid.pdf). Therefore, this questionnaire survey evaluates the results of enlightenment activities carried out in the process of starting activities in 2014 and completing the algorithm in 2017.

Questionnaires regarding DF diagnosis and treatment were sent to JMOG participating facilities in January 2015 (n = 67), before the algorithm was developed, and in May 2018 (n = 80), after it was published. The basic policy of the treatment algorithm for extra-abdominal desmoid is 'wait and see', and surgery is allowed only if it is expected that there will be no postoperative dysfunction. For medical treatment, less toxic drug is desirable at the beginning. Modified algorithm is provided as Supplementary Figure 1. The content of the questionnaire was designed to focus on important clinical issues in the diagnosis and treatment of DF. These were as follows: biopsy method, immunohistochemical staining and genetic mutation analysis in pathological diagnosis, treatment policy after definitive diagnosis (separate questions for resectable and unresectable cases), treatment policy in cases with recurrence or enlargement, and method of dealing with cases that eventually became uncontrollable (Table 1). Institutional review board approval was waived for this questionnaire because it does not handle patients' personal information. The implementation of the survey was approved by the JMOG Executive Committee and Plenary Session.

Results

Among the JMOG participating facilities, 46 of 67 facilities (69%) responded to the questionnaire in 2015 and 42 of 80 facilities (53%) in 2018. There were 26 facilities that responded to the questionnaire survey both times. The facility name is listed in the acknowledgment. The results of the questionnaire on biopsy methods for DF diagnosis are shown in Fig. 1A. More than 70% of the facilities chose needle biopsy for the first biopsy, and this trend did not markedly differ between the questionnaire results in 2015 and 2018. Although immunostaining for β-catenin and MIB-1 is performed at many facilities, only 2 (4%) of the responding facilities performed CTNNB1 mutation analysis in 2015 and 3 (7%) in 2018 (Fig. 1B). As for the initial treatment modality for resectable cases, as shown in Fig. 2A, the number of facilities choosing wide resection decreased from 10/46 (22%) in 2015 to 4/42 (9.5%) in 2018, however, not significant (P = 0.20), while the number of facilities choosing active surveillance increased from 10/46 (22%) in 2015 to 16/42 (38%) in 2018 (P = 0.093). In terms of medical treatment used for resectable patients (Fig. 2B), COX-2 inhibitors and tranilast were the most commonly used drugs in both 2015 and 2018, with this trend remaining unchanged. As for the treatment of difficult-to-resect cases, the results of the 2015 and 2018 questionnaires did not differ markedly. However, the number of facilities that chose active surveillance first increased (Fig. 3A). In both 2015 and 2018, the proportion of facilities performing radiotherapy was less than 10% (5 and 3 facilities, respectively). As a drug treatment for difficult-to-resect cases, in addition to COX-2 inhibitors and tranilast, methotrexate plus vinblastine and doxorubicin were the drugs of choice, and there was no marked difference between 2015 and 2018 (Fig. 3B). In DF, there are cases that cannot be controlled even after active surveillance, less toxic drug treatment, and surgery. As a treatment modality for such cases, in 2015, there were four facilities that used DOX-based chemotherapy, four facilities considering or continuing MTX + VBL, three facilities with radiotherapy, three facilities with marginal or palliative resection, and one facility

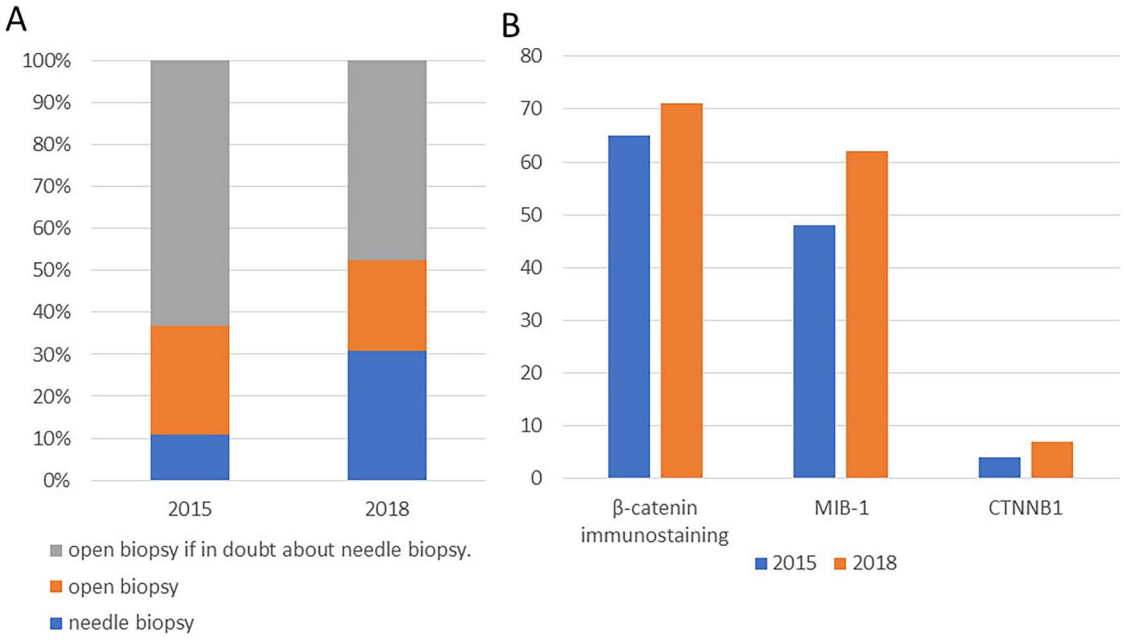

Figure 1. Results of questionnaire survey for biopsy and pathological diagnosis. (**A**) Biopsy methods. (**B**) Immunohistochemical staining for β-catenin and mutation analysis for CTNNB1.

Table 1. Questionnaire survey for diagnosis and treatment for DF

Facility name ( )
Questionnaire respondent name ( )
(1) Please select the biopsy method
( ) Needle biopsy ( ) Incision biopsy ( ) Incision biopsy if uncertain diagnosis by needle biopsy ( )Other
(2) Please select about pathological diagnosis
( ) Beta-catenin immunostaining is routinely performed
( ) MIB-1 index is evaluated routinely
( ) Beta-catenin gene (CTNNB1) mutation is being evaluated
If you have any other points to keep in mind, please write them down.
(3) Please select the treatment policy after the pathological diagnosis of desmoid is confirmed.
(i) If the tumor is resectable, the first choice of treatment
( ) Extensive resection ( ) Marginal resection
( ) Radiation therapy (in the case of postoperative treatment, its indication)
( ) Drug treatment: Drugs used ( )
( ) Follow-up (active surveillance)
Other
(ii) Please describe the next treatment when the tumor recurs or grows in (i) .
(iii) Which treatment is chosen if the tumor is unresectable?
( ) Radiation therapy
( ) Drug treatment: Drugs used ( )
( ) Follow-up (active surveillance)
Other
(4) If there is a desmoid case that eventually becomes uncontrollable, please describe how to deal with it.

with palliative medicine, while 14 facilities responded that they had never experienced uncontrolled DF cases. In 2018, there were four facilities with DOX-based chemotherapy, five facilities considering or continuing MTX + VBL, six facilities with pazopanib, four facilities with radiotherapy, two facilities with marginal or palliative resection, two facilities with amputation, two2 facilities with palliative care and 12 facilities with no uncontrolled DF cases (Table 2). Interestingly, the number of respondents who said they would use pazopanib was 0 in 2015, but 6 in 2018, showing a large increase.

Discussion

Accurate diagnosis is required for neoplastic diseases, not limited to DF. Especially in rare diseases, it is often difficult for pathologists to make a correct diagnosis because of the small number of cases they have experienced. Needle biopsy is often chosen for soft tissue tumors that are easy to approach. In this survey, needle biopsy was performed at 34/46 facilities in 2015 (74%), and at 33/42 facilities in 2018 (79%). However, it occasionally may be difficult to differentiate DF from other fibroblastic tumors with specimens obtained by needle

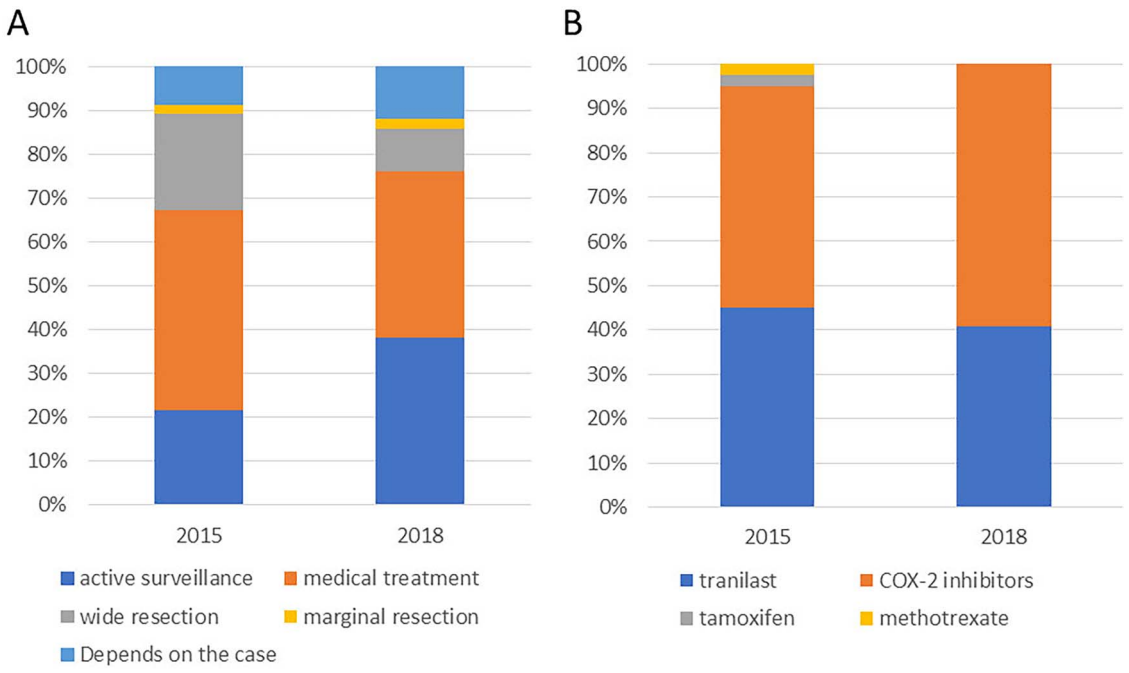

Figure 2. Results of questionnaire survey for initial treatment policy. (**A**) Initial treatment for resectable cases. (B) Pharmacotherapy for resectable cases.

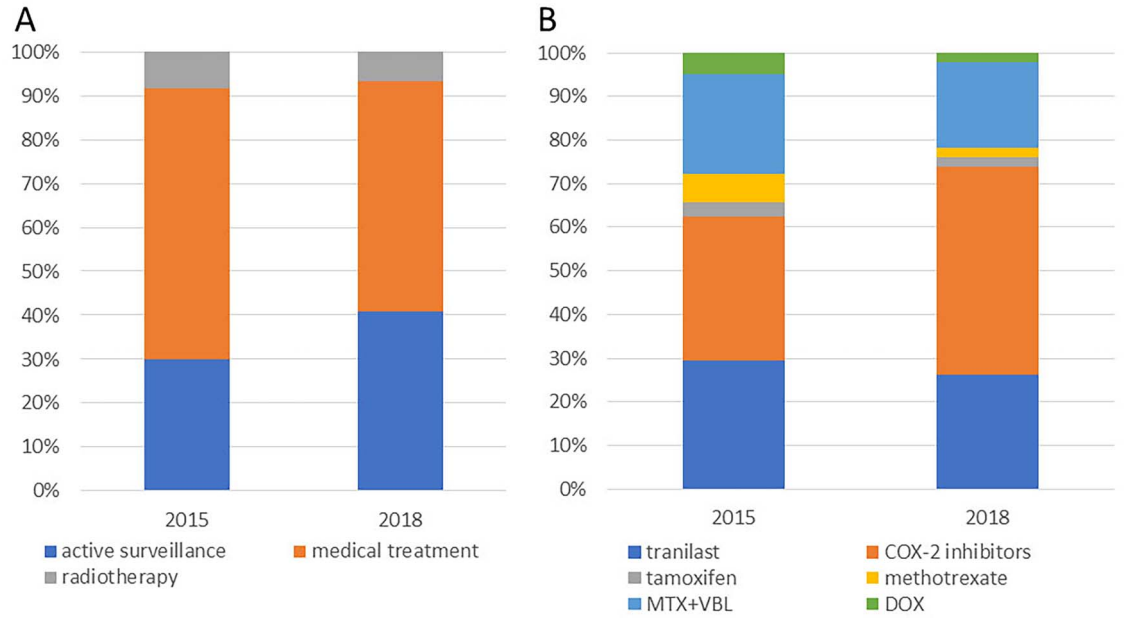

Figure 3. Results of questionnaire survey for difficult-to-resect cases. (**A**) Treatment modality for difficult-to-resect cases. (**B**) Drug treatment for difficult-to-resect cases.

biopsy due to the small sample volume, and incisional biopsy should be performed when the diagnosis is in doubt. In addition to the usual pathological evaluation, beta-catenin immunostaining is expected to help in the diagnosis of fibroblastic tumors when diagnosis by general pathological examination is difficult, and its usefulness is mentioned in the guidelines. On the other hand, some DF cases have been reported in which β-catenin was negative in the nucleus (8), and molecular biological methods may be necessary for a more accurate diagnosis. Mutations in CTNNB1 are often the etiological factor in DF, and many cases have been reported to have this mutation. In a report on cases in which histopathological diagnosis was difficult, 30 of 47 cases, in which the diagnosis of DF was not definite, could be diagnosed by CTNNB1 mutation analysis (15), and its usefulness has been suggested in many other papers (16–18). However, this mutation analysis is not widely used in daily practice in Japan partly due to the problem of insurance coverage. In contrast there might be many overseas sarcoma facilities that perform CTNNB1 mutation analysis in daily practice, because a global consensus paper for desmoid (12) reported a strong recommendation to perform a mutational analysis for DF to confirm diagnosis and guide the

Table 2. Treatment modality for difficult-to-control cases

Treatment modality	2015	2018
Dox-based chemotherapy	4	4
Low dose MTX + VBL	4	5
Pazopanib	0	6
Radiotherapy	3	4
Palliative or marginal resection	3	2
Amputation (for extremity)	0	2
Palliative medicine	1	2
Wait and see	3	2
No cases out of control	14	12
Introduction to another hospital	4	1
No answer	10	8

work-up. An important future task is to promote the use of mutation analysis tests to enhance diagnostic accuracy in Japan.

From the results of this survey, it can be seen that there is a decreasing trend in the selection of surgical treatment even in resectable cases, and that active surveillance as a treatment policy recommended by guideline/algorithm is becoming more widespread. The number of facilities that select and perform extensive resection is decreasing. Surgical treatment should be carefully selected taking into account the high recurrence rate and postoperative dysfunction. These policies seems to be consistent with the practice in Western countries (12). It is also important to consider that the site of occurrence may affect the surgical outcome, and it has been reported that the postoperative recurrence rate is higher in the extremities and lower in the abdominal wall (19). There is no clear evidence for the superiority of wide resection over marginal resection when surgical treatment is chosen, and it has been opined that marginal resection is preferable in consideration of residual postoperative function (2,11,20,21). Therefore, when surgery is performed, not only the indication, but also the surgical methods should be carefully determined in view of the recurrence rate and postoperative functional impairment. Even for resectable lesions, the number of facilities opting for surgical treatment decreased in 2018, with active surveillance/drug therapy being the treatment of choice instead. The survey showed that COX-2 selective inhibitors and tranilast were the most commonly used drug therapies in both 2015 and 2018. In particular, there are no reports of tranilast use from overseas, only case reports from Japan (22,23), which may indicate that it is a treatment unique to Japan. Tranilast is a drug covered by insurance in Japan as a keloid/hypertrophic scar treatment. Although the level of evidence for the efficacy of COX-2 selective inhibitors is not high, because of the low incidence of adverse events with COX-2 inhibitors, Japanese guidelines weakly recommend their use in limited cases. In contrast, they are not recommended in overseas guidelines (24,25). Therefore, attention should be paid to the future role of COX-2 inhibitors.

In the case of difficult-to-resect lesions, patients are often treated with observation or drug therapy, and few facilities in Japan choose radiotherapy. Considering the fact that extra-abdominal DF tumors are intermediate type tumors that are rarely life-threatening, physicians may be hesitant to choose radiotherapy because of the possibility of inducing a new malignancy.

More than half of the respondents answered that they would choose COX2 inhibitors or tranilast as drug treatment for difficult-to-resect cases. This may reflect a policy of using drugs with fewer side effects first if the patient's ADL/QOL does not deteriorate even if resection is difficult. MTX + VBL and pazopanib are two of the drugs for which there is evidence of efficacy (24–27). In particular, a paper with a high level of evidence on pazopanib was recently published (27). In this questionnaire survey, some facilities responded that they would use pazopanib for difficult-to-control cases in 2018. It has the potential to become a key drug in the future, when physicians in charge will avoid using drugs without evidence as much as possible. If there is concern that the patient's ADL/QOL will be worsened because of DF, the use of the above-mentioned drugs with evidence will be considered.

There is a question as to whether a three-year interval's questionnaire survey is appropriate for assessing the prevalence of clinical practice guidelines/algorithm. The validity of recommendations and the certainty of evidence at the time of preparation of clinical practice guidelines do not remain unchanged thereafter. 50% of clinical practice guidelines are reported to be 'outdated' in 5.8 years (28). Recommendations for clinical practice guidelines are based on systematic reviews of evidence, but about half of systematic reviews are said to require changes in 5.5 years (29). Together, it is considered desirable to revise the clinical practice guidelines within 5 years. It seems appropriate to disseminate guideline/algorithm quickly and evaluate them in about 3 years.

The limitation of this survey study is that the number of facilities that responded to the second survey was relatively small and may not accurately reflect the entire population. In addition, although this questionnaire was conducted at JMOG participating facilities specializing in bone and soft tissue tumors, in actual clinical practice, it is not uncommon for various departments such as plastic surgery, general surgery, and otolaryngology to treat DF, so it is necessary to investigate the actual status of treatment in these departments too. It is also necessary to widely disseminate guidelines for the treatment of DF. Since DF is a rare disease, there are no drugs that are covered by insurance. Therefore, the fact that the drugs for DF are not covered by insurance in Japan may strongly influence the treatment selection as evident in the questionnaire.

Conclusion

A questionnaire survey revealed the actual status and transition of treatment of desmoid-type fibromatosis at specialized bone and soft tissue tumor treatment facilities in Japan. The number of facilities that choose surgical treatment has tended to decrease, and several facilities are considering the use of pazopanib, which may reflect global guidelines for DF. It is necessary to continue to disseminate the contents of the guidelines in Japan published in 2019 and the global guideline paper published (12,25) not only to orthopedic oncologists, but also to physicians of other departments such as general surgery, thoracic surgery, plastic surgery, and otolaryngology, as well as to patients and their families.

Supplementary Material

Supplementary material is available at *Japanese Journal of Clinical Oncology* online.

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Facilities that responded to the questionnaire survey, 2015: Aichi Cancer Center Hospital, Ehime University, Osaka Medical College, Osaka City University, Osaka International Cancer Institute, Osaka University, Okayama University, Kagawa University, Kanmon Medical Center, The Cancer Institute Hospital of JFCR, Gifu University School of Medicine, Kyushu University, Kyoto University, Kyorin University, Kindai University, Kurume University, Gunma University Hospital, National Cancer Center Hospital, National Hospital Organization Osaka National Hospital, Kochi University, Kobe University, Sapporo Medical University, National Hospital Organization Shikoku Cancer Center, Shizuoka Cancer Center, Saitama Medical University International Medical Center, Jichi Medical University Saitama Medical Center, Juntendo University, Teikyo University, Teikyo University Hospital, Mizonokuchi, Tokyo Dental College Ichikawa General Hospital, The University of Tokyo, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tohoku University, Tokushima University, University of Toyama, Nagoya City University, Nagoya University, Nara Medical University, Niigata University, Hyogo Cancer Center, Fukushima Medical University, Hokkaido Cancer Center, Matsushita Memorial Hospital, Mie University, Yonago Medical Center, University of the Ryukyus.

2018: Aichi Medical University, Aichi Cancer Center Hospital, Ehime University, Osaka City University, Osaka International Cancer Institute, Osaka University, Okayama University, Kanazawa University, The Cancer Institute Hospital of JFCR, Gifu University, Kyushu University, Kyoto Prefectural University of Medicine, Kyorin University, Kurume University, Gunma University, Keio University, National Cancer Center Hospital, National Hospital Organization Osaka National Hospital, Saitama Prefectural Cancer Center, National Hospital Organization Shikoku Cancer Center, Juntendo University, Shinshu University, Teikyo University, Tokai University, The University of Tokyo, Tohoku University, Tokushima University, Tottori University, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Nagasaki University, Nagoya City University, Nagoya University, Niigata University, Hamamatsu University School of Medicine, Hyogo College of Medicine, Hyogo Cancer Center, Hirosaki University, Hiroshima University, Matsushita Memorial Hospital, Mie University, University of Yamanashi.

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Conflict of interest

The authors have no conflict of interest to report in conducting this study.

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